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Edited by

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B. Pertuiset, Paris
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M. G. Yaşargil, Zurich

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Preface

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

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

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

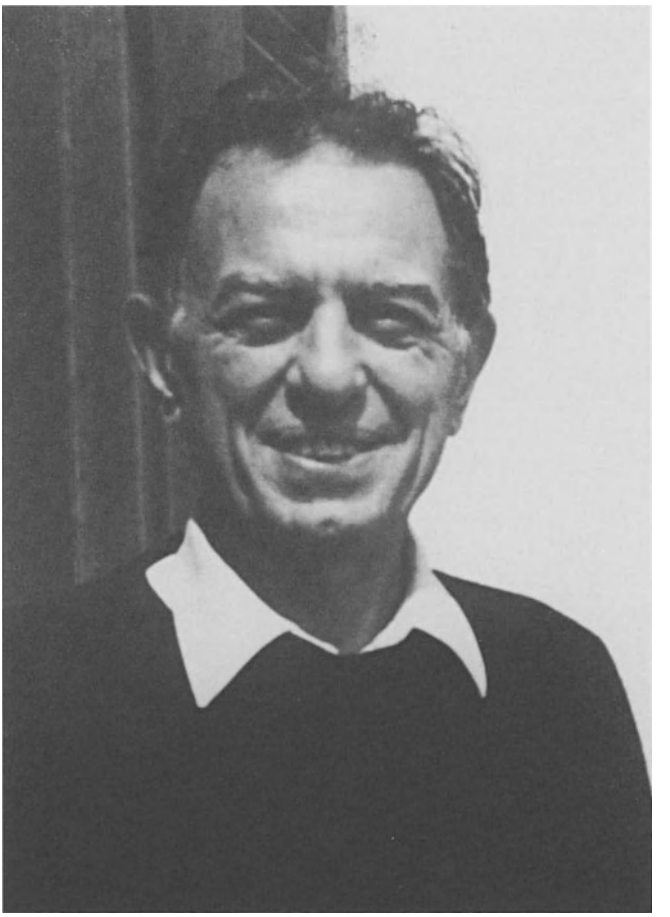
Our series is not intended to compete with the publications of original scientific papers in other neurosurgical journals. Our intention is, rather, to present fields of neurosurgery and related areas in which important recent advances have been made. The contributions are written by specialists in the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

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

The descriptions of standard operative procedures are a novel feature of our series. We intend that this section should make available the findings of European neurosurgeons, published perhaps in less familiar languages, to neurosurgeons beyond the boundaries of the authors countries and of Europe. We will however from time to time bring to the notice of our European colleagues, operative procedures from colleagues in the United States and Japan, who have developed techniques which may now be regarded as standard. Our aim throughout is to promote contacts among neurosurgeons in Europe and throughout the world neurosurgical community in general.

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

The Editors



Professor Beniamino Guidetti long associated with the Editorial Board of "Advances and Technical Standards of Neurosurgery" sadly died in July 1989. A full obituary will appear in "Acta Neurochirurgica".

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List of Contributors

Adamson, Dr. T. E., Neurochirurgische Klinik, Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland.

Caemart, Dr. J., Kliniek voor Neurochirurgie, De Pintelaan 185, B-9000 Gent, Belgium.

Calliauw, Prof. Dr. L., Kliniek voor Neurochirurgie, De Pintelaan 185, B-9000 Gent, Belgium.

Cohadon, Prof. F., Laboratoire de Neurochirurgie Expérimentale et Neurobiologie, Université de Bordeaux II, 146, rue Léo-Saignat, F-33076 Bordeaux-Cedex, France.

Cooper, Dr. P. R., New York Medical Center, New York, NY 10016, U.S.A.

Crockard, Dr. H. A., Department of Surgical Neurology, The National Hospitals for Nervous Diseases, Maida Vale, London W9 1TL, U.K.

De Tribolet, Prof. Dr. N., Service de neurochirurgie, CHUV, CH-1011 Lausanne, Switzerland.

Kelly, Dr. P. J., Department of Neurologic Surgery, Mayo Clinic, Rochester, MN 55905, U.S.A.

Lieberman, Dr. A., New York University Medical Center, New York, NY 10016, U.S.A.

Ostertag, Dr. Ch. B., Abteilung für Stereotaktische Neurochirurgie der Universität des Saarlandes, D-6650 Homburg/Saar, Federal Republic of Germany.

Pell, Dr. M., Gough-Cooper Department of Neurological Surgery, The National Hospital, Queen Square, London WC1N 3BG, U.K.

Ransford, Dr. A. O., The Royal National Orthopaedic Hospital, London, U.K.

Ransohoff, Dr. J., New York University Medical Center, New York, NY 10016, U.S.A.

Roth, Dr. P., Neurochirurgische Klinik, Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland.

Sarioglu, Dr. A. C., Neurochirurgische Klinik, Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland.

Sawamura, Dr. Y., Service de neurochirurgie, CHUV, CH-1011 Lausanne, Switzerland.

Symon, Prof. Dr. L., Gough-Cooper Department of Neurological Surgery, The National Hospital, Queen Square, London WC1N 3BG, U.K.

Yaşargil, Prof. Dr. M. G., Neurochirurgische Klinik, Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland.

A. Advances

Immunobiology of Brain Tumors

Y. SAWAMURA and N. DE TRIBOLET

Department of Neurosurgery, University Hospital, Lausanne (Switzerland)

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Definitions of Abbreviations:

ADCC	antibody-dependent cell-mediated cytotoxicity
AFP	alphafeto protein
APC	antigen presenting cell
BBB	blood brain barrier
BCDF	B cell differentiation factor
BCG	bacille de Calmette-Guerin
BCGF	B cell growth factor
BRM	biological response modifier
cAMP	cyclic adenosine monophosphate
CALLA	common acute lymphoblastic leukemia antigen
CEA	carcino-embryonic antigen
CD	cluster designation, cluster of differentiation antigens
CNS	central nervous system
CSF	cerebrospinal fluid

CR	complete response
CTL	cytotoxic T lymphocyte
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
GD	disialoganglioside
GFAP	glial fibrillary acidic protein
GM	monosialoganglioside
GM-CSF	granulocyte-macrophage colony stimulating factor
GMEM	glioma-mesenchymal extracellular matrix antigen
GT	trisialoganglioside
G-TsF (TGFβ2)	glioblastoma-derived T cell suppressor factor
HLA	human leukocyte antigen
Ig	immunoglobulin
IL	interleukin
IFN	interferon
kD	kilodalton
LAK	lymphokine-activated killer
LGL	large granular lymphocyte
MAb	monoclonal antibody
MCF	monocyte cytotoxic factor
MHC	major histocompatibility complex
MLTC	mixed lymphocyte-tumor cell culture
MR	minor response
mRNA	messenger ribonucleic acid
MTX	methotrexate
NK	natural killer
NKAF	natural killer activating factor
NKCF	natural killer cytotoxic factor
PBL	peripheral blood lymphocyte
PDGF	platelet-derived growth factor
PGE	prostaglandin E
PR	partial response
TAA	tumor-associated antigen
TCGF	T cell growth factor
TGF	transforming growth factor
TIL	tumor infiltrating lymphocyte
TNF	tumor necrosis factor
TR	transferrin receptor

Introduction

The treatment of malignant brain tumors continues to challenge neurosurgeons and basic scientists. The lack of major success with chemotherapy and radiation therapy has spurred further investigation into the biology of these tumors and host reactions to them.

Much of this research has centered upon evaluation of tumor cell antigenicity and the cell-mediated immune responses to the malignant tumors. Over recent years evidence has accumulated from monoclonal-antibody research for the presence of brain tumor-associated antigens. There has also been an increasing awareness of the ways in which a brain tumor can apparently evade host immune reactions. In addition, it is recognized that a host versus tumor reaction occurs at the site of tumor growth and that the cell-mediated immune system may have a central role for possible control of neoplastic growth. The discovery of cytokines is a major advance in modern immunology and has given insights into cellular communication and the development of the immune response.

In this review we will discuss the immunobiology of malignant brain tumors, particularly gliomas, with particular reference to the interactions between the tumor and the host immune system. In addition, given the pivotal importance of monoclonal antibodies in humoral immunity as well as cytokine-interactions in cellular immunity, ideas for potential therapeutic manipulation of host-glioma immune interactions will be critically reviewed.

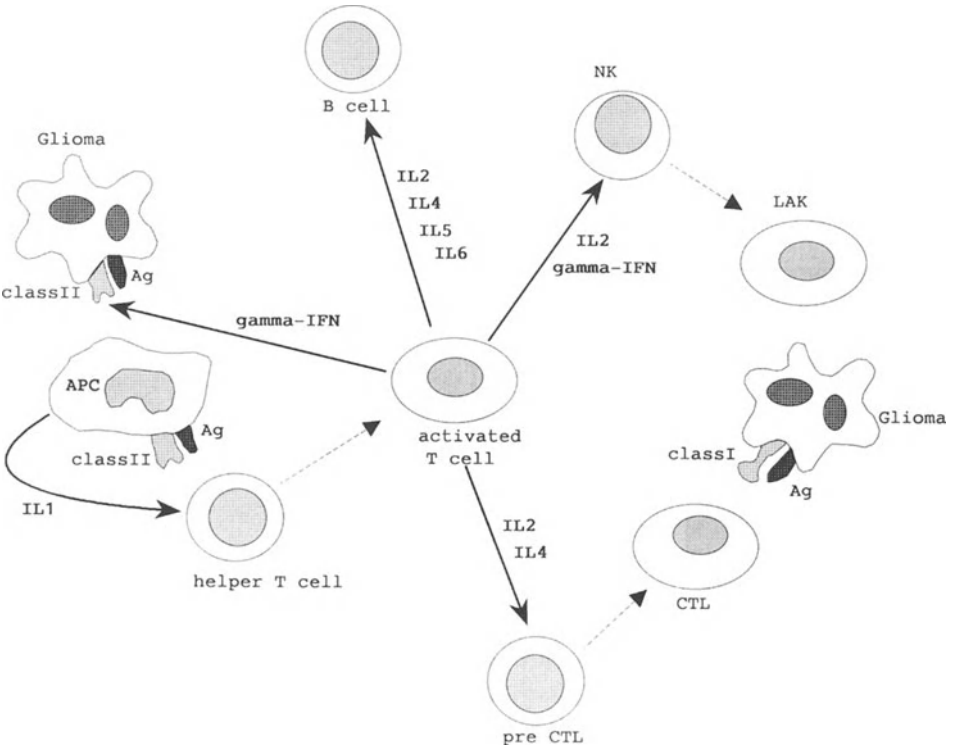


Fig. 1. Interaction of immune component cells and cytokines

We are including a brief introduction describing some of the basic concepts of immunology, which are also illustrated in Fig. 1.

One function of the immune system is to recognize foreign structures and trigger a series of reactions which eventually lead to their elimination. Effector function has therefore also to be tightly linked to recognition mechanisms in order to be focused on specific target molecules on foreign, infected or transformed cells and to avoid damage to normal cells. Antigen presenting cells (APC) possess the capacity to mediate antigen capture and processing as well as to secrete monokines such as interleukin-1 (IL1) and tumor necrosis factor (TNF). IL1 stimulates lymphokine release from T cells and stimulates IL2 receptor expression on T cells. TNF modulates the expression of major histocompatibility complex (MHC) class I antigens and is capable of inducing necrosis of cells including tumor cells.

T cells recognize an antigen only after the antigen is displayed on the surface of an APC in physical association with a MHC class II molecule. Activated T cells, in particular helper T cells, synthesize and secrete a number of lymphokines including IL2, IL3, IL4, IL5 and interferon-γ (IFN-γ) which can stimulate B cells as well as effector T cells. As a consequence of this activation, specific effector T cells. As a consequence of this activation, specific effector function of either T cells or B cells can be induced and amplified. Although antigens trigger only certain T and B cells by interacting with their surface antigen receptor and immunoglobulin, respectively, the lymphokines produced in response to activation are independent of the specific antigen initiating the immune response. IL2 binds to specific receptors on activated T and B cells, giving rise to the expansion of the activated clone. Finally antigen-specific cytotoxic T lymphocytes (CTL) recognize and kill the target tumor cells expressing the antigen in association with MHC class I molecules.

On the other hand it has become evident in recent years that some effector functions of killer lymphocytes are non-specific. For example natural killer (NK) cells display cytotoxicity towards certain tumor cell types independently of MHC expression and lymphokine activated killer (LAK) cells, generated by culturing peripheral blood lymphocytes with IL2, are non antigen specific killer cells supposedly capable of killing tumor targets in a non MHC restricted manner. NK cells normally exist in the organism whereas LAK cells can only be generated in vitro or in vivo by stimulation with high doses of IL2. The mechanisms by which LAK cells mediate cytotoxicity are still poorly understood.

I. The Immune System in the Central Nervous System

The host response to a brain tumor by either cellular or humoral immune mechanisms is unique. While it was originally thought that this occurred

because the brain was anatomically isolated from the immune system, it is now known that this is not entirely true.

The basis for classifying the CNS as an immunologically privileged site was initially derived from preliminary studies by Shirai in 1921, and from more comprehensive studies in 1923 by Murphy and Sturm. These investigators demonstrated that a xenograft of a transplantable murine sarcoma implanted into rat brain continued to grow and eventually killed its host, in contrast to extraneural implants which were universally rejected (reviewed by Neuwelt 1977, Murphy and Sturm 1923). However two decades later, evidence that revealed actual host immune responses against intracerebral allografts or xenografts led Medawar (1948) to suggest that the CNS is only partially privileged.

Moreover recent discoveries which are rapidly increasing along modern basic immunological knowledge, have demonstrated numerous interactions between the host immune system and brain malignancies as well as cancers originating from other organs. To establish an immune response, reactive astrocytes, microglia, endothelial cells and tumor cells interact with infiltrating host immune competent cells. In addition to releasing substances that stimulate the immune system tumor cells also release immune suppressive factors.

Regardless of whether the intact CNS may be a truly or partially immunologically privileged site, the brain at the site of tumor growth is no longer immunologically privileged.

Lymphatic System and Microglia

Anatomically there is no lymphatic system in the CNS as well as the anterior chamber of the eye, the thyroid and the testicle.

Microglia were first described by del Rio Ortega (1932) in silver-stained preparations at the light microscopic level. Microglia are morphologically distinct types of cells with long, branched and crenellated processes within the CNS. Their functions and particularly their origin, mesodermal, monocytic or neuroectodermal, have been controversial. If microglia were of monocytic origin it might have been expected that they would share cell surface antigens with monocytes. However a number of immunocytochemical studies have failed to demonstrate such shared antigens, Hayes *et al.* (1988) found that isolated microglia from adult human brain express some panmacrophage markers and are phagocytic in culture. Whereas nonspecific esterase staining, a characteristic of blood monocytes, is absent or weakly positive in microglia (Esiri and MacGee 1987, Hayes *et al.* 1988). Recently Perry and Gordon (1988) concluded that microglia are the resident macrophages of the brain, according to evidence that during embryonic development of the retina and brain, circulating monocytes enter and stay

Table 1. *Characteristics of Different Antigen Presenting Cells (APC)*

APC	Phagocytosis	Fc and C3 receptor	MHC class II expression	Presents to
Monocyte/macrophage	+	+	+/−	T and B cell
Dendritic cell	−	−	+	T cell
Microglia	+	+	+/−	T cell
(Activated astrocyte)	+/−	−	−/+	T cell

in these structures, and can be followed through a series of morphological transitions as they differentiate into ramified microglia.

Microglia express cell surface antigens including the Fc portion of immunoglobulin and complement receptors, and occasionally activated microglia in rat brain also express low levels of the CD 4 antigen (Perry and Gordon 1988). The expression of MHC class I and class II antigens has also been demonstrated on microglia in a variety of pathological conditions or upon stimulation by interferon-γ (DuBois *et al.* 1985, Suzumura *et al.* 1987), therefore it is suspected that microglia might function as APC, which have generally been considered to be class II positive macrophages and dendritic cells (Frei *et al.* 1987) (Table 1).

Besides functioning as APC, microglia can secrete various factors. (1) Microglia exposed to IFNγ or endotoxin develop antitumor activity and produce TNFα (Frei *et al.* 1987). (2) Microglia stimulated by lipo-polysaccharide synthesize and release IL 1 (Heiter *et al.* 1988). (3) Ameboid microglia activated in vitro release glia-promoting factors (GPFs) that stimulate the proliferation of specific glial subpopulations isolated from newborn rat (Giulian and Baker 1985). In addition IL 3 and GM-CSF are likely to be potent growth factors for microglia.

However it should be noted that there is no evidence of an increased number of microglia in malignant brain tumors in contrast to the frequent accumulation of macrophages.

Blood Vessels in Brain and Tumor

In normal brain vessels, adjacent endothelial cells are joined by continuous bands of tight junctions, no fenestrations are present, and the density of endothelial vesicles is very low. These vascular structures in combination with astrocytes constitute the blood brain barrier (BBB) which shields the brain to a certain extent from systemic humoral and cellular immunity. Immunoglobulins, IL 2 and IFNs would not be expected to effectively permeate the BBB because of their large molecular size. While some chemical characteristics such as small size of molecule, lipophilicity, low binding

to serum proteins, and carrier-mediated transport, are known to favor penetration of molecules across the BBB.

The progressive growth of a malignant tumor requires an adequate blood supply, which is furnished by newly formed vessels. Vascular transformation is a response to the nearby malignant process. It is assumed that pathological neovascularization is provoked by specific angiogenic factors including fibroblast growth factor, angiogenin, TGFα, TGFβ, TNFα and PDGF (Hermansson *et al.* 1988). PDGF, TGFα and TGFβ, known to be secreted by glioma cells may play a role in maintaining the integrity of the vascular wall as paracrine growth factors. Thus tumor cells invading normal brain can alter the structure and function of blood vessels in a variety of ways. As a result of tumor-induced endothelial changes or as a result of necrosis of the vessel itself, the blood vessels that grow and course through and around the tumor lose their BBB properties and become highly abnormal (Hirano and Matsui 1975, Stewart *et al.* 1987). The large pores in the altered vascular walls provide a pathway both for extravasation of larger molecules including serum proteins and conversely for many factors produced by tumor cells (Stewart *et al.* 1987). These factors then allow the interaction between the host immune response and the tumor cells. In addition abnormal endothelial cells in gliomas also express tumor-associated antigens of neuroectodermal type (Schreyer *et al.* 1986).

Neuropeptide Hormones and Neurotransmitters

Lymphocytes bear many receptors for a variety of agonists that deliver both positive and negative signals. These agonists include cytokines like IL 2 and IFNs, complement products, antibodies as well as helper and suppressor factors. In addition lymphocytes bear receptors for neuropeptide hormones and neurotransmitters.

These substances which have been reported to influence lymphocyte functions are; ACTH, endorphins, enkephalins, TSH, somatostatin, substance P, histamine, serotonin, dopamine, isoproterenol, epinephrine, norepinephrine. Binding of histamine, serotonin, or β-adrenergic agents to their specific receptors stimulates membrane-bound adenylate cyclase, thereby causing an increase in the intracellular concentration of cAMP (Plaut 1987). Since a rise in cAMP is associated with inhibition of various lymphokine functions (Goodwin *et al.* 1977, Rivkin *et al.* 1975), the physiologic effects of these adenylate cyclase-acting agonists on lymphocyte function is most often one of immunosuppression. These mechanisms of the neuropeptide hormones and the neurotransmitters have been reviewed extensively elsewhere (Blalock 1985, Payan *et al.* 1986, Plaut 1987, Roszman *et al.* 1985). A control of the immune function by the brain has been suggested and is called neuroimmunomodulation. A lesion in the anterior thalamus or the thalamus may suppress a variety of immune parameters, whereas a lesion

in the hypocampus, the amygdala, and the mamillary bodies may be facilitory when compared to the frontal cortex (Brooks *et al.* 1982, Cross *et al.* 1984, Forni *et al.* 1983, Imaya *et al.* 1988, Roszman *et al.* 1985). Furthermore Roszman (1985) speculated a remote effect of altered secretion of neurotransmitters on immunomodulation.
However in general these neuropeptide hormones or neurotransmitters at a physiological level do not seem to influence profoundly brain tumor immunity.

II. Brain Tumor Immunology

The central question in tumor immunology is whether tumor cells show differences from their normal cellular counterparts that can be recognized by the immune system. Antigens which are absolutely tumor-specific have yet to be discovered, or may not actually exist. There is, however, now evidence that primary malignant brain tumors are antigenic for the host immune system, and can elicit an immune response (Kuppner *et al.* 1988 a, Miescher *et al.* 1988).
Theoretically tumor-specific antigens would be the perfect targets for immunotherapy, but in practice absolute specificity does not seem to be necessary. A number of antigens, which are shared by histogenetically related tumors, have been found and characterized as for example the neuroectodermal antigens. Furthermore it does not matter from an immunotherapeutic point of view if a glioma antigen, which may exhibit therapeutically functional specificity, is also expressed by other brain tumors, since distinction from the host's normal tissue is the essential requirement. Moreover certain cytotoxic lymphocytes such as LAK cells appear to be capable of killing a variety of malignant tumor cells but not normal cells without recognition of tumor-specific antigens (Table 2).

Table 2. *Restriction of Lymphoid Cell Activation*

Function	Surface phenotype	Restriction
Helper T lymphocytes	CD3+CD4+CD8−	MHC class II + antigen
Cytotoxic T lymphocytes	CD3+CD4−CD8+ (or CD3+CD4+CD8−)	MHC class I + antigen (or MHC class II + anitgen)
NK cells and LAK cells	CD3−CD16+ or CD3±Leu19+	MHC non-restricted ? antigen

1. Tumor-associated Antigens (TAA)

Since most treatment modalities of malignant brain tumors have limited efficacy, attention has turned to more innovative techniques for selectively

identifying and destroying gliomas. To this end, there has been a major quest to identify specific antigens on the surface of glioma cells that are not shared by other normal cells of the brain and the body.

Some cytoplasmic antigens of brain tumors shared with normal brain have been described including glial fibrillary acidic protein (GFAP), S-100 protein, neuron-specific enolase (NSE) and vimentin. These are useful markers in immunohistological diagnosis and have been reviewed elsewhere (Bonnin and Rubinstein 1984, Esiri 1982). They will not be considered further here since they are normal antigens and sequestered within the cell and are therefore not suitable targets for an immune response against malignancy. In contrast cell surface membrane antigens are of greater relevance in tumor immunology.

The initial process of identification of these antigens was slow because the antibodies used to search for the "glioma antigens" were produced from either autologous sera of glioma patients, or heterosera of animals immunized with human brain tumor. These antisera had to be exhaustively absorbed on normal tissues in order to remove contaminating antibodies and very little specific antibody was left for study. Yet, using these techniques that may be regarded as outdated today, a great deal was learned (Coakham and Lakshmi 1975, Coakham 1984, de Tribolet and Carrel 1980, Pfreundschuh *et al.* 1982, Schnegg *et al.* 1981 a, Wahlström *et al.* 1974). The studies using antisera have demonstrated the existence of differentiation antigens which appeared common to astrocytomas (Coakham 1974, Schnegg *et al.* 1981 a) and also of oncofetal antigens which were expressed on various types of brain tumors as well as foetal tissues (Wahlström 1974, Wikstrand and Bigner 1979). Furthermore a group of common neuroectodermal antigens were detected, some of which were shared by melanomas (Kornblith *et al.* 1979, Pfreundschuh *et al.* 1978).

A major breakthrough occurred with the development of the monoclonal antibody (MAb) technology by Köhler and Milstein (1975). This technique utilizes the fusion of non-specific antibody-secreting myeloma cells with specific antibody secreting murine spleen cells. The somatic cells hybrids produced codominantly express immortality and specific antibody production, so that secretion can be fixed as a permanent property of an established cell line. Kennett and Gilbert (1979) were the first to generate an MAb against a neuroblastoma antigen which was also shared by fetal brain.

Three significant groups of antigens have been identified on brain tumor cells using MAb: (1) tumor-associated antigens, (2) MHC antigens, (3) lymphoid differentiation antigens.

In the past several years, MAbs against tumor-associated antigens have been produced. Glial antigens are primarily displayed on gliomas and MAbs directed to glial antigens have some additional minor specificity for other

nonneuroectodermal tissues and reactive astrocytes (de Tribolet *et al.* 1984a, Schnegg *et al.* 1981b). While neuroectodermal antigens form a major component of the surface antigens found on glioma cells, they are also present on other tissues derived from the neuroectoderm and tumors that arise therefrom. Neuroectodermal antigens have been detected on gliomas, melanomas, neuroblastomas as well as fetal brain cells and endothelial cells within gliomas (Cairncross *et al.* 1982, Carrel *et al.* 1982a, Dickinson *et al.* 1983, Kennett and Gilbert 1979, Piguet *et al.* 1985, Seeger *et al.* 1981). Screening with the MAbs has demonstrated that a number of these antigens may be present singly or in groups. The expression of melanoma-associated antigens on endothelial cells within malignant gliomas is a particularly interesting phenomenon (Schreyer *et al.* 1986). The presence of these antigens on tumor cells attests to their neuroectodermal origin, while the expression of the same antigen on endothelial cells suggests that a significant transformation has taken place. Using tissues from a large number of malignant gliomas and a panel of MAbs, the overall representation of these brain tumor-associated antigens has been studied and summarized elsewhere (Behnke *et al.* 1988a, de Muralt *et al.* 1983, Fischer *et al.* 1988).

It has become evident that a glioma is not a homogeneous collection of cells all having similar antigenic determinants, which means that a given antigen is not present on all the cells of a given tumor (de Tribolet 1982, Schnegg *et al.* 1981b). Cells of a malignant glioma have a constantly varying multiprobable antigenicity (Bigner 1981, de Muralt *et al.* 1985, Shapiro *et al.* 1981, Studer *et al.* 1985, Wikstrand *et al.* 1983). Furthermore many intrinsic and extrinsic factors can alter or induce changes in cellular antigen expression. In the case of a malignant glioma, these factors might include: cell age, state of each cell in its own cell cycle, heterogeneity of the original clonogenic cells, external humoral factors, external immune cell interactions with tumor cells and the effects of attempted therapy. All of these would have significant effects on some or all the cells within a malignant glioma and limit the probability that a single antigen would be resident on all or even a critical number of cells. This concept limits the possibility that single antibody directed therapy would be successful.

Following Coakham's opening-up of this field (Coakham 1974, Coakham and Lakshmi 1975), a large number of brain tumor-associated antigens detected by either antisera or MAb were reported. The following MAbs may have clinical value.

81C6 (anti-GMEM MAb)

The glioma mesenchymal extracellular matrix (GMEM) antigen localizes on the basement membrane of glioblastomas and associates with proliferative endothelium of the hyperplastic vessels. It is defined by the mono-

clonal antibody 81 C 6, obtained from a murine hybridoma supernatant immunized by a cell suspension of the glioma cell line U-251 MG. In antibody binding radioimmunoassay using 81 C 6, it has been shown that the GMEM antigen is present on most glioma and fibroblast cell lines and on some of the tested neuroblastoma, sarcoma, ovarian carcinoma and melanoma cell lines. Immunohistochemistry has also demonstrated binding to fetal and adult spleen, liver, adult kidney and mesenchymal cells, but not to normal adult brain (Bourdon *et al.* 1983, 1984, Bullard *et al.* 1986, McComb and Bigner 1985).

UJ 13 A

UJ 13 A recognizes all neuroectodermal tumors except melanomas and also reacts with normal brain, peripheral nerves, adrenal medulla, adult thyroid epithelium, fetal kidney tubules, and primary cultures of fetal myoblasts. It was raised after immunization with homogenates of human fetal brain (16 weeks gestation) and obtained from murine hybridoma ascites (Allan *et al.* 1983, Davies *et al.* 1985, Garson *et al.* 1985).

Mel-14

Mel-14 antibody raised against membrane-enriched fractions from the melanoma cell line Me-43 was obtained from murine hybridoma supernatants and ascites. Mel-14 (IgG 2 a) reacts with a 240 kD glycoprotein antigen found on a large number of melanoma cell lines and other neuroectodermal tumors. Cross-reactivity was not detected with the normal adult tissues tested (Carrel *et al.* 1980, 1982 a, de Tribolet *et al.* 1984 a).

Anti-EGFR MAb 425

The epidermal growth factor receptor (EGFR), which is the normal cellular counterpart of the viral erb B oncogene (Downward *et al.* 1984), may be an interesting target antigen for MAb (Woo *et al.* 1988). Large amounts of EGF are present in normal brain and may have a paracrine or autocrine role in the growth of brain tumors overexpressing EGFR. EGF enhances the growth of fresh glial tumor cells in serum-free conditions (Fallon *et al.* 1984, Frappaz *et al.* 1988). The EGFR molecule is a glycoprotein of 170 kD and is composed of an extracellular EGF binding domain linked by a transmembrane segment to an intracellular portion with tyrosine kinase activity (Hunter 1984). Antigenic determinants in the extracellular domain of the receptor can serve as a target for MAb which can be used for therapy (Basu *et al.* 1987, Rodeck *et al.* 1987). MAb 425 of IgG 2 a isotype was derived from mice immunized with A 431 epidermoid carcinoma cells and binds to a protein determinant on the external domain of the EGFR

(Murthy *et al.* 1987). The EGFR has been shown to be overexpressed in some 50% of malignant gliomas (Libermann *et al.* 1984), in addition our recent study on 60 samples of malignant glioma using MAb 425 also showed immunostaining in 37 samples (62%) (Strommer *et al.* 1989). EGFR is expressed rarely on normal brain tissue, and not at all on bone marrow and peripheral blood cells. There is a concomitant amplification of the EGFR gene in approximately 40 to 50% of malignant gliomas (Bigner *et al.* 1988, Libermann *et al.* 1985, Strommer *et al.* 1989).

Anti-GD 2 and GD 3 Ganglioside MAb

Gangliosides on certain malignant tumor cells are immunogenic membrane-associated glycolipids (Tai *et al.* 1985). MAbs OFA-I-2 and 14.18 react with diasialoganglioside GD 2. MAbs 11 C 64 and R 24 are reactive with the diasialoganglioside GD 3. OFA-I-2 was raised against EBV transformed PBL of a melanoma patient and recognizes cell surface GD 2 on glioma cells as well as other GD 2 positive cells (Cahan *et al.* 1982, Honsik *et al.* 1986, Houghton *et al.* 1985).

Major Histocompatibility Antigens on Tumor Cells

MHC class I antigens are expressed on all nucleated cell types except brain cells (Daar *et al.* 1984, Forman 1984). MHC class II antigens, including HLA-DR and HLA-DQ molecules, have a more limited tissue distribution; they are present on cells of the immune system, such as B lymphocytes, cells of the monocyte/macrophage lineage (including epithelial Langerhans cells and dendritic cells), thymic epithelium, and activated T cells (Hirshberg *et al.* 1982, Shackelford *et al.* 1982).

The expression of certain MHC class II antigens (particularly HLA-DR) is necessary for activation of the immune system to present new foreign antigens. A putative tumor antigen can be immunogenic only if it is recognized together with the self MHC molecule by APC. A key step in initiating an immune response is that the APC expresses MHC class II molecules in association with foreign antigens (Unanue *et al.* 1984). The necessity for coexpression of both the class II antigen and foreign antigen on the tumor cell and APC forms a double check system to guard against indiscriminate activation of the T lymphocytes by antigens. In addition MHC class I (particularly HLA-A) expression is required on the target cells for the lytic action of effector cells to take place (see Tables 1 and 2). Certain correlations have been reported between the clinical outcome and the expression of MHC antigens, in that several of the most aggressive tumor types with poor prognosis do not express MHC class I antigens (Bröcker 1985, Doyle *et al.* 1985). Marked lymphoid cell infiltration as a possible host immune response was present in a higher proportion of MHC

class II positive human tumors (Vànky *et al.* 1988), human melanoma cells expressing HLA-DR were able to induce the in vitro proliferation of autologous T cells whereas DR negative cells could not do so (du Pont *et al.* 1984).

Although normal resting brain astrocytes do not exhibit MHC class II antigens, a surprising finding is that some activated astrocytes and glioma cells as well as hyperplastic endothelial cells within the CNS can express HLA-DR (de Tribolet *et al.* 1984 b, Frank *et al.* 1986). However, on tissue sections of glioblastomas a small percentage of malignant astrocytes (5—20%) were shown to express HLA-DR, which is also expressed on only a fraction of glioma cells or cell lines in vitro. The question then arises how the HLA-DR negative tumor cells could be induced to express these antigens. In general IFNs have been known to enhance or induce the expression of MHC class I and class II antigens on normal lymphoid cells and macrophages, thereby modulating the immune response. Particularly IFNγ selectively modulates the expression of HLA-DR. Gerosa *et al.* (1984) and Piguet *et al.* (1986) have demonstrated that HLA-DR can be modulated by IFNγ on a number of glioma cell lines and their clones but not on all of them. Regarding the in vivo mechanism, after initial contact with brain endothelium and disruption of the vessel wall the invading preactivated T cells may release IFNγ locally into the tumor tissue, and thereby may trigger HLA-DR antigen expression on glioma cells and macrophages. Furthermore activated macrophages and microglia can secrete TNFα which in turn may enhance the expression of HLA-ABC (Zuber *et al.* 1988 a). In contrast TGFβ 2 which can be secreted by glioma cells produces a partial but significant decrease of constitutive and IFNγ induced HLA-DR surface antigen expression on glioma cells (Zuber *et al.* 1988 b).

Lymphoid Differentiation Antigens on Brain Tumors

Normal brain and tumors of neuroectodermal origin express lymphoid differentiation antigens. Included within this group are lymphoid antigens normally present on functioning lymphocytes (CD 3: recognized by Thy-1, HNK-1: by Leu 7) and antigens expressed by lymphocytes that have undergone malignant change (CALLA) (Carrel *et al.* 1982 b, Kemshead *et al.* 1982, Pesando *et al.* 1981, Seeger *et al.* 1982, Wikstrand *et al.* 1983). CALLA has been shown to be present on a broad panel of gliomas (Carrel *et al.* 1982 b, Ritz *et al.* 1980 a, 1980 b) and on normal brain. Recently Letarte *et al.* (1988) reported that CALLA is identical to neutral endopeptidase (NEP; known as enkephalinase) which inactivates several peptide hormones. This enzyme activity was actually found on CALLA-positive glioma cell lines (Monod unpublished data). In addition CD 4 known as a marker of T helper lymphocytes may be expressed on neurons, glial cells and microglia in the brain (Funke *et al.* 1987, Maddson *et al.* 1986, Perry

and Gordon 1988). The expression of these lymphoid differentiation antigens on glioma cells and astrocytes suggests common functional properties between lymphocytes and glial cells.

2. *Humoral Immune Response*

The humoral immune response of patients with CNS malignancies has been widely investigated. Populations of B lymphocytes are present within gliomas, but their ability to produce anti-glioma antibodies capable of participating in complement dependent or antibody dependent cell-mediated cytotoxic (ADCC) responses is doubtful.

The absolute values of serum immunoglobulin levels of brain tumor patients do not fall outside normal ranges, with the exception of IgM levels (Mahaley *et al.* 1977, Seeldrayers *et al.* 1984). Several laboratories have demonstrated the presence of limited antiglioma activity within the sera of a small number of patients harboring CNS gliomas (Apuzzo 1981, Appuzo and Mitchell 1981, Coakham 1984, Kornblith *et al.* 1974, 1979, Pfreundschuh *et al.* 1978). The presence of antibodies in glioma patients' serum which were cytotoxic against autologous tumor cells in vitro has been suggested to correlate with survival (Kornblith *et al.* 1983). This activity was stronger in patients with low grade gliomas and it may be constituted by an IgG or IgM antibody. In addition Garson *et al.* (1981) reported that the IgM fraction was more effective in mediating cytotoxicity than IgG.

It seems to be important to realize that a majority of these cytotoxicity assays were carried out with animal complement, however human complement seems relatively ineffective in mediating such antibody cytotoxicity against glioma cells (Woolsley *et al.* 1977). Furthermore a part of these studies were carried out allogeneically so that anti-HLA effects might be responsible for some of the reactivity observed. In another study using large numbers of patients, the antiglioma activity of patient's sera has been demonstrated to be largely nonspecific and to extend to other neuroectodermal tumors and to connective tissues, and this antiglioma activity could be readily absorbed out of the sera by cells of other tumors and by platelets (Martin-Achard *et al.* 1980 a). In addition Martin-Achard *et al.* (1980 b) demonstrated that some 28% percent of patients with malignant glioma had immune complexes in their sera. The mean survival in this group of patients was half of that observed in those who did not have such complexes.

Part of the serological response may originate from intratumoral lymphocytes, since Sikora *et al.* (1982) were able to isolate B cells from human gliomas which after hybridization with a human myeloma line were thought to produce monoclonal antibodies against glioma-associated antigens. Elevated immunoglobulin level in the CSF in certain patients with either malignant or benign glioma has been reported, while serum immunoglob-

ulin levels of these patients were normal (Neuwelt 1977). It is of interest to mention that IL 6 which can be secreted by glioma cells promotes immunoglobulin production by activated B lymphocytes.

3. Cell-mediated Immune Response

Killer lymphocytes can recognize malignant cells either in a MHC-restricted or non-MHC-restricted manner (Table 2).

The initial step of MHC-restricted antigen recognition is arbitrated by APC including macrophages, some reactive astrocytes and microglia (Fontana *et al.* 1984 a, Perry and Gordon 1988). After MHC-restricted antigen recognition by the antigen-specific T cell receptor (Ti), helper T lymphocytes ($CD3^+CD4^+$) carry out a wide variety of regulatory functions (Dalgleish 1986). Antigen binding in the presence of macrophage-derived IL 1 triggers synthesis and secretion of IL 2 and the transient expression of high and low affinity IL 2 receptors on helper T cells (Robb *et al.* 1981). Antigenic effector T cell activation is then initiated by antigen binding to specific T cell receptors present on the surface of resting T cells ($CD3^+CD8^+$) in association with MHC class I molecules. The subsequent interaction of IL 2 with its high affinity membrane receptor results in the clonal expansion of antigen-specific effector T cells. Finally the cytotoxic T lymphocytes lyse cells expressing MHC class I molecules. The expression of an intercellular adhesion molecule 1 (ICAM-1) on astrocytes or glioma cells as the ligand for lymphocyte-associated antigen 1 (LFA-1) may enhance the connection between effector and target cells. IFNγ can induce not only the expression of MHC class II antigen, but also the expression of ICAM-1 (Gupta *et al.* 1988).

In contrast the NK or LAK effects do not utilize the antigen-specific T cell receptor (Ti) and the MHC antigens on the target cells are not involved (non-MHC-restricted response). NK cells, which is a heterogeneous population of lymphocytes expressing Fc receptors ($CD16^+$) and exist mainly in the LGL (large granular lymphocyte) fraction of PBL, can lyse certain human malignant tumor cells, but not fresh solid tumors. Lymphocytes activated with IL 2 (LAK cells) acquire the capacity to kill almost all types of genetically unrelated tumor target cells which are resistant to nonactivated NK cells. The predominant cell type responsible for this lytic phenomenon defined as LAK activity is mainly represented by activated NK cells ($CD3^-CD16^+$). A minor population of IL 2-activated killer cells are also known to expresses $CD3^+CD4^-CD8^-CD16^-$ (Gerosa *et al.* 1988), $CD3^+Leu19^+$ or $CD3^-Leu19^+$ (Whiteside *et al.* 1988 a, 1988 b). Human LAK cells can recognize aspects of tumor cells that are absent on normal cells and lyse a wide spectrum of malignant brain tumors (Jacob *et al.* 1986 a, 1986 b). The molecular nature of target

recognition by these cells has not yet been clearly identified. The search for human NK-specific target structures in the past years has led to the discovery of several potential candidates such as the transferrin receptor (Alarcon and Fresno 1985), mannose-6 (Werkmeister and Pross 1985), proteoglycans (MacDermott *et al.* 1986) and GM 2 ganglioside (Ando *et al.* 1987).

It has been repeatedly emphasized that the cellular immune response in patients with a malignant brain tumor is significantly depressed according to the following evidence;

(1) Anergy in skin tests (Brooks *et al.* 1972).

(2) Reduction in the absolute number of PBL (Mahaley *et al.* 1977).

(3) Decreased count and impairment of rosette-forming T cells (Brooks *et al.* 1976).

(4) Increase in the number of lectin receptors on peripheral blood T lymphocytes (Roszman *et al.* 1982).

(5) Increase in the number of T suppressor lymphocytes (Braun *et al.* 1982, Gerosa *et al.* 1981, van Hawehr *et al.* 1984).

(6) Increase in peripheral blood monocyte suppressor cells (Braun *et al.* 1984, Wood and Morantz 1983).

(7) Decrease in the OKT 4/OKT 8 ratio (Uegaki *et al.* 1988).

(8) T cell suppression due to anticonvulsants, anti-inflammatory agents, and circulating antigen-antibody complexes (Gately *et al.* 1982 a, 1982 b, Sjögren *et al.* 1971).

(9) Impaired lymphocyte blastogenic response (Braun *et al.* 1982, Brooks *et al.* 1972, Elliot *et al.* 1984, Gerosa *et al.* 1981, Roszman *et al.* 1982).

(10) Inhibitory effect of patients' sera on lymphocyte responsiveness to T cell mitogens (Wahlstrom 1974, Young *et al.* 1976).

(11) Suppression of NK activity (Braun *et al.* 1984, Imaya *et al.* 1988).

(12) Reduced IL 2 production and IL 2 receptor expression of mitogen-stimulated T cells (Elliot *et al.* 1984, 1987).

It is generally accepted that the reaction of the host immune system to tumor tissue occurs predominantly at the site of tumor growth. Therefore functional analyses of tumor infiltrating lymphocytes seem to be important.

The first detailed report regarding the relevance of lymphocytic infiltration in gliomas was published in 1971 by Ridley and Cavanagh. Thereafter a number of reports have demonstrated that the degree of lymphocytic infiltration in CNS neoplasms has some relevance to the prognosis (Brooks *et al.* 1978, di Lorenzo *et al.* 1977, Mahaley *et al.* 1977, Maunoury *et al.* 1975, Palma *et al.* 1978, Ridley and Cavanagh 1971, Schiffer *et al.* 1974). However Safdari *et al.* (1985) evaluated 342 biopsy specimens of malignant glioma and observed that the presence of lymphocyte infiltration in the tissue was conversely associated with a poor prognosis.

According to immunohistochemical studies using MAbs to lymphocyte

subset markers, the mononuclear cells found in glioma tissue have been identified as being mostly T lymphocytes, with a predominance of the cytotoxic/suppressor ($CD\,8^+$) cell subset (Fig. 2). The infiltration was most pronounced at the tumor periphery (Stavrou *et al.* 1977) and NK cell, macrophage and B lymphocyte infiltration was also demonstrated. Lymphocyte infiltration in glial tumors is relatively scarce in contrast to that found in metastatic brain tumors or cancers of other organs (Brooks *et al.* 1978, di Lorenzo *et al.* 1977, Hitchcock and Morris 1988, Paine *et al.* 1986, Palma *et al.* 1978, Ridley and Cavanagh 1971, Saito *et al.* 1987, von Hanwehr *et al.* 1984). In addition the number of TIL isolated from gliomas is often extremely low in comparison to TIL derived from other tumor types (Heo *et al.* 1988, Itoh *et al.* 1986, Rabinowich *et al.* 1987, Topalian *et al.* 1988, Whiteside *et al.* 1988 b).

Recent work has shown that the tumor infiltrating lymphocytes (TIL) isolated from malignant gliomas can be cultured using a limiting dilution microculture system (Kuppner *et al.* 1988 a, Miescher *et al.* 1988). The lymphocyte cultures obtained by this method were capable of killing allogeneic and autologous tumor cells in vitro. The antitumor activity of the TIL against autologous tumor cells studied in limiting dilution system was significantly higher than that of the IL 2-activated PBL of the same patients suggesting that there may be a selective accumulation of lymphocytes at the tumor site (Kuppner *et al.* 1988 a).

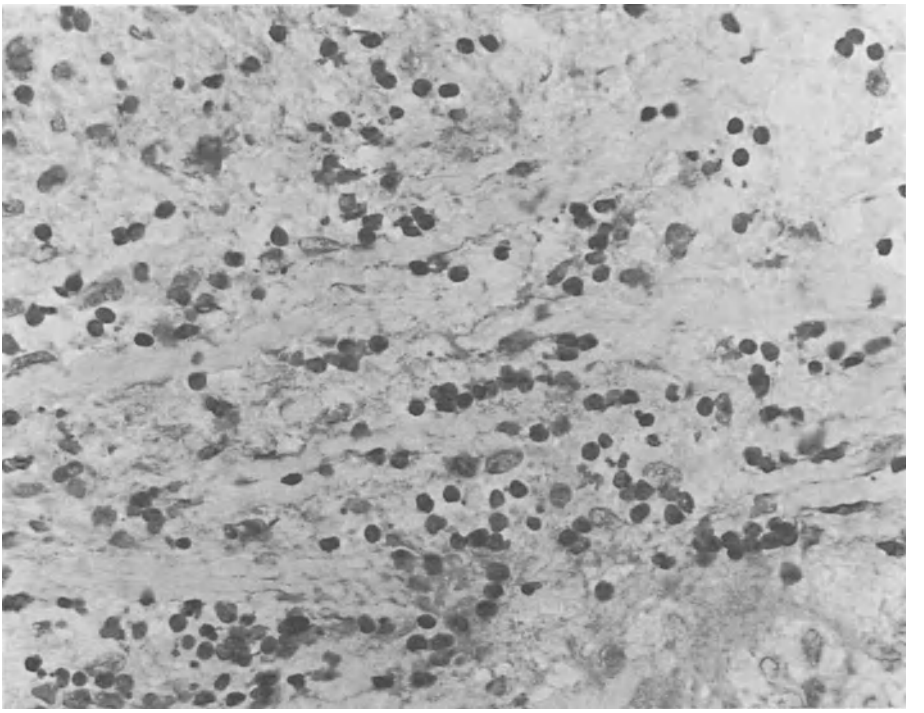
T lymphocytes isolated from brain tumors have been shown to be small nonblastic and negative for activation antigens (Miescher *et al.* 1988), however the maturation and activation of glioma-derived TIL can be generated after in vitro exposure to exogenous IL 2 (Sawamura *et al.* 1988 a). Therefore it is suspected that suppression of glioma-infiltrating precursors by the tumor cells in situ may be more profound than that of TIL in the cancers of other organs, since freshly isolated TIL from these cancers are more numerous in addition to being IL 2 receptor positive (Heo *et al.* 1988, Rabinowich *et al.* 1987, Topalian *et al.* 1988, Whiteside *et al.* 1988 b).

This evidence has lead us to consider a suppression mechanism of the host-immune response by gliomas.

4. Modulation of the Host-immune Response by Gliomas

Augmentation of immunity requires induction of increased effector function, and also requires concomitant abatement of regulatory (suppressor) activities. Human brain tumors can secrete a variety of immunosuppressive factors and this inhibitory role is thought to provide the means for tumor self-defense.

Several studies have shown the suppressive effect of supernatants derived from glioma cell cultures. Even a brief exposure of normal lectin-responsive

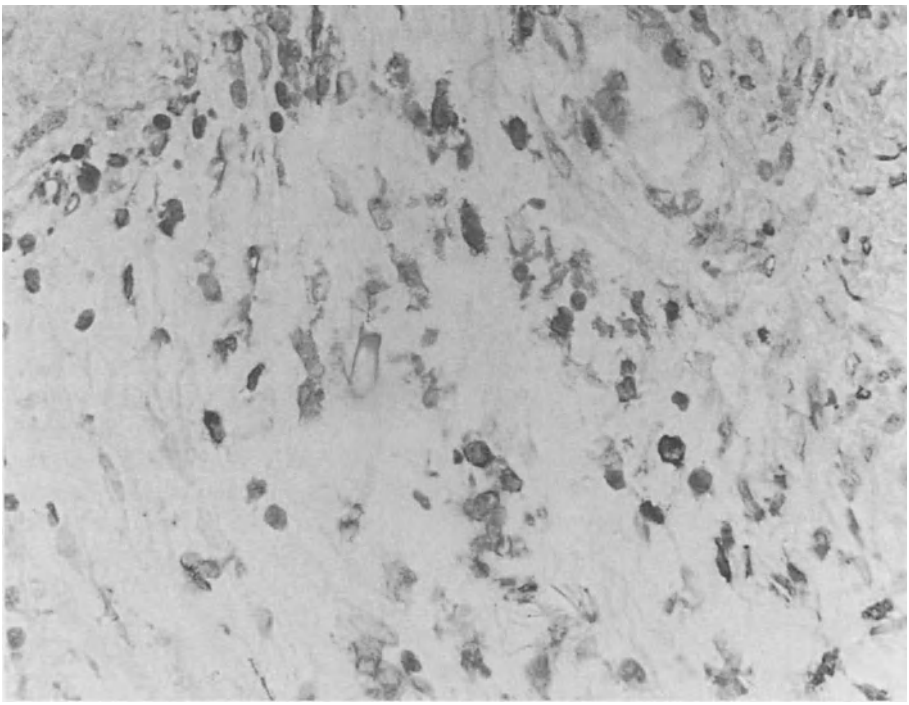


A

Fig. 2. Immunoperoxidase staining of human glioblastoma, demonstrating lymphoid cell infiltrations. A) Accumulation of CD 3-positive T cells. B) Accumulation of CD 14-positive macrophages

PBL to the supernatant of cultured glioma cells abolished the proliferative response of lymphocytes (Miescher *et al.* 1988). LAK cell activation by IL 2 was also considerably suppressed by coculture with glioma cells (Grimm *et al.* 1988). Furthermore we found that activation and proliferation of glioma-derived T lymphocytes were profoundly suppressed by addition of a supernatant obtained from their autologous glioma culture. In addition brain-tumor cyst fluid was found to inhibit the activation of mitogen-stimulated PBL (Kikuchi and Neuwelt 1983).

On the other hand certain glioma cell lines produce hyaluronidase-sensitive mucopolysaccharide coats on their cell surface which impair activation of lymphocytes and hinders direct interaction of glioma cells with other cells (Dick *et al.* 1983, Gately *et al.* 1982 b). The interference with cell to cell interactions by the glioma-cell coat may limit recognition and presentation of glioma antigens. In addition this coat also prevented tumor cell killing by specific cytotoxic allogeneic lymphocytes (Gately *et al.* 1984).



B

Recent studies have revealed that these observations can be explained by the action of molecules secreted by tumor cells (Fig. 3). It will be of interest to determine the therapeutic utility of pharmacologic manipulation of these suppressive factors.

TGFβ 2

TGFβ 2 may in part be responsible for the immunosuppression observed in glioma patients (Wrann *et al.* 1987).

A factor isolated from glioma cells maintained in culture has been demonstrated to antagonize profoundly the effects of interleukin 2 (Fontana *et al.* 1984 b). This factor has been termed glioblastoma-derived T cell suppressor factor (G-TsF) by Fontana and it is capable of suppressing both interleukin 2 dependent T cell proliferation and the generation of cytotoxic T cells in allogeneic mixed lymphocyte cultures. Recently this factor has been shown to be identical to TGFβ 2 (de Martin *et al.* 1987, Schwyzer 1985, Wrann *et al.* 1987).

TGFβ type 1 and type 2 have been shown to have a potent immunosuppressive effect on multiple immune functions such as; IL 2 dependent T cell proliferation, IL 2 receptor expression on stimulated T cells, IFN

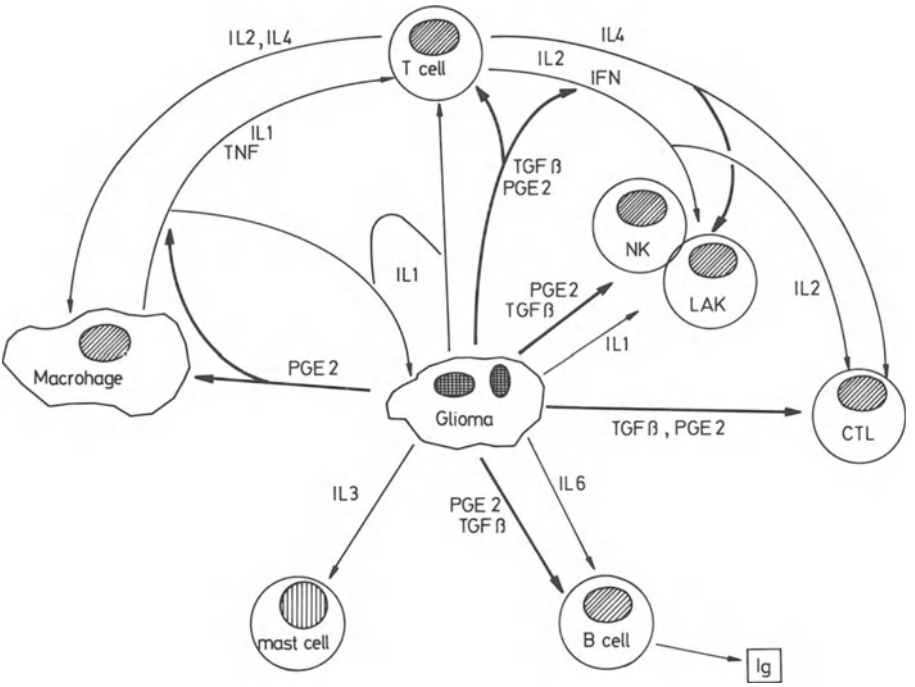


Fig. 3. Immunoregulatory factors secreted by glioma cells and leukocytes. TGFβ and PGE 2 are thought to be responsible for suppression of host-immune responses. →: suppression. →: enhancement

boosting of NK activity, cytotoxic T cell development in allogeneic mixed lymphocyte cultures, generation of LAK cells, IL 1 dependent lymphocyte proliferation, proliferative response of glioma derived TIL, cytotoxic activity of TIL against autologous glioma cells, IFN-induced class II antigen expression on tumor cells, immunoglobulin production and B cell proliferation (Fontana *et al.* 1984 b, Grimm *et al.* 1988 b, Kehrl *et al.* 1986 a, Kuppner *et al.* 1988 b, 1989, Spiel *et al.* 1988, Zuber *et al.* 1988 b, Wahl *et al.* 1988).

Increasing concentrations of IL 2 could overcome the suppressive activity of TGFβ on IL 2-dependent proliferation of stimulated lymphocytes and B cells (Kehrl *et al.* 1986 a, 1986 b, Mulé *et al.* 1988). TNF may partly reverse inhibition of cytotoxic T cell development (Ranges *et al.* 1987). However the inhibition of immunoglobulin secretion induced by TGFβ cannot be overcome by higher concentrations of the lymphokines (Kehle *et al.* 1986 b).

In addition TGFβ 2 secreted by tumor cells can augment tumor growth indirectly by effects on the stromal elements such as enhancement of both angiogenesis and formation of connective tissue (Roberts *et al.* 1988).

PGE 2

PGE is another major immunomodulator found to be secreted by glioma cells (Fontana *et al.* 1982).

Prostaglandins play a role in inflammation as modulators of the immune system. Prostaglandins of the E series (PGE), and in particular PGE 2 can increase vascular permeability and edema (Williams and Peck 1977), cause fever and sensitize pain receptors. Therefore they may cause a peritumoral brain edema.

PGE 2, which is produced in large amounts by monocytes and may be produced by microglial cells as well as glioma cells, exerts profound effects on a variety of immunological parameters and may be a means of local communication between cells which regulate the immunological response to antigen (Chouaib and Bertoglio 1988). (1) PGE 2 at physiological doses (10^{-8} to 10^{-6}mol) primarily exerts its inhibitory effect on lymphocyte proliferation through an inhibition of IL 2 production by T helper lymphocytes and downregulation of IL 2 receptor expression (Hancock *et al.* 1988, Rappaport and Dodge 1982). (2) PGE 2 to inhibits antigen and mitogen-stimulated T cell proliferation and lymphokine production, to alter accessory cell functions and the development of humoral responses. (3) PGE 2 also interferes with various aspects of cell-mediated cytotoxicity including the generation of CTL, NK activity, LAK cell-differentiation and macrophage-mediated cytotoxicity (Chouaib and Bertoglio 1988). (4) PGE 2 suppresses the proliferation of activated B lymphocytes as well as the generation of immunoglobulin secreting cells (Simkin *et al.* 1987). (5) PGE 2 inhibits the increased expression of MHC class II molecules on the cell surface of macrophages, thus potentially affecting their antigen-presenting capacity (Tripp *et al.* 1986).

Cytokines

Glial cells and hematopoietic cells, so-called neuroectodermal-hematopoietic cells, hold many properties in common. Glioma cells not only express lymphoid differentiation antigens as mentioned previously, but also have the ability to secrete some cytokines. The production of these cytokines by glioma cells could directly act on the functional activity of immune competent cells infiltrating a tumor (Table 3). Three cytokines have been found to be secreted in vitro by glioma cultures.

The first, IL 1 promotes the production of IL 2 from helper T lymphocytes. The production of IL-1 like activity in glioma cell cultures was found by Fontana *et al.* (1982, 1983). Recently Kasahara *et al.* (1988) and Lachman *et al.* (1987) reported that human astrocytoma cell lines exhibited a marked proliferative response to IL 1 in a dose-dependent manner. The data suggest an autocrine system of IL 1-mediated proliferation on gliomas.

Table 3. *General Properties of Human Interleukins*

IL-1 a	monocytes/macrophages	lymphokine release from activated T cells	LAF
IL-1 β	NK cells	IL-6 release from glioma cells	endogenous pyrogen
	endothelial cells	release of PGE 2	
	fibroblasts	IL-2 receptor expression	
	glioma cell lines	NK cell activation	
		growth of glioma cell lines	
		general fever	
IL-2	activated T cells	growth of activated T cells	TCGF
		lymphokine production by T cells	
		cytotoxic T lymphocyte activity	
		NK cell activation	
		LAK cell activation	
		monocyte cytotoxicity	
IL-3	lectin stimulated PBL	growth stimulation of multipotential stem cells	multi-CSF
	activated T cell clones		
	glioma cell lines		
IL-4	activated T cells	proliferation of cytotoxic T lymphocytes	BSF-1
	mast cells	inhibition of LAK cell activation	BCGF
		B cell stimulation	
		induction of CD 23 expression on B cells	
		activation of macrophages	
IL-5	T cells	IgG & IgM secretion by stimulated PBL	BCGF-II
		differentiation of eosinophiles	EDF
IL-6	monocytes	final differentiation of B cells into Ig secreting cells	IFN-β2
	glioma cell lines		BSF-2
	fibroblasts	MHC class I induction on fibroblasts	HGF
		activation of T lymphocytes	

An addition of exogenous IL 1 can stimulate IL 6 production by glioma cells (Kasahara *et al.* 1988).

The second, IL 3 is a lymphokine which is predominantly produced by activated T lymphocytes (Bowlin *et al.* 1984). Normal murine astrocytes and murine glioma cells secrete an IL 3-like factor (Frei *et al.* 1985). IL 3

has a wide range of biologic activities that affect growth stimulation and differentiation of different hematopoietic cells such as macrophages, mast cells, and T lymphocytes (Schrader *et al.* 1983). Therefore intracerebral production of IL 3 may be of importance for the maturation of macrophages infiltrating brain tumors.

The third, IL 6, which was originally designated B cell stimulating factor 2 (BSF 2) and is identical to IFNβ 2, induces the final proliferation and differentiation of B cells into antibody-secreting cells. IL 1, TNF, PDGF, IFNβ and virus infection can trigger or enhance expression of the IL 6 gene (Billiau 1988). Human astrocytoma cell lines produce high levels of IL 6 after a brief incubation with IL 1 (Kasahara *et al.* 1988).

IFNβ has been reported to be produced by many glioma cell lines in titres comparable to those produced by human fibroblasts and its production is inducible by viral or chemical stimulation (Larsson *et al.* 1978). However recently IFNβ 2 has been proven to be identical to IL 6 (Chen *et al.* 1988) and its functional property not closely related to the IFN family. Therefore the IFN-β-like antiviral activity reported by Larsson should be now distinguished from IL 6 (IFNβ 2) and IFNβ 1. There is a distinct possibility that glioma cell lines may be unable to produce IFNβ 1 and glioma-producing IFNβ-like activity might be identical to IL 6.

Finally, glioblastoma cell lines secrete both urokinase-type plasminogen activator and plasminogen activator inhibitor type 1 (Helseth *et al.* 1988). The activity of urokinase-type plasminogen activator is associated with invasiveness (Mignatti *et al.* 1986), and this proteolytic activity may assist distant infiltration of glioma cells into normal brain tissue protected by the BBB. TGFβ 1 has been shown to suppress the urokinase activity in glioblastoma cell lines. The molecular mechanism behind the decrease in proteolytic activity is partly due to increased synthesis of plasminogen activator inhibitor type 1 (Helseth *et al.* 1988). Recently Sawaya and Highsmith (1988) suggested that the fibrinolytic enzyme system may be responsible in part for the altered immune response detected in patients with brain tumors. For example, plasminogen activators were found to inhibit NK and specific CTL cytotoxicity. Similarly α-1-anti-trypsin which is present in brain tumors is capable of inhibiting cytotoxic reactions of lymphocytes including ADCC, T lymphocyte and NK cytotoxicity and complement activation (Breit *et al.* 1985, Sawaya *et al.* 1987, Wainberg *et al.* 1982).

Sialic Acid and Gangliosides

One of the characteristics of malignant tumor cells is the production of glycocompounds with a high content of sialic acid. Both the sialic acid-containing glycoproteins and gangliosides of the cell membrane are known to undergo significant alteration during malignant transformation. Ele-

vated sialic acid levels in the serum and also in the CSF of patients with malignant brain tumors have been described (Kakari *et al.* 1984, Marth *et al.* 1988).

Gangliosides comprise a family of glycosphingolipids which differ from each other in the number of carbohydrates in an oligosaccharide backbone and in the number of sialic acid moieties attached to the oligosaccharide. Several studies have found that the ganglioside compositions of human gliomas correlate with their histological grade (Eto and Shinoda 1982, Berra *et al.* 1985). Berra demonstrated that the degree of malignancy, passing from grade I to grade IV, is associated with a statistically significant increase of a ganglioside CD 3. An important modification in the ganglioside composition of human astrocytomas is the decrease in polysialylated species in parallel with increasing degree of malignancy (Berra *et al.* 1985).

Numerous studies have demonstrated the ability of gangliosides to inhibit lymphocyte proliferation during in vitro assays. (1) Gangliosides including GM 2, GD1a, and GT1b inhibit the IL 2-stimulated proliferation of T lymphocytes (Merritt *et al.* 1984). (2) Gangliosides can block the binding of IL 2 to the high affinity IL 2 receptor (Robb 1986). (3) Ganglioside alter the function of the CD 4 molecule. In vitro ganglioside pretreatment induces rapid and selective disappearance of the CD 4 molecule from T helper cells, the effect is dose-dependent and requires both the lipid and sialated oligosaccharide moieties (Offner *et al.* 1987). (4) Gangliosides can inhibit accessory cell function and interleukin 1 production by monocytes (Cavallion and Fitting 1986, Ladisch *et al.* 1984). In addition IFNβ 1 increases the total cellular ganglioside content of some human gliomas (Yates *et al.* 1988).

III. Immunotherapy

Intracranial malignant gliomas usually recur within 8 to 11 months notwithstanding the initial treatment with operation, radiation therapy and chemotherapy, and a median survival from the time of recurrence of approximately 35 weeks may be expected (Ammirati *et al.* 1987). The extremely poor prognosis of patients has stimulated the search for new strategies and previous therapeutic successes of immunology against infectious microorganisms led to hopes that a similar approach could be successful against malignant processes.

One can imagine therapeutic manipulation of the glioma cells and immune competent cells at several levels:

1) Appropriate MAbs might be used as carriers for chemotherapeutic and radiotherapeutic agents.

2) The cellular immune system could be manipulated by either administration of exogenous biological response modifiers (BRM) or by the transfer of activated lymphocytes.

3) Attempts might be made to reverse the effect of those factors produced by glioma cells that interfere with the development of a normal immune response.

4) Advances in molecular genetics might lead to a new range of tumor products coded by oncogenes which in turn might provide valuable tumor specific markers for diagnosis and therapy.

1. Monoclonal Antibodies

The possibility of using MAb as therapeutic agents is attractive. While this concept has been considered for many years, its realization has been hampered by major obstacles which include the following:

1) All antigens recognized by the MAb produced so far are known to have some secondary representation on other cells. In order for MAb directed therapy to be safe, the antigens must be fully characterized as discussed above and their expression on normal cells must be minimal.

2) The possibility of an anaphylactic reaction always exists, especially if MAb are employed repeatedly.

3) Within the central areas of gliomas, there would be free access for MAb, but at the actively growing peripheral areas of these tumors, access of MAb is hindered by the BBB.

4) One final problem in evaluation of MAb directed therapy is the antigenic heterogeneity of glioma cells. Because of this heterogeneity, a single MAb will not detect all the glioma cells of a given tumor. Even if a MAb linked to a noxious agent could kill 100% of the cells it links to, then only a portion of the tumor cells would be destroyed. The use of a group of MAb as a polymonoclonal antibody may have a better chance of destroying a critical amount of glioma cells.

Some MAbs directed to tumor-associated antigens, which were not conjugated with toxins or radioactive agents, have been shown to have an antitumor effect. Augmentation of antibody-dependent macrophage cytotoxicity (ADMC) and antibody-dependent cellular cytotoxicity (ADCC) were supposed to be responsible for the antitumor effect of some antibodies (Herlyn *et al.* 1980, Herlyn and Koprowski 1982, North and Dean 1983, Schulz *et al.* 1983, Seto *et al.* 1983). Although MAbs could potentially be used to kill tumor cells when infused alone, clinical studies using such native MAbs have been limited to patients suffering from leukemias or lymphomas and results have been disappointing.

Gangliosides still may be relevant target antigens for MAb-mediated immunotherapy of gliomas. The ganglioside CD 3 was found to be an effective target in vitro for both complement-mediated tumor cytolysis and ADCC by MAbs of the IgG 3 subclass (Honsik *et al.* 1986). Honsik showed that murine mononuclear splenocytes or LAK cells "armed" with anti-GD 2 and anti-GD 3 MAbs could eradicate progressively growing human

neuroectodermal tumors in a nude mice model. Houghton *et al.* (1985) using the MAb R 24 directed to GD 3 observed major tumor regression in 3 of 11 melanoma patients treated with this antibody in a phase I clinical trial. These results with antiganglioside MAbs warrant further study.

MAbs Carrying Toxins

Immunotoxins comprise a new class of cell-type specific cytotoxic heteroconjugates which consist of a MAb linked to a protein toxin. Recently immuntoxin-linked MAbs directed to EGFR have become available (Akiyama *et al.* 1984, Taetle *et al.* 1988, Vollman *et al.* 1987).

Abrin, ricin, and modeccin are related toxins which bind to similar glycoprotein cell surface receptors, enter the cell, and eventually inhibit the protein synthesis of the target cells. Ricin especially is an extremely powerful cytotoxin consisting of 2 subunits with different functional activities. The A chain is an enzyme that catalytically inhibits protein synthesis by inactivation of ribosomes in the cytosol. The binding to the surface receptor is mediated by the B chain following which the toxic A chain enters the cell and exerts its toxic effect. If the whole toxin structure is conjugated to a MAb, the antibody loses its specific capacity due to the remaining binding capacity of the B chain. This can be circumvented by conjugating only the toxic A chain with the MAb which takes the place of the B chain or by using the whole toxin and saturating the galactose binding sites in the B-subunit with lactose (Raso and Griffin 1980, Youle and Neville 1980). Immunotoxins have specific cytotoxic effects and fail to have any effect against target cells not carrying the antigen since the binding to the target is indispensable. Trials with these conjugates have been performed in vitro or in nude mice and mostly concern lymphoid antigens (Blythman *et al.* 1981, Raso *et al.* 1982).

Anti-EGFR antibodies and EGF itself have also been linked to Pseudomonas exotoxin or ricin A chain, and these immunotoxins displayed specific in vitro toxicity for human tumor cells (Akiyama *et al.* 1984, Vollman *et al.* 1987). Recently Taetle *et al.* (1988) reported that the recombinant-ricin A chain conjugated with anti-EGFR MAbs exhibited specific cytotoxicity for malignant EGFR-bearing cells with greater than 50,000 EGFR/cell. In vivo studies have not, however, been reported.

The transferrin receptor (TR) is a transmembrane glycoprotein which mediates cellular uptake of iron. Proliferating cells including glioma cells express much larger numbers of transferrin receptors than resting cells. Zovickian *et al.* (1987) demonstrated an in vitro selective toxicity of anti-TR-ricin immunotoxin with a ratio between tumor cells and normal brain of more than 150- to 1380-fold. On the other hand, a ligand-toxin conjugate (human diferric transferrin linked ricin A chain) has been shown to be more cytotoxic for glioma cells than the ricin A chain alone or BCNU,

but the addition of CSF reduced this toxicity by about 10-fold (Colombatti *et al.* 1988). Zovickian and Youle (1988) reported an in vivo study with percutaneous intracisternal injection of an antiidiotype MAb (M 6)-ricin conjugate 24 hours after intracisternal inoculation of tumor cells. This treatment produced prolonged survival in tumor-bearing animals. However this in vivo study only indicates an effect of the immunotoxin against tumor cells suspended in the CSF. In addition the transferrin receptor is clearly not a tumor-specific antigen.

MAbs Carrying Chemotherapeutic Agents

Another possibility of MAb targeted therapy is the antibody-drug conjugate aiming at high drug delivery to the target cells and reducing the toxic effect on normal cells.

Ford *et al.* (1983) have demonstrated that drug conjugation does not impair antibody targeting in patients with metastatic carcinoma using radiolabeled vindesin-anti-CEA conjugate. Uadia *et al.* (1985) have shown in vitro that human melanoma cells preferentially take up methotrexate (MTX) conjugated to a MAb directed against human melanoma cells. Pimm *et al.* (1982) reported the in vivo effect of an adriamicin-MAb conjugate against rat mammary carcinoma cells.

No such study has been carried out in a comparable brain-tumor system. The effectiveness of the chemotherapeutic agent-MAb conjugate depends on the drug sensitivity of the tumor cells as much as on the specificity of the MAb. This form of targeting does not resolve the major problem of drug resistence.

MAbs Carrying Radionuclides

MAbs can also act as carriers for radionuclides and this method is the most promising among MAb targeted therapies. As opposed to MAbs carrying toxins, MAbs carrying radionuclides can destroy antigen negative cells adjacent to antigen positive cells binding the antibody. Many murine in vivo studies have already been published. Radiolabeled MAbs against glioma-associated antigens have been shown to localize specifically in human glioma xenografts (Boudon *et al.* 1984, Bullard *et al.* 1986, Colapinto *et al.* 1988, Takahashi *et al.* 1987, Wikstrand *et al.* 1987). The administration of antiglioma MAb 81 C 6, labeled with ^{131}I, has induced growth delay of subcutaneous glioma xenografts in athymic mice and survival prolongation in intracranial glioma xenograft-bearing athymic rats (Lee *et al.* 1988).

In order to allow the achievement of therapeutic radiation doses to tumor tissue without excessive toxicity to normal tissue, various strategies are being investigated; such as MAbs of higher specificity, panels or batteries of MAbs directed against different antigenic determinants of a tumor, immunoglobulin Fab or $F(ab')_2$ fragments, blood brain barrier disruption,

regional therapy (e.g., intrathecal or intracarotid administration) or new methods of radiolabeling which produce more stable bonds between iodine nuclide and MAb (Colapinto *et al.* 1988).

In vivo Distribution of MAb

The aforementioned experimental results have not yet led to large clinical trials because of low specific localization of radiolabeled MAbs in human brain tumors (Behnke *et al.* 1988 b).

After intravenous administration to a cancer patient, the MAb is diluted into the circulating blood, where it can bind to pre-existing antimouse IgG. The possible existence of preexisting antispecies antibody is variable depending on the type of the tumor, on the individuality of the patient, and on the monoclonal antibody (Mach *et al.* 1980, Davies *et al.* 1986, Primus and Goldenberg 1980). After a second infusion of the MAb the level of circulating antimouse antibody is higher and there is an increased risk of anaphylactic reaction. Additionally in certain cases the radiolabeled MAb can be trapped rapidly into the reticuloendothelial system, specifically into the liver, therefore reducing the tumor uptake (Larson *et al.* 1983).

Another point to be taken into consideration is that the blood-to-tissue transport rate is influenced by the regional blood flow, the vascular permeability of the substance, the extent of vascularization and the extracellular fluid circulation (Blasberg *et al.* 1983 a, 1983 b). The regional blood flow in the tumor parenchyma is relatively high and the BBB is abnormal with an increased vascular permeability (Groothuis *et al.* 1982) which may allow the delivery of MAbs into the brain tumor. A problem is the lower blood flow in the adjacent brain surrounding the tumor parenchyma, where the BBB may be preserved.

Since whole immunoglobulin crosses brain and tumor capillaries passively, the smaller size of the fragments may lead them to enter the tumor more rapidly. Takahashi *et al.* (1987) has demonstrated relatively high mean tumor-to-tissue ratios of radioactivity ranging between 8.2 (blood) and 55.8 (muscle) after the injection of ^{131}I-labeled MAb 425 $F(ab')_2$ directed to EGFR-positive glioma xenografts. Colapinto *et al.* (1988) compared the localization of the radioiodinated MAb Mel-14 and its $F(ab')_2$ fragment with a nonspecific control MAb of the same isotype in subcutaneous and intracranial xenografts of human gliomas in athymic mice. The study showed a higher specific localization in the tumor tissue by the $F(ab')_2$ fragment of Mel-14 and a substantially higher radiation dose to the tumor than to normal tissue.

Attempts at artificially altering the vascular permeability and opening the BBB have been used as a means of enhancing MAb access (Neuwelt 1984). However mannitol opens the barrier in the normal brain as well as

the area with tumor infiltration resulting in a simultaneous increase in MAb localization in normal tissue.

A paired-label study in glioma patients was reported by Behnke *et al.* (1988 a, 1988 b) who demonstrated a definitive uptake of the i.v. injected Mel-14 MAb into glioma tissue due to its specificity but with low localization indices. Moseley *et al.* (1987) reported the distribution of ^{131}I-labeled 81 C 6 MAb following intracarotid injection in three glioma patients. On brain scintigrams an increased uptake of ^{131}I was observed in the region of tumor and the localization indices ranged between 1.4 and 12.6 indicating specific glioma uptake. However tumor samples obtained at operation 24 to 48 hours after injection contained only about 0.001 %dose/g (tissue) ^{131}I, which is clearly insufficient for therapy. In addition Jones *et al.* (1987) found only a small amount of tumor uptake with 0.0018 %dose/g to 0.01% dose/g after i.v. administration of radiolabeled UJ 13 A or 81 C 6 MAbs. Similar low tumor uptake of MAbs in patients with melanoma, breast, ovarian, and gastrointestinal carcinomas have been reported (Buraggi *et al.* 1985, Epenetos *et al.* 1986).

These findings in human studies have led some to question the feasibility of using radiolabeled MAbs for tumor therapy, reasoning that adequate radiation doses cannot be achieved in the tumor without unacceptable radiation exposure to normal tissues (Vaughan *et al.* 1987).

Clinical Therapeutic Trials

Despite the limitations mentioned above, a few experimental clinical trials have been attempted for brain tumor patients.

Epenetos *et al.* (1985) treated a patient with recurrent glioblastoma with an intracarotid infusion of the MAb A 9 labeled with 45 mCi of ^{131}I directed against the EGFR and blood group A antigens on erythrocytes. Four months after treatment a CT showed a partial regression of the tumor burden. Brady *et al.* (1988) infused 20 to 25 mCi of ^{125}I-labeled MAb 425 directed against EGFR into six patients with recurrent malignant glioma through the internal carotid artery. Five of six patients showed immediate signs of improvement within two weeks after injection and stabilization of the disease with no apparent side effect.

On the other hand, an attractive way of using MAb for antibody-guided irradiation is the intrathecal route for neoplastic meningitis. Under these conditions the neoplastic cells are disseminated within the subarachnoid space, thus being more accessible to MAb than cells in the solid mass. Coakham *et al.* (1984, 1988) have obtained clinical remissions using the intrathecal application of a radiolabeled MAb in patients who suffered from neoplastic meningitis secondary to pineal tumors or melanomas. Some isotopes were slightly detected in the blood circulation, but there was no detectable liver and spleen uptake as demonstrated by scintigraphy.

These pilot studies revealed at least the tolerability of single infusion of murine MAb in the treatment of malignant glioma. The production of human MAb to tumor-associated antigens would allow to completely resolve the problem of the human immune response to murine antibodies. The possible application of human MAbs in diagnosis and therapy of cancer has been reviewed by Thompson (1988).

2. Biological Response Modifiers (BRMs)

Adjuvant immunotherapy with immunomodulating agents is an attempt to enhance or stimulate the suboptimal immune response of patients with brain malignancies. Early attempts at this type of therapy used the immunization with mycobacteria, either bacille de Calmette-Guerin (BCG) or Corynebacterium parvum. The application of these agents in experimental animal systems had been encouraging but when they were employed as part of a therapeutic protocol for patients, there was no significant prolongation of survival (Decarvalho *et al.* 1977, Mahaley *et al.* 1983, Selker *et al.* 1978). Similar disappointing results have been reported with the immunoregulatory drug levamisole (Mahaley *et al.* 1981).

Recent studies have concentrated on the use of immunomodulating drugs for the treatment of cancer particularly cytokines (lymphokines and monokines). There are recombinant DNA-derived forms of IFNs and interleukins, and some agents have reached the stage of clinical trials for brain tumor treatment. General properties of human interleukins and interferons are summarized in Tables 3 and 4.

Interleukin-2

IL 2, which currently became available as purified recombinant interleukin-2, is a 15 kD glycoprotein secreted by helper T lymphocytes in response to various immunologic stimuli such as bacteria, alloantigens, and mitogenic lectins. The primary role for IL 2 is that of a growth factor (IL 2 was originally designed T cell growth factor or TCGF), and is the obligatory second signal responsible for clonal expansion of antigen primed lymphocytes.

A huge dose of intravenous IL 2 is required to achieve an adequate IL 2 dose (approximately 6 U/ml) in the CSF (Rosenberg *et al.* 1984), which can activate LAK-precursor lymphocytes and/or maintain LAK cells. Saris *et al.* (1988) found that IL 2 was detectable in the lumbar CSF 4 to 5 hours after the initial intravenous infusion (10^5 U/kg), and rose to a plateau of 3 to 9 μ/ml after repeated infusions every 8 hours, and cleared to the limits of detection over 8 to 12 hours after the last dose.

The clinical application of IL 2 in malignant gliomas was initiated by Jacobs *et al.* (1986 a). In a preliminary study they reported no toxicity when

IL 2 was administrated in escalating doses intracerebrally into the peritumoral area of glioma patients during surgery. In contrast in our studies we found frequent headache, moderate-grade fever (< 38.5 °C), nausea, chill or occasional dysesthesia in lower limbs after intratumoral or intrathecal injections of IL 2 (dose ranged 10^3 U to 2×10^4 U) (Sawamura, unpublished results). In addition it has been found that an intravenous high-dose IL 2 therapy elicits transient mental status changes (confusion, disorientation, or lethargy) in one third of patients (Denicoff *et al.* 1987).

Systemic administration of IL 2 alone in clinical trials for cancer patients usually does not result in tumor regression (Rosenberg *et al.* 1987, West *et al.* 1987), furthermore the patients with intracranial metastasis have been principally excluded from the protocols of IL 2 therapy. At present IL 2 has been utilized locally in combination with LAK cell transfer.

Interleukin-4 (IL 4)

Although IL 4 was first characterized as a B cell stimulatory factor (BSF-1) (Howard *et al.* 1982), IL 4 is now known to modulate T cell activation. IL 4 can inhibit the proliferation and induction of LAK cells in PBLs cultured in IL 2. This suppression is specific for the induction phase of LAK activity in CD 16+ NK cells and can be overcome by adding IFNγ (Han *et al.* 1988). It is interesting to be note that IL 4 in combination with IL 2 can promote the growth of autologous tumor specific cytotoxic T cells and reciprocally inhibits nonspecific populations (Kawakami *et al.* 1988).

IFNα and IFNβ 1

IFNα and IFNβ share the same receptor (type 1 receptor) on the target cell surface (Table 4). Numerous studies have shown that human IFNα and IFNβ can inhibit the growth of human neuroectodermal tumors in murine models and in vitro studies have suggested that IFNβ has a more marked growth inhibitory effect on human glioma cell lines than either IFNα or IFNγ (Bradley *et al.* 1983, Cook *et al.* 1983, Hirakawa *et al.* 1983, Lundblad and Lundgren 1981, Nederman and Benediktsson 1982, Yates *et al.* 1985, Yung *et al.* 1987). A similar growth inhibitory effect of IFNβ has been reported on human glioma xenografts in nude mice (Tanaka *et al.* 1983).

These growth inhibitory effects of IFNs are variable according to the type of IFN and the type of cell under investigation. Furthermore it has been shown that clones resistant to the antitumor effect of IFN can develop in vitro after prolonged exposure to IFN (Gresser *et al.* 1974, Kuwata *et al.* 1976).

Several types of IFNs such as human fibroblast IFNβ, recombinant IFNα, IFNβ and IFNγ are now available for clinical use. A 0% to 40%

Table 4. General Properties of Human Interferons

	IFN-a	IFN-β	IFN-r
Old classification	Leukocyte	Fibroblast	Immune
Primary natural source	virus-activated lymphocytes	fibroblasts	T lymphocytes
Recombinant form	available	available	available
Type of receptor	a/β (type I)	a/β (type I)	r (type III)
Tumoricidal activity against glioma cells	++	++	+
Clinical trials for brain tumor	undergone	undergone	undergone
Clinical efficacy	positive <	positive	poor

response rate was reported in early work on various IFNs in malignant brain tumor patients (Boëthius *et al.* 1983, Feun *et al.* 1982, Hirawaka *et al.* 1983, Nagai and Arai 1984, Salford *et al.* 1981).

Three large series using IFNβ were conducted in Japan. Nagai and Arai (1984) treated 47 patients with malignant brain tumors. In this study IFN-α and IFNβ were administered daily in doses ranging from 3.0 to 9.0×10^6 IU/body locally or intravenously (IFNβ) or intramuscularly (IFNα), which were continued for at least eight weeks. The relative optimal responsiveness (40%) was obtained with IFNβ (1 CR and 7 PR in 20 cases) compared to IFNα (3 PR in 12 cases). A cooperative clinical trial with IFNβ reported 12 responses (22%) (CR and PR) out of 54 patients with gliomas treated either locally or intravenously in doses of 1×10^6 to 6×10^6 IU/body, daily for a period of 8 weeks or longer. The efficacy via the local route was similar to that of systemic administration. Long-term continuous administration of IFNβ was favorable in the suppression of tumor recurrence and growth (Nagai 1983). Another cooperative study using IFNβ in Japan obtained a 13.5% response rate (5 PR in 37 patients) (Takakura 1987). In the largest clinical series using IFNα, Mahaley reported reduction of tumor size in 7 (41%) of 17 patients with recurrent gliomas who received 9×10^7 IU/m^2 systemically. Obbens *et al.* (1985) administered IFNα intraventricularly in 4 patients with leptomeningeal metastases, whereby the CSF became free of malignant cells, while clinical improvement was less dramatic.

According to a cooperative study in Japan, side effects of IFNβ occurred in 61% of patients, including transient fever (54%), lassitude (12%), chills (8%), seizure, hypotension, nausea and vomiting. Abnormal laboratory findings were seen in 41% of cases, including leukopenia (25%), thrombocytepenia (11%), anemia (7%), and elevated serum GPT (17%). The

suppression of hematopoietic function and liver dysfunction were mild and generally returned to normal without withdrawal of the medication (Nagai 1983). However in certain cases bone marrow suppression was profound enough to interrupt the therapy. In addition Obbens *et al.* (1985) reported that acute side effects such as fever, nausea, vomiting, and headache occurred almost exclusively with intraventricular injection of IFNα.

The overall results have been equivocal. In addition no controlled phase III studies have been carried out.

IFNγ

The receptor (type 2) for IFNγ differs from the receptors for IFNα and IFNβ. IFNγ showed low direct antiglioma activity in vitro in comparison to IFNα or IFNβ. However a combination of IFNγ and IFNβ may be effective in suppressing glioblastoma growth in cultures exhibiting innate resistance to IFNs (Vita *et al.* 1988). Until now, the only well-directed clinical trial of IFNγ in glioma patients appears to be that of Mahaley *et al.* (1988), who obtained disappointing results. The side effects of IFNγ are generally so severe in comparison with IFNβ that clinical trials of IFNγ have been interrupted (Shitara *et al.* 1987).

Manipulation of the enhancement of tumor antigenicity and effector cytotoxicity is another potential area for IFNγ. One might hypothesize that the administration of IFNγ would be a major stimulus for the expression of HLA-DR on astrocytes and glioma cells in vivo. If a critical amount of antigen could be presented in this manner, then a cellular immune response might be initiated. IFNγ has been shown in vitro to activate lymphocytes to produce specific cytotoxicity in the presence of IL 2 (Bogdahn *et al.* 1984, Takiguchi *et al.* 1985). Furthermore it has been recently demonstrated that an administration of TIL plus IFNα, which could enhance MHC-class I expression on tumor cells, produced a substantial synergistic therapeutic effect (Cohen *et al.* 1987, Rosenberg *et al.* 1988). In a similar way IFNγ at a proper dose might be utilized in order to enhance tumor immunogenicity in combination with the other immunotherapeutical approaches.

OK-432 and PS-K

The two largest selling drugs by dollar value in the cancer chemotherapy market including malignant brain tumors are the two immunomodulators OK-432 (lyophilized powder of Streptococcus pyogenes preparation) and PS-K (protein-bound polysaccharide Kureha form Basidiomycetes). It is noteworthy that their use is largely limited to Japan.

It has been reported that OK-432 possesses various immunopharmacological activities such as; (1) augmentation of cytotoxic activity of CTL, NK cells, LAK cells and macrophages, (2) stimulation of cytokine pro-

duction including IFNα, IFNβ, IFNγ, IL 1, IL 2, NKAF, NKCF, MCF and TNF, (3) reduction or elimination of suppressive activity of macrophages (Ishida 1986).

According to an early preliminary report of a cooperative study (Takakura 1982, Shibata *et al.* 1987) using OK-432 with chemoradiationtherapy including ACNU and vincristine conducted by 21 neurosurgical institutes in Japan, the survival rate of patients receiving postoperative irradiation, chemotherapy, and OK-432 was 60% at the end of 18 months, whereas the survival rate of patients receiving chemoradiationtherapy only, was 43% for the same period. The difference was reported to be statistically significant with a 5% difference in risk rate as proven by Cox-Mantel analysis. In contrast another cooperative study demonstrated that 1- and 3-year survival rates of glioma patients were 70% and 30%, and that there was no clinical effect of OK-432 (Shibata *et al.* 1987).

3. Adoptive Immunotherapy

More than ten years ago empirical attempts have been made to infuse leukocytes directory into the intrathecal or intratumoral space in patients with brain tumors, this did not, however, result in any definitive benefit (Steinbok *et al.* 1984, Takakura *et al.* 1975, Trouillas 1970, Young *et al.* 1977). Steinbok *et al.* (1984) injected autologous peripheral blood mononuclear cells into the postoperative cavity of four recurrent glioblastoma patients and obtained four autopsies, two of which were performed seven days after the last lymphocyte infusion and one was after three weeks. No lymphocytes were seen in the tumor tissue around the injected site and no significant perivascular lymphocyte accumulations were present in all the glioblastomas. This evidence suggests the inability of adoptively transferred lymphocytes to migrate actively into the autologous tumor tissue.

Lymphokine-activated Killer Cells (LAK)

In 1982, it was first reported that cancer patients' or normal persons' lymphocytes could be activated by in vitro incubation with IL 2 (lymphokine-activated killer cells: LAK cells) to a tumoricidal state (Grimm *et al.* 1982). Jacobs *et al.* (1986 b) reported that LAK cells generated from glioma patients' PBLs could kill autologous fresh glioma tumor targets in short-term cytotoxicity assays. LAK cells are able to bind very tightly to allogenic tissue-culture glioma targets within 30 minutes of coculture and cause death of glioma cells in less than 1 minute (Hook *et al.* 1988). All fresh normal cells were LAK-resistant. In addition LAK have been injected into human brain peroperatively around the tumor cavity with no obvious deleterious effects (Jacobs *et al.* 1986 a).

For clinical application, at least 10^9 LAK cells are required for local

injection. Precursor autologous PBLs are obtained by leukapheresis and are then activated in an in vitro culture system in the presence of high concentration of IL 2 (1,000 to 2,000 U/ml medium) for approximately 2 to 8 days. Although glioma patients are known to have an impaired cell-mediated immune response, it is possible to activate PBLs derived from patients who have been treated by chemotherapy, irradiation or corticosteroid administration after surgery. In addition the cytotoxic activity of LAK cells derived from glioma patients was similar to that of LAK cells from healthy control subjects (Bosnes and Hirschberg 1988). However the number of PBL obtained from patients receiving chemotherapy was significantly reduced. Therefore the volume of patient's blood required to generate the same number of LAK cells was larger in glioma patients than control subjects. In certain patients with leukocytopenia the number of clinically available LAK cells was insufficient. Furthermore there is also the problem of obtaining sufficient numbers of PBL to generate LAK cells in infants. George *et al.* (1988) have described a culture method whereby the final oncolytic potential derived from a limited number of PBL obtained from children with medulloblastoma could be increased four- to sixfold over IL 2 alone by simultaneously stimulating the cultures with anti-CD 3 MAb. On the other hand, after in vitro cultivation of PBL, nonadherent and adherent LAK cells can be harvested. Adherent LAK cells have been known to be more potent in killing glioma cells than nonadherent populations (Whiteside *et al.* 1988 a).

Adoptive immunotherapy, where lymphokine-activated killer (LAK) cells are transferred to patients with malignant brain tumors in combination with interleukin 2 (IL 2), has been reported in six preliminary clinical trials (Grimm 1988 a, Jacobs *et al.* 1986, Merchant *et al.* 1988, Nakamura *et al.* 1987, Sawamura *et al.* 1988 b, Shimizu *et al.* 1987, Yoshida *et al.* 1988).

(1) Jacobs *et al.* (1986 a) and Grimm (1988 a) have administered IL 2 (up to 10^6 U) and/or LAK cells (up to 1×10^{10} cells) to a total of 11 malignant glioma patients in a phase I trial. In this study no toxicity was reported, but the patients' clinical outcome was not described.

(2) Merchant *et al.* (1988) have treated 13 patients by intralesional or intrathecal infusion of autologous LAK cells (total dose: range 1×10^9 to 9×10^9, median: 3.6×10^9) and IL 2 (total dose: range 7×10^6 to 10^7, median: 8×10^6 U). The therapy did not appear to have a significant impact on patient survival.

(3) In our studies we have administered LAK cells (1.2×10^9 to 1.4×10^{10}, median: 2.5×10^9) in combination with IL 2 (5×10^4 to 3×10^5 μ, median: 1.2×10^5 U) directly into the tumor bed or intrathecally to 9 malignant glioma patients and one meningeal carcinomatosis due to lung cancer. Only one minimal response (MR) was obtained. The median

number of transferred LAK cells was relatively low, because therapy had to be interrupted by progressive tumor growth (unpublished data).

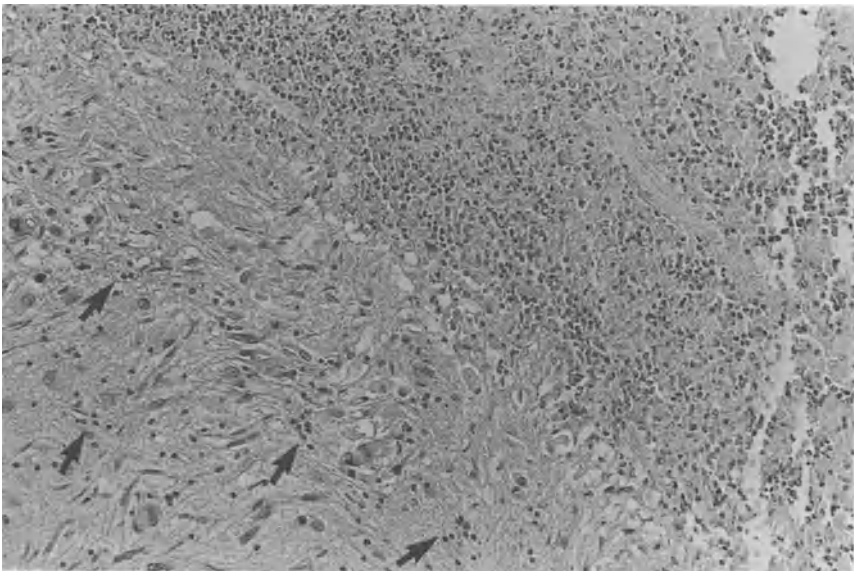
(4) Nakamura *et al.* (1987) reported positive responses to LAK-cell therapy in 7 patients with recurrent malignant gliomas. They injected LAK cells (total dose: 1.3×10^9 to 6×10^9, median: 3.6×10^9) plus IL 2 (total dose: 2×10^5 to 9×10^5 U, median: 5×10^5 U) into the postoperative cavity. Headache and fever were common, but these side effects resolved within two to three days. Six patients showed no tumor recurrence for more than 1 to 9 months after treatment. Furthermore of three patients with measurable residual tumors on postoperative CT, one patient reached a complete response (CR) and another patient showed a partial response (PR) to the therapy.

(5) Yoshida *et al.* (1988) injected LAK cells plus IL 2 directly into the postoperative cavities of 23 recurrent glioma patients; 1.2×10^8 to 3.2×10^{10} (median: 4.5×10^9 cells) and 8×10^2 to 5.4×10^3 (median 1.9×10^3 U) units of IL 2 were infused into the brain through an Ommaya reservoir. Definite tumor regression, improvement of some clinical symptoms, and remission over 6 months or more were observed in 6, 9 and 3 patients, respectively. There were no marked side effects, except for slight fever in 8 patients and chill in 3 patients.

(6) Shimizu *et al.* (1987) used LAK cells in two patients; one with meningeal gliomatosis and the other with meningeal carcinomatosis. He concluded that adoptive transfer of LAK cells was very effective in reducing clinical symptoms and signs, and in eliminating malignant cells from CSF.

Improvement of clinical symptoms and tumor regression provided by LAK therapy have been demonstrated. A majority of these remissions were transient. The intracranial injection of large amounts of LAK cells caused cerebral edema (Merchant *et al.* 1988) increased intracranial pressure and hydrocephalus. The local adoptive immunotherapy using LAK cells with IL 2 caused no irreversible toxicity (Jacobs *et al.* 1986 a, Merchant *et al.* 1988, Nakamura *et al.* 1987, Yoshida *et al.* 1988). Reversible side effects include frequent fever, nausea, vomiting, headache, fatiguability and occasional mild somnolence. Furthermore repeated local injections of LAK cells may cause serious infections, especially due to mycotic organisms, and replacement of an obstructed reservoir was frequently required.

Successful adoptive immunotherapy presumably depends on the accumulation of transferred effector cells at the site of tumor growth, and effector cells must physically bind to the tumor cells to kill (Hook *et al.* 1988, Hosokawa *et al.* 1988). Intratumoral injection would be most likely to maximize cell to cell contact between killer lymphocytes and postoperative residual glioma cells (Jacobs *et al.* 1986 a, Merchant *et al.* 1988). Regarding the distribution pattern of LAK cells noted on the scintigrams after intrathecal and intratumoral injection in our clinical trials using LAK



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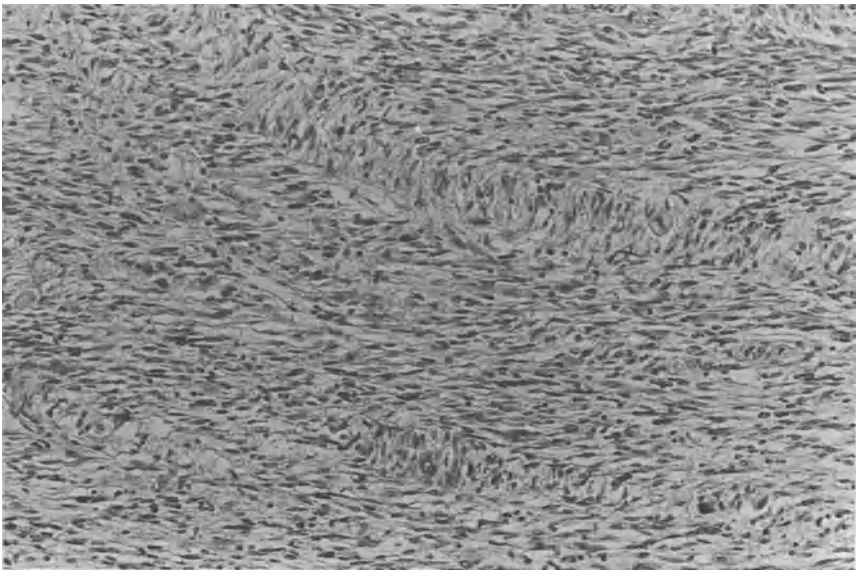

B

Fig. 4. Distribution of LAK cells injected into the tumor cavity in an autopsied case with glioblastoma. An accumulation of numerous mononuclear cells (LAK cells) could be seen in the tumor tissue adjacent to injected site and seemed to be making a tumor necrosis (upper-right side of Fig. 4 A). A few LAK cells infiltrated into tumor parenchyma (as indicated by arrows in lower-left side of the figure). However there was an active tumor growth next to the site of LAK cells accumulation (Fig. 4 B)

cells, these transferred cells did not migrate preferentially to the site of tumor growth. Furthermore, the postmortem examination in our three autopsied cases also revealed that the LAK cells injected into the cavity surrounding the glioma remained localized at the injection site and did not infiltrate into tumor tissue (Fig. 4). A study of i.v. injected LAK cells into mice showed that among normal organs the liver and the spleen had the highest uptake of transferred LAK cells, 60% dose/g organ and 67% dose/g organ respectively, whereas the brain tissue showed extremely low values with 0.1%dose/g organ (Sawamura *et al.* 1988 b). It thus appears that one of the major limitations of therapy with LAK cells is their inability to migrate and localize to the tumor tissue.

Tumor Infiltrating Lymphocytes (TIL)

It is known that the degree of lymphatic infiltration of gliomas has some relevance to the prognosis of glioma-bearing patients. It has also been reported that in certain cases glioma-derived tumor infiltrating lymphocytes (TIL) in microculture systems possess selective lytic activity against autologous tumor cells (Kuppner *et al.* 1988 a). Adoptive immunotherapy using autologous TILs in place of LAK cells has already been administered to cancer patients with the exception of brain tumor patients.

Many recent experiments have demonstrated that TIL isolated from human cancers with the exception of brain tumors proliferate briskly in IL 2 (Anderson *et al.* 1987, Belldegrum *et al.* 1988, Heo *et al.* 1988, Itho *et al.* 1986, Kradin *et al.* 1987, Muul *et al.* 1987, Rabinowich *et al.* 1987, Rosemberg *et al.* 1986, Sawamura *et al.* 1988 a, 1989). However it has been found that glioma-infiltrating lymphocytes cultured in the presence of IL 2 have a strikingly reduced proliferative potential (Miescher *et al.* 1988).

Recently we investigated the possibility of glioma-derived TIL for clinical use. If TIL are to be more effective in vivo as adoptively transferred effector cells than LAK, the following requirements have to be fulfilled in vitro (Rosenberg *et al.* 1986, Topalian *et al.* 1988): (1) IL 2-expanded TIL must be cytotoxic T cells; (2) cytotoxicity assays must show that TIL effect greater lysis of autologous target than do LAK cells; (3) TIL must exhibit lytic specificity for the autologous target cells. Furthermore it is estimated that over 10^{10} TIL per patient will be required to induce a clinical response after i.v. injection (Topalian *et al.* 1988).

In our study (Sawamura *et al.* 1989) glioma-infiltrating lymphocytes were separated from twenty-four glioma specimens and cultured in medium containing IL 2. Within 20 to 42 days after the initiation of culture, 20 out of 24 cultures of glioma derived lymphocytes expanded with a substantial increase in cell numbers, of at least 5×10^8 cells up to 5×10^9, with a simultaneous elimination of contaminating autologous glioma cells. After several weeks of proliferation the lymphocytes ceased to grow in all cultures.

Many reports on TIL isolated from human solid tumors have demonstrated that the majority of TIL cultures ceased to grow within six or eight weeks losing their cytolytic activity (Heo *et al.* 1988, Itoh *et al.* 1986, Topalian *et al.* 1988, Whiteside *et al.* 1988 b). Therefore expanded TIL, which could be obtained at the peak of cell number or later, might be quiescent or be reaccumulating into the resting phase (Smith 1988), and may no longer be suitable as adoptively transferred effector cells.

The expanding glioma-derived lymphocytes consisted of approximately 90% $CD3^+$ T cells including both $CD4^+$ and $CD8^+$ subpopulations. CD 16 was expressed on $4 \pm 5\%$ of the cells and three cultures studied exhibited 14% + 1 of Leu 19 positive cells. There was no evident specificity or selectivity for lysis of autologous glioma, insomuch as the bulk TIL cultures were cytotoxic against both autologous and allogeneic glioma targets. The quantitative differences in the activities could vary, depending on factors such as relative expansion, time of culture, or sensitivity of tumor cell targets of lysis. This observation is consistent with other reports that lytic preference for autologous vs. allogeneic tumors was observed only in bulk cultured TIL from human melanomas (Itoh *et al.* 1986, Muul *et al.* 1987, Topalian *et al.* 1988). In addition the cytotoxic activity of long-term cultured LAK cells obtained from the same patients appeared to be similar to that of glioma-derived lymphocytes in killing autologous tumor cells.

Even though glioma-derived TIL at the clonal level possess a selective cytolytic activity against autologous tumor cells, these cloned TIL may not be able to lyze the entire spectrum of heterogenous cells within the individual glioma. The issue of the specificity of glioma-derived TIL for autologous targets may not be entirely answered by previous in vitro observations (Kuppner *et al.* 1988 a, Miescher *et al.* 1988), and the existence of a selective activity of glioma-derived TIL in bulk culture against autologous tumors remains to be confirmed before the TIL are applied in the clinical situation. Recently it has been suggested that using IL 4 in combination with IL 2 might enhance the selective activity of glioma-derived TIL (Kawakami *et al.* 1988).

Since antigen primed lymphocytes have a site-selective homing potential during the efferent phase of an in vivo adoptively transferred immune response (Spangrude *et al.* 1984, 1985), and since the most motile subpopulations of IL 2-stimulated lymphocytes contain a $CD4^+$ subset significantly poorer in LAK and NK activity (Ratner and Heppner 1988), it may be that $CD4^+$ glioma-derived TIL exhibiting low LAK like activity and possessing primed antitumor activity may have a more favorable distribution in vivo.

In conclusion these results could lead one to initiate a clinical protocol utilizing TIL in the immunotherapy of malignant gliomas. However the

definitive benefit of TIL over LAK cells as transferred effector cells is still not clear.

Autologous Specific Cytotoxic T Lymphocyte Clones Derived from PBL

In many animal models the therapeutic efficacy of tumor-specific cytotoxic T lymphocytes (CTL) has been repeatedly emphasized. In contrast to TIL, which have been hypothesized to be activated at the tumor site, attempts to sensitize patient's PBL in vitro against autologous tumor cells have also been performed. With the recent development of cytokines and cell cloning techniques it seems possible to generate human lymphocyte clones specifically sensitized in vitro against autologous tumor cells. Clones of cytotoxic T cells with autologous specific antitumor activity in an MHC-restricted manner might be isolated from PBL, and could be further activated in vitro by mixed lymphocyte-tumor cell culture (MLTC) and expanded in the presence of IL 2 and feeder cells.

The efficacy of such specific CTL clones has been demonstrated in an experimental methylcholanthrene induced murine glioma model (Yamasaki *et al.* 1984), which was a highly antigenic tumor for the induction of syngeneic CTL clones.

The existence of brain tumor-specific killer cells present in patients' PBL was suggested in early reports (Levy 1978, Rainbird *et al.* 1981), their specificty was, however, doubtful. Although Miyatake *et al.* (1988) established human T lymphocyte clones with some specific cytotoxic activity derived from a patient with gliosarcoma, the term of specificity in this report remains misleading. Kitahara *et al.* (1987) administered cytotoxic lymphocyte cell lines specific for autologous glioma to five patients (total dose: 5×10^8 to 10×10^8, median: 6×10^8 cells) and reported that 2 tumors regressed more than 50% in diameter. However the specificity of the transferred cells was ambiguous, since the lymphocyte cell lines stimulated by MLTC showed only preferential killing of autologous tumor cells.

One should remember that a single human solid tumor is composed of heterogenous populations of cells with respect to susceptibility to lysis by autologous CTL clones (Anichini *et al.* 1986). There is considerable variation in the cytotoxic activity of T cell clones against various autologous targets suggesting quantitative differences in the expression of antigen or in the ability to repair membrane damage of tumor cells. This implies that a therapeutic modality must be capable of activating the overall immune response to the tumor rather than being directed at a single entity (Anichini *et al.* 1986, Vose *et al.* 1987).

Summary and Conclusions

In summary, many actual interactions between tumors in the CNS and the immune system have been demonstrated. The normal brain does not

possess a lymphatic system and is partially hidden from the systemic immune system by the BBB, furthermore brain cells do not express MHC antigens which are necessary for the initiation of an immune response. In pathological conditions however, immunocompetent cells may find their way through transformed endothelial cells. Microglia and astrocytes may function as antigen presenting cells. Glioma cells when stimulated by cytokines such as IFNγ can be induced to express MHC class I and class II antigens, thus making them more susceptible to an immune attack. In addition glioma cells are capable of secreting several cytokines including IL 1, IL 3 and IL 6 also involved in the generation of an immune response. Indeed, a functional analysis of lymphocytes infiltrating gliomas has revealed the accumulation at the tumor site of cytotoxic T lymphocytes as well as NK cells. However host-immune responses against gliomas seem to be weak in comparison to other cancers. Glioma cells are known to secrete TGFβ 2 and PGE 2 which may in part be responsible for this lack of immune response, thus shielding themselves from immune attack.

In order to be recognized by the immune system the tumor cells must express TAA in addition to MHC antigens, and such TAA have been identified by MAbs. These MAbs can be used for "targeted" therapy when coupled to toxic agents or radionuclides. Preclinical studies have shown that, after intravenous or intracarotid injection, there is specific accumulation of the MAb in the tumor but in insufficient amounts for therapeutic use. The relatively small amount of MAb binding to the tumor in vivo can be due to several factors: not all the cells in a single tumor express a given tumor-associated antigens, the MAb may have a low affinity for the antigen, the BBB may hinder the passage of the MAb. Attempts have been made to overcome these drawbacks by opening the BBB for example. In addition MAbs can readily be used for the treatment of carcinomatous meningitis.

There has been little success in the development of immunotherapy with IFNβ 1 and even less with adoptive immunotherapy using LAK cells plus IL 2. TIL as well as LAK cells can be expanded in vitro with IL 2 and it is feasible to reinject these cells into the tumor site. However the problem is that the cells remain localized to the injection site and do not migrate actively into the tumor tissue. Overall augmentation of immunity requires induction of increased effector function, in addition to concomitant abatement of suppressive activities.

Research in the immunology of brain tumors has enabled us to gain some insight into how we may augment the immune response to these tumors and thus in turn may help in the design of novel and effective immunotherapeutic approaches to the treatment of these tumors.

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Adrenal Medullary Transplants as a Treatment for Advanced Parkinson's Disease

A. Lieberman, P. R. Cooper, and J. Ransohoff

New York University Medical Center, New York, New York (U.S.A.)

It is no coincidence that human neural transplantation currently focuse on Parkinson's Disease. In PD, of all the neurodegenerative disorders, there is the clearest relationship between the pathology [the loss of catecholamine containing pigmented neurons in the substantia nigra pars compacta (SNpc)], the neurochemistry [the loss of striatal dopamine (DA)] the pathophysiology (the disinhibition of the striatum), and the clinical symptoms. Moreover, the loss of tissue in PD is small and restricted to the SNpc. It was reasonable to expect that if a transplant could substitute for the lost SNpc neurons in patients with PD, then symptoms might improve.

In PD, symptoms appear after the number of pigmented neurons in the substantia nigra pars compacta and the level of dopamine in the striatum are reduced by 80%. Compensation for the striatal DA deficiency is achieved by administering levodopa which is converted to DA in the remaining nigral neurons and by the development of supersensitivity in the striatal DA receptors. Whereas treatment for patients early in the course of PD is good, treatment late in the disease is not[1, 2].

The main problem in treatment of PD is the large number of patients who, after initially responding to levodopa, become more symptomatic. Deterioration of parkinsonian symptoms is usually accompanied by diurnal fluctuations. These are mainly "wearing-off" phenomena, or "end-of-dose deterioration" but they may also occur as abrupt, random fluctuations, or "on-off" phenomena. The patient's increased disability results mainly from the continuing loss of catecholamine containing pigmented neurons in the SNpc, with the remaining neurons being unable to convert levodopa to DA in sufficient quantities to stimulate the striatal DA receptors. Because most of the symptoms of PD result from the loss of SNpc neurons and because of the limitations of levodopa as a substitute for that loss, investigators began to consider replacing the lost SNpc tissue[3, 4].

Animal studies indicate that fetal cells can survive and reverse symptoms when they are transplanted into the striata of adult parkinsonian animals[3–7]. However, because the use of fetal tissue raises complex social issues, investigators turned to other sources, such as the adrenal medulla, which is embryologically related to the catecholamine containing cells in the SNpc. Animal studies reveal that fetal or juvenile adrenal medulla may be transplanted into striata, survive, and reverse PD symptoms[5, 8].

The observation that autografts of adult adrenal medullary cells may also reverse parkinsonian symptoms led to the present interest in transplantation. Although adult adrenal autografts do not reverse parkinsonian symptoms as well, or survive as long as fetal grafts, they offer certain advantages. The use of a patient's own tissue avoids the problem of host-graft rejection and the necessity for immunosuppressive drugs, and it bypasses the social issues involved in fetal transplantation.

Investigators in Sweden originally transplanted suspensions of autologous adrenal medullary tissue into four patients with advanced PD[9, 10]. Two implants were placed stereotaxically into the caudate nucleus and two into the putamen. Only two patients transiently improved and the procedure was abandoned.

Undeterred by these negative results, investigators in Mexico modified the procedure and reported marked improvement in two patients[11]. Subsequently they reported improvement in 18 of 40 patients. The improvement has been maintained in 13 of the 18 patients for at least one year. Four deaths occurred. Autopsies on two patients revealed that the autologous adrenal grafts were necrotic. Other investigators have reported more modest results[12].

The Mexican and Swedish studies differed in that the Mexican team used more adrenal tissue, did not make the tissue into a suspension, implanted the tissue directly in to the caudate, and anchored the tissue in such a way that some of the adrenal cells remained in contact with the ventricular fluid. Because of the improvement reported in their first two patients, we and other investigators in the United States began clinical studies to determine the efficacy of autologous adrenal medullary transplantation[12].

Methods

Between July 8, 1987 and April 28, 1988 12 autologous adrenal medullary to caudate nucleus transplants were performed at the New York University (NYU) Medical Center. This paper presents the effects in the patients up-to December 31, 1988. Patients selected for autologous adrenal medullary to caudate nucleus transplantations were patients with advanced PD who were no longer responding satisfactorily to antiparkinson medication in spite of manipulation or changes in dosage and type of medication (11

patients) or were unable to tolerate antiparkinson medications because of adverse effects consisting of confusion and hallucinations (one patient). The patients and their relatives consented to the surgery by signing a detailed explanation of the procedure approved by the NYU Institutional Review Board.

The mean age of the patients was 55.1 years (range 37–65 years), and the mean duration of their PD was 11.7 years (range 4–40 years). Eleven of the patients were on levodopa/carbidopa (Sinemet). The mean dose of levodopa was 1,438 mg (range 500–3,500 mg). The mean dose of carbidopa was 243 mg (range 0–550 mg). Ten of the patients had diurnal response fluctuations consisting of "wearing off" phenomena and "on-off" phenomena. One patient, III, was "off" all of the time despite medication. The mean stage of the patients in the "off" period was 4.8 (range 4–5) (12 patients).

Most of the patients had previously also been treated with other antiparkinson medications.

Prior to surgery all 12 patients were assessed using the Unified Parkinson Disease Rating Scale (UPDRS)[13]. All patients were assessed on the UPDRS both in an "on" and an "off" period. All patients were also rated on the Hoehn and Yahr Scale in both an "on" and an "off" period. On this scale Stage 1 is mild unilateral disease; Stage 2, bilateral involvement, no gait disturbance; Stage 3, mild gait disturbance; Stage 4, moderate to marked gait disturbance, able to walk or stand unassisted but markedly incapacitated; Stage 5, confined to wheelchair.

Patients were asked to keep "on/off" diaries to assess the percent of waking hours spent "off". Diurnal response fluctuations and dyskinesias were also monitored using questions from a subset of the UPDRS. Assessments were made at baseline, at twice weekly intervals in the hospital and at four monthly intervals outside the hospital.

Preoperatively, 11 of the patients underwent magnetic resonance imaging (MRI) of the brain, and one underwent computed tomography (CT). Cortical atrophy was found in only two patients (III, XI). In all patients, CT scans of the abdomen demonstrated two adrenal glands. All of the patients were evaluated preoperatively by an internist and an intensive care unit specialist. Patients underwent cardiac evaluations including tilt table examinations to monitor orthostatic hypotension. All patients underwent neuro-psychological testing and quantitative evaluations of tremor and postural stability.

In the first six patients a right frontal craniotomy was used as described by Madrazo[11]. The dura was opened and an ultrasound probe was used to locate the right lateral ventricle. When the caudate nucleus was identified an incision was made into it and a single bed for the adrenal transplant was created. The adrenal medullary tissue was then placed into the caudate

bed. The largest piece was placed last and was clipped to the edge of the hole in the caudate so that it remained in contact with the lateral ventricle.

In the next 6 patients the lateral ventricle was entered through a transcallosal approach. The corpus callosum was opened for 0.5 cm and the right lateral ventricle was entered. Three separate beds were made in the caudate allowing for a wider dispersal of the adrenal medullary tissue with the idea that such a dispersal might promote a longer survival of the grafted tissue. In all patients, the left adrenal gland was removed via an abdominal approach. Because the adrenal cortical tissue may inhibit the integration of the medullary tissue into the caudate, an attempt was made to achieve a complete separation of cortex from medulla, although some cortical tissue always remained. Usually 3 to 15 fragments of adrenal tissue are removed, the fragments weighing into up to 1 gram. The adrenal medullary and caudate tissue are assayed for tyrosine hydroxylase (TH) activity, and the caudate tissue was further assayed for DA, homovanillic acid (HVA), and dihydroxyphenylacetic acid (DOPAC)[14].

Changes in patient functioning from baseline to December 31, 1988 were analyzed using non-parametric methods. The primary mode of evaluation was the Wilcoxon matched-pair signed-rank test. Both one tailed and two tailed tests were performed. Level of significance was set at $p < 0.05$.

Results

The results of the surgery are summarized in Tables 1–3. The main finding for the group was a 35% reduction in levodopa post-operatively compared to pre-operatively ($p < 0.01$). There was a 13% reduction in the patient's stage in the "off" period. This reduction is significant ($p < 0.05$) and reflects decreased "off" time and less abrupt, unpredictable "off" periods.

Table 1. *Results of Adrenal Medullary Transplantation (Mean ± SD)*

	Number of patients	ID	CD	Stage "on"	Stage "off"
Pre	12	1437 ± 1037	243 ± 222	3.3 ± 0.83	4.8 ± 0.45
Post	12	929 ± 892	140 ± 113	2.6 ± 1.1	4.2 ± 0.83
Change		−35%[a]	−42%[b]	−21%[b]	−13%[c]

[a] $p < 0.01$.
[b] Not significant.
[c] $p < 0.05$.

Table 2. *Results of Adrenal Medulary Transplantation: UPDRS (Mean ± SD)*

	Number of patients	ment (16)	sympt "on" (52)	sign "on" (108)	sympt "off" (52)	sign "off" (108)	fluct (20)
Pre	12	3.9 ± 3.1	19 ± 10.4	39 ± 15.8	32 ± 7.3	56 ± 11.1	± 8.5 ± 3.1
Post	12	4.9 ± 5.2	13 ± 16.6	26 ± 23.2	30 ± 13.4	48 ± 19.8	5.9 ± 2.6
Change		+25%[a]	−32%[a]	−13%[a]	−6%[a]	−14%[a]	−30%[b]

[a] Not significant.
[b] $p < 0.05$.

Table 3. *Adverse Effects*

		Patients											
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
CNS	Seizures	+										+	
	Psychosis	+		+			+		+	+			
	Depression	+		+		+			+	+			+
	Infarction					+						+	+
	Hemorrhage											+	+
	Dyskinesia				+								
	NMS	+			+								
CV	Arrhythmia	+			+								+
	Hypotension	+			+								+
Pulm	Vocal Cord	+			+	+							
	Atelectasis		+	+		+						+	
	Pneumothorax	+		+					+			+	+
	Aspiration	+			+	+			+			+	+
	Infection	+			+	+			+			+	+
	Embolism												
GI	Hemorrhage	+											
GU	Infection	+											
Endo	Hyperglycemia												+
Hem	Thrombocytopenia												+
	Dic												

Three patients had excellent responses to the surgery. Patient III, a 58-year-old man with progressive disease experienced his first symptoms 4 years before surgery as manifested by making a turn while skiing. Two years later, he could not ski, one year later he could not walk, and six months later, he could not speak. Before surgery, he was dependent on his wife for all activities of daily living and was confined to a wheelchair. He was bradykinetic and, although he could stand, he fell spontaneously. He was a Stage 5 parkinsonian and was "off" all of the time. He was on levodopa 1,200 mg/day, carbidopa 300 mg/day, and deprenyl 10 mg/day. Improvement began two weeks after surgery via a transfrontal approach. One month after surgery he was able to walk unaided and speak. He continued to receive levodopa 600 mg/day, and carbidopa 150 mg/day. One year later, the patient improved further. Now, 16 months later, he is able to go outside by himself, drive a car, and has returned to work as a psychiatrist part-time.

Patient VII is a 56-year-old man with a 21 year history of PD. He had diurnal response fluctuations. In his "on" period he was a Stage 3 and in his "off" period he was a Stage 5. His "on" periods lasted less than 25% of his waking day. The patient, a college teacher, always needed assistance at work. He waas on levodopa 1,750 mg/day and carbidopa 750 mg/day. He had been treated with anticholinergics; amantadine, bromocriptine, and deprenyl. He underwent the surgery (transcallosal approach) uneventfully and one month later was moderately improved. He was "on" for up to 50% of his waking day. His speech however was impaired by a tongue tremor (which he had not previously had).

Four months later, the patient began to regress and three months later, he was back to his baseline state. At this time, without any change in his medication, he again began to improve. Ten months after surgery the patient is Stage 2 in his "on" periods and Stage 3 in his "off" periods. He is "on" for up to 75% of his waking day and can now work unaided. The tongue tremor disappeared. He is on levodopa 1,000 mg/day and carbidopa 100 mg/day.

Patient X, a 46-year-old man, had a nine year history of PD. He had initially responded to levodopa but now had diurnal response fluctuations. In his "on" period he was Stage 3 and in his "off" periods he was Stage 5. His "on" periods occupied less than 25% of his waking day and were complicated by peak dose dyskinesias. He was on levodopa 500 mg/day and carbidopa 50 mg/day. He had not been helped by DA agonists. The patient underwent operation uneventfully and began to improve two weeks later. Two months later he was a Stage 2 in his "on" periods and Stage 3 in his "off" periods. He was "on" for up to 75% of his waking day. He was now able to walk up and down the six flights of stairs from his apartment and to do his own shopping. He was on the same dose of

levodopa/carbidopa. At this time the patient, who lived alone, died suddenly.

An autopsy failed to reveal the cause of death. There were no surviving adrenal medullary cells in the caudate nucleus. This patient with typical PD, no history of toxic exposure and a typical response to levodopa had few pigmented cells in the SNpc but there were no Lewy bodies.

Three other patients improved moderately. Patient VI, a 37-year-old female with a 7 year history of PD was "on" for 25% of her waking day and was able to go for less than 8 hours between her last dose of levodopa at night and her first dose of levodopa in the morning. Now 14 months after surgery she is able to go 18 hours between her last dose of levodopa at night and her first dose of levodopa in the afternoon. She has reduced her medication from levodopa 800 mg/day and carbidopa 200 mg/day to levodopa 500 mg/day and carbidopa 75 mg/day.

Patient VIII is a 60-year-old man with a 12 year history of PD. Before surgery he was "on" for less than 50% of the waking day and would rapidly and unpredictably fluctuate between his "on" and "off" periods. Two months after surgery the patient was "on" for up to 75% of the waking day and his fluctuations were less abrupt. However, the patient did not maintain his improvement and 10 months later he is back to his baseline state.

Patient IX is a 65-year-old woman with a 12 year history of PD. Before surgery she was "on" less than 50% of the time. Her "off" periods were abrupt and often unpredictable. She began to improve one month after the surgery (transcallosal approach). She is now "on" for more than 50% of the day and her "off" periods are less abrupt and more predictable. Her medication has been reduced from levodopa 1,400 mg/day and carbidopa 140 mg/day to levodopa 900 mg/day and carbidopa 75 mg/day.

Two patients (II, IV) after uneventful operations (transfrontal approach) did not improve. Patient IV, a 52-year-old physician, was severely affected by PD and died 4 months after the surgery of unrelated causes. Post mortem examination revealed few pigmented neurons in the SNpc and the presence of Lewy bodies. Examination of the caudate nucleus revealed clusters of surviving adrenal medullary cells that stained positively for chromaffin granules but negatively for tyrosine hydroxylase.

Four patients had major complications from surgery. Patient I, a 58-year-old woman with a 40-year history of PD had cardiac arrest one week after surgery related to a vagal response to suctioning. She was promptly resuscitated and had a pacemaker inserted. However, 17 months after surgery, her parkinsonism is improved in that she is "on" longer but she has some mental impairment. Patient I also experienced a number of other adverse effects. These included the neuroleptic malignant syndrome (NMS) related to discontinuation of levodopa. The NMS abated with reinstitution

of levodopa and the addition of bromocriptine. Based on this experience, levodopa treatment is either maintained at preoperative dose levels or lowered by no more than 50%. The initial reason for trying to discontinue levodopa was the observation by Madrazo *et al.* (pers. comm.) that the best results occurred in patients in whom levodopa was discontinued.

Patient V, a 60-year-old man with a 4 year history of PD suffered a right cerebral infarction (transfrontal approach) resulting in a left hemiplegia.

Patient XI, a 59-year-old woman with a 9 year history of PD suffered a right frontal venous haemorrhage (transcallosal approach). The patient slowly recovered and 8 months later she is at her preoperative level of functioning with no sequelae of the right frontal haemorrhage.

Patient XII had a right frontal venous infarction after a transcallosal approach. He subsequently developed thrombocytopenia and a disseminated intravascular coagulopathy (related to an antibiotic used to treat an aspiration pneumonia). The patient then haemorrhaged into the sight of the right frontal infarction, the retroperitoneal space, and had a pulmonary embolus. He was eventually discharged from the hospital but died 5 months after surgery. Adverse effects in the entire series are summarized in Table 3.

Discussion

Neural transplantation is a new and experimental treatment for a major debilitating neurodegenerative illness. The present operations are prototypes that will be refined so that their results are more predictable and with fewer complications.

Three of our patients improved markedly with major changes in their lifestyle, changes that could not be achieved with medication. The improvement in two of these patients was biphasic suggesting two separate mechanisms related to graft placement. An initial mechanism may be related to release of trophic factors from the caudate or from inflammatory cells attracted to the graft, and a second mechanism may be related to the reinnervation of caudate neurons by collateral sprouting from the remaining nigrostriatal neurons. The collateral sprouting may be induced by trophic factors. The improvement is probably not related to the survival of the grafted cells.

Three other patients improved moderately with an increased time spent in their "on" periods and a decreased disability in their "off" periods. This improvement, in 50% of patients, is similar to the improvement reported at the American Academy of Neurology (Cincinnati, Ohio, 1988) by 7 institutions on 47 operated patients. We experienced 4 serious adverse effects (33%) which is higher than that reported at the Academy.

In view of the improvement noted in our patients and in others it is

relevant to ask why, 2 years after Madrazo's report, there is disillusionment about the efficacy of the operation. Unfortunately the surgery is not uniformly beneficial and poses major risks. Madrazo reports that his best responses occurred in patients in their 30s and 40s[11]. In general, with some exceptions, the best responses in the U.S. have been noted in patients of the same age and is analogous to results obtained in animals where the best results are obtained by transplanting fetal or juvenile adrenal medullary tissue. This suggests that after a certain age autologous adrenal medullary tissue is less suitable for transplantation, either from the loss of adrenal medullary tissue that occurs with aging or as an effect of the disease on the adrenal tissue. In addition, young patients are in better physical condition and better able to undergo simultaneous adrenalectomy and craniotomy.

However, if only younger patients are considered for surgery then the usefulness of the operation is limited because the great majority of patients with advanced disease are over age 60.

In order for the surgery to become more accepted the mortality and morbidity of the operation must decrease. The high morbidity is related to performing two operations on debilitated patients who, because of their underlying PD have specific medical problems. Thus many patients with advanced PD (excluding those with Shy-Drager syndrome) have some degree of autonomic insufficiency, including vocal cord paralysis, dysphagia, sialorrhea, seborrhea, orthostatic hypotension, sweating abnormalities, urinary incontinence, and impotence. Patients with advanced PD who have clinical evidence of autonomic insufficiency or in whom autonomic insufficiency is suspected should undergo autonomic nervous system testing. The problems in these patients may be classified as those that involve the central nervous system (CNS), the cardiovascular system, the respiratory system, and the gastrointestinal system.

Some patients are unresponsive for 2 to 7 days after surgery. The unresponsiveness resembles the clinical state of patients who are sedated with narcotics and has been attributed by Madrazo to the high levels of methionine enkephalin secreted by the graft[11]. It is noteworthy that many of these patients have little or no postoperative pain. Six patients experienced significant postoperative depression requiring psychiatric counseling and antidepressant medication. In all patients, the depression cleared.

Three patients had arrhythmias during the postoperative course. In two, these were transient but in one patient a bradyarrhythmia related to autonomic insufficiency required the placement of a pacemaker. One or more respiratory complications occurred in 9 of the 12 patients. Increased vocal cord paralysis manifested by stridor developed in two patients (both had a history of vocal cord dysfunction, not uncommon among persons with

advanced PD). Both required a tracheostomy, and in one patient, it proved to be permanent. One patient already had a tracheostomy before surgery because of vocal cord paralysis. In one patient, a pneumothorax related to the placement of a central venous catheter developed. It was promptly recognized and appropriately treated. Six patients with histories of aspiration pneumonia before surgery had several episodes after surgery. Further episodes of aspiration were prevented in these and other patients by meticulous suctioning and careful positioning of the patients by the nursing staff.

At this time removal of adrenal tissue via laparotomy and implantation of this tissue in the CNS via craniotomy is fraught with considerable morbidity in these chronically ill patients. One way of improving morbidity might be to employ a stereotactic rather than an open approach for transplantation of adrenal tissue. Efficacy might be improved by staging the operation. Thus, initial stimulation of the caudate nucleus presumably with release of trophic factors followed at a later date by transplantation may yield more consistent benefits. In addition, with the stereotactic approach, tissue can be transplanted to multiple sites in the caudate and putamen. Implantation of tissue to the putamen may be especially important because the most marked DA depletion occurs at this location.

Another means of improving the result of operation would be to use adrenal medullary tissue from organ donors, i. e., people who are giving up their kidneys for transplantation. This approach bypasses the need for an adrenalectomy and allows the harvesting of at least two adrenal glands. This approach coupled with methods to preserve and culture adrenal medullary tissue and modify its antigenicity (so that the host does not reject it) will allow the development of tissue banks. This may enable the surgery to be done safely, even on patients with advanced disease.

Another development is the use of fetal nigral tissue. At present, fetal transplants have been performed in China, Mexico, Cuba, Sweden, Great Britain, and the United States. Animal data indicate that nigral cells are more effective than autologous or fetal adrenal medullary tissue in alleviating PD. A disadvantage to using fetal tissue is the requirement for using immunosuppressive drugs. The brain can no longer be regarded as immunologically privileged and although the fetus is immunologically immature, the surgery does disrupt the blood brain barrier and it is conceivable that the host will reject the graft. A prolonged requirement for immunosuppressant drugs will limit the use of fetal implants. However, thus far, there have been no reports of rejection with or without immunosuppressive drugs. Although the animal work is promising and there have been some anecdotal reports of marked improvement in patients receiving fetal tissue, it is too early to judge this approach.

Conclusion

Neural transplants have opened a new era. The transplants are forcing neurologists and neurosurgeons to rethink their ideas on how the brain is organized and are forcing neurosurgeons to play a more active role in treating neurodegenerative disorders. At this time adrenal transplantation in humans with PD is an experimental procedure. Although there have been encouraging results in some patients, the morbidity of the procedure is considerable and a high percentage of patients receive no clinical benefit. Results have been difficult to evaluate because of heterogeneous operative techniques, non-uniform patient selection and difficulty in judging clinical improvement in a disease whose course may be variable.

On a more basic level there is considerable debate and confusion regarding the interaction between operative manipulation of the caudate nucleus and the disease process and the exact mechanism by which the grafts may ameliorate PD.

It is clear that before this procedure can be utilized more widely in the management of PD, additional investigations will have to be performed in animals. Issues to be resolved include (1) the relative efficacy and viability of fetal versus adult transplants, (2) autologous versus homologous transplants, (3) mechanisms by which grafts and operation exert a beneficial effect (4) techniques of implantation that reduce morbidity and mortality and at the same time maximize the clinical effect of the procedure.

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Stereotactic Imaging, Surgical Planning and Computer-Assisted Resection of Intracranial Lesions: Methods and Results

P. J. KELLY

Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota (U.S.A.)

With 21 Figures

Contents

Historical Background

Robert Henry Clarke described the stereotactic method and had a stereotactic instrument constructed in 1906 (Clarke and Horsley 1906). He and Sir Victor Horsley used the technique for a study of the cerebellar nuclei (Horsley and Clarke 1908). Horsley scoffed when Clarke suggested the application of the stereotactic technique to human neurosurgery. This ended their well known association. Later, in a monograph of 1920, Clarke described several types of stereotactic instruments and proposed human stereotaxis (Clarke 1920).

Human subcortical stereotaxis began in 1947, when Spiegel and Wycis performed a dorsal medial thalamotomy in an attempt to provide a less destructive alternative to frontal lobotomy (Spiegel and Wycis 1947). Talairach (1949) in Paris and Leksell (1949) in Stockholm also developed stereotactic instruments and methods for placing subcortical lesions for psychiatric disease, pain, and movement disorders. Other centers acquired stereotactic technology and in the late 1950s and 1960s many neuroablative procedures were performed for the treatment of movement disorders, particularly the tremor associated with Parkinson's disease. The availability of L-dopa in the 1960s brought about an abrupt end to stereotactic surgery in most centers. Nevertheless, a few centers continued to apply stereotactic methods for other purposes: for the drainage of tumor cysts, for the placement of subcortical electrodes in the evaluation of epilepsy, and for the biopsy and interstitial irradiation of subcortical tumors (Szikla *et al.* 1961).

Nevertheless, general applications of stereotaxis to the diagnosis and treatment of intracranial tumors remained limited, because most tumors could not be visualized on plain stereotactic radiographs. Their position had to be inferred from ventricular system shifts detected on positive contrast ventriculography. The advent of computed tomography (CT) brought about new possibilities for stereotaxis in general and for its application to tumor neurosurgery in particular. CT scanning provides a precise three-dimensional data base that can be incorporated into the three-dimensional coordinate system of a stereotactic frame. Intracranial tumors can also be visualized directly on CT.

Several methods for determining stereotactic coordinates on CT slices evolved in the late 1970s. These included: 1) transposition of CT slice data to standard stereotactic radiographs (Kelly *et al.* 1978), 2) calculation of

coordinates from screen and scout views when these options became available on later generation scanners (Gildenberg *et al.* 1982), 3) utilization of CT table and screen coordinates when scanning the patient in the stereotactic frame (Bergstrom *et al.* 1976 and Boethius *et al.* 1980) and finally 4) utilizing a reference localization system which created fiducial reference marks on each stereotactic CT slice from which stereotactic coordinates could be calculated (Brown 1979, Goerss *et al.* 1982, Perry *et al.* 1980). This latter method was derived from the inclined plane concept originally described by Goodenough (Goodenough *et al.* 1975) and evolved into the familiar "N"-shaped localization system used on several CT based stereotactic systems.

Volumetric Stereotaxis

Our interest in imaging directed stereotactic surgery began in late 1977 when we adapted techniques for the biopsy and interstitial irradiation of centrally located and deep-seated intracranial tumors (Kelly *et al.* 1978) from the methods developed by Talairach and Szikla (1961). Unlike classical functional stereotactic surgery where a target is considered as a point in space, tumor stereotaxis is more complex because tumors are, in fact, volumes in space. To be sure, a surgeon may biopsy a *point* within a CT defined tumor volume or place a series of radionuclide sources at several three-dimensionally defined points (Apuzzo and Sabshin 1983 and Kelly 1978 and 1979). However to accurately plan treatment of intracranial tumors, they must be considered as volumes in space. Interpolation of tumor boundaries detected on CT slice data allows the representation of the tumor as a three-dimensional object in space.

We first employed volume stereotaxis in attempts to more accurately plan interstitial radionuclide source placements so that the resultant isodose contours more conformed to CT-derived tumor contours. In order to do this, life size clay models were constructed from slice contour templates derived from photographically enlarged CT axial slices and reconstructions (Kelly *et al.* 1979). These models could then be suspended in a phantom stereotactic apparatus and sliced perpendicular to the intended radionuclide source implantation angle. These para-axial slice contours were then transferred to paper and then to a radiotherapy planning computer. Simulated sources were placed with the isodose contours for each of the slice contours. This was effective but cumbersome and time consuming.

Independently we had been using an operating room computer system to model and display a computer resident stereotactic atlas used during functional neurosurgery. Here digitized outlines of the atlas substructures were suspended in three-dimensional computer image matrix. This was eventually published in 1985 (Kall *et al.* 1985). The computer could reconstruct and model atlas sections which were displayed along any arbitrary

plane, usually parallel or orthogonal to a probe trajectory during functional procedures. Noting the similarity with the problem of tumor slice reconstruction, we rapidly adapted this software to do the same thing with outlines of tumors digitized from CT slices (Kelly *et al.* 1982). Thus the CT slices were read into the computer and the surgeon could simply digitize the outline of the tumor on each slice. The computer would then suspend those slices in a three-dimensional image matrix, interpolate intermediate slices and then create a volume in space by filling in each of the digitized interpolated slice with 1 mm cubic voxels (Kelly *et al.* 1983 a and b; 1984 a and b). The computer could then slice the tumor volume perpendicular to the intended surgical radionuclide source implantation angle (Kelly 1983 a and Kelly *et al.* 1984 a).

Stereotactic Resections

Many lesions were too geometrically complex to permit fitting of a precise isodose configuration produced by a finite number of sources to a series of slices from a complex tumor volume. In addition, other lesions were too large to consider interstitial irradiation as a safe therapeutic option, as the addition of the peritumoral edema following implantation could precipitate herniation. Finally, highly malignant glial neoplasms grew so rapidly, so that by the time the therapeutic dose of radiation had been delivered the tumor had grown beyond the therapeutic isodose limits.

The deep-seated location of most of the subcortical tumors in our patients precludes conventional surgical resection for several reasons. First the surgeon risks getting lost while attempting to find a deep subcortical tumor. This risk increases the deeper the procedure extends below the cortical surface. In addition, the margins between superficial and deep glial neoplasm and surrounding brain tissue is not always clear, especially later on in the procedure when bleeding is encountered. Finally, many of these lesions were irregular in shape and maintaining orientation within the lesion was also difficult.

Therefore, in order to resect deep and centrally located tumors as completely and as safely as possible, we began performing craniotomies in the stereotactic frame (Kelly and Alker 1981). The computer slice reconstructions developed for interstitial irradiation dose planning modified for display during open resections, were referred directly to the surgical approach (Kelly *et al.* 1982 and 1983 b, Kelly 1986). The stereotactic method not only allows precise spatial localization of the tumor but also a method by which the margins of the lesion could be identified. Specifically the reconstructions are sliced perpendicular to the trajectory angles set in the stereotactic frame in the surgical field by showing the position of the edges of the tumor as defined by the imaging studies, first CT, and later magnetic resonance imaging (MRI).

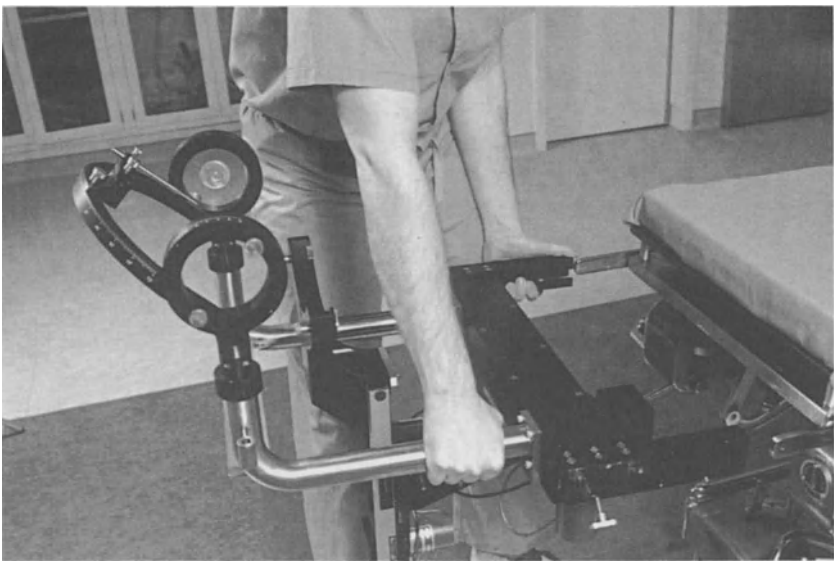
Development of Stereotactic Instrumentation

We originally used the Todd-Wells stereotactic frame for our tumor resection procedures. In this instrument, the patient's head, held in a rigid head holder attached to a three-dimensional slide system, is moved in X (right, left), Y (anterior, posterior) and Z (superior, posterior) in order to place an intracranial target into the focal point of a fixed arc-quadrant. The approach trajectory to the target is defined by two angles: arc (angle from the verticle plane) and collar or quadrant (angle from the horizontal plane). Any probe inserted perpendicular to a target of the arc-quadrant and to a depth equal to the radius of the arc-quadrant will always arrive at the target point. We modified the Todd-Wells system for computed tomography compatibility and later devised localization systems for magnetic resonance imaging and digital angiography. Unfortunately the Todd-Wells frame was originally designed for radiographically based functional neurosurgical procedures. Based on the limitations in the original design and applying our own set of requirements, including tumor stereotaxis, we totally redesigned the system around the arc-quadrant principle of the original Todd-Wells instrument. The intermediate system consisted of a large 400 mm radius movable arc which was indexed into a servomotor controlled three-dimensional slide system. While this intermediate system was being used in our surgical practice, further limitations related to the cumbersome 400 mm arc were noted.

Present Instrumentation for Stereotactic Resection

Stereotactic Frame

The stereotactic instrument which we now use consists of a three-dimensional slide controlled by computer driven stepper motors (Kelly *et al.* 1988 c). We retained the simplicity of the cartesian arc-quadrant system: the patient's head, held in a stereotactic head holder, is moved in three-dimensional space to place an intracranial target point in the center of a 160 mm radius fixed arc-quadrant (Fig. 1 A and B). The present system attaches to a standard operating table or to a floor mounted base unit. Movements of the three-dimensional slide system are accomplished by one of three methods: automatically by computer activated stepper motors, manually through a remote control panel, and mechanically by hand crank/worm gears on the X, Y and Z axis. Computer-controlled automatic movements of the slide system are enabled only when a foot pedal is depressed by the surgeon. Stereotactic coordinates are registered by three axis optical encoders which transmit them to the computer and to a digital display unit. In addition, mechanical vernier scales are provided for each X, Y and Z axis as backup to the optical encoders. The basering of the stereotactic



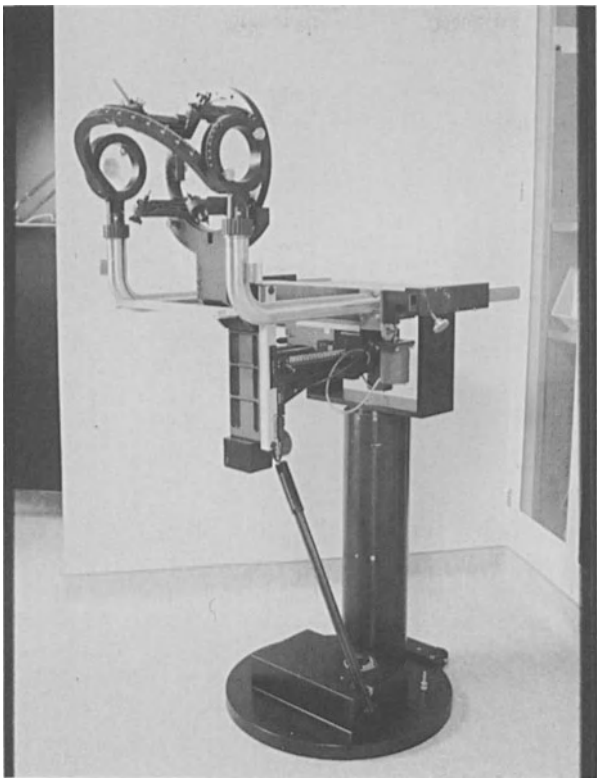
A

Fig. 1. Arc-quadrant stereotactic frame which attaches to: A) standard operating table or B) floor mounted base unit. The unit consists of a three-dimensional slide which moves the patient's head which is mounted in the stereotactic head holder in order to place the intracranial target point in the center of the fixed arc-quadrant. The movements of the three-dimensional slide are accomplished by computer driven stepper motors. The stereotactic coordinates are detected by three axis linear optical encoders

head holder is round and easily detaches and rettaches to the receiving yoke of the three-dimensional slide system. The base ring is also indexed at 5 degree increments which align to an indexing reference mark at the base of the receiving yoke. Thus the patient can be rotated to any position which will provide a comfortable working situation for the surgeon, and the degrees of rotation read off the basering and entered into the computer. The computer then recalculates the stereotactic coordinates of the target point and reformats the volumetric data base to account for this rotation. Using this system, all orthogonal and oblique approaches and target points in all parts of the head and neck are possible utilizing the appropriate combinations of arc and collar angle, patient rotation, and head frame placement (standard for supratentorial procedures and inverted for posterior fossa operations).

Stereotactic Retractors

For tumor resections we developed a series of stereotactically directed cylindrical retractors which are mounted on the 160 mm radius arc-quad-



B

rant. These maintain exposure of a deep tumor, are always directed at the focal point of the arc-quadrant and provide a fixed reference point within the surgical field (Burger *et al.* 1983). The computer displays the circular outline of the cylindrical retractor and the tumor slice reconstruction which corresponds to the configuration of the tumor at the depth to which the retractor has been inserted. The retractors are also used in the approach to deep tumors. An internal dilator is inserted into the retractor in order to dilate a subcortical incision up to the diameter of the retractor before the retractor is advanced. In order to use the 140 mm long retractors effectively, extra long bipolar forceps, suction tips, dissectors and scissors were manufactured on a custom basis.

Intramicroscope Graphics

A "heads-up" display system (similar to that used in fighter aircraft) projects the computer generated slices images of a tumor volume and a circular image corresponding to the cylindrical retractor into a standard free floating operating microscope (Zeiss Contraves, Carl Zeiss, Inc., West

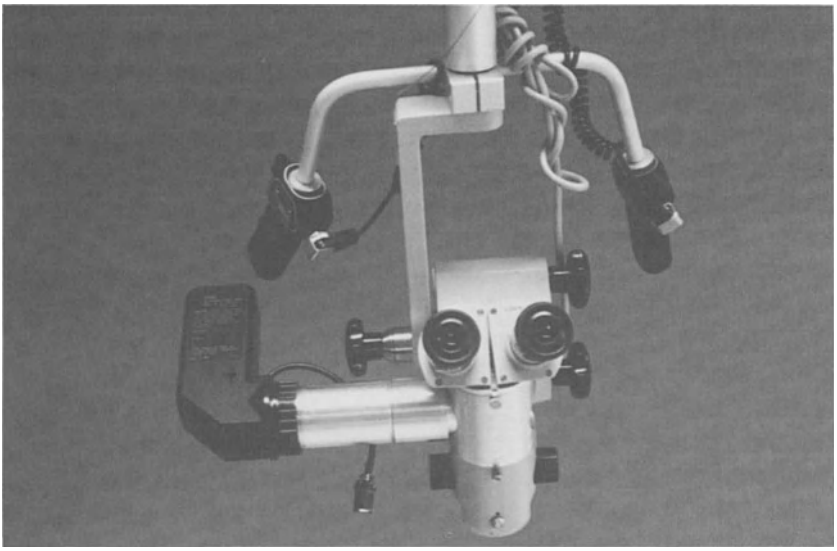


Fig. 2. "Heads-up" display unit for the Zeiss operating microscope. This consists of a video display monitor with optics which scale the computer image to align with the surgical field

Germany) and superimposes these images upon the surgical field (Fig. 2). The retractor image and tumor slice image dimensions are scaled by the computer so the projected images are actual size when viewed through the microscope. The operating microscope is optically indexed to the stereotactic surgical field as follows: During surgery, the surgeon adjusts the microscope so that the image of the stereotactic retractor projected into the microscope is superimposed over the actual retractor in the surgical field. Alternatively for superficially located tumors a scaled image of a circular trephine is superimposed over the actual cranial trephine placed stereotactically.

The surgeon communicates with the operating room computer system by means fo a sterile "mouse" on the operating table. This moves a cursor on a menu system which is also projected into the operating microscope by the "heads-up" display unit. Thus, without taking his eyes off of the surgical field, the surgeon can communicate with the computer to change image displays and make stereotactic frame adjustments.

The Stereotactic Laser

The carbon dioxide laser provides several advantages over conventional methods of tissue removal in the stereotactic resection of deep-seated intracranial lesions. First, it is a convenient tool for removing tissue from

the bottom of a deep cavity. One less instrument must be inserted into the channel which is used to expose the deep tumor since only a beam of light is being used to remove tissue. Second, the laser beam can be controlled and monitored by computer in the surgical field. Third, the laser is relatively haemostatic in the vaporization of tumors. Finally a laser incision is precise and results in tissue damage of less than 300 microns on either side of the incision. This factor is very important when attempting to resect a tumor from neurologically important areas such as the thalamus or in the brain stem.

Operating Room Computer System

The computer system makes volumetric stereotactic tumor procedures practical. Certainly volumetric stereotaxis can be performed without a computer system (Kelly *et al.* 1979 and Kelly and Alker 1981). However, the calculations are complex and would require many hours to perform using manual or graphic methods. In addition, intraoperative changes in target point or trajectory would be impractical due to the time necessary to perform these calculations manually. A dedicated operating room computer system can perform volumetric calculation in seconds to minutes and reformat and display tumor slices during a surgical procedure.

The computer system (Data General MV 9800) is located directly above the operating room (Fig. 3). It communicates with an image processor (Vicom) which transmits images to video monitors in each stereotactic operating room and to the "heads-up" display on the operating microscope.

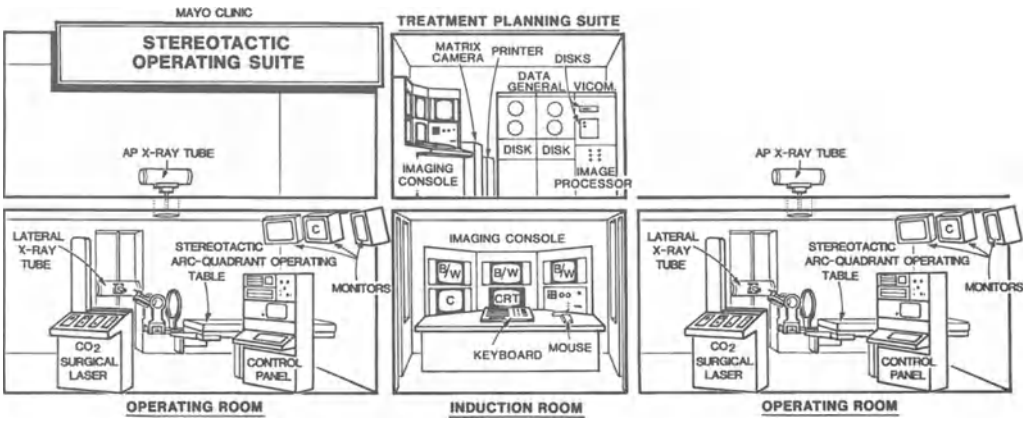
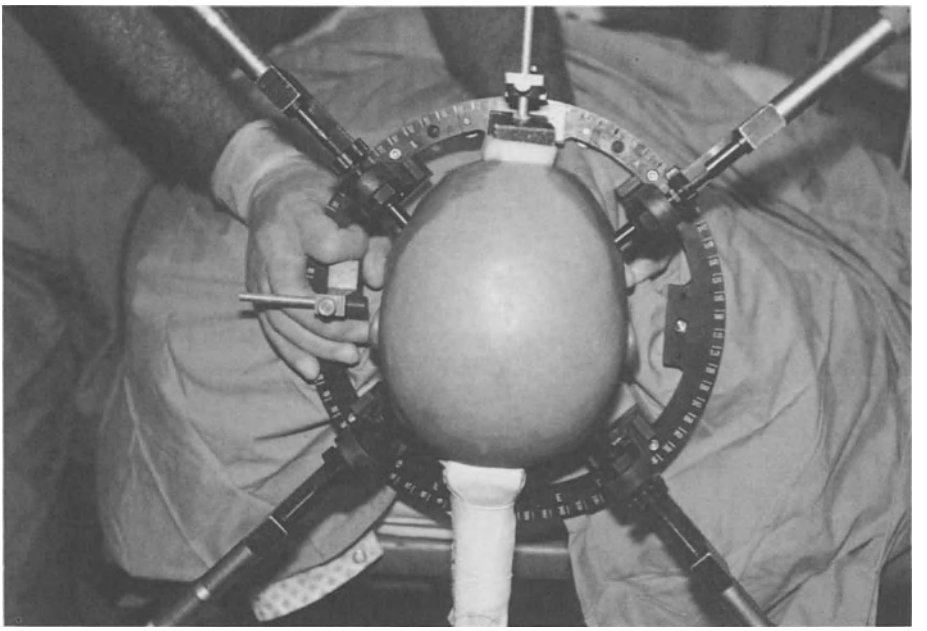


Fig. 3. The stereotactic operating room. A computer room is located above two operating rooms equipped for stereotaxis. Each operating room has a stereotactic frame, fixed tube AP and lateral laser collimated teleradiography and video display monitors for the display of computer generated images. Image display consoles are located between the operating rooms and in a treatment planning area above

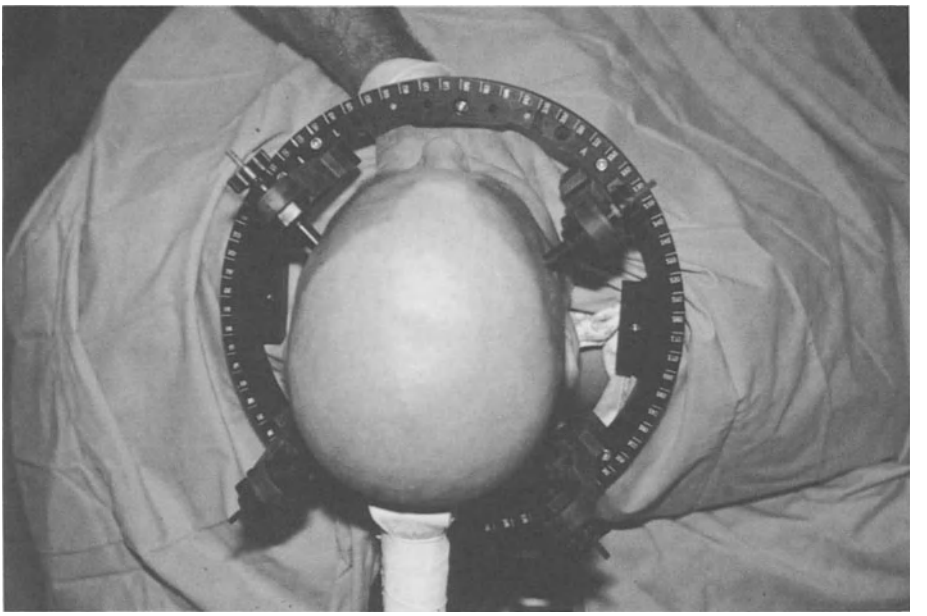


A

Fig. 4. The stereotactic head frame consists of four vertical supports and round base ring. The frame is fixed to the skull by means of carbon fiber pins which are secured to the vertical supports. Detachable micrometers are used to measure the length of the carbon fiber pins with respect to the vertical supports (A). This provides a mechanism by which the frame can be applied, removed, and reapplied in precisely the same manner. Head frame with micrometers removed (B). Note index marks at 5° intervals which are inscribed on the base ring. The patient may be rotated 360° in the stereotactic apparatus in order to provide a comfortable working position for the surgeon. The reading of the index mark on the base ring is transmitted to the computer which then calculates stereotactic coordinates in that rotation

The computer is used to process data from CT scanning, MR imaging and digital angiography. During surgical planning the computer relates the position of stereotactically directed instruments to slice reconstructions derived from an interpolated CT and MRI based tumor volume, where a tumor points selected from stereotactic CT or MRI slices are displayed on arterial or venous phases of the arteriogram or on a mask image which demonstrates the position of the major cortical sulci and fissures. This is very useful in planning of the surgical approach trajectory.

Computer-assisted stereotactic procedures are performed in three phases: data base acquisition, treatment planning and the interactive pro-



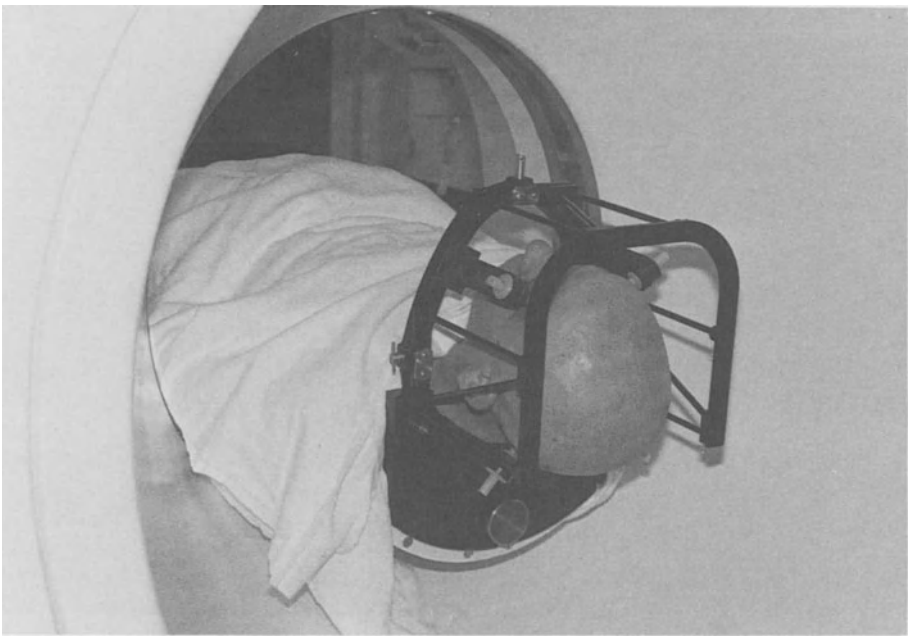
B

cedure. A replaceable stereotactic headholder is employed so that the head holder can be applied for data base acquisition and reapplied for the actual surgery. This is convenient since data base acquisition and surgery can be performed as separate procedures on two separate days.

Data Acquisition

Using neuroleptic sedation and local anaesthesia, the A CT/MRI compatible stereotactic head frame is placed on the patient's head. The head frame is secured by flanged carbon fiber pins which are inserted into $^{1}/_{8}$ inch twistdrill holes which extend through the outer table of the skull into the diploe. Four (4) detacheable micrometers attach to the vertical supports of the head frame to measure the length of the carbon fiber fixation pins with respect to the fixed vertical support elements (Fig. 4). These measurements are recorded in the patient's chart. Reapplication of the frame is straightforward and accomplished by tapping the four carbon fiber pins into the previously made skull fixation holes, reproducing the micrometer measurements and securing the fixation system. This provides a mechanism for accurately replacing the frame for subsequent data acquisition or surgical procedures.

Following frame application, the patient undergoes stereotactic CT, MRI and digital angiographic examinations as follows:



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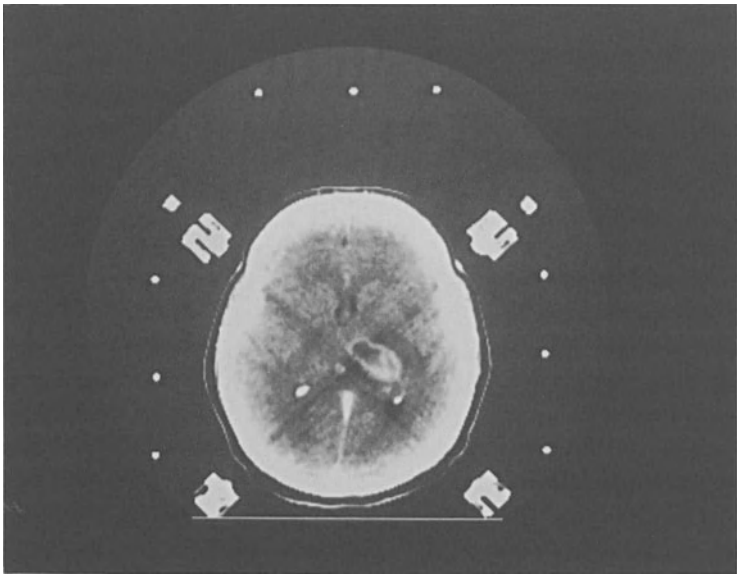


B

Fig. 5. A) CT localization system which contains "N"-shaped carbon fiber rods bilaterally and anteriorly. B) The localizing system produces nine reference marks on each CT slice from which stereotactic coordinates are calculated

Stereotactic CT Scanning

The stereotactic head holder secures to a CT table adaptation plate. A CT localization system which consists of nine carbon fiber localization rods arranged in the shape of the letter "N" located on either side of the head and anteriorly to create nine reference marks on each CT slice (Fig. 5 A and B). At our institution stereotactic CT scanning is performed on a General Electric 9800 CT scanning unit. Intravenous Iothalamate Meglumine is administered for contrast enhancement. Five (5) mm slices are gathered through the lesion, utilizing a medium body format. It is important that the examination encompass the entire lesion so that normal slices inferior and superior to the lesion are obtained.

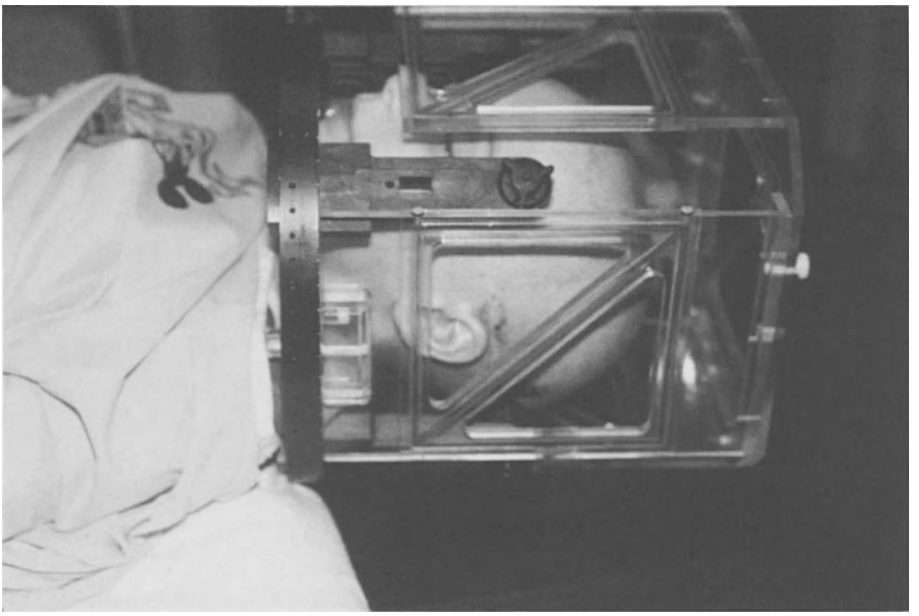
Stereotactic Magnetic Resonance Imaging

Stereotactic MRI examinations are performed on a General Electric 1.5 Tesla Signa unit. The stereotactic head holder is MRI compatible. The MRI localization system consists of plates containing capillary tubes filled with copper sulfate solution arranged in the shape of the letter "N" (Fig. 6 A and B). Plates are arranged bilaterally, superiorly, anteriorly and posteriorly. This allows sagittal, coronal and transverse image data acquisition. Nine reference marks are created on each sagittal, coronal and axial MRI image. Recently MRI studies have been performed utilizing Gadolinium DPTA contrast. In general, axial slices are useful for interpolation of tumor volumes. Sagittal and coronal images are useful in surgical approach planning.

Digital Angiography

Stereotactic digital angiography is employed for the localization of important blood vessels which must be preserved in the surgical approach and tumor resection. In addition, sulci may also be placed in stereotactic space utilizing stereoscopic pairs and a method well described by Szikla *et al.* (1977).

The stereotactic head holder fits into a DF table adaptation plate on the General Electric DF 3000 or 5000 Digital Angiographic units. A digital angiographic localization system consists of lucite plates which contain nine radioopaque reference marks and are located on either side of the head, anteriorly and posteriorly (Fig. 7 A). These create 18 reference marks on each AP and lateral DA image (Fig. 7 B). The mathematical relationships between the fiducial marks and their locations on the DA images are the basis from which stereotactic coordinates for intracranial vessels can be calculated, and stereotactic target points derived from CT and MRI can be displayed on angiographic images. Digital angiography is performed



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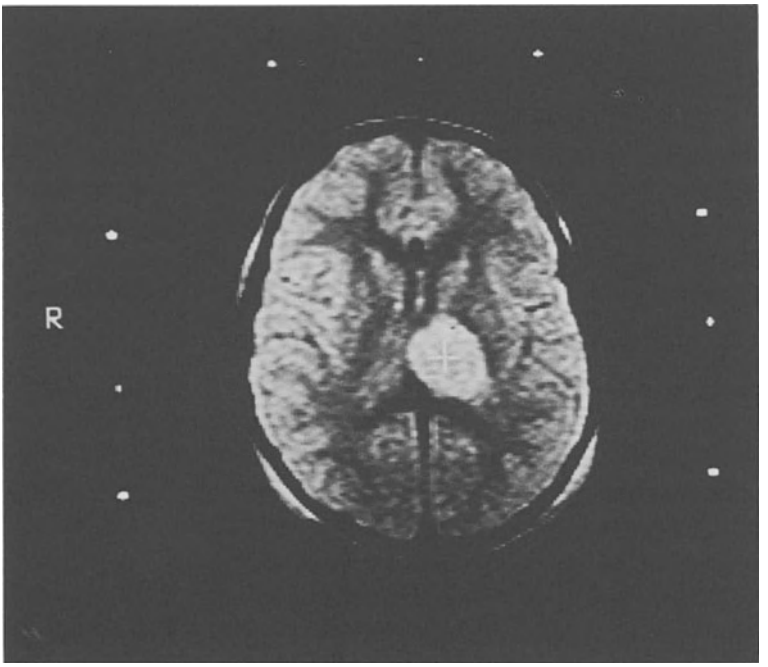
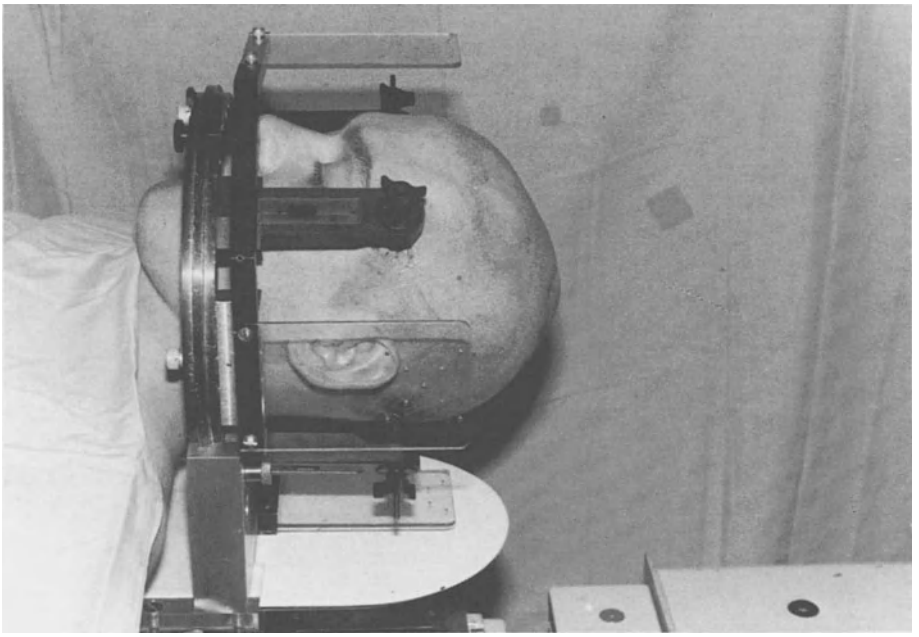


B

Fig. 6. A) MR localization system which consists of plates bilaterally, anteriorly, posteriorly and superiorly. Each plate contains capillary tubes filled with copper sulfate solution which produce reference marks on sagittal, axial and coronal MR images. B) MR image demonstrating a thalamic lesion. Note the nine reference marks produced by the localization system



A

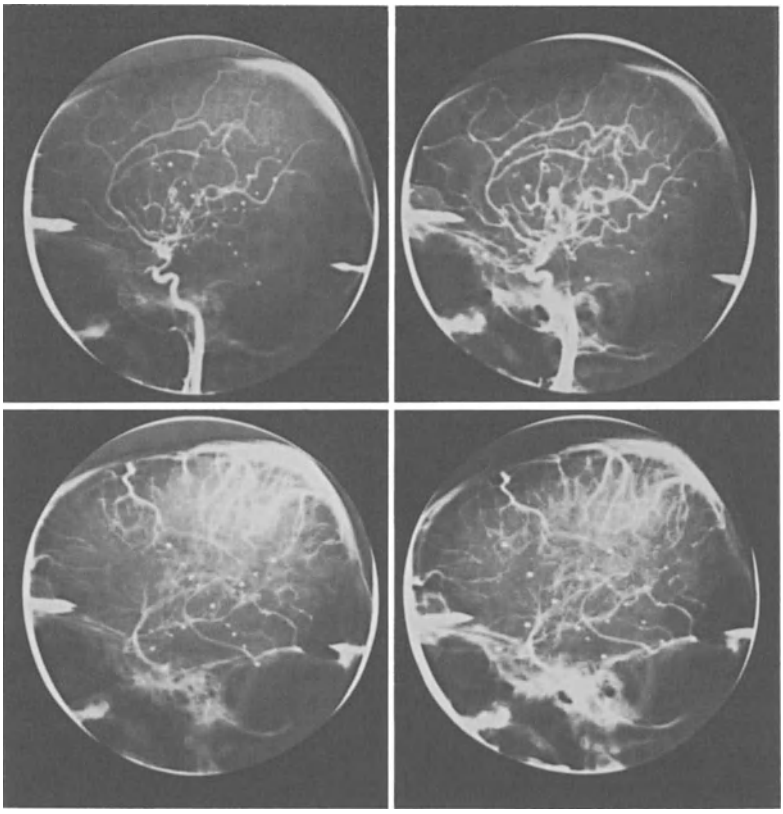
Fig. 7. A) Arteriographic localization system which attaches to the base ring of the stereotactic frame. This consists of four plates on either side of the head anteriorly and posteriorly. Each plate contains nine radiopaque reference marks. B) Stereoscopic lateral stereotactic arteriogram in orthogonal and 6° oblique projections. Note the 18 reference marks produced by the arteriographic reference system from which stereotactic coordinates can be calculated and points on CT and MRI displayed and cross correlated to the arteriogram images

utilizing a standard femoral catheterization technique. Orthogonal and six degrees oblique arterial and venous phases are obtained in orthogonal and 6° rotated stereoscopic pairs.

Surgical Planning

Tumor Volume Interpolation

Following data acquisition, the archived data tapes from the CT, MRI and DA examinations are read into the operating room computer system. The surgeon views each of the CT slices and MRI images which demonstrate the image and digitizes them as follows: the nine reference marks on each CT slice and MR image are detected automatically by an intensity detection algorithm. This suspends the position of each slice in a three-dimensional



B

Fig. 7

computer image storage matrix. Utilizing cursor and trackball, the surgeon traces around the outline of the lesion defined by CT contrast enhancement, around that defined by CT hypodensity, and around the contours of the lesion defined be the T 1 and T 2 weighted signal abnormalities of the MRI. Each of these digitized contours are suspended in a separate computer image matrix. A computer program then interpolates the intermediate slices at 1 mm intervals between the digitized contours and creates separate volumes in space by filling in each of these slices with 1 mm cubic voxels (21) (Fig. 8). Thus, volumes defined by CT contrast enhancement, CT low attenuation, T 1 and T 2 signal abnormalities on MRI are each established in the computer matrix. Each volume is assigned an identifying gray level which may be displayed individually or all together on a computer display monitor.

Surgical Planning and Approach

The surgical approach is selected which will preserve the patient's neurologic function by avoidance of injury to essential neurologic tissue. There-

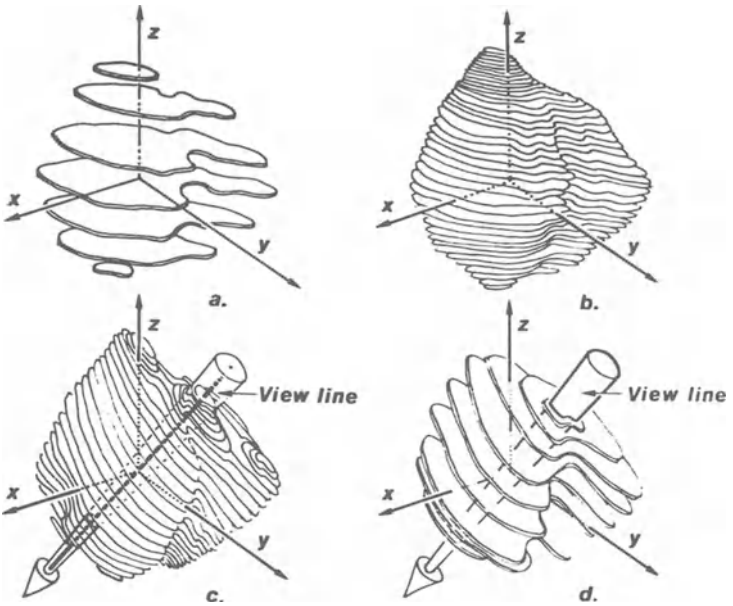


Fig. 8. Steps for tumor volume reconstruction from digitized CT or MRI data. Top left: Digitized slices are suspended in a three-dimensional computer image matrix in relationship to their position in stereotactic space. Top right: Intermediate slices are interpolated at 1 mm intervals. The digitized and interpolated slices are then filled in with 1 mm cubic voxels. Bottom left: The image data is then reformatted perpendicular to a specified viewline which is defined by arc and collar settings on the stereotactic frame. Bottom right: The computer slices the tumor volume with the image matrix perpendicular to the specified viewline. These slices are then displayed on a video monitor in the operating room and in the "heads-up" display unit on the operating microscope

fore, the stereotactic position of important neural and vascular structures and their relationship to the tumor volume must be established and the surgical approach planned to avoid them. Lesions which extend to within a few millimeters of the cortical surface usually are exposed by means of an incision in the crown of the overyling and nonviable gyrus. Deep lesions, on the other hand, are approached transcortically through nonessential brain tissue in a direction parallel to major white matter projections or through a deep sulcus.

The major cortical fissures and sulci are localized by the identification of the deep segments of arteries and veins apparent on stereotactic stereoscopic DA images using a variation of a method first described by Szikla *et al.* (1977). The surgeon views the stereoscopic pairs and traces each vascular deep segment utilizing the cursor and mouse. The computer retains

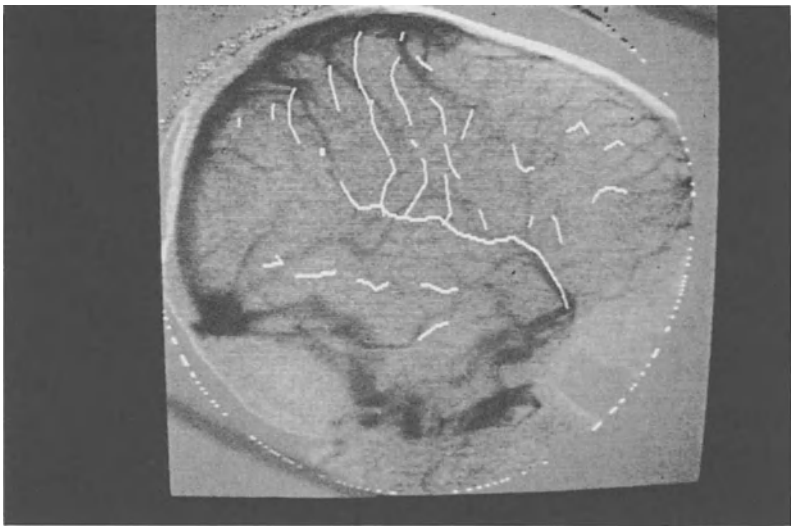


Fig. 9. The stereotactic stereoscopic digital arteriogram can be displayed on a computer-based videomerge unit. The surgeon traces the deep segments of the cortical arteries and veins. The computer retains the position of each of these digitized deep segments. This delineates the position of the major sulci of the brain

each of these line segments in an image displayed on the scout view mask image. This procedure clearly identifies the Rolandic and Sylvian fissures as well as the pre- and postcentral sulci (Fig. 9). In addition other sulci such as the superior and middle frontal sulci, superior temporal sulcus and interparietal sulcus can be identified and stereotactically localized in each and every case. This information is important in planning a trajectory to a deep tumor for two reasons. First the precentral and postcentral convolutions must be avoided by the approach trajectory. Secondly, deep sulci can provide a route to the depth of the hemisphere. The superficial aspect of a sulcus overlying a tumor can be chosen as a stereotactic entry point in the trajectory to expose a subcortical tumor. In addition, infiltrating tumors can be resected in nonessential brain tissue. Thus, determination of resectability is made after viewing the limits of the tumor displayed on the mask image which shows the sulcal localization.

The stereotactic surgical approach to the lesion is then planned, taking into account the three-dimensional shape of the tumor and important overlying cortical regions, subcortical white matter pathways and important vascular structures which must be preserved. First the surgeon reviews the DA image on which the central point within the tumor is displayed. A cursor is manipulated to simulate the approach on lateral and anterior-posterior images in order to select a trajectory which avoids major arterial

and venous vascular structures. The computer calculates and displays the angular settings for the arc and collar of the stereotactic frame which will provide this trajectory in the patient during the surgical procedure. In addition, collar and arc settings can also be calculated by computer from entry and target point coordinates.

Surgical approaches to a variety of deep-seated lesions have been adapted from conventional techniques or developed specifically for our methods. The following general points may be useful in planning the surgical exposure. The precentral convolution cannot be traversed if neurologic deficit is to be avoided. Therefore, deep precentral lesions are approached anteriorly through a microsurgically split precentral sulcus with the patient supine (0° rotation). Posterior approaches which are performed with the patient prone (180° rotation) are selected for lesions located posterior to the central sulcus.

Anterior thalamic lesions are exposed by means of a retracted incision through the anterior limb of the internal capsule. Lesions of the posterior and ventral thalamus are approached through a cortical and white matter incision at the temporal occipital junction, with the patient prone (180° rotation) or semiprone (135° for left- or 225° for right-sided lesions). Dorsal thalamic lesions are exposed through the superior parietal lobule and lateral ventricle.

Midline posterior fossa lesions are exposed through an incision in and retraction of the inferior vermis; lateral lesions through cerebellar hemisphere. Midline pontine lesions which elevate and extend to the floor of the fourth ventricle are resected through a midline incision in the floor of the ventricle. Lateral pontine lesions are exposed through a dilated incision in the middle cerebellar peduncle.

The surgical approach is expressed in terms of patient rotation (which will depend on whichever working position is most comfortable for the surgeon) and arc and collar angles (which will depend on the safest line of attack to the lesion). During the surgical procedure, the computer continuously displays the patient rotation, the arc and collar angles, and the stereotactic frame settings along with the image displays.

The actual surgical approach (or viewline) is expressed in stereotactic frame adjustments (collar: angle from the horizontal plane; arc: angle from the vertical plane) which access a selected point with the interpolated tumor volumes from an entry point on the surface of the brain. The CT and MRI defined tumor volumes residing within the image storage matrix are sliced perpendicular to the intended surgical approach angles.

Surgical Procedures

Computer-assisted stereotactic surgery is useful in superficial or deep-seated lesions. In superficial lesions, the stereotactic instrument is used to

center a circular trephine having a known diameter over the tumor. The relationships between the computer display of the circular trephine superimposed by the "heads-up" display onto the actual trephine in the surgical field and slices from the CT- and/or MRI-defined tumor volumes, will orient the surgeon during dissection around the removal of the neoplasm. This procedure ensures that the trephine is directly over the tumor, that trephine need be no larger than the largest cross sectional slice of the tumor and that no more brain tissue than necessary need to exposed to potential injury. Deep tumors are removed through a stereotactically directed cylindrically shaped retractor. Both procedures are described below.

Superficial Lesions

Procedural Aspects. The patient is placed under general endotracheal anesthesia. The stereotactic head frame is replaced using the same pin holes in the skull, pin placements and frame micrometer settings utilized during the data acquisition phase. The patient is then positioned in the stereotactic frame. In our system, the patient in the stereotactic head frame may be rotated to any rotation which will provide a comfortable working situation for the surgeon. The frame rotation angle is entered into the computer program and the computer calculates frame adjustments which place the center of the tumor into the focal point of the stereotactic arc-quadrant accounting for this rotation. After prepping and draping the head, the stereotactic arc-quadrant is positioned. The selected arc and collar approach angles are set on the instrument. Through a stab wound in the scalp a pilot hole is drilled in the outer table of the skull by a stereotactically directed $^1/_8$" drill. The scalp is then opened by a linear incision. A craniotomy is performed using a power trephine centered on the pilot hole. The size of the trephine selected is equal to or slightly larger than the largest cross-sectional area of the tumor viewed from the selected surgical approach angles which have been determined during the planning phase.

The computer displays the configuration of the trephine in relationship to the reformatted tumor outlines into the "heads-up" display unit of the operating microscope (Fig. 10). The surgeon then superimposes the graphics image of the trephine over the actual trephine in the surgical field using the most superficial computer generated tumor slice as a template. A section of cortex having the same size and configuration as this computer generated image is removed with bipolar and scissors. The dissection is then carried to deeper levels as a plane is developed around the tumor utilizing the bipolar forceps, cavitron or microscope mounted CO_2 laser. During tumor resection, the computer displays successive slice configurations of the lesion at successively deeper levels. The depth of the resection is calculated against the fixed arc-quadrant. Incidentally the arc-quadrant serves also as a convenient hand rest during the dissection.

In the resection of superficial tumors, the lesion is first isolated from surrounding brain tissue and the specimen is kept intact. The interior of the lesion should not be entered until late in the procedure because the walls of the lesion may collapse in on themselves and render subsequent

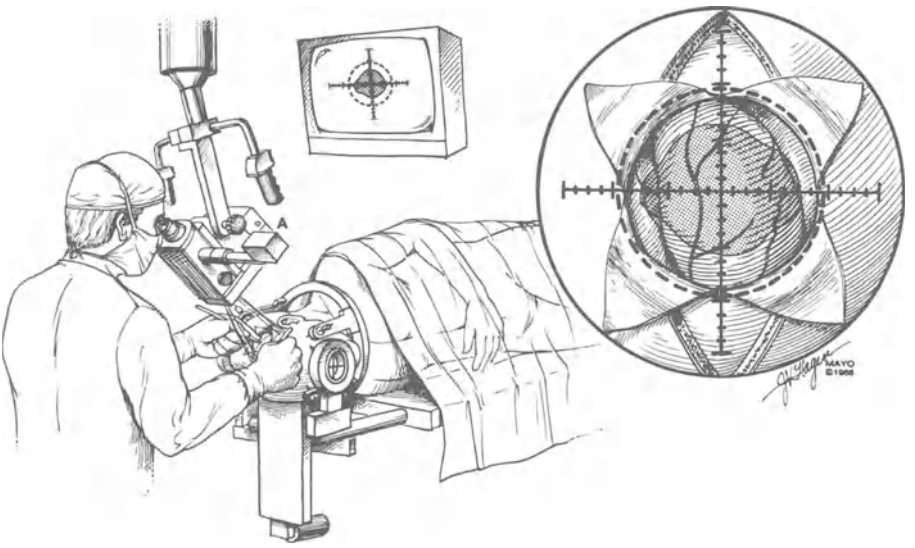


Fig. 10. Method for stereotactic resection of superficial tumors using "heads-up" display unit. This superimposes the computer generated tumor slice image over the surgical field viewed through the operating microscope. The cranial trephine is placed stereotactically. The surgeon superimposes the computer display image of the trephine over the actual trephine in the surgical field. This accurately places the image of the tumor directly over the surface of the brain when viewed through the operating microscope. The displayed tumor slice image then serves as a template, useful in establishing a plane of dissection between tumor and surrounding brain tissue. (Mayo Clin Proc 63: 1186–1198, 1988)

computer generated slice images no longer accurate. When this method is employed, intermediate and high-grade gliomas can be removed as intact specimens. During decompression with the volumetric stereotactic technique the lesion is first separated from its blood supply and bleeding is negligible. Similarly the technique is also very useful for arteriovenous malformations which are also dissected from surrounding brain tissue and their arterial feeders, identified in the stereotactic field, ligated. In addition, infiltrated areas of brain parenchyma in low-grade gliomas identified by increased T 2 signal on MRI and located in nonessential brain tissue can also be resected in a similar manner.

Deep Tumors

Stereotactic resection of periventricular, intraventricular, basal ganglia or thalamic tumors requires stereotactic retractors, extra long bipolar forceps and dissecting instruments.

Cylindrically shaped stereotactic retractors described previously are mounted on an internal stereotactic arc-quadrant (Fig. 11). The position of the deep end of these retractors with respect to the stereotactic target point and slices through the tumor volume is indicated on the computer display terminal in the operating room and is projected into the "heads-up" display unit of the operating microscope. The cylindrical retractor when viewed by the surgeon is circular and is represented as a circle in the computer display in relationship to the tumor slice. During surgery, the computer-generated image of the retractor projected into the "heads-up" display unit is superimposed on the actual retractor viewed through the operating microscope.

The selected target point within the tumor volume is positioned into the focal point of the stereotactic arc-quadrant. In order to monitor possible movements of the tumor during the procedure, a series of $^1/_2$ mm stainless

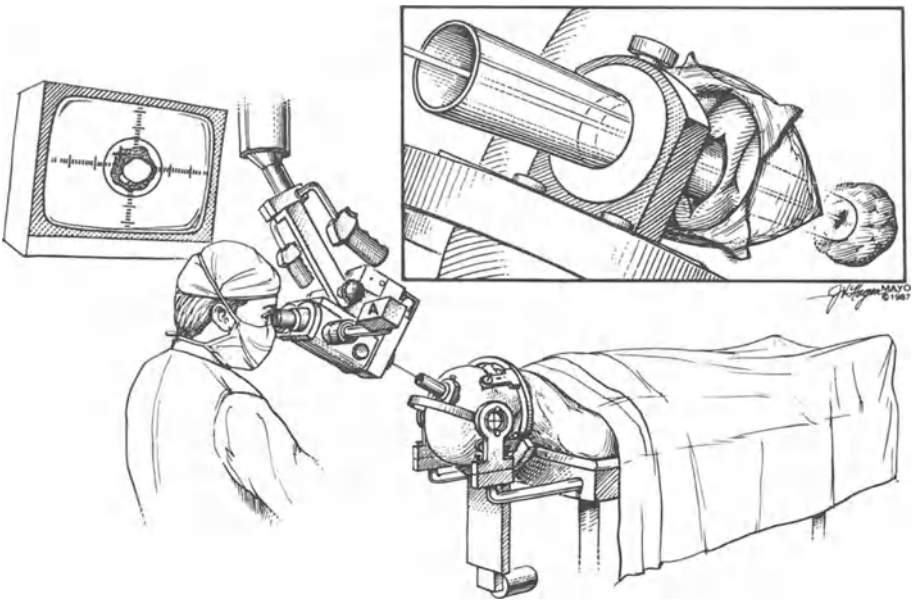


Fig. 11. Deep-seated lesions are removed utilizing a stereotactically directed cylindrical retractor. The image of the retractor and a slice of the computer generated tumor volume cut perpendicular to the specified viewline are displayed on a computer monitor in the operating room and into the "heads-up" display of the operating microscope (*A*). (Mayo Clin Proc 63: 1186–1198, 1988)

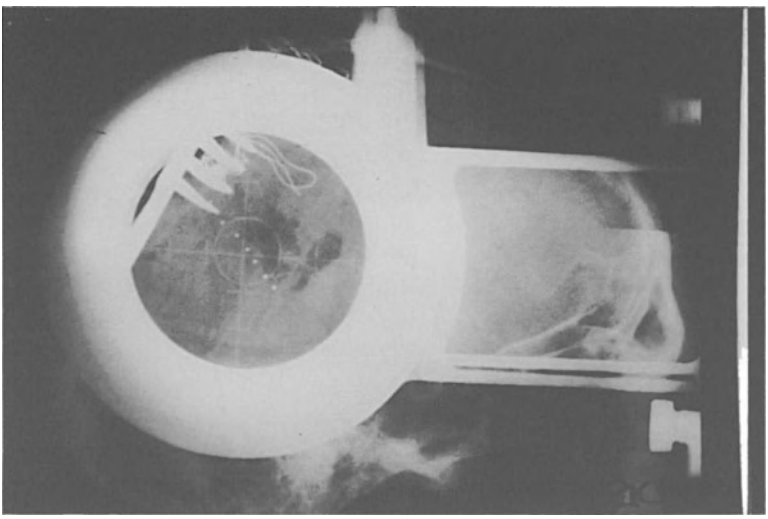


Fig. 12. Cystic tumors or those located near the ventricular system are first traversed with a stereotactically directed cannula inserted through a twistdrill opening in the skull. A series of stainless steel balls are deposited along the stereotactic viewline. AP and lateral teleradiographs are used to document the position of the steel balls which then are used to monitor possible shifts which may occur after trephine craniotomy, dural opening and possible entry into cyst or ventricular system. If shifts are detected, the position of the tumor in the computer matrix is changed accordingly

steel reference balls are deposited at 5 mm intervals along the surgical viewline in the tumor by a stereotactically directed biopsy cannula inserted through a $^1/_8$ inch drill hole in the skull. AP and lateral radiographs are obtained. The position of these steel balls on subsequent radiographs serve as indicators of shifts in the position of the tumor which may occur following craniotomy, opening of the dura and exposure of the lesion (Fig. 12). This step is especially important in lesions associated with a cyst or in lesions near the ventricular system since they can shift in position when cyst fluid or ventricular fluid are drained.

The scalp is opened with a linear incision. A $1^1/_2$" trephine craniotomy is performed and a cruciate opening of the dura accomplished. In general we try to use a convenient sulcus identified stereotactically and opened microsurgically to gain access beneath the cortical surface. The sulcal banks are gently retracted and the cortex at the bottom of the sulcus is incised to the subcortical white matter. Then the subcortical white matter incision is progressively deepened and dilated utilizing the stereotactic retractor and dilator. The CO_2 laser directed from the operating microscope and manipulated by a microslad is particularly suited to the application. The

direction of the subcortical incision has been planned to traverse non-essential brain tissue and progress in a direction parallel to major white matter fibers. As the incision is deepened, the stereotactic retractor is advanced to maintain the developing exposure.

The computer has calculated the range of the tumor along the surgical viewline. Since the length of the retractor (140 mm) and the distance of the retractor mounting bracket on the arc-quadrant (125 mm) are known, measurements from the mounting bracket to the superficial end of the retractor serve to confirm the depth of the distal end of the retractor from the target point. At the calculated outer border of the tumor, the laser beam is deflected laterally to expose the superficial aspect of the tumor and the retractor is advanced in order to create a shaft from the surface to the outer border of the tumor. Then using the computer display of the superficial slices of the tumor against the position of the retractor as a guide, the surgeon creates a plane of dissection around the lesion with the laser or extra long bipolar forceps, advances the retractor and deepens the incision circumscribing the tumor. Tumor tissue within the retractor is vaporized with 65–85 watts of defocused laser power or removed by suction or biopsy forceps. In order to prevent the tumor collapsing in upon itself following internal decompression and rendering subsequent stereotactic slice images inaccurate, it is important that tumors are first isolated from surrounding brain tissue before removal or removed slice by slice extending from the most superficial slices to the deepest. Hemostasis is secured utilizing the extra long bipolar forceps. AP and lateral teleradiographs are obtained to document the progress of the procedure and record possible movements of the reference balls (which are removed as they are encountered during the procedure).

Tumors larger than the retractor opening can be removed as follows. First, one side of the tumor is positioned under the retractor and the surgeon creates a plane between this side of the tumor and brain tissue. The display image is then translated on the computer display terminal to position the other side of the lesion under the retractor. The computer calculates new stereotactic frame adjustments which are duplicated on the stepper motor driven slide mechanism of the stereotactic frame. These motors can be controlled directly by computer or manually by means of a remote control panel. Then this side of the tumor is separated from brain tissue. After isolating the lesion from surrounding brain tissue it may then be vaporized by laser as described above. We have removed lesions as large as 5.0 cm in diameter through a 2.0 cm diameter retractor by employing this method.

Posterior Fossa Procedures

The data acquisition phase for a posterior fossa biopsy or resection procedure varies from that described for supratentorial work in that the

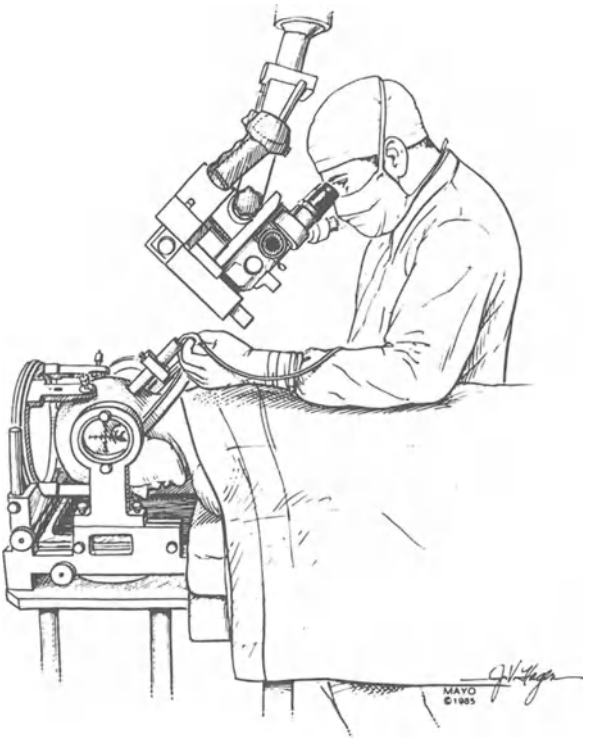


Fig. 13. Stereotactic resection of a posterior fossa tumor. The frame is placed in the inverted position. The surgeon stands to the side of the patient and deep-seated posterior fossa tumors are resected utilizing a stereotactically directed retractor

stereotactic headholder is placed in an inverted manner for data base acquisition and for the surgical procedure (Kelly *et al.* 1986). Following data acquisition and planning, the surgical procedure is performed with the patient 180° prone for lesions which are to be approached in a transcerebellar fashion or rotated 30–40° off the straight prone position to provide in midline lesions a comfortable working position for the surgeon. The surgeon stands at the patient's side facing cephalad (Fig. 13). Vertical linear scalp incisions, suboccipital craniectomy and transcerebellar hemisphere or inferior transvermian surgical approaches are utilized. We have found that the 2.0 cm diameter stereotactic retractor can be used safely in the cerebellum. For obvious reasons the retractor is not advanced into the brain stem. In the resection of brain stem lesions, the edges of the retractor are superficial to the brain stem, maintain exposure through the overlying cerebellum and provide a stereotactic reference structure against which slices of the lesional volume may be displayed. During brain stem proce-

dures in an attempt to recognize potential injury to the intact brain stem and avoid it, we routinely monitor median and tibial somatosensory evoked responses, brain stem auditory evoked responses and occasionally cranial nerve electrical activity.

Clinical Material

Two hundred and twenty-six (226) patients underwent computer assisted stereotactic craniotomies at the Mayo Clinic between August 1984 and August 1987. Some of the following information has recently been published elsewhere (Kelly 1988 a). The preoperative and postoperative neurologic condition of the 226 patients in this series are listed in Table 1 which also shows the number of patients having lesions in various anatomical locations. Two hundred and three (203) patients had lesions in supratentorial areas, 23 had lesions infratentorially. Lesions histologies and surgical results are summarized in Table 2. There were 115 glial tumors, 67 nonglial tumors and 44 nonneoplastic mass lesions. Patients ranged in age from 2 to 78 years, with an average age of 46.8 years.

General Results and Complications

Preoperative neurological examinations revealed that 105 of the 226 patients were normal neurologically (36 of these had intractable seizures). Preoperative neurologic deficits were documented in 121 patients. Postoperative neurologic examinations performed upon discharge from the hospital or two weeks following surgery, demonstrated that 109 patients were improved from their preoperative level (see Tables 1 and 2). This includes 36 patients who presented with medically intractable seizures; all were seizure-free postoperatively and remained seizure-free for at least three months. Ninety-six (96) patients were neurologically unchanged: 66 were normal preoperatively and remained normal postoperatively; 30 patients had deficits preoperatively which did not improve following surgery.

Twenty-one (21) patients had new neurological deficits or worsening of a preoperative deficit following surgery; 7 of these had been neurologically normal preoperatively. Of the 21 patients who were worse following surgery, postoperative neurologic deficits were consistent with trauma caused by the surgical approach in 9 patients. Seven (7) developed contralateral visual field deficits following posterior temporo-occipital approaches to mesial temporal or ventral thalamic lesions (partial superior quadrantopsia in 4, complete superior quadrantopsia in 2 and homonymous hemianopsia in 1). One patient had increased gait dystaxia following a trans-Vermian approach to a deep midline partially thrombosed AVM and another was noted to have right-sided dyspraxia following a trans-Sylvian approach to a metastatic tumor beneath the left insular cortex. Eleven (11) other patients

Table 1. *Results of Pre- and 1–2 Week Postoperative Neurologic Examinations Correlated with Location*

Location	No. of patients	Side		Deficit	Preop. normal	Seizures	Improved	Postop. same	Worse
		R	L						
Supratentorial (203)									
Frontal	45	23	22	19	19	7	19	25	1
Central	17	10	7	9	2	6	14	2	1
Parietal	36	16	20	21	9	6	18	17	1
Temporal	27	12	15	6	10	11	13	10	4
Occipital	6	4	2	2	1	3	4	2	—
Temporo-parietal	13	3	10	9	2	2	8	3	2
Parieto-occipital	5	3	2	4	—	1	4	1	—
Temporo-occipital	5	2	3	4	1	—	3	1	1
Thalamus	20	3	16	15	5	—	8	9[a]	3
Basal Ganglia	11	5	6	7	4	—	4	5	2
Third Ventricle	12	—	—	2	10	—	2	9	1
Lateral Ventricle	4	1	3	2	2[b]	—	1	2	1
Corpus Callosum	2	—	—	2	—	—	1	—	1
Infratentorial (23)									
Cerebellar Hemisphere	8	3	5	6	2	—	3	4	1[c]
Cerebellar Vermis	3	—	—	2	1	—	—	2	1
Midbrain	1	—	—	1	—	—	1	—	—
Pons	6	—	—	5	1	—	3	3	—
Medulla	5	—	—	5	—	—	3	1	1
	226			121	69	36	109	96	21

[a] Normal exam in five patients.
[b] Ventricular system obstructed in one patient.
[c] Infection.

Table 2. *Summary of Pre- and Postoperative Neurologic Examinations on Patients with Various Histologic Lesion Types.* Numbers with parentheses in patients who are preoperatively normal indicate the number presenting with intractable seizures

Lesion	No.	Preop.		Postop.			% Morbidity	% Mortality
		Normal (seizures)	Deficit	Improved	Same	Worse		
Glial tumors (115)								
Grade 4 astrocytomas	44	6	38	21	18	5	11	
Grade 3 astrocytomas	7	2	5	3	2	2	28	
Grade 2 astrocytomas	10	6	4	2	3	5	50	
Grade 1 astrocytomas	3	3 (3)			3		—	—
Pilocytic astrocytomas	24	11 (2)	13	11	11	2[b]	8	4
Oligoastrocytomas	8	4 (2)	4	4	4	—	—	
Oligodendrogliomas	11	9 (4)	2	6	5	—	—	
Gangliogliomas	3	3 (1)	—	1	2	—	—	
Subependymoma	1	1	—	1	—	—	—	
Ependymoma	3	1	2	1	2	—	—	
Medulloblastoma	1	—	1	1	—	—	—	
Nonglial Tumors (67)								
Metastatic tumors	44	13	31	21	21	2	4.5	
Hemangioblastomas	2	—	2	2	—	—	—	
Meningiomas	7	6	1	—	6	1[c]	14	
Colloid cysts	9	9	—	—	9	—	—	
Lymphomas	4	—	4	2	2	—	—	
Choroid plexus pap.	1	—	1	1	—	—	—	

Nonneoplastic Lesions (44)							
Vascular Lesions[a]	29	23 (18)	6	20	5	4	13
Radiation necrosis	5	1 (1)	4	3	2	—	—
Gliosis (epilepsy)	5	5 (5)	—	5	—	—	—
Tuberous sclerosis	1	—	1	1	—	—	
Abscess	1	1	—	1	—	—	—
Cystocercosis	1	1	—	—	1	—	—
Hematomas	2	—	2	2	—	—	—
Totals				109	96	21	

[a] Include AVMs, cryptic AVMs, caverous hemangiomas.
[b] One of three patients died.
[c] Death from pulmonary emboli.

were worse because of local trauma to perilesional tissue during the resection of the lesion (hemiparesis in 3, monoparesis in 2, recent memory impairment in 1, apraxia in 2, somnolence in 1, and nonpermanent apnea following resection of a medullary astrocytoma in 1). Another of these 11 patients deteriorated because of paroxysmal lateralizing epileptiform discharges (PLEDs). This patient, a 75-year-old man with metastatic bronchogenic carcinoma ultimately died two months postoperatively due to pulmonary decompensation. One patient had a postoperative infection.

Two patients died within 30 days of the surgical procedure. One patient died eight days postoperatively: a 29-year-old man following resection of a thalamic astrocytoma with infiltration into the brain stem apparent on MRI. Another patient, a 64-year-old man, hemiparetic postoperatively, sustained fatal pulmonary emboli 14 days following resection of a large meningioma from the left lateral ventricle.

Table 2 summarizes the postoperative results following stereotactic resection of various histologic lesion types. Patients having certain histologic types do better than others. In general the more histologically circumscribed the lesion, the better the postoperative results.

High-Grade Gliomas

Forty-four (44) patients underwent resection of the contrast enhancing portion of grade 4 astrocytomas: 38 had preoperative neurologic deficits, 21 of them improved, 12 were unchanged and 5 were worse. In each case postoperative deficits were consistent with trauma to perilesional tumor cell infiltrated parenchyma. Average postoperative survival was 47.8 weeks (mean survival 43.5 weeks) in this group of patients. In seven (7) patients having grade 3 astrocytomas resected, 3 of 5 patients with preoperative deficits improved while 2 were worse; 2 preoperatively normal patients were normal postoperatively.

We cannot cure malignant gliomas. Computer-assisted stereotactic resection can remove all CT-defined contrast enhancing portions of glioblastomas from neurologically important subcortical areas (Fig. 14) with acceptable levels of mortality and morbidity (Kelly *et al.* 1986 and Kelly 1988 a). Postoperative CT studies usually demonstrate absence of contrast enhancement around the surgical defect. Nevertheless death in grade 4 astrocytomas treated by this method is due to tumor "recurrence" and progression. New areas of contrast enhancement develop within low density areas close to and in some cases remote from the surgical defect. Histologic examination of stereotactic biopsy specimens obtained from CT hypodense and MRI T 2 prolonged areas outside regions of CT contrast enhancement reveal intact edematous brain parenchyma infiltrated by aggressive isolated tumor cells (Burger 1983, Daumas-Duport *et al.* 1982 and 1987, Kelly *et al.*

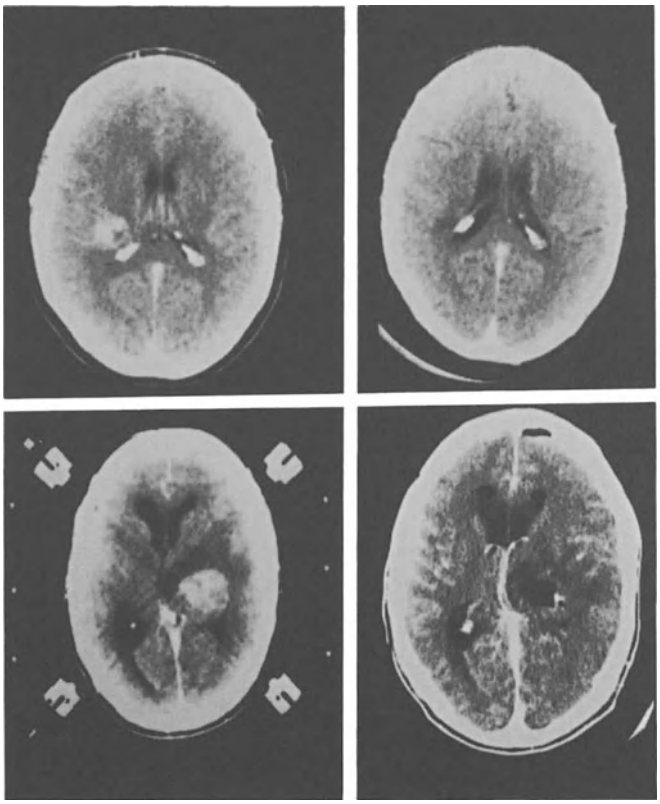


Fig. 14. Pre- (left) and postoperative (right) CT scans in patients with grade 4 astrocytomas resected from the deep parietal area in a 38-year-old man and from the left thalamus in a 43-year-old man. Neither patient was neurologically worse postoperatively

1987a and b). Nevertheless, the average survival of grade 4 astrocytoma patients (Kernohan classification), treated by computer-assisted stereotactic laser resection and external beam radiation therapy was slightly better than average survival times quoted in other series from the literature (37 weeks) (Frankel and Gorman 1959, Godan and Walker 1977, Hitchcock and Sato 1964, Jelsma and Bucy 1967), in which a high percentage of patients harbored lesions in the frontal and temporal lobes which are more amenable to radical surgical resection by lobectomy.

However, comparisons between any contemporary surgical series and historical controls are probably unfair. Many of the historical series of high grade gliomas were accumulated before the availability of CT scanning. CT scanning allows earlier detection of glial neoplasms. Therefore patients in older series may have had more advanced disease at the time of surgical diagnosis.

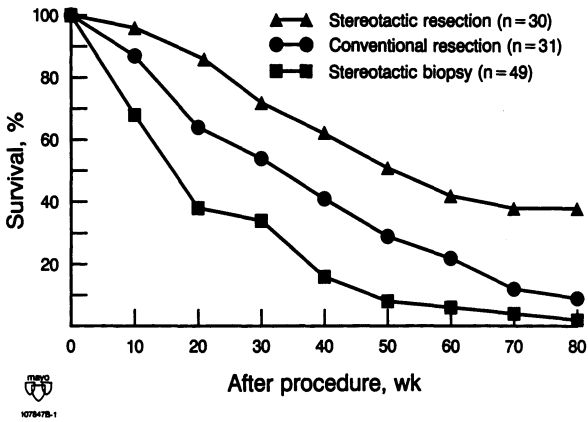


Fig. 15. Life table analysis of patients undergoing stereotactic biopsy and radiation therapy, conventional nonstereotactic craniotomy and radiation therapy, and stereotactic resection followed by radiation therapy

Therefore, survival was compared in 110 consecutive patients harboring grade 4 astrocytomas treated at the Mayo Clinic between August 1984 and January 1987 who underwent stereotactic biopsy (49 patients) standard nonstereotactic resection (31 patients) and computer-assisted stereotactic resection (30 patients) followed by external beam radiation therapy (Fig. 15). The patients who underwent conventional craniotomy had nonpolar grade 4 astrocytomas and were referred to other neurosurgeons at our institution. There was a 29.5 week average survival following biopsy and radiation, a 38 week average survival following conventional craniotomy and resection followed by radiation therapy, and a 47.5 week survival after stereotactic resection and radiation therapy. It should be stressed, however, that this is a nonrandomized retrospective series. Patients undergoing stereotactic resection are selected for that procedure because they appear to have relatively circumscribed lesions on CT scanning.

Low-Grade Gliomas

Fibrillary Astrocytomas

Ten (10) patients with grade 2 astrocytomas (6 normal and 4 with deficits preoperatively) did less well: 5 had mild postoperative neurological deficits (4 of these had been normal preoperatively). Three patients with very low grade (grade 1) astrocytomas presenting with a long history of medically intractable partial complex seizures did well postoperatively.

The resectability of grade 1–2 astrocytomas, oligodendrogliomas and oligoastrocytomas depends on the degree of histological circumscription in that individual neoplasm. In adults the tumor is usually manifest by an

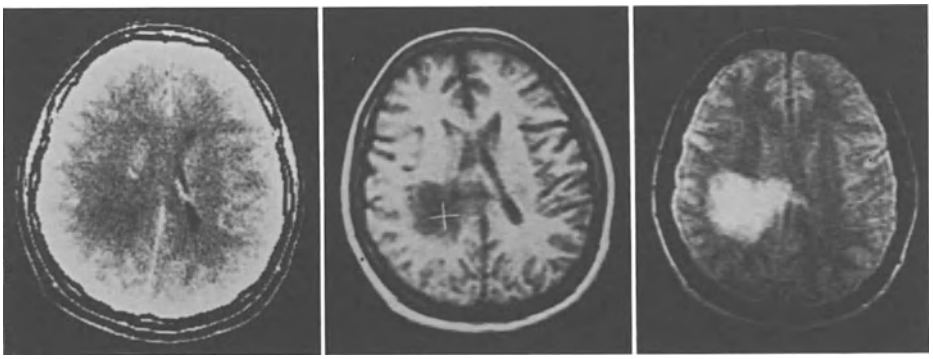


Fig. 16. CT (left), T 1 (middle) and T 2 (right) MR images in patient harboring a grade 2 astrocytoma. Biopsy showed intact parenchyma infiltrated by isolated tumor cells. Resection of a lesion such as this is, in fact, resection of functioning brain tissue

area of low density on CT scanning and prolongation of signal on MRI (Kelly *et al.* 1987 a and b). Figure 16 shows a typical example of an adult low-grade glioma. Stereotactic serial biopsy studies of these so-called fibrillary astrocytomas, oligodendrogliomas and mixed gliomas reveal that the tumor is usually comprised of infiltrated intact parenchyma with little tumor tissue proper (Daumas-Duport 1987, Kelly *et al.* 1987). In important brain areas, stereotactic resection of intact but infiltrated parenchyma defined by low density areas on CT scanning and signal prolongation on MRI results in postoperative neurologic deficit (Kelly *et al.* 1988).

Pilocytic Astrocytomas

In general, 24 patients with pilocytic astrocytomas in various deep-seated locations did well as a group; 11 noted improvement of preoperative neurologic deficits. However 2 patients were worse following the surgery. One patient with a left posterior medial temporal pilocytic astrocytoma, sustained a partial contralateral superior quadrantopsia due to the surgical approach (posterior-lateral transtemporal). The other patient had a pilocytic astrocytoma of the right thalamus associated with components of an ordinary astrocytoma which infiltrated through subthalamic area, midbrain and pons. Removal of the thalamic component of the neoplasm was followed by massive brain stem edema and death eight days later. Nevertheless, pilocytic astrocytomas are usually circumscribed histologically. The borders of these lesions are accurately defined by the contrast enhancement that these tumors exhibit on CT scanning (Daumas-Duport *et al.* 1987, Kelly *et al.* 1986). In spite of the fact that many are located in the thalamus and

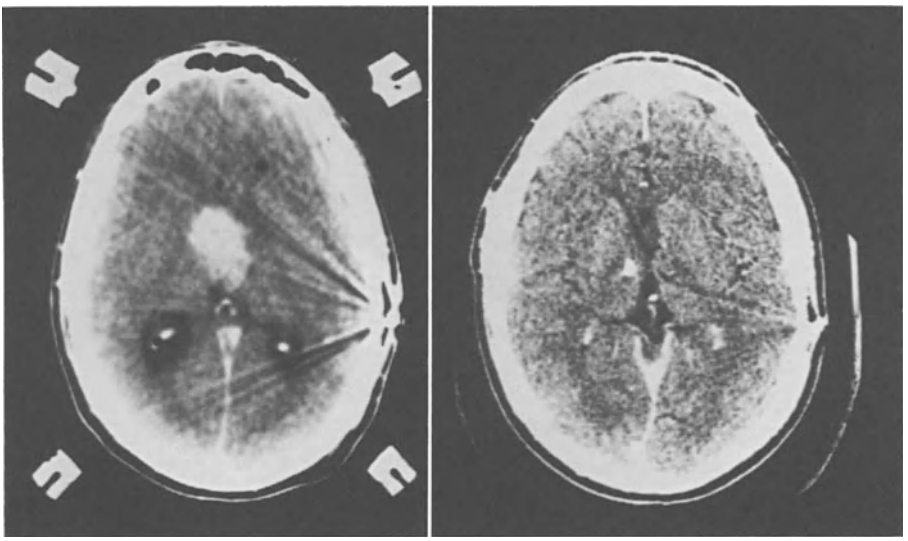


Fig. 17. Pre- and postoperative CT scans of medial thalamic pilocytic astrocytoma. Increased density in the right thalamus on postoperative scan is a distal element of a previously placed ventricular shunt

other deep-seated locations, they can be completely resected by computer-assisted stereotactic technique with excellent postoperative results (McGirr *et al.* 1987) (Figs. 17 and 18).

Metastatic Tumors

Following resection of 44 metastatic tumors, 21 of 31 patients with preoperative neurologic deficits improved postoperatively, but 1 of these 31 was worse postoperatively. Twelve of the remaining 13 patients who were normal preoperatively were normal postoperatively. However one patient, neurologically normal preoperatively, sustained a monoparesis of the left arm following resection of a metastatic adenocarcinoma from deep within the right precentral convolution. This had resolved three months postoperatively.

Stereotactic resection can be advantageous in the resection of the superifical metastases as well as the deeply situated lesions. Stereotactic localization helps center small cranial trephines directly over superficial lesions (the trephine need be no larger than the cross-sectional area of the neoplasm). The approach is therefore selective, direct and no more brain than absolutely necessary need be exposed. Since metastatic tumors are histologically circumscribed, they can be completely resected by the computer-assisted stereotactic craniotomy (Fig. 19). Our postoperative mor-

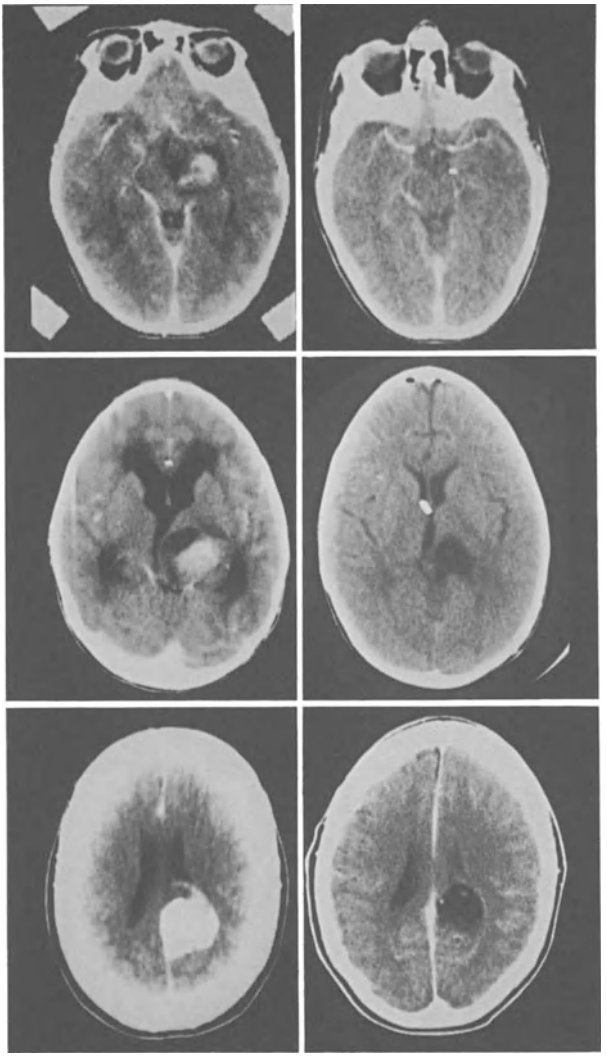


Fig. 18. Pre- and postoperative CT scans in three patients having pilocytic astrocytomas. Top: Eight-year-old boy with tumor resected from left thalamus. Postoperative scan was obtained 5 years following surgery; Middle: Five-year-old girl with tumor in left posterior ventral thalamus. This lesion was removed utilizing a posterior-inferior approach to the thalamus and medial parietal area. Bottom: Twenty-seven-year-old woman with medically intractable sensorimotor seizures and tumor in left anterior medial parietal lobe. None of these patients had neurologic deficit postoperatively. (Reprinted with permission from the Mayo Clin Proc 63: 1186–1198, 1988)

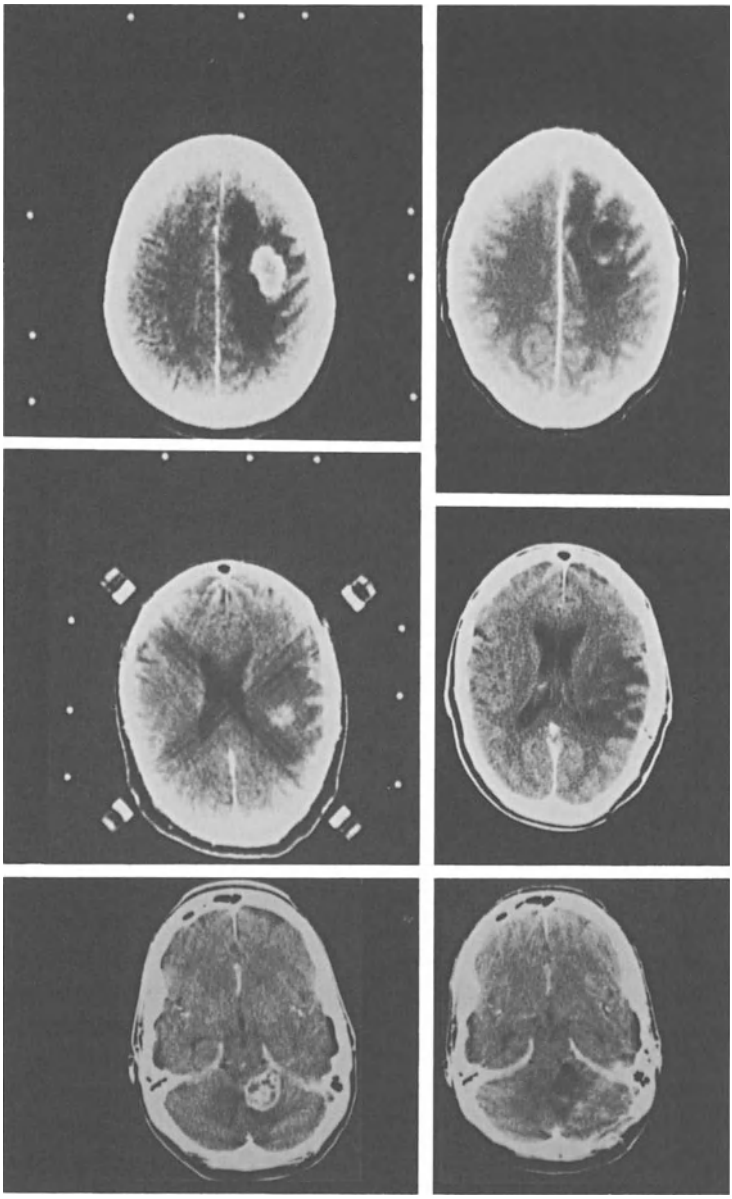


Fig. 19. Pre- (left) and postoperative (right) CT scans on patients having metastatic tumors resected from the left posterior frontal area. (Top) from subinsular area utilizing a trans-Sylvian approach (middle) and from middle cerebellar peduncle (bottom). Neurosurgery 22: 7–17, 1988

bidity for stereotactic resection of centrally located and deep-seated metastatic tumors (mortality 0, morbidity 9.0%), compares favorably with that associated with conventional craniotomy for metastatic neoplasms reported in the literature (mortality 11%) (Haar and Patterson 1972, MacGee 1971). External beam radiation therapy has followed surgery in most of our patients in order to treat possible microscopic metastatic lesions not visible on CT scanning.

Vascular Lesions

Cryptic or thrombosed AVMs, cavernous hemangiomas and small arteriovenous malformations provide a circumscribed target for stereotactic removal. Eighteen of 29 patients with vascular lesions and medically intractable seizures had complete cessation of the seizures following removal of the lesions. Four (4) of these 29 patients had postoperative deficits due to the approach in 2 patients (superior quadrantopsias following resection of medial temporal lesions) and in 2 due to local surgical trauma (hand weakness in one following resection of a lesion in the motor strip and lethargy following removal of a lesion in the ventral thalamus, subthalamus and midbrain).

Cryptic AVMs and cavernous hemangiomas are well circumscribed lesions which can be completely removed stereotactically with relatively low risk. A by-product of establishing the histology is that a cessation or significant reduction of seizures, when present, usually results.

Small deep-seated active arteriovenous malformations may also be resected utilizing similar techniques. The position of the feeding vessels is established in the three-dimensional surgical planning matrix and these are approached and clipped or coagulated first, before the remainder of the lesion is dissected away from the surrounding parenchyma.

Miscellaneous Lesions

Patients having other circumscribed neoplastic and nonneoplastic lesions have done well in general following volumetric stereotactic resections. Intraventricular lesions such as colloid cysts, meningiomas and choroid plexus papillomas are easily removed by the technique with relatively low morbidity.

Intraventricular Lesions

A direct approach to intraventricular lesions can be made stereotactically. Brain and ventricular incisions need to be only large enough to introduce and manipulate the stereotactic retractor. Even large lesions of the lateral ventricles and septum pellucidum can be removed through a 1.5 inch trephine and 2 cm cylindrical retractor (Fig. 20).

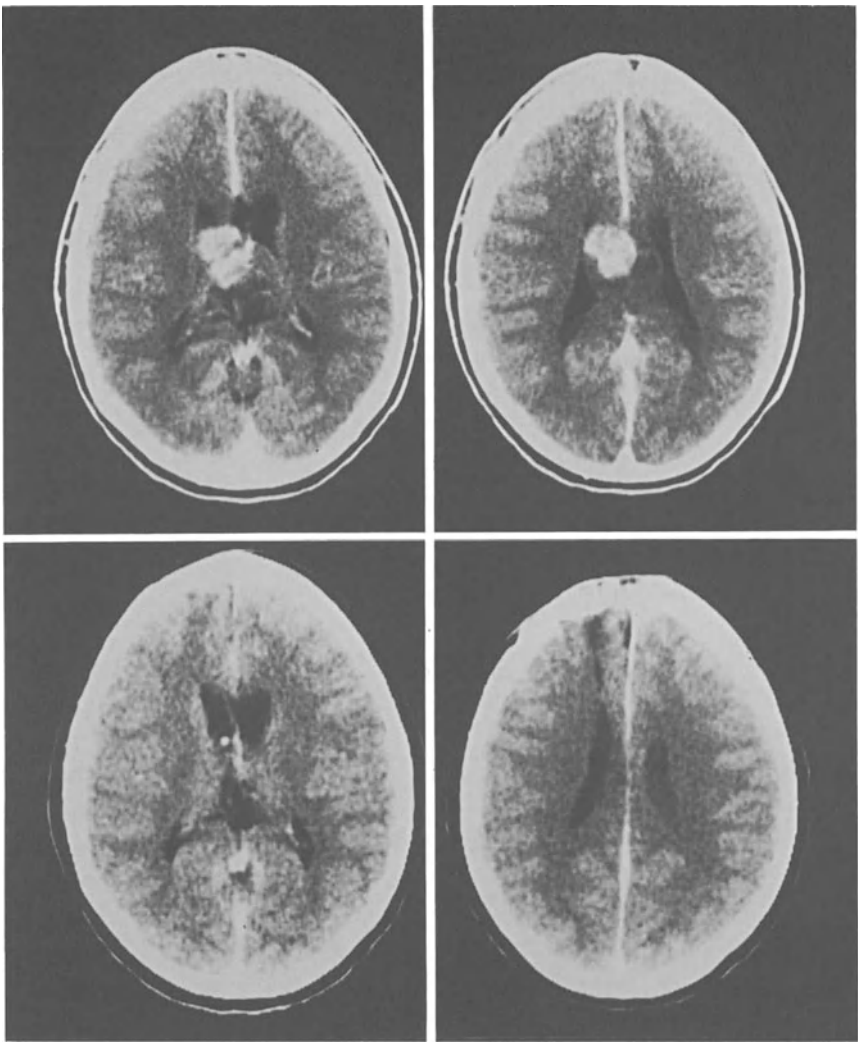


Fig. 20. Pilocytic astrocytoma of the septum pellucidum and right lateral ventricle. Pre- (top) and postoperative (bottom) scans are shown. Note surgical tract on bottom right image

Third ventricular lesions are approached through the right lateral ventricle. Colloid cysts can be removed through the foramen of Monro through which the cyst extends. The lesion is exposed by means of the stereotactic retractor and large colloid cysts can be removed by this method (Fig. 21). In large solid third ventricular lesions one fornix can be divided in order to extend the stereotactic retractor into the lesion. Here an internal decompression of the lesion is performed until only a thin rim of the capsule

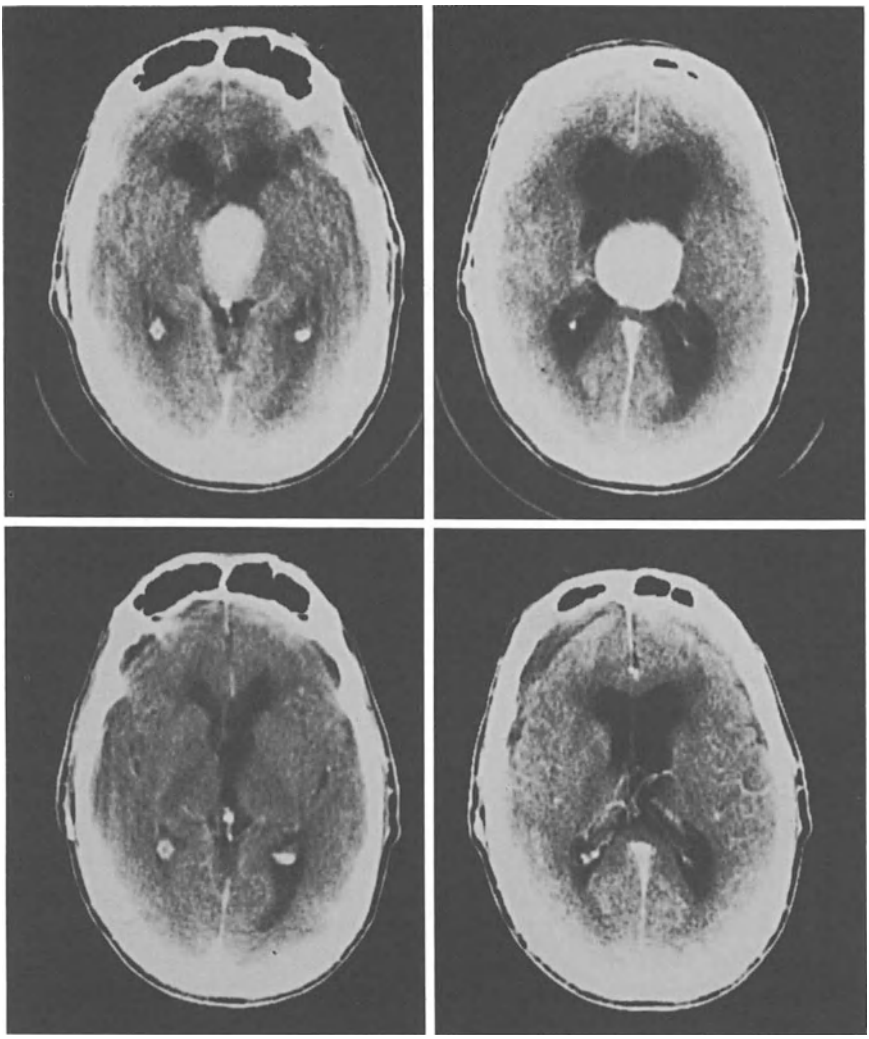


Fig. 21. Pre- (top) and postoperative (bottom) CT scans in patient harboring a giant colloid cyst of third ventricle

remains. The computer display of the cross-sections of the digitized tumor volume are extremely useful in this step as the surgeon can be quite aggressive within the tumor with no risk of extending through the capsule and damaging the walls of the third ventricle. Following this internal decompression, the retractor is withdrawn to the level of the roof of the third ventricle and the capsule is carefully dissected from the walls of the third ventricle and removed.

Discussion

In computer-assisted volumetric stereotactic microsurgery, tumors in important subcortical areas are exposed by means of a preplanned approach with traverses nonessential brain tissue. The surgeon monitors not only the surgical field but also a computer generated image of the surgical field derived from CT scanning and MR imaging. Thus, surgeons are more secure in performing a more complete resection of deep-seated and centrally located neoplasms when using the computer-assisted stereotactic technique than they would be utilizing a conventional technique alone.

The limitations of the computer-assisted stereotactic procedure in glial neoplasms lie in the constraints established by the disease process: unresectable intact parenchyma which is infiltrated by isolated tumor cells. However, patients harboring histologically circumscribed (noninfiltrating) deep-seated or centrally located lesions will derive the most benefit from the procedure.

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B. Technical Standards

Surgical Techniques in the Management of Colloid Cysts of the Third Ventricle

With 16 Figures

Contents

Introduction

Dandy was the first to describe the successful removal of a colloid cyst in 1921[10]. Initially a variety of open surgical approaches were described mainly through the frontal horn of the lateral ventricle or through the corpus callosum and although these were attended by considerable mortality and morbidity in the past[12, 13, 23, 24, 34], modern microsurgery has revolutionized the management of these conditions[1, 27]. The two series reported here by classical neurosurgical techniques, from Zürich and London, indicate that complete excision of these tumours may now be achieved with low mortality and morbidity. Since 1975, an increasing number of reports have described aspiration techniques avoiding craniotomy[5, 11, 15, 17, 29, 30, 31], and a series from Homburg/Saar is described using these techniques. The ventriculoscope has been employed stereotactically or freehand[29] (Calliauw) and a brief description of the modern ventriculoscope is appended from Brussels.

The Transcortical Approach

(L. SYMON and M. PELL)

Between 1949 and 1988, 42 patients with colloid cyst verified at operation have been seen at the academic department of the National Hospital for Nervous Diseases based at Queen Square, London. Of these 42 patients, 13 of them were seen in the last 5 years. All cases were operated upon by Professor Valentine Logue or Professor Lindsay Symon.

The sex incidence is unequal with males being more commonly affected than females. In this series there were 30 males and 12 females with ages ranging from 12 to 65 years. The disease predominated in young middle age, with 23 patients being between the ages of 31 to 50 (55%). The age and sex distribution are shown in Table 1.

Table 1. *Age and Sex Distribution*

Sex	0–20	21–30	31–40	41–50	51–60	61+	
Male	3	6	7	10	2	2	30
Female	1	4	4	2	1	0	12
Total							42

Signs and Symptoms (Table 2)

The main symptoms on presentation were headache, nausea and vomiting, disturbances in mentation, visual disturbance and motor weakness. In a number of cases these disturbances could be properly regarded as drop

Table 2. *Neurological Symptoms in Patients with Colloid Cysts*

Symptoms	No. of cases
Headache	37
Blurred vision	18
Disturbed mentation	16 (8 unconscious)
Vomiting	13
Gait disturbance	6
Motor weakness	7
Diplopia	2
Drop attacks	3
Dizziness	2
CSF rhinorrhoea	1

Table 3. *Neurological Signs in Patients with Colloid Cysts*

Signs	No. of cases
Papilloedema	26
Mental impairment	14 (9 were drowsy or semicomatose)
Seventh nerve palsy	8
Hyperreflexia	6
Plantar extensor response	8
Incoordination	5
Motor weakness	5
Tremor	1
No signs	2

Table 4. *Duration of Symptoms*

	Months			Years			
	1	1–6	6–12	1–2	2–3	over 3	Total
No. of cases	7	10	7	10	3	5	42

attacks in which patients usually in association with a sudden headache but without loss of consciousness would collapse to the floor quite unexpectedly. However, this is not a symptom of such invariable presence that it could be relied upon as a diagnostic feature. Occasionally quite unusual drop attacks were encountered. One lady of 37 invariably dropped to the ground while hanging her washing up on her washing line. The accompanying extension of her neck was thought to be the precipitating factor and cervical spondylosis was suspected. Only on further neurological examination and CT scanning was the true diagnosis of a colloid cyst with moderate hydrocephalus established, the drop attack being occasioned no doubt by change in venous pressure induced by hyperextension of the neck. 37 patients had headache, with only 5 patients not complaining of headache. 16 patients gave a history of disturbance in mentation which in recent years has been confirmed by neuro-psychological testing. 8 patients presented in coma or with episodes of unconsciousness. 20 patients had visual disturbance (mainly blurring of vision; 2 patients complained of diplopia), 6 patients had difficulty walking and 7 patients noted weakness of the legs. One patient presented with CSF rhinorrhoea.

On admission, 14 patients showed some degree of mental retardation and 9 of these were confused or semiconscious; 26 patients had papill-

Table 5. *Classification of Symptoms According to Kelly*

	No. of cases
Group I	20
Group II	7
Group III	14
Unclassified	1

oedema on presentation; an upper motor neurone seventh cranial nerve palsy was present in 8 patients; 5 patients showed motor weakness with hyperreflexia, extensor plantar response and incoordination. Two patients had no signs because of previous shunting procedures at other institutions (Table 3).

The interval between the first symptom and admission to hospital ranged from hours on the day of onset to 7 years. Prior to 1983 the majority of patients presented more than 6 months after the initial symptom, but in recent years the interval between onset and presentation has reduced and more patients presented in under 6 months (Table 4).

In his 1951 classification of presenting symptoms, Kelly proposed 3 main groups:

Group I: Headache, papilloedema and no localizing features.

Group II: Fluctuating or progressive dementia.

Group III: Cases with so-called classical features—some episodic headache and drop attacks.

Almost half (48%) presented in Group I. To this classification a fourth group had to be added as one case who presented solely with CSF rhinorrhoea associated with hydrocephalus could not be classified in any of Groups I to III of Kelly (Table 5).

Diagnosis

The advent of CT scanning has made the radiological diagnosis of colloid cyst a relatively simple and safe procedure[9, 16]. Prior to 1981, when the CT scan came into general use, ventriculography had been the principal investigation. This revealed symmetrical hydrocephalus of the lateral ventricles with slight dilatation of the anterior third ventricle, and a rounded defect of the third ventricle directly behind the foramen of Monro. CT scanning is now well established as the most reliable diagnostic method and commonly shows a high density or isodense mass in the anterior third ventricle not enhancing on CT scan. Kendall *et al.* characterized colloid cysts on CT scan as generally of increased density (69%), less commonly

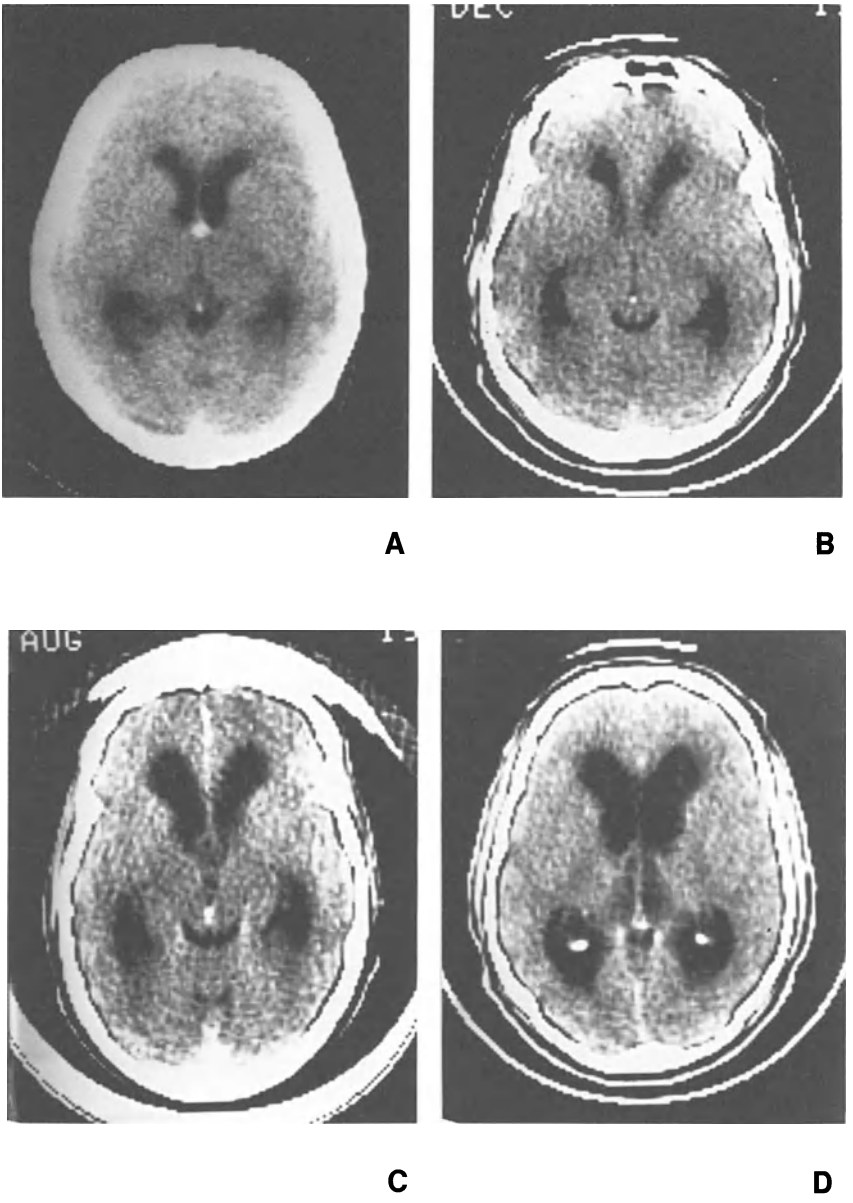


Fig. 1. Three colloid cysts of differing density. A) Shows a typical hyperdense lesion, (unenhanced), B) shows an isodense lesion which can just be made out in the foramen of Monro. C) and D) the lesion is undoubtedly hypodense with a ring of hypodensity which does not enhance. Two cuts are shown in C) and D). Doubt about the diagnosis in this case prompted the ventriculogram shown in Fig. 2

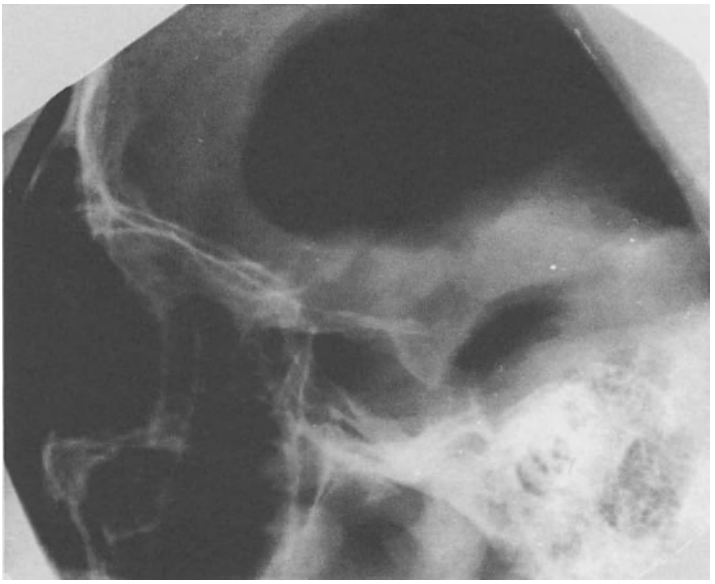
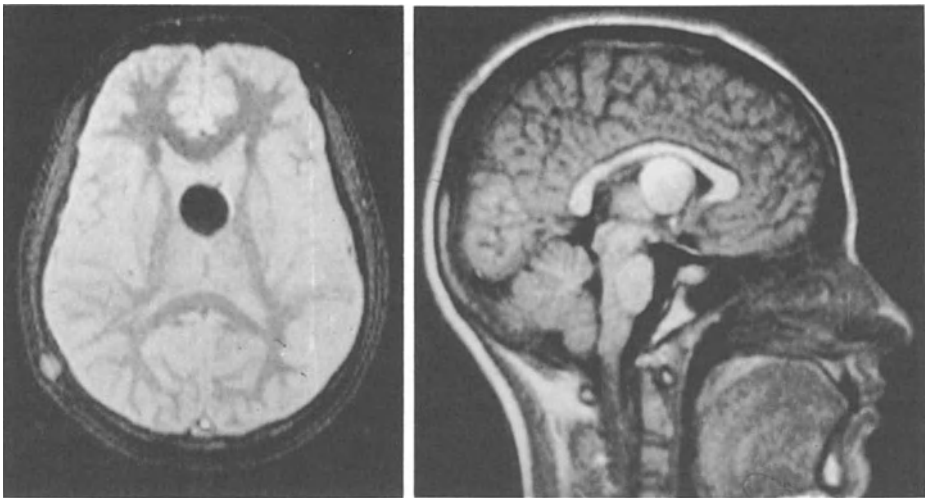


Fig. 2. Ventriculogram from the case shown in Fig. 1 C and D. The rounded filling defect in the upper part of the third ventricle just in the posterior part of the foramen of Monro can be made out on this air study. The diagnosis is therefore confirmed

of isodensity (29%) and very rarely of low density (Fig. 1). The margins of the cyst are smooth in 71% and there is lateral ventricular dilatation in 94% of cases.

The confidence of diagnosis with CT scan is such that no other radiological investigation is usually necessary. As Yaşargil in his contribution to this chapter points out, the rare case of an isodense colloid cyst on CT scanning or more commonly one on which the CT scan as a result of thick slices has failed adequately to demonstrate the foramen of Monro, does constitute a difficulty in diagnosis from time to time. Under these circumstances clinical suspicion is paramount, and the straightforward easy option of ventriculo-peritoneal shunt for the undiagnosed biventricular hydrocephalus can only be undertaken when obliteration of the foramen of Monro by a colloid cyst or other pathology can be confidently excluded. Even today ventriculography may be required (Fig. 2) if MR scanning is unavailable.

Occasionally a very posteriorly placed colloid cyst may occasion mistaken diagnosis. One such case occurred in our series in which the initial diagnosis of third ventricular glioma was made and the patient relieved from symptoms by a shunt procedure. He was then lost to follow-up, but



A B

Fig. 3. MR sequences of a colloid cyst, already treated by a shunt operation elsewhere. A) Shows the low signal on the T 1-weighted image, in a transaxial cut, B) the high signal on the inversion recovery sequence, in a sagittal section. This large cyst was removed by a transcallosal approach in view of the small ventricular size

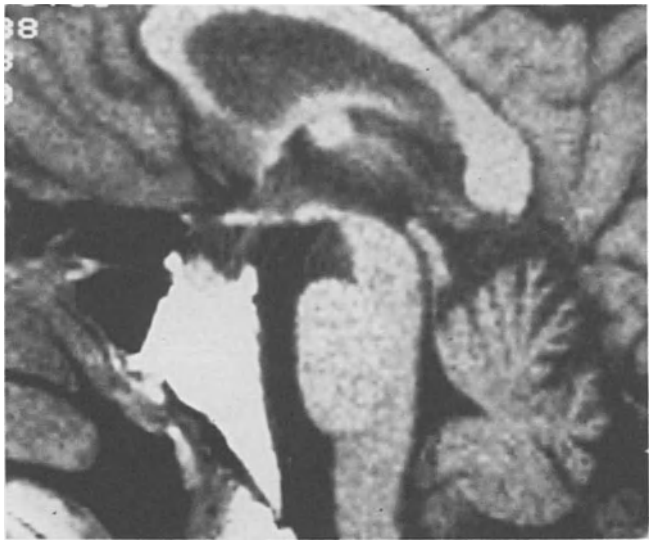


Fig. 4. A small and asymptomatic colloid cyst incidentally discovered on MR scan. The excellent detail of the cyst, the foramen of Monro, the fornix and the third ventricle are easily made out. This cyst, asymptomatic, remains in situ

reappeared in the clinic after recurrent complaints of headache and transient impairment of consciousness suggestive of intermittent hydrocephalus, with a shunt system which was functioning and intracranial pressure which was normal. A huge colloid cyst compressed the upper midbrain, and although it was possible to remove the lesion the patient, by this time in very poor neurological condition, survived only a few months and subsequently died. This case demonstrated that the option of shunting colloid cysts advocated by a number of authors, may in the end be unsatisfactory. Angiography is not usually necessary but may be undertaken to outline the venous displacement of colloid cysts, with elevation of the internal cerebral vein and deformation of the septal vein. Before the advent of effective CT and MRI vertebral angiography was often undertaken in atypical cases to exclude a high basilar aneurysm. More recently MRI scanning has been utilized showing a low signal cyst on the T^1 weighted image and high signal on the inversion recovery sequence (Figs. 3 and 4). If available it is the diagnostic method of choice.

Operation

The standard operation performed for excision of colloid cysts in the University Department of the National Hospital has been a transventricular exposure of the right foramen of Monro. The patient is positioned on his back with about 20° of foot down tilt and the head moderately flexed. The surgeon should be aiming to get a direct vertical sight from his cortical incision down to the foramen of Monro. The position of the scalp and bone flap is shown in Fig. 5. The scalp flap should reach the midline but need not transgress it, and it is the author's practice to use a small four burr hole flap which posteriorly should just reach the corona and which extends on the midline some 3 cm anteriorly. Laterally it reaches almost to the superior temporal line. A smaller triangular flap may be used but we have always found a small four burr hole flap to be convenient. The two midline burr holes are placed on the sagittal sinus with care to avoid damage to that structure, and the flap is cut out with a Gigli saw. Not only does this avoid laceration of the dura particularly in the parasagittal area, but it also ensures a relatively small bone defect. The relief of hydrocephalus following such surgery can result in falling in of the bone flap if a wide bony cut is made as for example, with the modern craniotomes, unless careful wedging of the flap is carried out postoperatively. The dura is hitched to the bone edges except parasagittally where hitching stitches are unwise lest the sagittal sinus circulation be impaired, and the double post for the Yaşargil self-retaining retractor system placed on the posterior margin of the bone flap. We have never used external fixation for self-retaining retractors, preferring to retain the option to move the head during

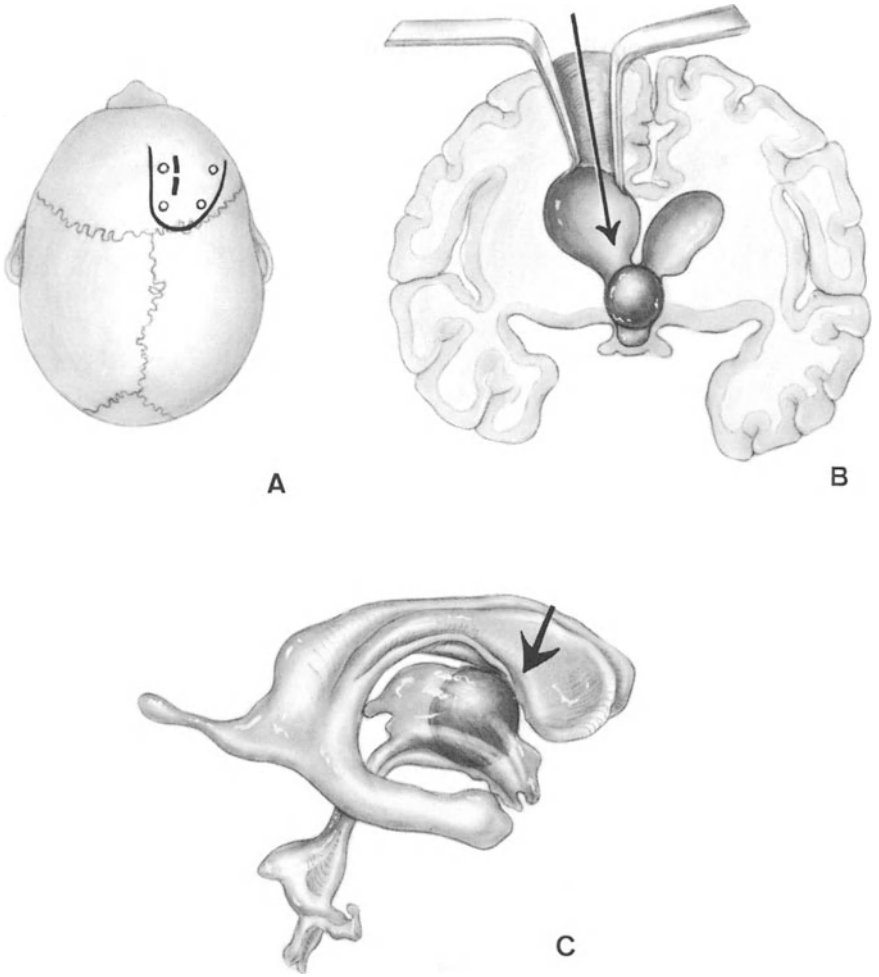


Fig. 5. A) Position of scalp and bone flap for transcortical excision of colloid cyst of the third ventricle. B) and C) Transcortical exposure of Foramen of Monro

the procedure. For similar reasons pin fixation has not been employed. If intracranial tension is high a preliminary nick in the dura is made in the centre of the craniotomy about one inch in front of the coronal suture and 3 cm parasagittally. The outer angle of the eye palpated through the drapes and the midline palpated at the nose form a good double landmark to pass a brain needle down into the frontal horn of the lateral ventricle. A sufficient volume of CSF to lower the tension and enable comfortable dural opening is then withdrawn. The dura is opened in an anteroposterior linear incision 3 cm from the midline overlying the middle frontal gyrus. If the ventricle has not up to now been needled, a brain needle should be passed from the

centre of the exposure into the lateral ventricle and the track of the brain needle followed down along a pair of bayonet forceps to enter the lateral ventricle. It is important as this small track is made to haemostase cortical vessels and small crossing vessels in the white matter with bipolar diathermy or silver clips. Generally it is unwise to follow a gyrus down as more bleeding will be encountered. The roof of the ventricle contains several crossing veins and these must be haemostased with bipolar coagulation before the ventricle is widely opened. The small track may be enlarged sufficiently by the insertion of half inch brain retractors and the edges held apart. The use of the operating microscope enormously reduces the length of the necessary cortical incision and it was never the practise in this department to excise a cone of cortex. If the direction of the approach to the ventricle has been accurate then as soon as the microscope is brought in, the area of the foramen of Monro will be evident. Figure 6 shows the relevant anatomy. The most prominent feature of any ventricle is the choroid plexus of the lateral ventricle which being followed forward, leads to the foramen of Monro. Here the thalamostriate vein coursing along the interval between the bulge of the head of caudate nucleus and the thalamus can be identified crossing the floor of the ventricle to reach the foramen of Monro, where it coalesces with the larger of the two septal veins in the formation of the internal cerebral vein. There are usually two or three septal veins, but only one is sufficiently large to demand its careful preservation. Where there is appreciable hydrocephalus it is usually comfortable now to open the septum by suction coagulation between the veins and drain the opposite lateral ventricle. The two self-retaining retractors should retract the cortical incision but should not be passed down into the ventricle to retract the lateral wall of the ventricle. The genu of the internal capsule is almost subependymal at the groove between the head of caudate nucleus and thalamus and transgression of the ependyma here with a retractor may very well produce injury and transient motor weakness or worse.

The curve of the column of the fornix arching over the superior and anterior border of the foramen may then be gently freed with a blunt hook from the bulge of the colloid cyst which presents coming from the postero-superior margin of the foramen. The colloid cyst is usually covered by a thin glial membrane containing several small vascular branches coming from the choroid plexus and these may be coagulated. It is interesting that having identified this layer, the stripping of the wall of the colloid cyst particularly from the wall of the third ventricle becomes much easier. This layer is not part of the wall of the colloid cyst, but appears to be a superadded glial layer taken from the ependyma. It is not always present. It is then usually most convenient to pass a needle into the colloid cyst to aspirate its contents as far as possible. Whilst these contents are often referred to as gelatinous and amenable to aspiration, this is far from usually

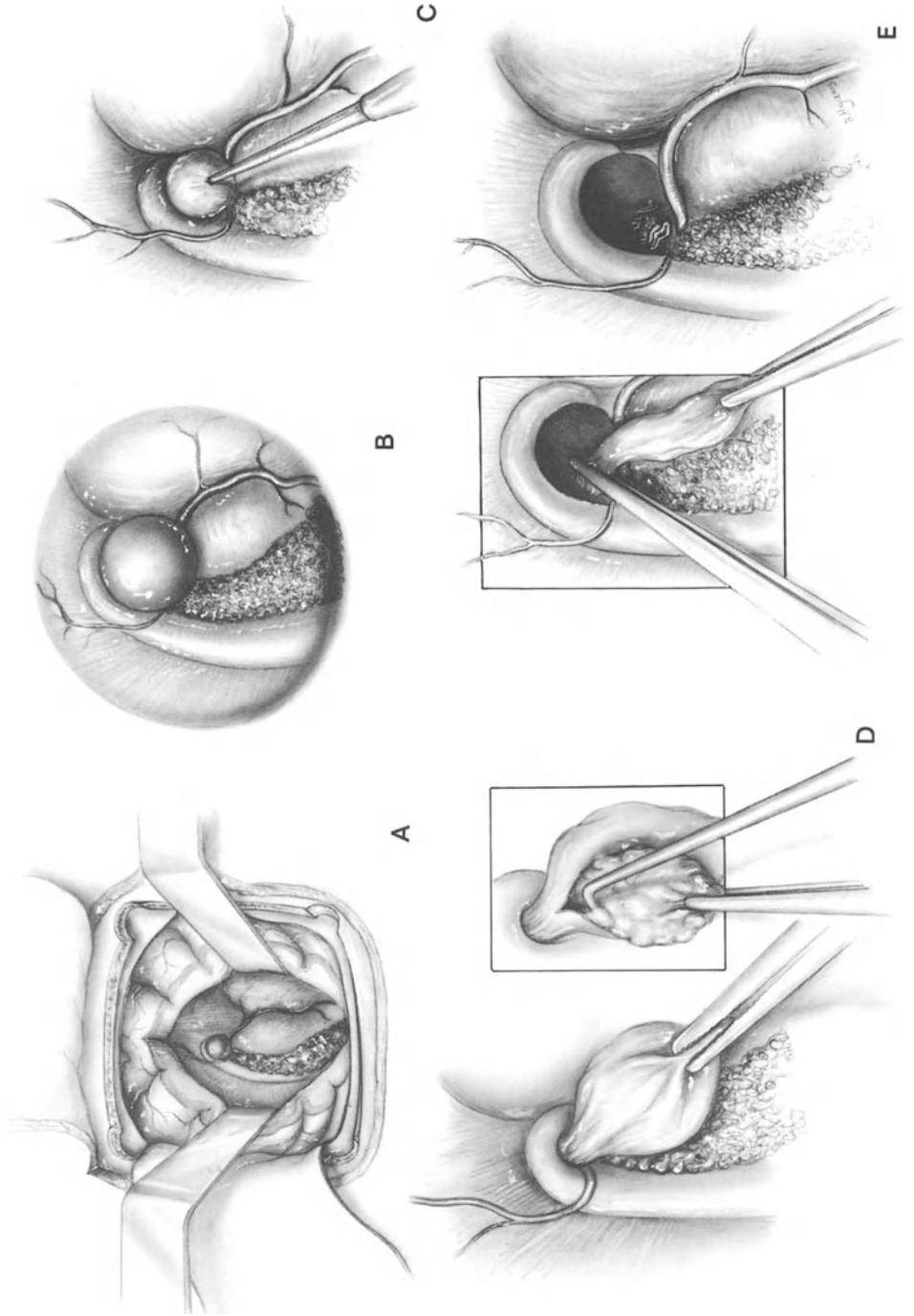


Fig. 6. A) Foramen of Monro and associated structures visualized through the lateral ventricle. B) Enlarged view of A). C) Aspiration of the cyst. D) The cyst is delivered into the lateral ventricle. E) The base is coagulated or clipped and the cyst removed

the case. In almost all the colloid cysts we have operated upon the material has at least in a good part been semisolid and has required extraction with a blunt hook. It is seldom necessary to employ Ronguers. As the material is aspirated from the cyst a patty placed in the ipsilateral lateral ventricle will prevent the material spilling into the back of the ventricle. While it does no harm to the ventricle itself, it may, after removal of the cyst, slip down into the third ventricle and block the aqueduct. As the cyst is emptied, its wall may be seized in fine forceps, and carefully dissected from adhesion to the lateral walls of the third ventricle. Such adhesion is not usually significant unless the cyst has reached an appreciable size when small paraventricular veins in the wall of the third ventricle may require gentle coagulation to free the cyst wall completely. This is without danger. The cyst wall may then be gently drawn up into the lateral ventricle and its pedicle freed from its attachment to the postero-superior margin of the foramen of Monro. As a rule vascular attachments here require gentle bipolar coagulation and it has been our practice to complete the dissection by placing a clip across the attenuated neck of the cyst and cutting the wall free. Frequently this last procedure is unnecessary and with bipolar coagulation of the vascular pedicle the wall comes free without the necessity for a clip. Injury to the septal and thalamostriate veins should be avoided.

It cannot be overemphasized that the use of the operating microscope, microscopic techniques and bipolar coagulation has rendered the excision of the colloid cyst one of the easiest and most rewarding procedures in neurosurgery. It should be without morbidity apart from the pre-operative morbidity occasioned by a patient who has suffered from appreciable hydrocephalus and possibly short-term memory loss which may take some time to recover. Occlusion of the thalamostriate and other veins at the foramen of Monro have been implicated as causing drowsiness, hemiplegia, mutism and haemorrhagic infarction of the basal ganglia (Hirsch *et al.* 1979). Occasionally an external ventricular drain has been left in situ for a number of days post-operatively as a precaution against reactionary swelling; none of these patients required definitive shunting.

A small number of cases have presented to this institution following ventriculo-peritoneal shunting, making the transventricular route difficult. In such instances, the transcallosal route was used. One patient underwent ligation of the shunt 3 days pre-operatively followed by the standard transventricular route and excision of the colloid cyst.

Results

Our results may be classified into 4 groups:

Group I: Excellent results, no neurological abnormality, uneventful course of life.

Table 6. *Operative Results with Relationship to the Use of the Operating Microscope*

Group	No. of patients	Results	Without microscope	With microscope (1976 onwards)	Total
I	20	excellent	6	12	18
		good	1	1	2
		poor	0	0	0
II	7	excellent	1	2	3
		good	1	2	3
		poor	1	0	1
III	14	excellent	3	4	7
		good	4	1	5
		poor	1	1	2
Unclassified	1	excellent	0		
			1		
			1		
Total			18	24	42

Group II: A good result though the patent had minimal neurological abnormality and was not handicapped in everyday life.

Group III: A poor result, the patient showing distinct neurological abnormality and being handicapped in everyday life.

Group IV: Death.

The operative results before and after the operating microscope are shown in Table 6. Twenty-eight of 42 patients had excellent results and a further 10 had good results with minimal morbidity in every life. There was no operative mortality but 3 patients had a poor result because of persisting memory deficit in one cell and in the second operated upon in coma, persisting confusion and memory loss. There were 2 late deaths in the series at 4 and 5 years respectively. One patient in the poor group died at 6 months from massive pulmonary embolism whilst in the rehabilitation unit.

The Interhemispheric-transcallosal Approach

(M. G. YAŞARGIL, A. C. SARIOGLU, T. E. ADAMSON, and P. ROTH)

From 1967 to 1988 20 patients with colloid cysts were operated microsurgically in the University Hospital of Zürich.

The age and sex, duration of symptoms, clinical presentation and neuroradiological findings are presented in Tables 7 to 10.

Table 7. *Age and Sex*

	Female	Male	Total no.	
11–20	—	1	1)	
21–30	1	1	2	8
31–40	1	4	5	
41–50	2	2	4)	
51–60	1	3	4	12
61–70	1	2	3	
71>	—	1	1	
	6	14	20	

Table 8. *Duration of Symptoms*

	No. of cases	
Acute-subacute	6	(30%)
1–2 months	2	
3–6 months	2	
7–12 months	3	
1–2 years	2	
3–5 years	2	(35%)
5> years	3	

Table 9. *Clinical Presentation*

		No. of cases
a)	Patients with symptoms and signs of raised ICP	11 (55%)
b)	Urgent admission (subcoma)	5 (25%)
c)	Paroxysmal attacks	5
d)	Mental symptoms	10 (50%)
e)	Choked disk (papilloedema)	3
	Hemiparesis	1
	Oculomotor palsy	1
	Aphasia	1
	Headache with reclination of the head	1
	Severe obesitas	1
f)	No neurological deficits	7 (35%)

Table 10. *Radiological Investigations*

	No. of cases		Pathological findings
Ventriculography	6	6	(1 case unilateral)
CT	16		
Enlargement of ventricle			
a) Symmetric		14	(in 11 cases diagnosis
b) Asymmetric		3	correct, in 5 unusure,
c) Space occupying		15	in 4 wrong).
d) Hyperdensity		15	
e) Enhancement		15	
MRI	5	5	(clear diagnosis)

One unfortunate case, a 28-year-old female patient was diagnostically difficult. After she had suffered an acute headache for the first time in her life, the diagnosis of subarachnoid haemorrhage was made, but not confirmed by lumbar puncture. Nevertheless, her husband, a medical doctor insisted that cerebral angiography be performed. It was normal in every aspect, with no displacement of the vascular structures, and no sign of hydrocephalus. CT scan was not available in Zürich at that time. The asymptomatic patient with no neurological or mental deficit was allowed to return to her home country due of headache 3 days after angiography. Arriving at the airport she again complained of severe headache, fell into a coma and died within a short time, before she could be transferred to a hospital. Autopsy revealed a 2 × 2 cm colloid cyst of the third ventricle.

Consequently, in every case with an unusual attack of headache simulating a subarachnoid haemorrhage, but with normal angiography, the CT and MR images should be checked again for a "hidden" colloid cyst. The diagnosis of a colloid cyst however, is not always possible on a CT scan. In two patients of the present series who suffered an acute headache, the diagnosis of a subarachnoid haemorrhage was made in another hospital. Lumbar puncture failed to confirm a haemorrhage and the condition of the patients deteriorated rapidly. They were transferred to Zürich in a semicomatose state. CT scan revealed, in both cases, bilateral hydrocephalus and visualization of the third ventricle, but no other pathological finding. Urgently performed shunt procedures were life-saving. The post-shunting CT scans showed, in both cases, only a suspicious finding in the third ventricle. Surgical exploration revealed colloid cysts. MRI seems a more reliable procedure in the diagnosis of colloid cyst, as we have experienced in 5 cases since 1983. In the near future therefore, we may see colloid cysts diagnosed more frequently.

Operative Approaches

Early in the series (1971 and 1972), two patients with third ventricular lesions underwent transcortical-transventricular exploration. In each case a colloid cyst was found and removed. Both patients showed, post-operatively, slight transient weakness on the left side, but recovered within a few days. One patient was discharged home 3 weeks after surgery and returned to his former profession. The other patient succumbed, after a pulmonary embolus 14 days post-operatively.

The interhemispheric anterior-transcallosal approach had already been employed for arteriovenous malformations of the anterior third of corpus callosum with good results and therefore, the idea developed to use the same approach for tumours of the third ventricle, in particular for colloid cysts. In the 18 cases since 1973, the unilateral anterior-transcallosal, transseptal biformaminal approach was used for the removal of colloid cysts. This technique will be described in detail.

The Anterior-Transcallosal Approach

Of critical importance to this operation is proper positioning of the patient. Particular care should be taken with regard to flexion of the neck (Fig. 7) and the correct degree of head elevation. The patient should be supine with the head somewhat flexed to allow the sitting surgeon to look perpendicularly through the corpus callosum to both foramina of Monro. During positioning of the head great attention should be paid to ensure

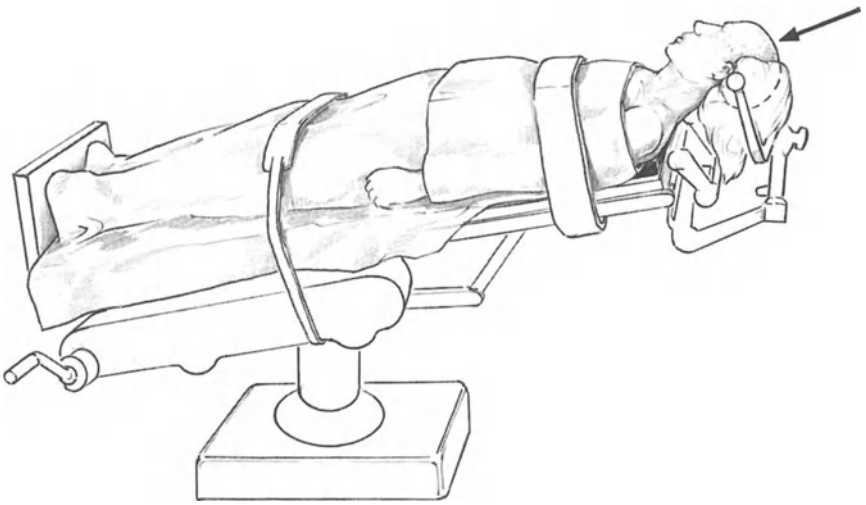


Fig. 7. Position of the patient on the operating table. The arrow indicates the direction of the exploration towards the foramina of Monro

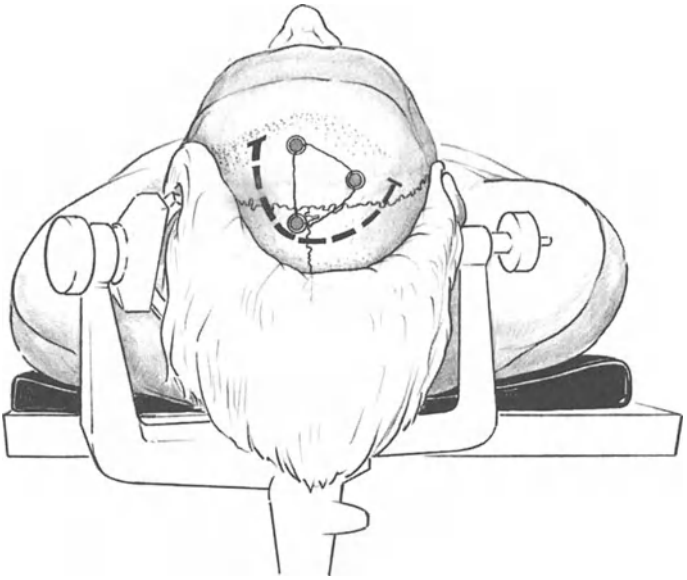


Fig. 8. Parasagittal craniotomy in relation to the coronal and sagittal sutures

that the trachea and jugular veins are not compressed. Tilting the table may also help to bring the head into the desired position.

A small semicircular skin incision is made either bifrontally or unilaterally, about 1 cm posterior to the interauricular line which is 10–15 mm posterior to the foramina of Monro (Fig. 8). The coronal suture is also usually perpendicular to the foramina of Monro. Gross chronic hydrocephalus, large frontal sinuses or various ethnic difference in skull structure may alter the calvarium such that the coronol suture is displaced posteriorly. The general rule therefore is as follows:

The foramina of Monro are perpendicular to the interauricular line which can easily be palpated during positioning of the patient and after sterile draping. They may occasionally be perpendicular to, or up to 1 cm anterior to the coronal suture. Initially, the skin flap is retracted anteriorly and the periosteum is elevated as a separate layer and retracted with the skinflap.

The size of the parasagittal craniotomy will be related to the experience of the surgeon. Although a small 2 × 2 cm craniotomy is sufficient for an interhemispheric transcallosal approach to the foramen of Monro for removal of a colloid cyst, each surgeon has to decide for himself which size of craniotomy he will feel most comfortable with. One, two or three burr holes can be used for a parasagittal frontal craniotomy, usually on the right side. The first burr hole is placed in the midline 1–2 cm in front of

the coronal suture, the second 1 cm behind the suture, and the third 2–3 cm paramedian.

For the craniotomy Gigli's saw or a craniotome can be used, but before this, the dura, especially the superior sagittal sinus should be carefully dissected and freed to prevent inadvertent injury. The midline cut of the bone is placed just over the sagittal sinus preferable 1–2 mm to the left of the midline to the opposite side. After removal of the free bone flap the dura is incised 1 $^1/_2$ to 2 cm longitudinally and 1 cm in width and fixed to the left side with a suture.

There are several points of surgical technique that are important, when using the transcallosal approach to gain access to midline structures. The craniotomy, although small and elongated anteroposteriorly, could be smaller if one could positively identify the location of the bridging veins to the sagittal sinus. Direct inspection determines the direction of dissection, anterior or posterior, to these venous structures that are to be preserved if possible. If a large group of veins is encountered, dissection of their arachnoid sheaths from the pia and dura mater will permit further mobilization and wrapping them in small muscle fragments limits venous oozing. When necessary, moderately sized veins can be sacrificed in order to facilitate an otherwise complicated dissection: excessive time should not be lost attempting to preserve them. Experience with the present series and with the surgery of aneurysms, AVMs and tumours which were approached interhemispherically, has not resulted in ischaemic changes to parasagittal structures that could have been attributed to the elimination of these moderate sized veins.

Exploring the medial surface of the frontal lobes is generally uncomplicated but, if the brain is very tight due to hydrocephalus, several approaches can be taken. When the sulci are large they can be opened to provide adequate drainage. If this fails or the sulci are small, the ventricle can be punctured. Occasionally, small veins on the medial surface of the frontal lobe cross the subarachnoid space to the falx and must be coagulated and divided. Separating the falx and cingulate gyrus is usually straightforward. Sometimes, however, the falx has a fibrous network with numerous large defects. In this instance the falx varies in depth and this indicates fusion of the cingulate gyrus in the midline which requires precise microsurgical dissection. Care should be taken not to confuse the ipsilateral opposed cingulate gyrus for the corpus callosum, under which circumstances the callosomarginal arteries within their respective sulci can be mistaken for the pericallosal vessels.

Occasionally, the arteries of the medial surface of the frontal lobes and, rarely the callosomarginal and pericallosal arteries, supply small (0.1 mm) branches to the falx. Inadvertent avulsion of these is of no consequence.

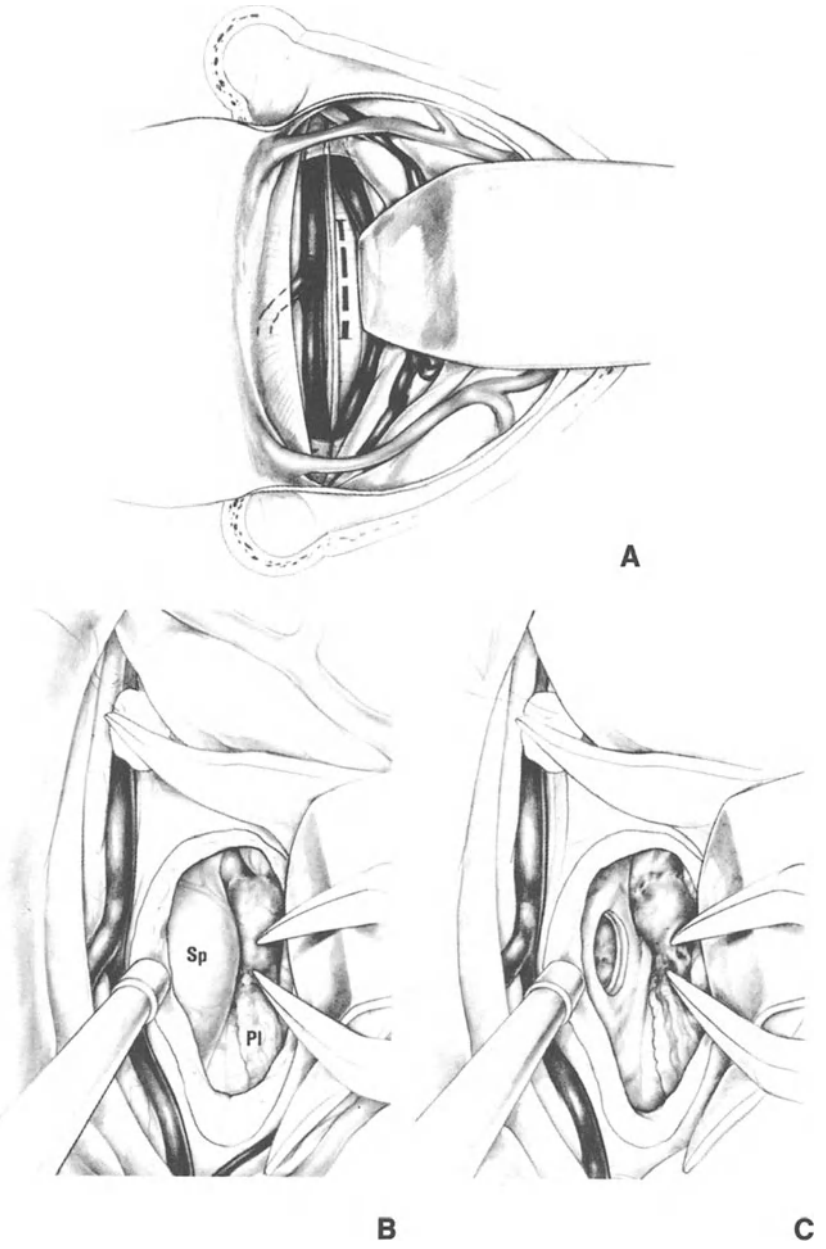


Fig. 9. A) Interhemispheric exploration and callosal incision between the pericallosal arteries. B) The right ventricle is decompressed. The septum pellucidum (*Sp*) is bulging to the right. (*Pl*) Plexus. The tips of the forceps rests on the tumour surface. C) The septum pellucidum is opened. The tumour is now visible in both foramina of Monro

However, avulsion of the parent vessels will lead to troublesome haemorrhage, and possible central infarction.

Upon reaching the body of the corpus callosum it is important to realize that there may be one to three A 2 arteries. The arterial pattern in this region should be carefully studied on the pre-operative angiograms and correlated with the surgical anatomy. The lateral sulcus should always be inspected beneath the cingulate gyrus for accessory A 2 vessels. Normally, the dissection proceeds by approaching the corpus callosum between the two pericallosal arteries, but, in some cases, anatomic variation forces the dissection to remain lateral to the right pericallosal artery. To avoid potential mechanical vasospasm during dissection, cottonoids soaked with papaverine are applied locally (Fig. 9).

Using bipolar forceps, a 10 to 15 mm opening into the corpus callosum is made. This allows free flow of CSF and decompression of the right ventricle. Unless there are natural openings in the septum pellucidum, the left ventricle will remain intact and the septum pellucidum will bulge to the right, obscuring the view of the surgeon. A 10 mm incision in the septum pellucidum will decompress the left ventricle, and give the surgeon good access to both foramina of Monro.

Dissection of the Lesion at the Foramen of Monro and in the Third Ventricle

At this point, the foramina of Monro should be inspected to ascertain the course of veins draining into the internal cerebral veins. In particular the septal, frontal subependymal, caudate, thalamostriate and several smaller posterior to anteriorly directed veins should be identified. All of these follow a course to the posterior inferior corner of the foramen of Monro and are usually covered by choroid plexus. The yellow-green cyst can be observed protruding through the foramina. There is almost always a very small network of arteries supplying the cyst. These can be coagulated at their insertion into the posterior medial choroidal arteries which are found near the previously located veins passing into the third ventricle (Fig. 10).

Dissection of the tumour proceeds bilaterally within the foramina, beginning at the posterior inferior corner. Once this portion of tumour has been freed it is then isolated using cottonoids and the cyst punctured and aspirated. This manœuvre is rarely adequate and the cyst wall needs to be opened and the residual detritus removed by suction. It is very important to avoid spillage of the cyst contents within the ventricles. A deeper and more detailed inspection of the third ventricle is now possible and the origin of the aqueduct and massa intermedia (compressed superiorly and posteriorly) can be seen. At this stage it is very important to establish a clear

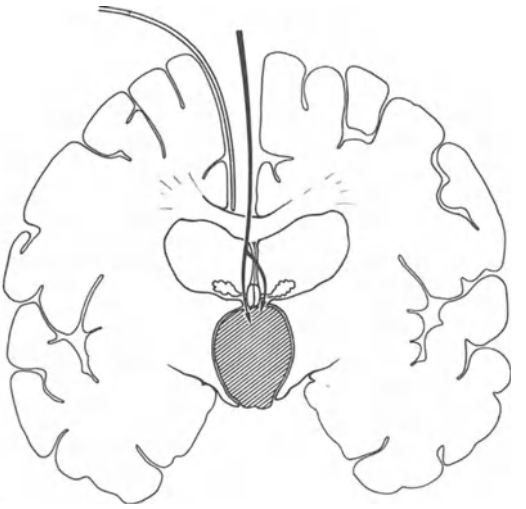


Fig. 10. Schematic drawing illustrating the direction of the transeptal biforaminal exploration of the tumour

plane between normal tissue and the cyst wall to prevent damage to the peraqueductal structures and delicate wall of the dilated third ventricle. Careful dissection of the cyst continues through both foramina until it is completely free and can be removed.

Following close inspection to ensure exact haemostasis, and the dura is closed using tight running suture. The bone flap is then replaced and the scalp closed in 2 layers.

Discussion

In the present series of 18 transcallosally operated cases the average duration of surgery was 1–1 $^1/_2$ hours and the hospital stay 5–10 days. A right-sided approach was used in all cases except one, where only the left ventricle was dilated. This is feasible in most instances, as there is usually symmetrical enlargement of the ventricle. Asymmetrical enlargement, especially left-sided, is rare. The enlargement of the foramen of Monro caused by the cyst, was adequate in all of the present cases to permit removal of the tumour without compromising surrounding structures. The interforniceal or subchoroidal approach, with mobilization of the choroid plexus and tela choroidea and with division of the thalamostriate vein was never performed. During dissection of the cyst wall, a clear plane of cleavage was identified and no adhesions or infiltration into the caudate nucleus were seen. Results are summarized in Tables 11 and 12.

Usually 10–20 mm in diameter and well encapsulate, spherical or ovoid colloid cysts rarely contain homogenous fluid. Surgical exploration in the

Table 11. *Operative Approaches and Results*

	No. of cases	Good	Fair	Death
Transcortical-transventricular	2	1 (1)	—	1
Transcallosal	18	17 (3)	1	—
	20	18	1	1*

* Pulmonary embolus 2 weeks later.
() Preoperative shunt procedure.

Postoperative complications:
After transcortical approach, 2 patients had a transient weakness.

Table 12a. *Discharged Home*

5–7 days	3
8–14 days	11
1–2 months	5

Table 12b. *Working Capacity*

Full	18
No	1
Death	1

Table 13. *Cyst Contents*

Real cyst	4
Gelatinous	8
Caseous	8

present series more frequently revealed colloid cysts containing semi-solid, creamy or caseous cellular debris, with or without the presence of crystallization, which was very often unsuitable for aspiration (Table 13).

There was one death due to a pulmonary embolus, which occurred 2 weeks post-operatively in a patient who was otherwise well. There was one post-operative wound infection. No extra-axial fluid collections or porencephalic cysts were observed.

There were no instances of transient or permanent hemiparesis following a transcallosal approach. Whether these deficits, as reported in other series, were secondary to interruption of venous drainage or were a direct result of trauma from the brain retractor, is unclear. Over the period of years covered by this present series, the initial dependence on the "constant" retraction of a self-retaining brain spatula has evolved into a "passive" system which utilizes the non-dominant hand controlling the suction tube to provide gentle intermittent retraction. This technique permits the surgeon

to work within the confines of natural "tunnels" in the brain: 15–20 mm in length, 10–15 mm in width and 10–12 cm in depth.

Three patients required shunt procedures pre-operatively, because of severe hydrocephalus and impairment of consciousness. In none of the cases was it necessary to perform a shunt procedure after removal of the colloid cyst. There have been no cases of recurrence (Fig. 11).

In this series the transcallosal approach has proved a very safe and effective method for the removal of colloid cysts.

The Stereotaxic Endoscopic Approach

(Ch. B. Ostertag)

It appears that with improved digital computed imaging techniques colloid cysts of the third ventricle are becoming easier to diagnose and therefore, are apparently more commonly encountered.

This report deals with the experience of stereotactic management of colloid cysts and emphasizes the use of stereotaxic techniques.

Clinical Details (Table 14)

Fifteen patients with colloid cysts of the anterior third ventricle have been seen over a five-year period. The majority of patients presented with episodic headaches and other signs of raised intracranial pressure. Three

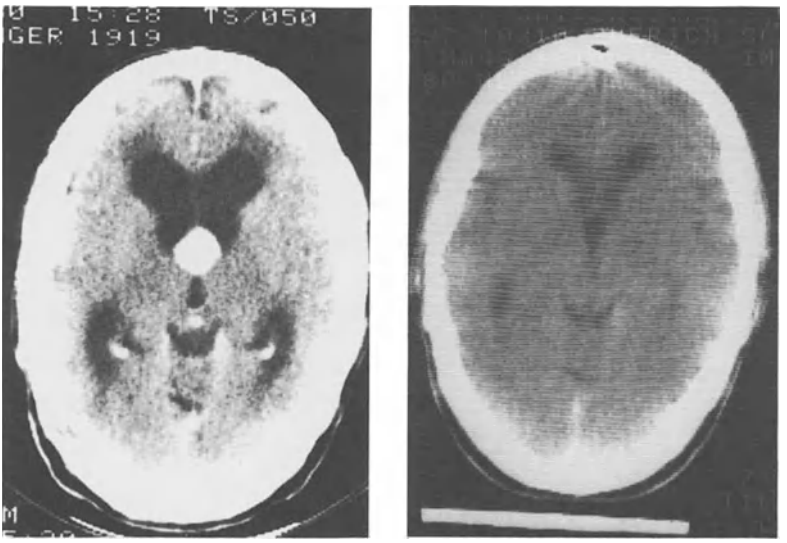


Fig. 11. A) An average sized colloid cyst visualized on pre-operative CT. B) Post-operative CT after transcallosal removal of the tumour

Table 14. *Clinical Details, Treatment and Outcome of Third Ventricle Colloid Cysts*

Case no.	Age years	Sex	Leading symptoms (duration year)	CT findings		First treatment	Causal treatment	Progress	
				Colloid cyst	Hydrocephalus			Karnofsky	Follow-up time years
1	56	m	episodic headache, lethargy, vomiting (2)	hyperdense mass	+ + +	shunt	stx. aspiration	100	5
2	14	m	lethargy (2)	hyperdense mass	+ +	—	stx. aspiration	100	5
3	50	m	headache vomiting (1)	hyperdense mass	+ +	—	stx. aspiration	100	5
4	48	f	headache vomiting (0.5)	hyperdense mass	+ +	shunt	stx. aspiration	100	5
5	21	f	headache gait disturbance (1)	hyperdense mass	+ +	shunt	stx. aspiration	100	4.5
6	63	m	psychosyndrome (0.5)	hyperdense mass	+ + +	shunt	stx. aspiration partial	100	4

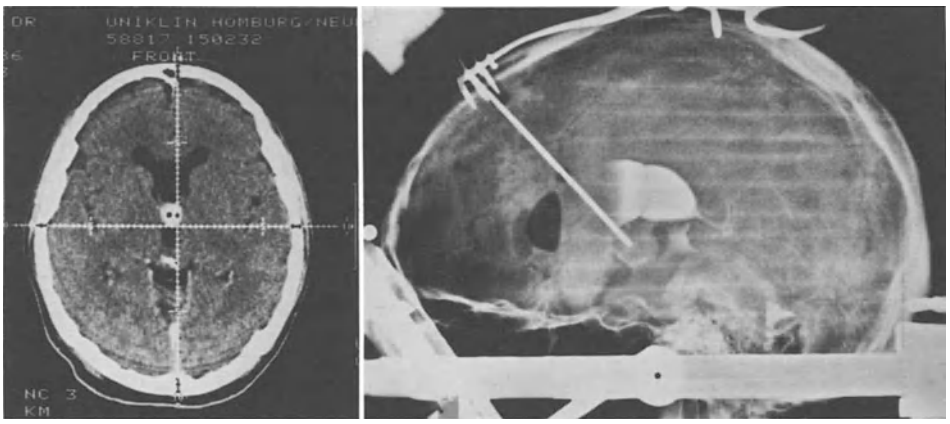
7	64	m	psychosyndrome headache (1)	hyperdense mass	+ + +	ventricular ext. drainage	stx. aspiration	100	4
8	25	m	gait disturbance, psychosyndrome (1)	isodense mass	+ +	shunt	stx. aspiration	100	3
9	54	m	episodic acute motor weakness (1.5)	hyperdense mass	+ + Cavum septi pellucidi	—	stx. aspiration Rickham-catheter	100	3
10	36	f	headache (0.5)	hyperdense mass	+ +	shunt	stx. aspiration	100	3
11	52	m	episodic headache (4)	mixed isodense-hyperdense mass	+ + +	craniotomy shunt	stx. aspiration	100	2.5
12	34	f	episodic headache CSF-spont. leakage (6)	hyperdense mass	+ + +	—	stx. aspiration	100	2
13	29	f	episodic headache (1)	hyperdense mass	+ +	—	stx. aspiration partial	90	2
14	30	m	episodic headache (1)	hyperdense mass	+ +	shunt	stx. aspiration	100	1.5
15	47	m	psychosyndrome	hyperdense mass	+	—	stx. aspitation partial	80	0.5

Abbreviations: Hydrocephalus mild (+) to severe (+ + +).

patients presented into fluctuating mental disturbances. One patient (case no. 15) had a minor fluctuating dementia and a history of brain trauma. Only one patient had a history of paroxysmal attacks. Of the 15 colloid cysts, 14 were well delineated hyperdense masses on CT scan, only one was isodense. Contrast enhancement was of no particular value. Mild to severe hydrocephalus was presented in all patients with unilateral ventricular enlargement in 2 patients. Seven patients were referred after a bifrontal shunt procedure. In one patient a craniotomy and a transcortical transventricular approach to the foramen of Monro had been performed. The colloid cyst, however, had not been removed. In one patient who became acutely ill with a severe hydrocephalus prior to the stereotaxic aspiration, a bifrontal ventricular external drainage was instituted and was removed later.

Method

A CT-based stereotaxic approach was used in all patients including stereotaxic angiography and ventriculoscopy. The stereotaxic headring, part of a modified Riechert stereotaxic system, was secured on the patient's head under local anaesthesia with four plastic posts, each holding a Mayfield pin[28]. Target localization was carried out in a standard CT scanner (Somaton DR) with the headring fixed. Coordinates of the frame can be directly derived from the CT image without further calculation once the image cross hair and the axes of the headring are made to coincide (Fig. 12 A). The accuracy of the stereotaxic procedure is guaranteed when the coordinate system of the imaging and the localization procedure and that of the intervention are in a fixed relationship. After CT scanning the patient was transferred to the operating room. Cerebral angiography was carried out under stereotaxic conditions[25]. After the target had been localized and the burr hole side was determined, the stereotaxic guidance system was attached to the headring. A 2 cm skin incision and paramedian precoronal 5 mm burr hole in the line of the probe was made. After incision of the dura and a point like coagulation of the pia mater a guide cannula was replaced by a guide cannula with a trocar. This trocar was then removed and a ventriculoscope (Stortz, Tuttlingen, type Hopkins forward viewing endoscope with a 2.6 mm diameter) was introduced down the guide cannula. The right frontal horn the foramen of Monro were then inspected and the colloid cysts identified including the position of the thalamostriate vein and the choroid plexus. The colloid cyst usually was a green or greyish mass filling the foramen of Monro. After having identified a site of penetration into the cyst free of blood vessels, the 2 mm guide cannula was reintroduced with a smaller sharp trocar and the cannula placed in the centre of the cyst (Fig. 12 B). The cyst contents was then aspirated by suction applied to the cannula with a syringe. If the cyst contents was too viscous[26]



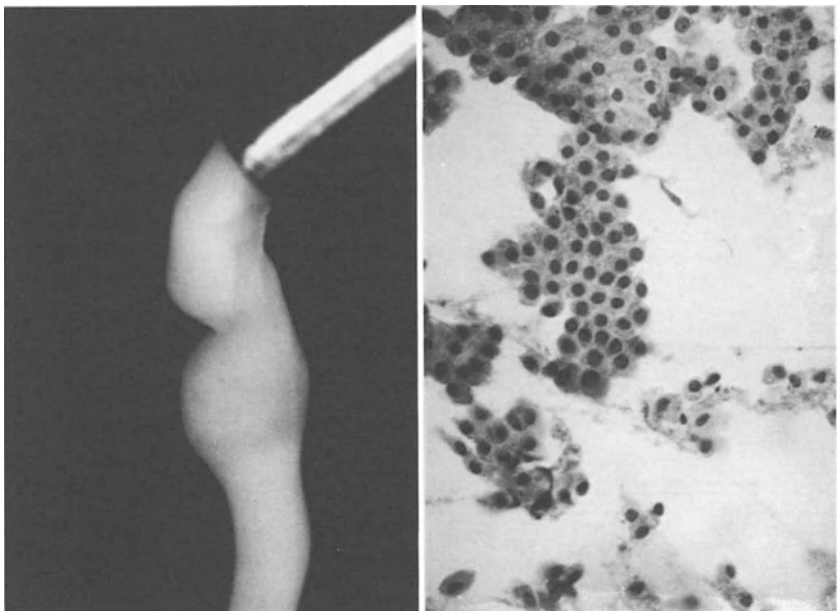
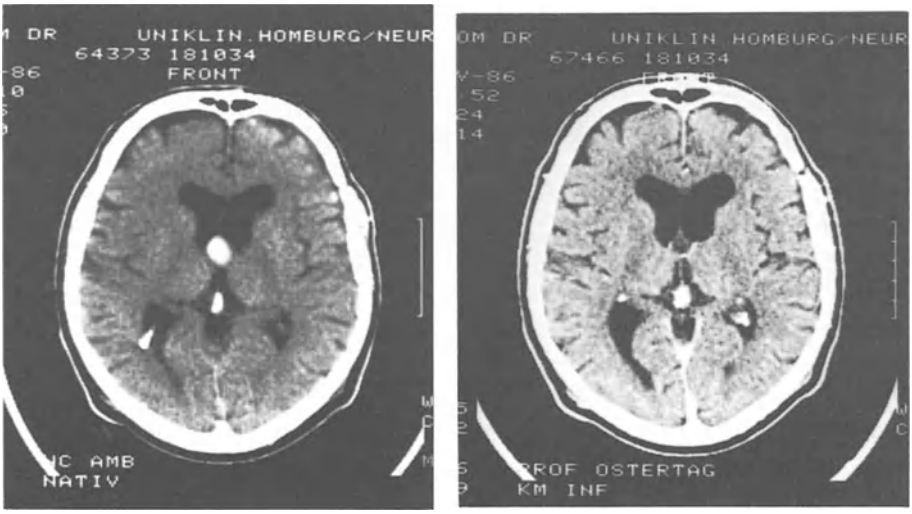


Fig. 12. A) CT scan (4 mm slice) of a colloid cyst of the third ventricle. Coordinates (black dot in the centre of the cyst) can be directly derived from the CT image in relation to the image cross hair. B) Lateral X-ray of the patient's head fixed in the stereotaxic frame. A 2 mm cannula is introduced into the centre of the colloid cyst. The contents of the cyst are delineated with the injection of a drop of contrast medium mixed with saline solution. Note the additional representation of the cavum septum pellucidum cyst with positive contrast medium and air. C) The cyst content is a mucous yellowish fluid of varying viscosity. The aspirated fluid is pressed out of the cannula. D) A biopsy from the cyst wall demonstrates the typical epithelial lining (smear preparation stained with Loeffler's methylene blue)

careful irrigation with a physiological saline solution was carried out (Fig. 12 C). A drop of contrast medium mixed with saline solution helped to delineate the size of the cyst and the definite evacuation (Fig. 12 B). The completeness of the evacuation depended on the consistency of the contents. The cannulas were withdrawn after ensuring that there was no bleeding into the ventricles. The incision was closed. The procedure under local anaesthesia and mild sedation usually took 1–1 $^1/_2$ hours including CT-scanning and angiography.

Results

Angiography under stereotaxic conditions was carried out in 7 out of 15 patients and could exclude in all patients a vascular pathology. Diagnostic ventriculoscopy was used in 10 patients. It could be used only if the ventricles were dilated enough to accommodate the 2.6 mm diameter endoscope. In 12 cases the stereotaxic aspiration of the cyst contents could be carried out totally (Figs. 13 A, B). In 3 cases only partial evacuation could be achieved (< 50% of the cyst volume left). This partial aspiration so far (6, 24, 46 months follow-up) proved sufficient to relieve the patient's symptoms. The one isodense cyst had a mucous-liquid content. In 3 cases a biopsy of the cyst was achieved which demonstrated the typical epithelial lining (Fig. 12 D). In one case (case 9) the pre-operative CT scan had



A B

Fig. 13. A) Typical CT appearance of a rounded hyperdense colloid cyst of the anterior portion of the third ventricle. B) CT scan after aspiration of the cyst contents, 3 months later

demonstrated an extended cavum septum pellucidi in addition to the colloid cyst (Figs. 12 A, B). This cavum was penetrated and a Rickham-reservoir catheter was placed within the cavum which connected to the frontal horn. In another case a Rickham-reservoir catheter was left after the aspiration of the cyst contents. This catheter, however, had to be removed because of meningitis. The meningitis observed was the only complication due to the procedure in 15 patients.

Except for one patient who has had a previous brain injury and a short follow-up period after the stereotaxic evacuation of the colloid cyst, all of our patients are in good health having a Karnofsky-index of 90–100 and follow-up periods of up to 5 years. Seven of our patients, however, had a shunting procedure prior to the stereotaxic aspiration, having entered the institution after the first treatment. These shunts were left in place after stereotaxic aspiration. Seven other patients, however, are well without CSF drainage after the stereotaxic aspiration (Figs. 13 A, B). Refilling of a colloid cyst so far has not been observed.

A Note on the Use of a Modern Endoscope

(J. Caemart and L. Calliauw)

The use of an early endoscope was reported by Powell (1983) to coagulate colloid cysts, and by Auer *et al.* (1988) who commented on one case of colloid cysts treated successfully in 109 endoscopic operations. The surgeon can remove part of the wall of the cyst with such an endoscope. Experience in a number of clinics would indicate that a simple puncture of the cyst is sooner or later followed by recurrence. The principles of endoscopy were described in Volume 14 of Advances in Technical Standards (Griffith) and this contribution is limited to the description of the endoscope

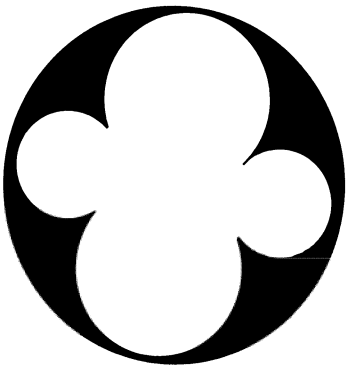


Fig. 14. Cross-section of the lumen of the endoscope

currently used in Brussels. The endoscope available offers in addition the possibility to use bipolar coagulation and the Neodymium Yag-Laser.

To be suitable for our stereotactic device (Leksell C.U. Frame) the length of the endoscope shaft should be 28 cm. This is necessary to permit placement of the video camera on the ocular so that it will not be blocked by the instrument carried on the arc at the time of introduction.

This new type of endoscope has, beside two channels for a telescope and working element, two further channels i.e. an inlet and outlet for flushing. The lumen of the shaft now has a clover-leaf profile (Fig. 14). At the top of the instrument on one of the flushing channels, a side window of 7 mm length is made. Through this opening a balloon catheter (Fogarty type) can be inflated to keep the ventricular cavity open after puncture should it entirely collapse after puncture. At the tip of the lumen of the working channel, the first lumen is bent over 5° so that the working element deviates terminally to come under perfect view of the telescope. A further advantage is that the action radius of the working element is thereby much enlarged. The telescope itself can be provided with a lens at its top and is bent over 10° so that the view of the working element is even more aligned. The shaft is introduced through an outer tube with blunt mandrin. The outer diameter of this tube is 6 mm and its section is round. A sliding depth-stop allows us to determine the depth of endoscopy to the chosen limit which can be altered during the intervention. A suitable stop and guide should be made for the specific type of stereotactic device into which the round introductory tube should fit. It is important to decide which of the two channels (either the working one, or that for the telescope) will be in the middle of this stop and guide, as this channel will be the only one directed straight at the target. The other channel immediately beside the central channel is thus eccentrically placed in the stop and guide. At the proximal end of each flushing channel and also at the working channel, a threeway cock is necessary. During aspiration these channels should be closed airtight. Through the working channel different instruments can be introduced. Simple punctures of cystic tumours are possible with a stiff catheter broadening just behind its tip to permit aspiration of the cyst contents after perforation with the top of the catheter, while the opening in the cyst wall is filled with the broadened end of the catheter. In this way cyst contents cannot escape freely into the ventricles. Through the broad lumen of this catheter aspiration of even very viscous material is possible. It is also possible to introduce. Small micro-forceps on a flexible axis for biopsies or to grasp cyst walls or other elements. In the same manner small micro-scissors and a bipolar coagulation forceps can be used. The working channels permit the use of a laser probe to coagulate small tumours under endoscopy. Finally a probe with an terminal electrical cutting-loop of variable diameter at its tip can be introduced.

Technique

Endoscopy may be performed free hand, but with such instability in manipulating the shaft that unavoidably a larger lesion is made in the cortex and on the trajectory through the white matter in the frontal lobe.

This disadvantage could be solved by a fixation system allowing one in a non-stereotactic way to introduce the endoscope into a guide which is movable, but which can be fixed in the desired position. We have no such fixation system.

Another advantage of stereotactic endoscopy is that the angle of introduction can be determined very accurately beforehand. This can be done on a stereotactic CT scan with sagittal and oblique reconstructions. The plane of the CT scan is the same as the horizontal plane in the stereotactic coordinate system. The angle between the frontal burr hole and the foramen of Monro can be determined in this way. A burr hole 2 cm in front of the coronal suture gives a good view of the foramen of Monro and permits one to make the desired manipulations.

A hole with a diameter of 8 mm permits us to coagulate and incise the dura in a cruciform fashion. Coagulation of the flaps of this cross gives a further retraction of the dura so that it cannot hinder the introduction of the endoscope. The underlying cortex is coagulated and with a fine spatula is linear 5 mm incision is made in the cortex. The endoscope is now introduced in the stereotactic stop and guide and carefully advanced through the cortex. The outer tube with its blunt mandrin is now introduced just through the ependyma of the ventricle, based on the measurements of the CT scan. After retraction of the mandrin the shaft with the different working channels is introduced and through the telescope we can now follow the further events either with the naked eye or with the video-camera on the ocular. The endoscope is advanced in towards the foramen of Monro. The stiff catheter with its broadened tip can now be introduced to puncture the cyst. The contents of the colloid cyst are usually viscous but this catheter permits aspiration. It is then absolutely necessary to make as big an opening as possible in the capsule of the colloid cyst either with the laser, the bipolar coagulator or a cutting-loop. Small forceps may be used to free the capsule from the foramen of Monro. One should be very careful not to pull on the capsule because the choroid plexus is often adherent. During these manipulations the view may become somewhat turbid from a few drops of blood mixed with the CSF. This can be solved by flushing with physiological saline using the in- and outlet channels of the endoscope. After this the foramen of Monro is open and there is free passage to the third ventricle. After retraction of the endoscope the burr hole is filled with Gelfoam to protect the underlying cortex. Local chloromycetin powder is applied and the wound is carefully closed.

Comments

As we have already mentioned, the route followed by the endoscope is the same as that followed in the classical transcortical, transventricular open surgery. Compared with the stereotactic puncture, the endoscopic approach has the advantage of visual control of the procedure. The normal view of the anatomical structures as seen through the endoscope is illustrated in Fig. 15. The presence of the cyst in the foramen often changes these anatomical structures. The choroid plexus in particular can be shifted laterally or protrude in the direction of the endoscope. The puncture needle can possibly damage a displaced thalamostriate vein. Neither CT nor NMR imaging can predict these anatomical displacements. By simple correction of the angle the endoscope can be directed so that damage to the choroid plexus is avoided. This is illustrated in the drawing of Fig. 16.

— Furthermore, the endoscopic approach not only permits accurate puncture of the cyst but also partial removal of its wall. This can be done either by grasping forceps, or cutting-loop, or by a Yag Laser. By means of coagulation the cyst can also be shrunk and coagulated. This procedure holds out the hope that recurrence of the cyst will not occur. However only a larger series of cases with a longer follow-up will be able to prove that partial removal of the cyst gives the same guarantee of complete cure as the total removal.

— There is no doubt that an open transcortical, transventricular ap-

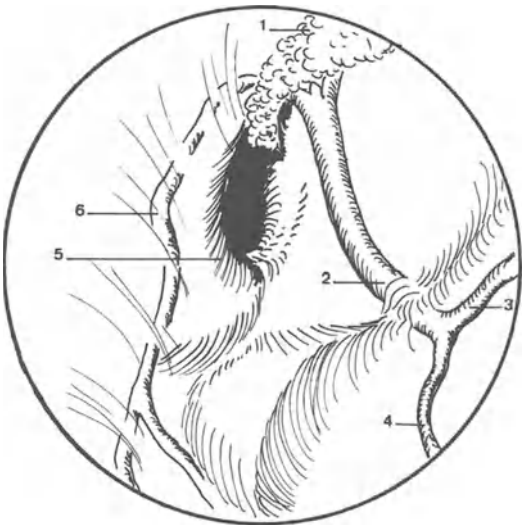


Fig. 15. Anatomical structures around the foramen of Monro, as seen through the endoscope. *1* Choroid plexus, *2* angulus venosus, *3* vena thalamostriata, *4* vena nuclei caudati, *5* fornix, *6* vena septi pellucidi

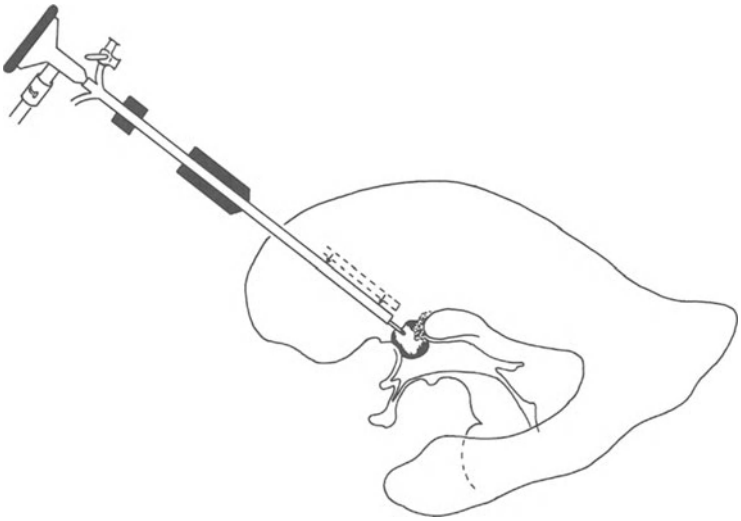


Fig. 16. Manœuvre to correct the trajectory of the endoscope

proach creates better access for more comprehensive manipulations around the foramen of Monro, but this method entails damage to a larger part of the cerebral cortex.

A further advantage of the endoscopic treatment for colloid cysts, is that the whole procedure can be done under local anaesthesia, allowing us to treat patients even when they are in a bad general condition.

By the use of this technique we have successfully managed two cases of colloid cyst with follow-up of 6 months in one case and of 1 year in the other. In both instances repeat CT scan has shown disappearance of the cyst.

A Short Critique of the Variety of Approaches to Handle Colloid Cysts

This chapter describes what one might regard as classical neurosurgical approaches to colloid cysts and two techniques which have been more recently suggested.

The alternative approaches of the classical type, the transcallosal and the transcortical, each have their advocates and the data presented in the chapter indicates that both may be successful. As in so many other aspects of neurosurgery it is to some extent dependent upon what the neurosurgeon has become used to and prefers. It is clear however that the transcallosal approach is easier to perform than the transcortical approach if the ventricles are of normal size or are only minimally enlarged. The transcallosal approach however, has the disadvantage of potentially disturbing the anterior cerebral vessels, and although in careful hands as demonstrated in

this chapter, this is not necessarily a problem, the approach does demand separation of the two hemispheres sometimes with irritating venous bleeding if the cingulate gyri are closely adherent, and has been recorded as producing damage to the anterior cerebral vessels.

In this approach also the two pillars of the fornix are more directly in the surgeon's view than in the transcortical approach and occasionally opening into a cavum septi pellucidi may cause confusion although it is soon clear there are no actual intraventricular structures present.

The transcortical approach is easier if the lateral ventricles are enlarged. Under these circumstances with perforation of the septum an excellent view of the foramen of Monro is obtained with the advantage that the approach is oblique and the foramen is therefore thrown into a more open form. While it is more difficult to expose the lateral ventricle on the opposite side than through the transcallosal approach, this is not significant in relation to colloid cysts where the lesion may be collapsed before contralateral adhesions to the third ventricular wall cause concern. In all these approaches the position of the self retaining retractors is extremely important. Yaşargil emphasizes the necessity for gentleness in his chapter and the Queen Square Group indicate the dangers to the genu of the internal capsule from unwise retraction of the lateral wall of the lateral ventricle just anterior to the thalamic bulge.

Much has been made of the relative risks of epilepsy in these two approaches. It is clear however that while the transcortical approach undoubtedly transgresses cortex, the transcallosal approach retracts cortex and may involve the division of small but not necessarily insignificant parasagittal veins. Although statistical evidence is lacking, it is likely that the relative incidence of epilepsy in the two forms of craniotomy is probably somewhat similar.

The transcallosal approach has been alleged to be not without some functional consequences if careful neuropsychometric is performed[20, 32], although it may be difficult to attribute exactly the cause of some mild functional impairment in a patient who may have presented with dementia and confusion and who may besides a small callosal incision, have experienced appreciable distortion of the septal region by the tumour and hydrocephalus. Our own and Yaşargil's recent experience would indicate that in a patient with small ventricles and no neurological deficit (including careful psychometric examination) pre-operatively, a small anterior transcallosal incision produces no detectable deficit.

Calliauw's description of the endoscopic treatment creates new horizons, but it is clear from his own description that complete removal of the cyst wall is unlikely by this method and the risk of haemorrhage from avulsion of attachments to the choroid plexus or damage to the veins, must be ever present. The senior Queen Square author has experience of a colloid cyst

which recurred after imperfect removal elsewhere and there seems no doubt that complete excision of the wall is the only way to be absolutely certain that the cyst will not recur, unlikely through this may appear. The endoscopic techniques therefore can be regarded as an interesting potential development but hardly one which could be regarded as routine.

Ostertag's description of his endoscopic stereotactic technique on the other hand recommends a procedure in which the wall of the cyst is not removed. Imperfect removal of these tumours even by open operation can be attended by recurrence, and there is little doubt that sooner or later some incompletely removed cyst will recur. The question of cost effectiveness is raised, the stereotaxic aspiration is carried out under local anaesthesia and is alleged to require the minimum amount of manpower and resources compared with open surgery. On the other hand it does require a complete stereotaxic system, it occupies computerized tomographic time and in Ostertag's hands at least requires stereotaxic angiography. It is doubtful therefore whether the question of cost effectiveness is a genuine advantage. In the elderly however, or in patients in poor general condition, stereotactic aspiration is unquestionably a lesser procedure than open craniotomy.

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Stabilization of the Spine

H. A. Crockard and A. O. Ransford

The National Hospitals for Nervous Diseases and The Royal National Orthopaedic Hospital, London (U.K.)

With 21 Figures

Contents

Introduction

The theme of this chapter is the prevention of spinal instability and deformity secondary to trauma, surgery and diseases of the spine. The treatment of established scoliosis and/or kyphosis is not within its remit. The bony and ligamentous damage consequent on trauma can produce deformity in later years. It comes as a shock to some clinicians that wide surgical destruction of the supportive elements of the vertebral column will also have the same effect. In part, this attitude has been engendered by the short survival prospects of many malignant "spinal" patients. A sequential approach has been adopted on the grounds that if the patient survived long enough, secondary corrective surgery might be considered. The problems of course are complex; maximum exposure for neurosurgery will mean almost certain spinal instability and/or deformity. Despite improved surgical awareness, there are far too many occasions when a simple laminectomy in an adult is undertaken in such a way that the pars interarticularis is knowingly or unknowingly fractured with the consequential risk of segmental instability. A more devasting error is widespread excisive laminectomy for spinal tumour in the immature skeleton without any consideration of the effects of the bony destruction on longitudinal spinal growth.

Ultimately spinal surgeons competent to treat diseases of the spinal column as well as the contents of the spinal canal will evolve. Until this is achieved, a multidisciplinary approach by neurosurgeon and orthopaedic surgeon should be planned for any condition which, after radical microneurosurgery, leaves spinal stability in doubt. The participants should have some knowledge of the potential benefits available through other specialities, and the aim must be *definitive one stage* neurosurgery and spinal stabilization (Crockard and Ransford 1990).

In this chapter we outline the basic anatomy and pathology which renders the spine unstable. Consideration is given to possible methods of spinal stabilization following trauma, and "old fashioned" neurosurgical laminectomy. Finally an outline plan is presented for combined approaches to complex spinal lesions.

Spinal Biomechanics

It is perhaps easier to understand spinal mechanics if a simple model is considered. This model divides the vertebrae into three columns (Dennis

1983). The anterior column is the front of the vertebrae, the middle column is the back of the vertebral body and the posterior column consists of the laminae, facets and posterior ligaments. Provided two of these columns are intact, the bony spine is stable; if two are destroyed, the spine is unstable (Fig. 1).

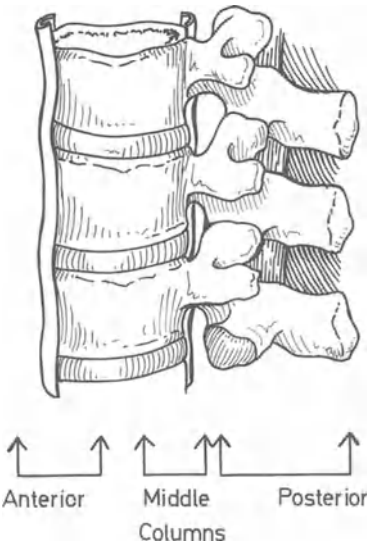


Fig. 1. The three vertebral "columns" on which stability depends are illustrated in this diagram

Bone under compression is stronger than bone under tension. In the lumbar spine, because of the lordosis, the laminae are the strongest part of the vertebrae. The vertebrae and discs obey Wolfe's Law. The discs of a labourer are stronger than those of a clinician. It is the doctor who is likely to have a prolapse disc. As one descends the spine, the discs get gradually larger; the L 4/5 and L 5/S 1 discs are the largest. The consequence of an upright posture is the production of sheer stresses at these two levels causing the annulus to fail in people with "weak discs" allowing the nucleus pulposus to prolapse posteriorly.

Massive trauma has predictable effects. A weak pars interarticularis can result in a stress fracture. It is instructive to consider this point further. A person with a large spinal canal has thinner laminar bone. Because he has less laminal bones he is predisposed to fracture the pars. The healing reaction (pseudarthrosis mass) only occasionally produces symptoms because of the large spinal canal. Other causes of pars interarticularis fracture are destruction by surgery or weakening by surgery and subsequent stress

fracture. This can happen with a small canal and thus more likely to cause compressive problems.

The vertebral body segments articulate together at the intervertebral discs and facet joints. Intersegmental stability is maintained provided one or other of these structures is normal. When both are diseased or damaged, spondylolisthesis or frank segmental instability can develop (Fig. 2 a).

Intersegmental instability implies damage to the discs and facet mechanisms at the same level.

The facet mechanism can be indirectly damaged surgically by destroying the accessory ligaments whilst approaching the canal. It is obvious, but not always remembered, that the supraspinatous ligament, the interspinous ligaments, the ligamentum flavum and the various spinal muscles are protective to the facet joints while the integrity of the facet capsule, nerve supply and blood supply are all equally important. As in any other joint, articular damage can produce pain and eventual osteoarthrosis.

Loss of disc height from degenerative disease or surgery causes facet subluxation and eventual loss of facet bone and subsequent loss of align-

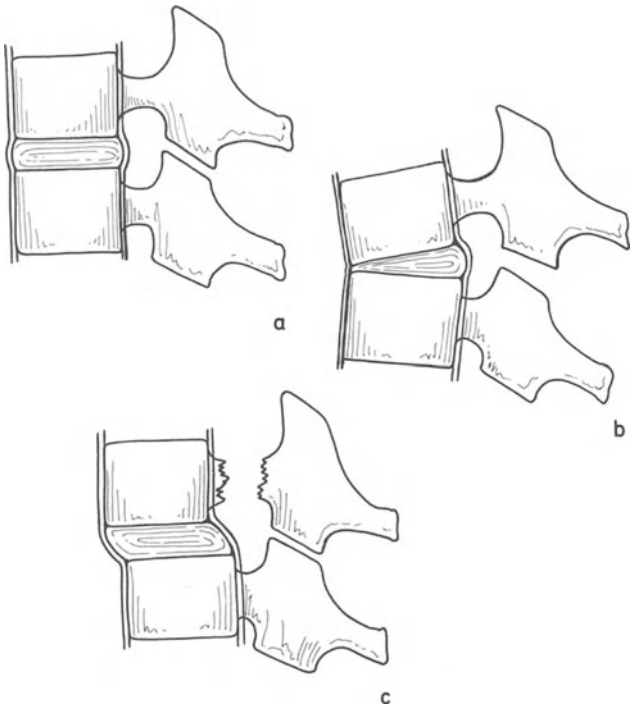


Fig. 2. a) Segmental stability depends on intact intervertebral facet joints. b) Loss of disc height will cause facet subluxation. c) Fracture of the pedicle will isolate the facet joint leaving stability to the longitudinal ligaments

ment (spondylolisthesis) (Fig. 2 b). The amount of "slip" is dependent on the disc height. A normal disc can only move a small amount before the annulus, anterior and posterior longitudinal ligaments become taut and prevent further slip. If the disc height is completely lost the two vertebrae can move nearly a centimetre before longitudinal fibres arrest the movement. A pars interarticularis fracture defunctions the facet joint and alignment is then totally dependent on the integrity of the disc and associated anterior and posterior longitudinal ligaments (Fig. 2 c).

Spinal Movements

Segment on segment movement, the so-called "vertebral coupling", depends on the configuration of the facets and the disposition of the ligaments; extra constraints occur in the thoracic spine by "external" splintage of the ribs.

At the *craniocervical* junction, tough capsular ligaments and the shape of the joints limits movement to one plane—nodding the head. The *atlanto-axial* joint movements are very much more complex to allow lateral rotation. At these two joints 85% of all neck movement normally occurs, a fact which must be taken into account when fusion is planned in this area. The C 1/C 2 joint is bascially an "axle in socket" joint whose plane of

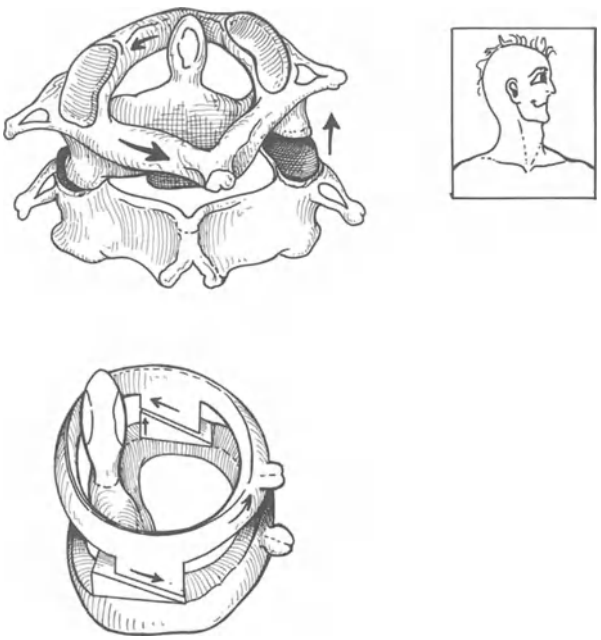


Fig. 3. Lateral rotation at the C 1/C 2 joint is accompanied by "up and down" movement

movement is altered by the sloping shoulders of their lateral masses (Fig. 3). Thus lateral rotation is accompanied by an elongated "concertina" movement which accounts for vulnerability to dislocate at the extremes of movement in Down's Syndrome. Also, the continuous wear and tear will allow progressive migration of the odontoid peg into the foramen magnum as noted in advanced rheumatoid arthritis (van Gilder *et al.* 1987).

The transverse ligament holds the odontoid peg tightly against the back of the arch of C 1 (the "socket" for the odontoid axle). Its rupture will render the joint unstable, but only slightly, provided the apical and alar ligaments are intact. Thus a large interval between dens and anterior arch with an intact odontoid process, can only occur when these and the transverse ligament are all damaged. Their other function is to limit lateral rotation and if they are deficient or lax, as in Down's Syndrome, the peg may dislocate.

The *subaxial spine* is reasonably resistant to deforming forces provided it is in normal alignment. If the neck is flexed, the superior and inferior facets slide apart leaving the bone at the cephalad tip of the inferior facet as the only guard against abnormal forces. This can now easily fracture if an abnormal loading force is applied. In the cervical region C 5/6 is at the apex of the curve and thus most vulnerable to acute injury and spondylytic changes. If subluxation has occurred the inherent unstable shape will cause further distortion ultimately compromising the spinal cord and adjacent nerve roots. A "wait and see" management policy therefore may lead ultimately to progressive cord compression and even more difficult surgery some years later.

The *cervicodorsal junction* is as vulnerable as the thoracolumbar junction presumably in part due to the loading forces which may be applied. In any area where the sagittal spinal curve is reversed there are special problems in acute trauma and also with degenerative "wear and tear".

The chest cage and sternum provide some extraspinal fixation for the *thoracic spine*. Quite marked vertebral destruction can occur without spinal instability or cord damage. Obviously this effect is lost in the region of the floating ribs.

The change in the sagittal curve at the *thoracolumbar* junction leaves the area vulnerable. The mobile lumbar segments in relation to the fixed thoracic segment invokes the "law of lever" also putting an extra strain on the joints. These factors are probably more important than the change in alignment of the facets from the thoracic to lumbar configurations. Movements at this region allow some flexion but mostly rotation.

Flexion, extension and lateral flexion and rotation occur in the *lumbar spine,* the former movements being most marked at the lumbosacral junction and rendering it most at risk to excessive movements and the effects of degenerative disease.

As one descends along the spine, the bones, ligaments and discs get larger—the largest being L 4/5 and L 5/S 1. The weight of the body acts through a vertical plane from foramen magnum to the anterior surface of S 1 with the spinal curves undulating across this line. The sites of altered curve are most at risk from shear forces and the lumbosacral area most vulnerable. Thus the high incidence of degenerative disc disease in the upright posture, and the painful back syndromes associated with abnormal movements following disruptive surgery in the area.

The *lumbosacral junction* is particularly vulnerable to acute deforming injury not only in the young healthy but also the degenerate spine. The loading and shear forces are at their maximum and this area is particularly prone to disc rupture and annular tear. Inappropriate surgery for disc disease may compound the problem by damaging the facet joint either directly or indirectly by destruction of its capsule, nerve supply, vascular supply, accessory ligaments or segmental muscles. It may be overstating the problem, but only slightly, when we contend that the continuation of symptoms following disc surgery is due to one or more of these factors; (1) inappropriate level of surgery, (2) wrong side, (3) inadequate disc removal and (4) surgical damage to the bony elements or the accessory ligaments.

Some conditions are inherently unstable for example the L 5/S 1 spondylolisthesis in the young male. This is usually due to congenitally deficient facets or a fractured pars interarticularis. Surgery here must involve some form of stabilization. Osteoarthritic L 4/L 5 spondylolisthesis is a degen-

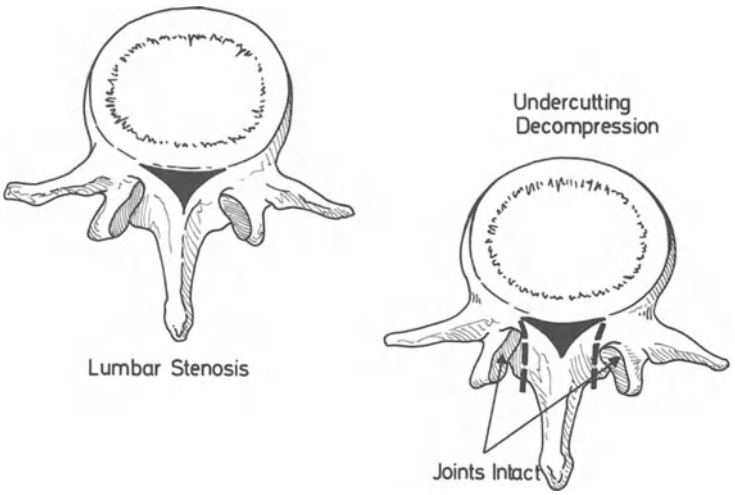


Fig. 4. A diagram to illustrate spinal stenosis. Decompression must not interfere with stability and so an "undercutting" procedure is used sparing the facet joints

erative condition almost always in elderly women; it is stable and will remain so provided the surgeon does not remove the facet joint. An "undercutting" type of internal decompression will expand the spinal canal and maintain stability (Fig. 4).

Pathology

a) Trauma

In *general,* the injuring force may damage the load bearing parts, usually the vertebral body, the articular elements, the ligamentous supports and the intervening intervertebral disc. The actual end result will depend on the direction of forces and special local anatomy. So often the "bony" deformity as noted on radiography is given primary if not exclusive consideration. Frequently it is forgotten that the ligamentous damage may render the level permanently unstable. It should be obvious that a fracture dislocation which does not easily reduce may be caused by interposed soft tissue. The basic rules mentioned in the Biomechanics section must be remembered when treating these injuries.

Fortunately vertebral bodies have an excellent blood supply and vascular necrosis is rarely a problem. The one exception is the tip of the odontoid peg and this fact (as well as interposed transverse ligament) accounts for the high (40%) incidence of non-fusion of fractures in this area.

The soft tissues have been mentioned, and, while injury can be anticipated by the thoughtful clinician, and inferred from plain radiographs, it may be identified with MRI scans and these will be used increasingly in the future in management. In the older person with prominent osteophytes, severe cord injuries may occur without any obvious bony or ligamentous injury. An acute prolapse of a cervical intervertebral disc may also cause severe neurological deficit and may only be seen on MRI, high definition CT scans or myelography. With less severe injury, the patient may recover, forget about the injury and, years later, present with a progressive myelopathy due to post traumatic osteophytes or a syrinx. In the authors' experience, cervical myelopathy in the young adult or middle aged person almost invariably has a history of trauma if the clinician remembers to ask.

Ligamentous injury is probably underdiagnosed. In Down's syndrome, the incidence of cord injury is almost certainly underestimated; in other genetic abnormalities e.g. Morquio's syndrome, ligamentous laxity is certainly the cause of their neurological deterioration (Fig. 5). In milder cases a capsular injury may allow excessive movements and may ultimately cause severe unilateral joint disease and associated intractable pain.

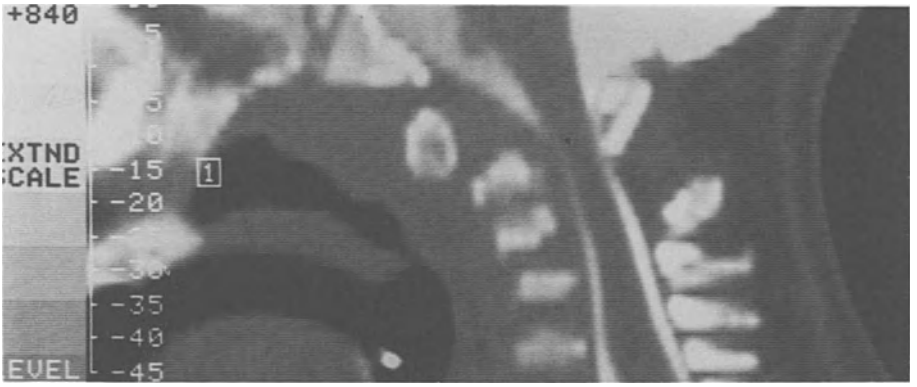


Fig. 5. Computed myelotomogram of the craniocervical junction in a child with Morquio Brailsford's syndrome. Note the compression at the craniocervical junction

b) Infections Which Cause Deformity

Bacterial spinal osteomyelitis, once a common and usually fatal paediatric problem, has been virtually eliminated with antibiotics in the Western World. It may still cause problems either acutely associated with an extradural abscess or chronically, 10 to 20 years later with progressive deformity in the adolescent due to disturbed growth patterns.

Tuberculous disease is the commonest deforming infection of the spine. In the acute stage appropriate medical therapy will control the infection and, if appropriate precautions taken, the spinal deformity may be minimized. The thoracic and thoracolumbar areas are especially involved in late kyphosis causing neurological problems.

Spinal hydatid disease, though rare, is an extremely difficult condition to manage. Ideally total excision would cure the problem, but often adjacent soft tissues are involved. The current medical therapy (the anti-helminthic Mebendazole) for the bony involvement is, in our experience, unimpressive (Levack *et al.* 1986).

c) Tumour

There are a wide variety of primary and secondary neoplasms which involve the spinal column. They usually cause pain, often night pain, and the expansion of the lesion or destruction of the vertebral body causes neurological signs. Most neoplasms, benign or malignant, involve the vertebral body or pedicle (Fig. 6). This important point must be taken into account when planning surgery as the posterior elements may be the only remaining stable column (Findlay 1984, Crockard 1987).

Metastases from breast, thyroid, kidney, lung and prostate are common in the vertebral body. Neurological presentation usually occurs once a

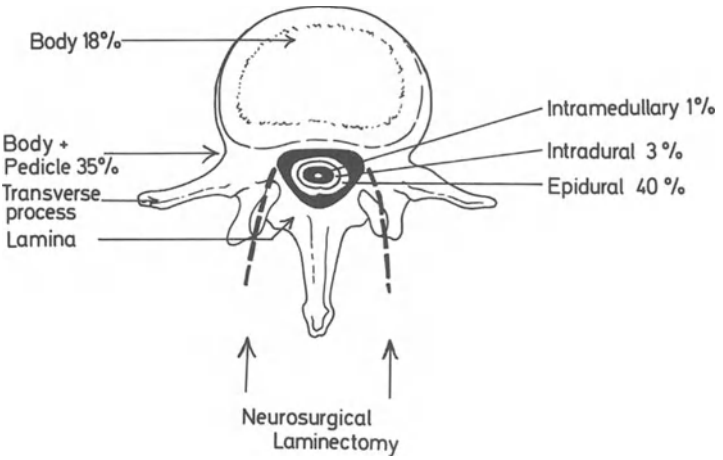


Fig. 6. The incidence of metastatic involvement of the vertebral body. A "neurosurgical" laminectomy removes the only area of bone which is rarely involved with the tumour

pedicle is involved and the spinal canal becomes compromised. This has profound implications for the surgical approach as will be outlined later. Manifestly the standard "neurosurgical" laminectomy will remove the only remaining stabilizing elements en route to the tumour (Paraicz 1987).

If there is a solitary metastasis or if there is a solitary plasmacytoma, radical excision may be worthwhile from a combined anterior and posterior approach (vide infra).

Primary tumours are relatively rare with a tendency to recur after inadequate excision and range from relatively benign (aneurysmal bone cysts, osteoid osteoma and osteoblastoma) to locally recurrent (chordoma and osteoblastoma) and frankly malignant osteosarcoma. It is fair to say that the goal must be complete excision, as for all these lesions, biopsy and its variants plus conventional external beam radiation have had very disappointing results. They seem to become even more locally aggressive at each recurrence.

Tumours of the spinal cord or nerve roots may present as a spinal deformity; in fact the first sign in the growing child may be the painful stiff back or an increasing scoliosis. Schwannomas may cause a "pain avoiding" scoliosis. It is rare for meningiomas to produce spinal deformities, but they, as with most other intradural lesions, are associated with all too common secondary iatrogenic deformities (McSweeney 1976).

d) Degenerative Conditions

Spondylosis implies a degenerative condition of the spine due to "wear and tear". Associated with degenerative disc disease there may be a pro-

liferative arthropathy and production of osteophytes; in conjunction they can effectively narrow the spinal canal and root foramina. The effects are more noticeable in those with a congenitally narrow spinal canal, the prime example being the lumbar spine in achondroplasia. A strong family history or certain races seem to be predisposed. If widespread, spinal stenosis will be the result. In most of these conditions, instability is rarely a problem.

Osteoporosis as such does not produce any neuraxial compression unless associated with a fracture. *Osteopetrosis* or Marble bone disease will produce spinal stenosis but not instability. *Ossifying posterior longitudinal ligament* disease is very common in the Orient and rare in Caucasians. In this condition the ligament ossifies and effectively reduces the canal diameter, only in its treatment is there the potential of instability.

e) Inflammatory Diseases

Rheumatoid arthritis, psoriatic arthropathy, a variety of collagen diseases and ankylosing spondylitis produce spinal deformities, cord compression and challenging conditions for the surgeon to treat. In many of them, there is a proliferative phase which can compress the cord and nerves. Later, in the "burnt out" phase disrupted ligaments allow subluxation.

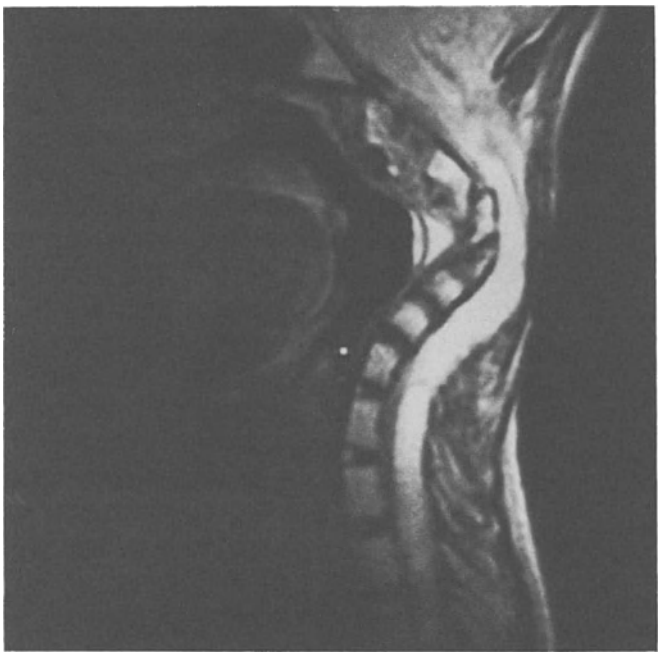


Fig. 7. The effects of extensive laminectomy and radiotherapy for a cervical cord cyst in a child are shown in this radiograph

Later still, osteoarthritis and spondylotic changes supervene and any or all of these factors may produce deformity and neural compression. Even in ankylosing spondylitis compression may occur. The "last joint syndrome" describes the hypermobility at the only remaining moving joint; this may also be associated with a proliferative situation, the so-called "Romanus lesion" which looks so like infection. Fracture dislocations may occur as the stiff spine is inadvertently deformed. Traction here is very dangerous as all the ossified soft tissues have also ruptured.

f) Iatrogenic

Inappropriate, or ill-informed treatment of many spinal conditions can render the spine unstable (Fig. 7). It is necessary to re-emphasize that over-enthusiastic posterior decompression surgery will damage the pars interarticulares or weaken the pars sufficiently that it can fracture later. Posterior surgery for anterior segment disease i.e. in the vertebral body, not only provides poor surgical access but removes often the only remaining stabilizing element at that spinal level. Anterior spinal surgery without anterior or posterior stabilization may result in further deformity. While the effects of surgery occur relatively soon, the deformity due to radiotherapy may be quite delayed but are most striking in the growing child.

Spinal Stabilization

In this section the general principles of surgery to prevent destabilization as well as the methods of stabilizing the unstable spine will be covered. It is obviously impossible to cover every technique and all diseases in a chapter of this length. It is hoped however that the reader will deduce the outline of the authors' approach. As with many other branches of surgery, there are many different ways to solve a problem, and, this is particularly true in an evolving speciality. Preservation of segmental structure is a philosophy common to all recent advances. The protection of junctional anatomy between the fused and unfused segments is of fundamental importance to prevent or minimize late junctional symptoms.

Table 1 provides a list of "do's" and "dont's" which will avoid many of the iatrogenic causes of the unstable spine. Clearly some or all of the rules may have to be broken to achieve the surgical objectives. At such times, the aim should be a *planned* decompression or excision combined with a fixation procedure.

Whether to stabilize internally or externally is a point which generates a great deal of debate. In some situations, as for example in a stable non-compressing crushed lumbar vertebra, external support would be the approach of most clinicians. At the other extreme, radical excision of several

Table 1. *For Spinal Stability After Surgery*

Do	Don't
Limit laminectomy	Damage the pars
Try a hemilaminectomy for malignancy	Damage the facets
Use a pediculectomy to decompress anteriorly	Use posterior acrylic fixation
Preserve interspinous ligament	
Undercutting decompression in stenosis	
Planned one stage excision and fixation	
Maintain vertebral height after excision	

vertebral bodies will usually require internal (and possibly external) fixation.

The authors often err on the side of internal fixation for any condition where life expectancy is short, or the risk of intercurrent disease or complications of recumbency are high. As with other types of surgery, a bad operation may be worse than no operation at all. The corollary of this is that the best results are in the hands of a team frequently engaged in complex spinal surgery. Each group will have preferences for one type of fixation system and with ever new developments in spinal surgery, there may not ever be a universally accepted or applicable system. On the one hand there is the relatively low technology approach of a sublaminar wire fixation system; on the other hand, the excellent Caspar and Cotrel Debousset systems require a large amount of expensive interconnecting equipment to perform the procedure.

Whether to stabilize from the front or back will depend on the original pathology but will also be influenced by the surgeon's experience.

a) Types of Stabilization

1. Bone Grafting

Osteosynthesis should be the ultimate aim of all of these procedures. The Cloward (1958) dowel graft and the Smith Robinson (1955) (Fig. 8) type graft are widely used in the cervical spine and produce satisfactory results. Following vertebral body excision the bone graft must be carefully shaped and be slightly "taller" than the space into which it is placed. Bone graft will incorporate better and faster when under compression. If the tumour is incompletely removed there seems to be little point in inserting

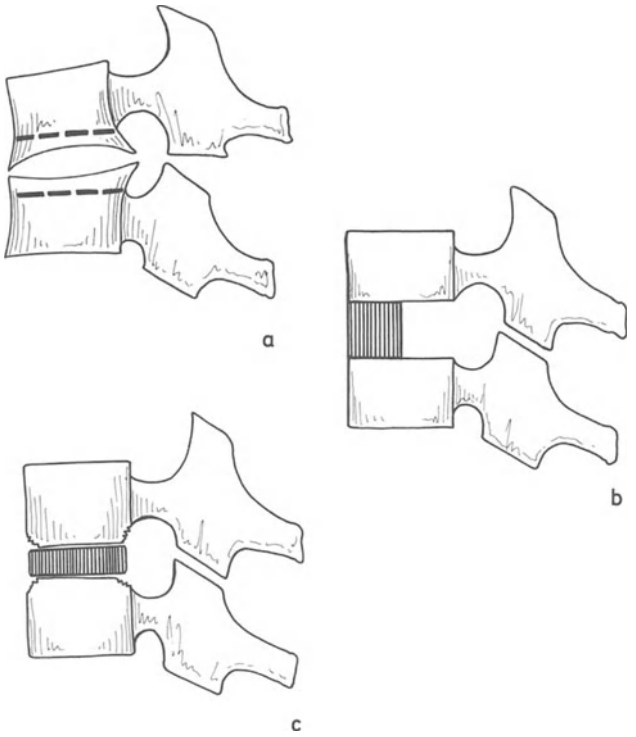


Fig. 8. The Cloward dowel and Smith Robinson interbody fusion techniques allow access to posterior osteophytes without destabilizing the vertebral column. a) osteophytes, b) Cloward, c) Smith Robinson

bone into the tumour bed; instead an artificial vertebral body implant or acrylic might be used (Pasztor *et al.* 1987).

When the grafting is posterior, cancellous bone chips are recommended associated with metal fixation. For specific purposes a cortical and cancellous graft is shaped to prevent loss of height during the fixation with sublaminar wires (the H-shaped graft).

Generally we favour iliac crest as the donor site for anterior and posterior graft procedures. Its cortex is sufficiently strong to provide a well-shaped graft, and there is usually sufficient cancellous bone. In small children, bilateral tibial and lower femoral grafts may be required as there is no substance to the paediatric iliac crest. We rarely use fibular grafts; while it provides a solid graft, it contains little cancellous bone, and may require prolonged external fixation to allow firm union. In the elderly it may be very much firmer than the bone into which it is being grafted and may "cut into" the operative site. Bank bone and synthetic bone both require further evaluation.

2. Bone Cement

In inexperienced hands, bone cement (Methyl methacrylate), is easy to use and provides initially a satisfactory implant or anchor point for sublaminar wires. The appearances, however are short-lived as there is absolutely no incorporation of the cement. It is to be recommended only in those situations where the patient's life expectancy is less than six months. A vertebral body may be replaced with it in association with an A.O. or Caspar plate. The practice of posterior cement implant with sublaminar wire fixation has little to commend it. Historically, it was used prior to the development of satisfactory metal implants. The latter are much less reactive in the tissue and, if infection supervenes, it can sometimes be controlled. Devastating tissue destruction occurs when attempts to remove an infected acrylic implant.

3. Vertebral Body Replacement

In the non-malignant conditions or following radical tumour excision, a bony fusion should be the aim anteriorly. In anterior surgery for the isolated vertebral metastasis with only subtotal excision some form of "spacer" must be used to maintain vertebral height. Bone cement is most used but there are a variety of prosthetic vertebral replacements either metal or ceramic which are currently undergoing evaluation. It must be emphasized that an implant must resist extension as well as compressive forces. Unless some anterior tension band system is incorporated in the design to prevent extension and rotation, a stabilising posterior fixation will always be necessary.

4. Wire Fixation

Malleable stainless steel segmental sublaminar wires are widely and successfully used for posterior stabilization. There are certain technical aspects which will improve the long-term outcome. Interspinous wiring is easy but is not supportive, will slip or fracture the spinous process and cannot be recommended unless the wire is passed through a drill hole at the very base of the spine. Sublaminar wires will provide best support and fixation. There are the obvious dangers of dural penetration and cord damage (even with the dura intact). A flavumectomy will reduce considerably the danger and the wire will pass more easily between dura and the undersurface of the lamina. Doubled wires or single wire with preformed blunted tips may be shaped to pass around the lamina. A variety of flavum dissectors and wire guides are available (Figs. 9 and 10). If there is any neural compression it is extremely dangerous to pass the wires. If there has been a loss of CSF either due to dural tear or previous anterior transdural surgery, the cord is particularly vulnerable; the intact dural sac with

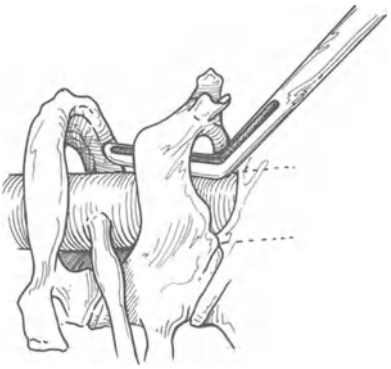


Fig. 9. An illustration of the sublaminar wiring technique. The ligamentum flavum has been removed and a wire guides (Codman and Shurtleff) passed under the lamina

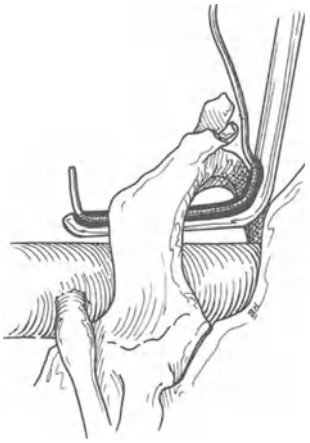


Fig. 10. A sublaminar wire is now passed in the groove of the wire guide

CSF provides a very effective hydraulic cushion for the spinal cord. At the craniocervical junction the most difficult site to pass wires is at the foramen magnum due to bony irregularities and dural attachment (not to mention the marginal venous sinus in 5% of individuals). Our recommendation here is paired 3 mm diameter burr holes in the occipital bone through which the wires may be passed (Ransford *et al.* 1986).

5. Screw Fixation

Anatomical repair of a fractured vertebra using screws can be obtained in two circumstances. A translaminar to pedicle screw (Buck's fusion) on each lamina for a bilateral pars interarticularis fracture compressing bone

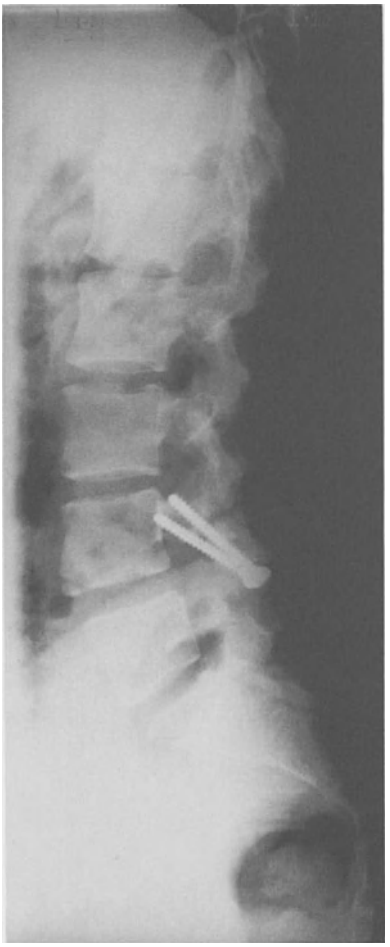


Fig. 11. A translaminar to pedicle screw fixation (Buck's fusion) for undisplaced pars interarticularis fractures

graft at the cleared out pseudarthrosis site can facilitate healing of the stress fracture and effectively restore segmental stability without intersegmental fusion (Fig. 11). The other circumstance is paired screw fixation of the fractured odontoid process via bilateral neck incisions and using biplanar radiographic guidance (Fig. 12).

Transarticular facet screws can stabilize adjacent vertebrae while awaiting bony fusion in two situations. Magerl and his colleagues have described C 1/C 2 fixation by this method (Grob and Magerl 1987). It is clearly an easier operation if the odontoid peg is intact and C 1 can be held against the peg whilst drills are replaced by screws (Fig. 13). The other fixation is that of Boucher in the lumbar spine. Here a screw is passed via the cephalad

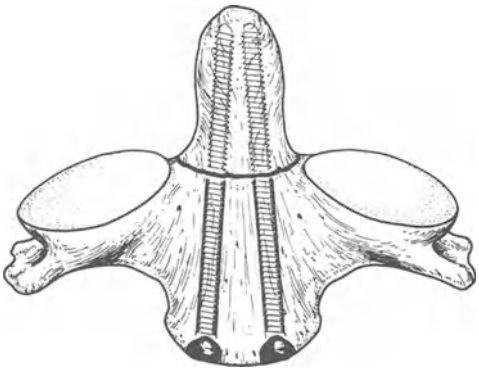


Fig. 12. Screw fixation of an odontoid fracture. Biplanar radiology and bilateral incisions are required

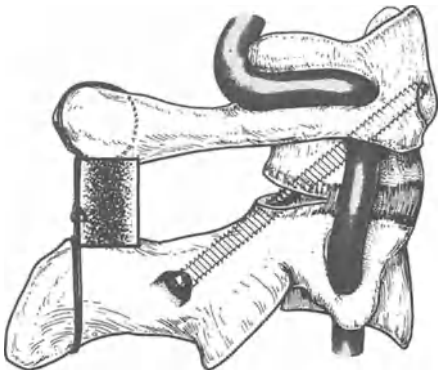
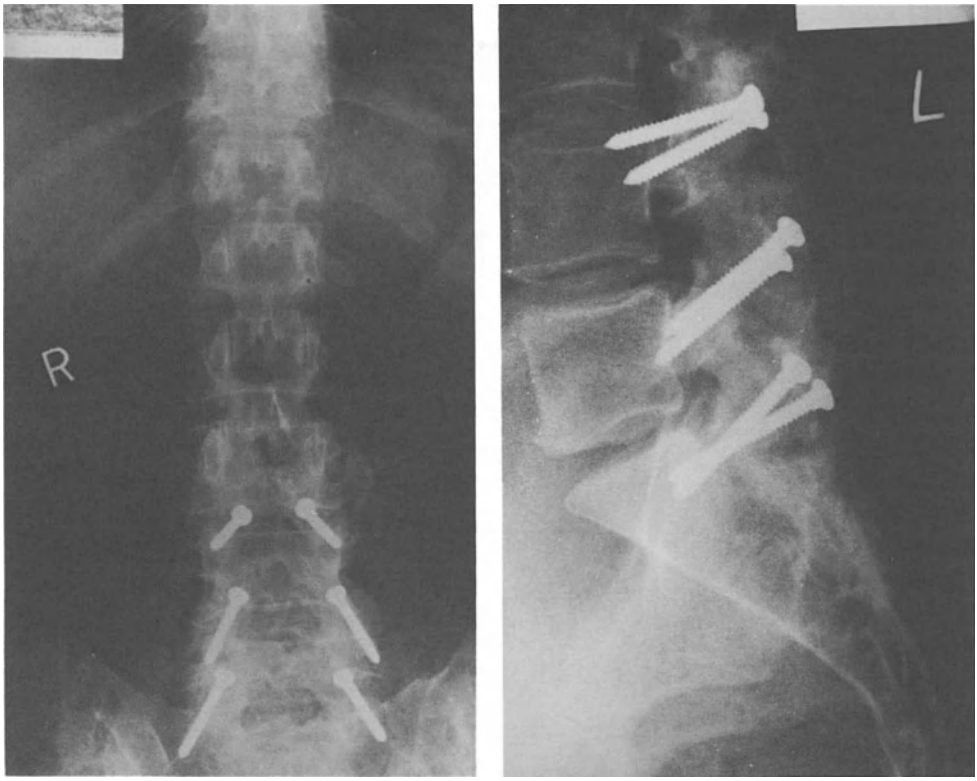


Fig. 13. C 1/C 2 lateral mass fixation

lamina through the facetal joint well into the pedicle of the vertebra below. The two screws end up at right angles to each other providing excellent stability (Fig. 14).

Pedicle screws imply a screw passed from posteriorly down the pedicle into the vertebral body. The diameter of the pedicles increases as we descend the spine so any screw system must incorporate 4–6.5 mms diameter screws. The entry into the pedicle is immediately caudal to the facet joint and great care must be taken to avoid facetal damage. Single pedicle screws can "toggle" or "windshield wipe" in the vertebral body if excessive forces are applied to them (i.e. in the correction of a deformity). Alone, therefore, they are not ideal for the correction of a deformity. A laminar bridge joining a pair of pedicle screws on the same vertebra may help solve this problem.



a b

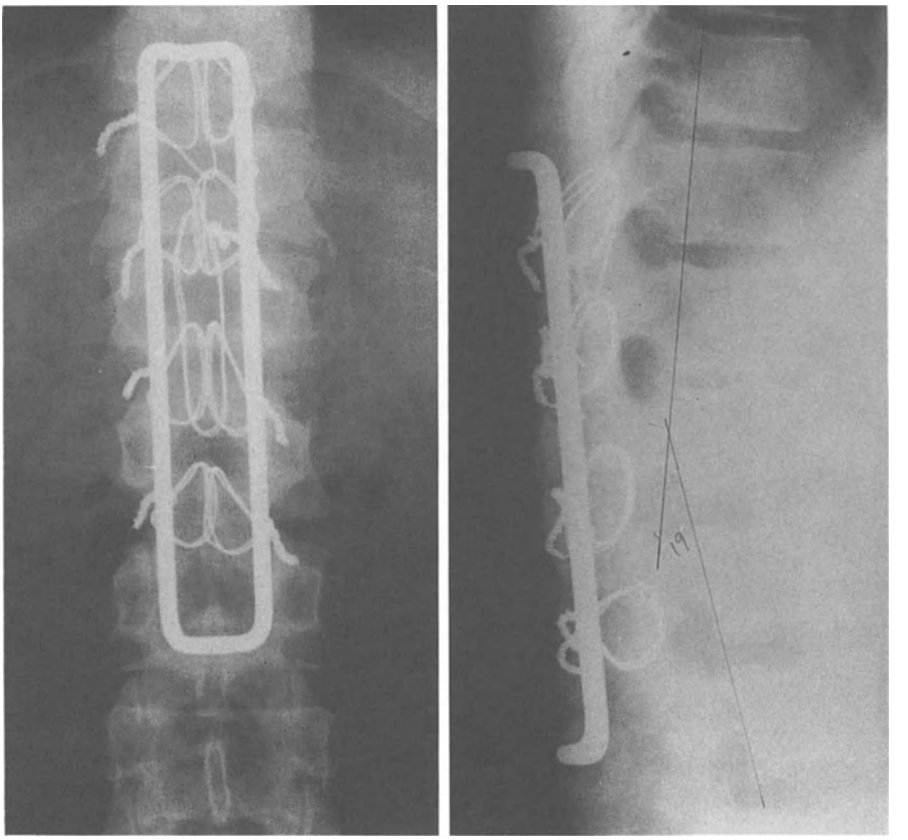
Fig. 14. Radiographs showing a three level Boucher type fusion

Laminar clamps are being developed. These are superior and inferior hooks around a single lamina. The fixation here is still not ideal as they can rotate around the lamina. However, pedicle screws will be required where there has been a laminectomy. Several systems are currently being evaluated (Luque, Steffee, Cotrel Debousset, Webb-Morley, A.O. (Dyk)).

6. Preformed Metal Implants

There are a variety of metal implants designed for different anatomical areas and with differing purposes. The most widely used system in the past has been the Harrington rod system. It provided firm fixation and also hold the injured part in distraction. It has stood the test of time.

Implants contoured to meet the regional anatomy and/or pathological curves were pioneered by Luque and these, having been bent to the individual's shape, are held in position with segmental sublaminar wires. The



a b

Fig. 15 a, b. A radiograph showing the Hartshill rectangle with sublaminar wire fixation in a thoracolumbar deformity

Luque and Hartshill rectangles (Fig. 15) are developments of the original rod technique and have great inherent strength. Their disadvantage, as with all "rodding" techniques, is the length of the exposure required to maintain stability (at least 2 segments above and below a thoracolumbar fracture dislocation). This inevitably leads to a long stiff segment. The Hartshill rectangle is currently enjoying a vogue of popularity in low lumbar fusions for back pain. The authors have a particular interest in occipito-cervical fusion using the Hartshill Ransford Loop. The occiput should not be included in a fusion unnecessarily. Clamp fixators have been designed to fix adjacent laminae and these can span up to 3 or 4 segments (Halifax clamp) (Fig. 16). Their chief advantage is the extremely firm fixation of adjacent segments and a small block of bone interposed between the laminae

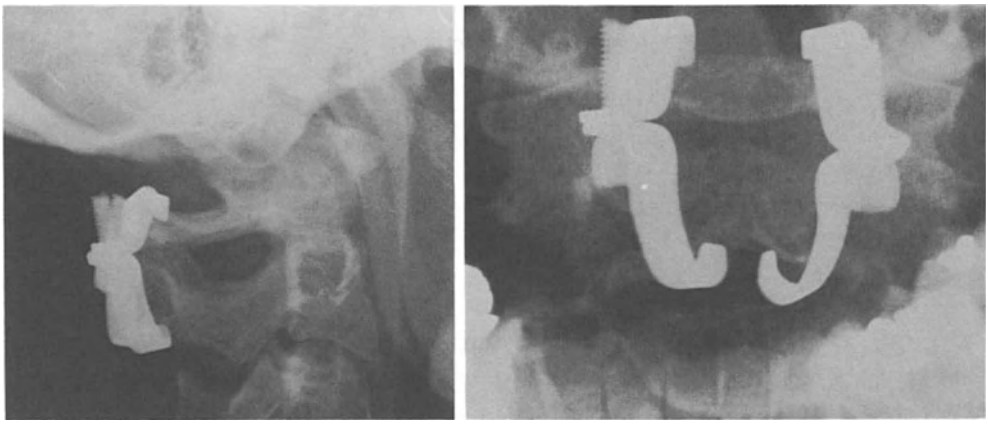


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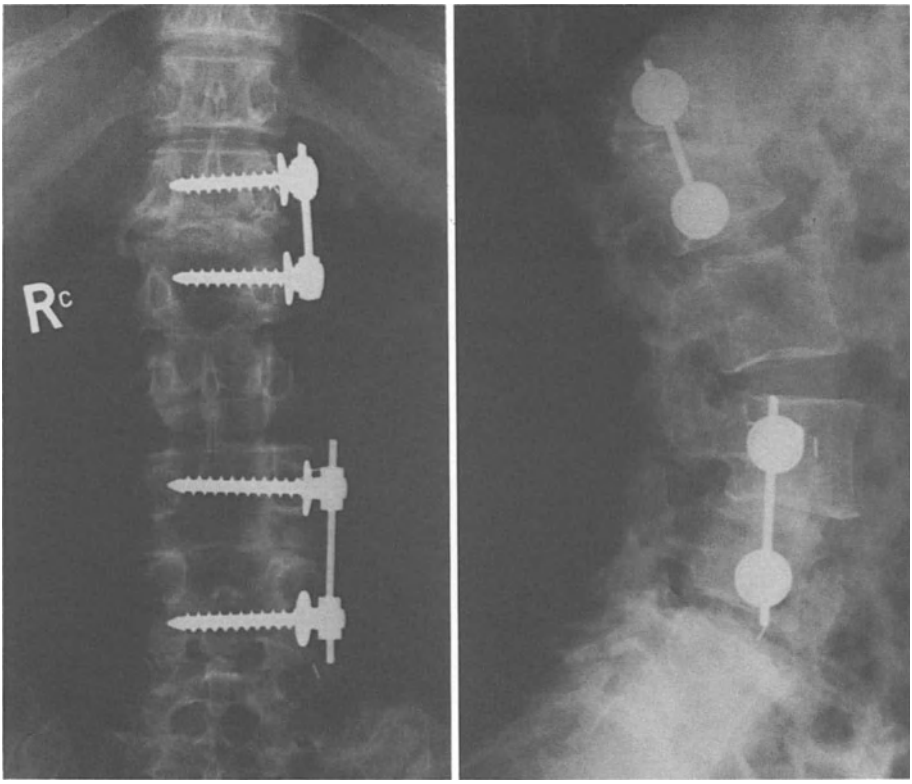
Fig. 16 a, b. The Halifax clamp is an excellent fixation system for posterior cervical stabilization. A C 1/C 2 fixation is shown here



a b

Fig. 17. The Zielke rod and screw fixation system has been used to provide anterior stability

avoids lordosis. There is a Hartshill rectangle attached to pedicle screws system which require further evaluation. Zielke or Webb-Morley screws and heavy duty rods are useful in the lumbar region (Fig. 17).

Posterior plate fixation in the spine is not successful and in the authors' opinion should be avoided. Interspinous plate fixators like interspinous wiring are easy to apply and just as easy to move, slip or result in very poor fixation.

7. External Fixation

A whole range of techniques have been used ranging from skull traction in bed through to Halo Pelvic metal fixation. The conventional Minerva jackets have stood the test of time and while requiring a great deal of expertise to apply and an equal amount of fortitude to wear for up to six months, the results of this form of stabilization are superior in many instances to internal fixation in the hands of the occasional exponent. There are a wide variety of preformed strut and plastic vests which are more comfortable and radiolucent. They suffer from the fact that the patient may adjust them or take parts off from time to time.

Stabilization in Trauma

It is not within the scope of this chapter to consider the treatment of all spine injuries. As with other conditions, general guidelines will be provided (Garlick and Crockard 1988).

As with all spinal conditions the non-invasive scanning techniques with multiplanar reconstructions have greatly improved the understanding of the pathology and aided the planning of treatment. In trauma, the position of retropulsed fragments and the anatomical integrity of the cord can be determined (Fig. 18). For our part we would now tend to be much more

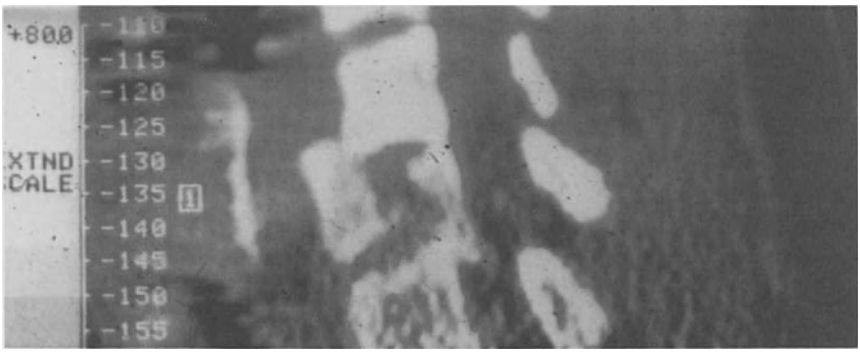


Fig. 18. Computed myelotomography showing a "retropulsed" fragment with cord compression in the cervical spine

agressive surgically in any partial cord lesion in the acute stage, and unstable fractures whatever the acute neurological condition on the grounds that the slightest repetitive movement at the fracture site might be producing cord concussion and further cord damage. The soft tissue element of an injuring mechanism can also be identified on MRI or CT myelography and the acute prolapsed disc can also be dealt with.

The scanning techniques have shown more clearly the exact disposition of the fracture lines and on reconstructions pedicle and facet fractures can be more easily deduced than on plain X-ray tomography.

In general terms, we would favour surgery on the conditions mentioned in Table 2. Obviously the total clinical picture must be taken into account. In our experience, a more active surgical policy is justified with present day imaging techniques, microneurosurgery and definitive one stage spinal stabilization, than the conservative "Guttman philosophy" of a generation ago.

At the craniocervical junction there are particular problems which are amenable to active intervention. With *fracture of the Axis* it is important to realize that the shape of the wedged shaped lateral masses will tend to be driven laterally if the transverse ligament is ruptured. In such, the anterior and posterior arches may be reduced and held with plate and screw fixation. Many *odontoid* fractures heal with conservative treatment but if the expertise is available, a compression fixation with two A-O screws can be performed by a lateral cervical approach. It must be emphasized again that if the fragments are widely separated it is likely that the transverse ligament is trapped between them. The *Hanged Man's Fracture* is a fracture through the pars interarticularis of the atlas; this will usually heal with external fixation. Bilateral pars interarticulares screw fixation from behind, or C 2/C 3 fixation by a dowel bone graft transorally have been used successfully.

In the thoracolumbar area the question of "ligamentotaxis" needs care-

Table 2. *Spinal Trauma Suitable for Surgery*

Recurrent subluxations
Ligament tear
Acute disc herniation
Fracture dislocations with preserved neurology
Retropulsed vertebral fragment with function
Deteriorating neurology with fracture
Deformation due to crushed vertebra
Cord transection but severe radioculopathy
CSF fistula
Penetrating wounds

ful consideration. This technique implies that the posteriorly prolapsed fragment of a vertebral body (the so-called "culprit fragment" seen on computerized tomography scanning) will reduce if the vertebral body height is restored and the posterior longitudinal ligament placed under tension. In our opinion, this should be done with spinal cord monitoring.

Complex Spinal Problems

Because of the constraints of space it is possibly only to provide examples of such problems. We choose one example for each region to illustrate the widening field of spinal surgery.

a) Craniocervical Instability

In rheumatoid arthritis there is the combination of instability due to ligamentous damage, bony erosion and hypertrophic synovitis which leads

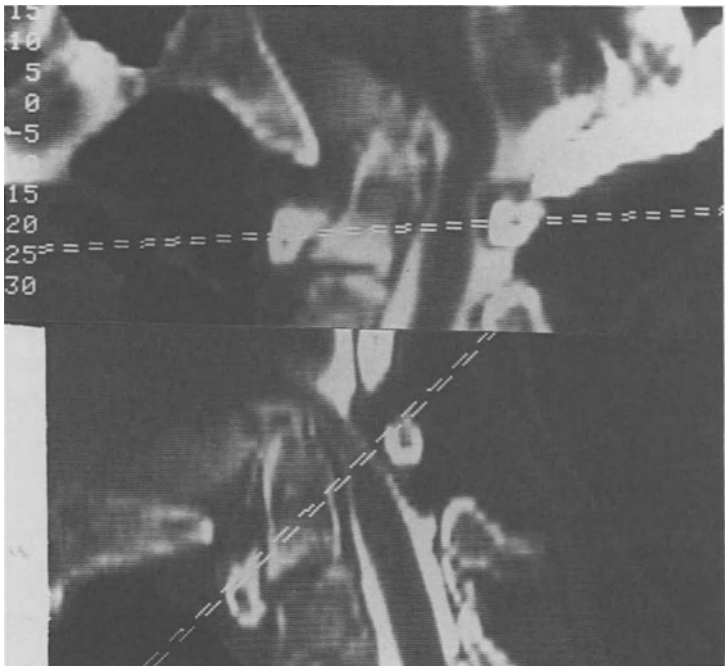


Fig. 19. Dynamic CT myelography is essential in identifying the problems associated with atlantoaxial compression in rheumatoid arthritis. Note the instability, the odontoid translocation and the brain stem compression

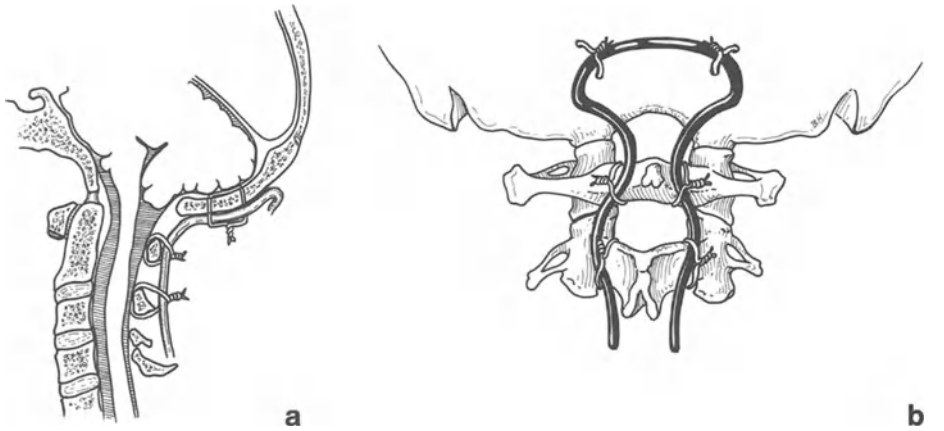


Fig. 20 a, b. An illustration of occipitocervical fixation using the Hartshill Ransford loop. The "flare" at C 2 is designed to prevent translocation. The occipital fixation is by wires passed through the occipital bone

to recurrent intermittent cord compression and with the arthritic pannus and possible translocation of the odontoid peg, there may be a permanent anterior deforming mass over which the craniocervical junction is compressed (Fig. 19). It is our contention that in such instances a one stage transoral removal of the anterior compressive mass and posterior occipitocervical fusion (Hartshill Ransford Loop) is a treatment which is well tolerated by the patient with a lower morbidity than conventional posterior surgery and significant improvement in neurological condition. The patient is placed in the lateral position on the operating table to allow access front and back. Tracheotomy is rarely required, instead fibreoptic nasotracheal intubation is used. Details are given elsewhere (Crockard 1988).

If there is craniocervical instability without anterior compression, then a posterior procedure will suffice (Hamblen 1967). In rheumatoid disease we often use a Hartshill Ransford Loop if C 1 is weak (Fig. 20). The value of a bone graft in such patients is currently being evaluated. Occipitocervical fusion is a major disability and the technique is reserved for patients with widespread joint involvement or in patients with metastatic involvement in the area. If there is simply a C 1/C 2 instability problem we favour lateral mass screw fixation or a Halifax clamp.

b) Midcervical Kyphus

One of the problems caused by multiple level vertebral disease in the cervical region is anterior collapse leading to a kyphus. It may be caused

by rheumatoid disease, tumour involvement of the vertebrae or previously extensive cervical laminectomy and radiotherapy (Fig. 7).

It is important to excise the whole of the anterior kyphus and this may extend over three vertebral bodies. In our experience fibular struts in this area are basically unstable and may slip backwards even with external fixation. A bone block and anterior plate fixation will hold the bone in position but there will be a tendency to further angulation unless there is a posterior rectangle extending well above and below the kyphos. (The alternative is to maintain the patient in a Halo Cuirasse for up to six months.)

c) Cervicodorsal Pathology

Lesions in the vertebral bodies at C 7 to T 2 are particularly difficult to deal with especially if there has been anterior collapse. Often the chin is touching the sternum and making tracheostomy impossible. Again as in all our "cervical instability" practice we favour fibreoptic nasotracheal intubation for anaesthesia. The pathology may be approached by a median sternotomy taking great care to preserve the innominate vein (one will have to work above or below it). Ligation of the vein may so severely compromise the cerebral drainage, that the patient may not recover from the anaesthetic. A C 7/T 1 disc may be approached by a low neck incision with division of scalenus anterior. A clavicular osteotomy and manubrial flap reflection is an alternative to a sternal split.

d) Thoracic Spine T 2–T 10

The stability of this area is enhanced by the ribs and sternum. Several vertebral bodies can be removed if the rib cage and posterior elements are intact. Bone graft under compression is the method of stabilization and osteosynthesis. Anterior metal implants are dangerous and have on occassion ruptured into a bronchus, the aorta or the heart itself. Only in those of short life expectancy will one depend entirely on a posterior implant. Unless there is good anterior osteosynthesis, the weight of the body will tend to "concertina" down the remaining vertebral column and this is more important the more caudad the pathology.

The blood supply of the spinal cord between C 7 and T 10 is conventionally considered to depend extensively on the Artery of Adamkiewicz. While this may be true in the normal situation or the acute compressive lesion, it will certainly not be true in the longstanding thoracic kyphoscoliosis. Great care therefore should be taken of all the intersegmental arteries especially at the apex of the kyphos. The classical posterolateral approach, satisfactory for lower thoracic disc, may be dangerous if extended over several segments with sacrifice of intercostal neurovascular bundles. A standard thoracotomy provides excellent access and the intercostal vessels

can be easily identified and preserved. A posterior retropleural thoracotomy may be used with resection of one or two necks of ribs and associated transverse processes. This will allow good access to the front of the dural sac and removal of a bony kyphos. An anterior bone strut of the anterior aspects of the vertebral bodies should be preserved to reduce the risk of further kyphos formation. Cancellous bone chips may be used in this situation, behind the "bridge" to promote further bone formation.

e) Thoracolumbar Junction

In terms of pathology, the area is particularly vulnerable to injury, and, after the acute phase, there is likely to be further deformation leading to a progressive angulation. Metastatic involvement in this area will result rapidly in spinal deformity. From the surgical point of view access is complicated by the diaphragm and great vessels. The natural tendency is to hope that the least possible surgical intervention will suffice. In patients with a rapidly advancing malignancy a *transpedicular* approach through the diseased pedicle will allow anterior decompression. Stabilization is achieved with a long Hartshill rectangle wired in, at least three levels above and below the decompression. This may be satisfactory for the remaining six to twelve months of the patient's life but he has a stiff back. Too much strain over a long rectangle may result in fracture of the laminae or sub-laminar wires. For patients with a good life expectancy alternative methods are recommended in which an anterior or anterolateral approach is used. Access will require a thoracolumbar incision with division of the diaphragm and a retroperitoneal exposure of the upper lumbar vertebrae. Vertebral body replacement, after decompression, and Zielke fixation may be the way ahead. Even after grafting and internal fixation, immobilization in plaster jacket for six months may be required.

f) Lumbar Spine

Tumoural involvement of a vertebral body may require total vertebrectomy, removal of the two adjacent discs and exposure of the vertebral end plates. Any vertebral prosthesis must articulate with the strong bone at the insertion of the annulus. Acrylic is used in the "malignant" situation but its long-term viability is very poor. It is expected that satisfactory vertebral body prostheses will be developed soon and when available will allow more extensive lumbar surgery than has been hitherto possible. If posterior rectangular implants are used, great care must be taken to shape the implant to maintain the normal lumbar lordosis. A "flat" back is a great disability in sitting, standing and walking.

g) Lumbosacral Junction

With maximal curve and minimal loading at this junction fixations will only be successful in the long-term if there is an excellent osteosynthesis.

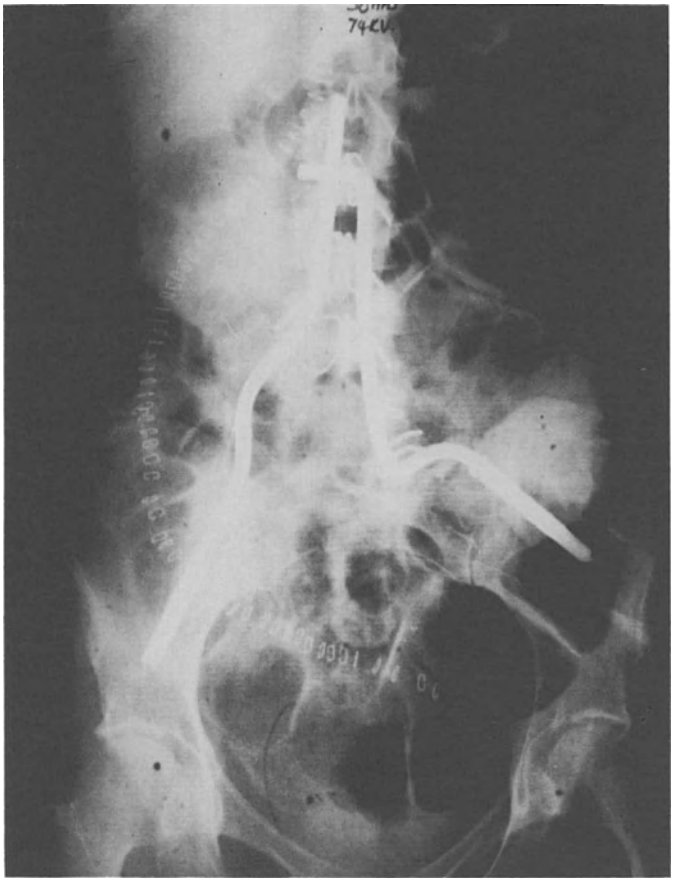


Fig. 21. Lumbosacral instability due to a breast cancer metastasis treated by threaded rod inserted into the ilium and held to the lumbar laminae by sublaminar wires

Metal fixation may be satisfactory for the short life expectancy of a patient with malignant disease but for the longer term, great efforts must be made to create a bony fusion. With malignant involvement at this level, shaped Luque or Cotrel Debousset rods sunk into the ilium on both sides and fixed to the lumbar spine by sublaminar wires and pedicle screws have been used successfully (Fig. 21).

Conclusions

As cancer patients survive due to better treatment an enormous chasm has appeared between the outcome of conventional surgical techniques and the expectation of the patients and his relatives. As public knowledge grows

there will be an increasing demand for more and more sophisticated surgery which cannot be performed on an emergency or ad hoc basis. Surgical advances in orthopaedics and neurosurgery together with combined procedures have provided the basis for a novel approach to old problems and ultimately the development of speciality spinal surgeons. These advances have coincided with the general availability of imaging techniques will provide greater understanding of the anatomy of pathological processes before and after surgical intervention, and provide objective data on the effects of the procedure. The combined effect of these factors, increased life expectancy, improved imaging, new surgical technique and increasing public awareness, must result in the abandoning of "after hours" semi-planned surgery and lead to dedicated hospital beds, assigned "daytime" operating sessions and the establishment of spinal surgery to cope with these new developments.

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Indications for Surgery in the Management of Gliomas

F. COHADON

Clinique Universitaire de Neurochirurgie, Hôpital Pellegrin, Bordeaux, (France), et Laboratoire de Neurochirurgie Expérimentale et Neurobiologie, Université de Bordeaux II, Bordeaux (France)

With 1 Figure

Contents

"About the group of gliomas
it is difficult to say anything
intelligent concerning them."
(Percival Bailey)

I. Introduction

The conventional wisdom among neurosurgeons and oncologists is that gliomas are not curable by surgery—nor by any other therapeutic approach—and yet that surgical resection is a necessary step in their treatment. It is not our intention to challenge this opinion, but to illustrate its daily application in the vast variety of individual gliomas in individual patients. If surgery were curative, the indication would be rather straightforward: we should only have to weigh the risks against the certainty of the cure. Surgery being palliative, its indication ought to be more carefully assessed: what does palliation mean in this patient? At what cost, to what extent and for how long will the disease be controlled? It is the aim of this paper to analyze possible answer to these questions leading to the decision for or against surgery in an individual patient presenting with a likely diagnosis of glioma.

Virchow (1863) in an attempt to classify the tumors of the central nervous system according to cell type coined the term glioma for those tumors derived from glial cells. This term, definitively established with the book of Bailey and Cushing (1926) is still in use. It encompasses tumors originating from astrocytes i.e. astrocytomas and glioblastomas, from oligodendrocytes i.e. oligodendroglioma, and from ependymocytes, i.e., ependymomas. Choroid plexus papilloma and colloid cysts, sometimes considered as ependymal derivatives (Russel and Rubinstein 1977) will not be considered here since their surgical treatment is so specific. Gliomas are an extremely heterogeneous group of tumors. In order to focus our discussion we will consider only the most common, i.e., hemispheric gliomas in the adult.

This paper is centered on the indications for surgery. A considerable part of the available data and current discussions in the literature of gliomas will not be reviewed. Molecular biology (see Schmideck 1987, Martuzza *et al.* 1988 for reviews), immunological biology (see Fischer *et al.* 1988, Sawamura and De Tribolet, this volume for reviews), radiotherapy (RT) (see Sheline 1977, Leibel and Sheline 1987, Morantz 1987, for reviews), and chemotherapy (ChT) (see Edwards *et al.* 1980, Shapiro and Byrne 1983, Kornblith and Walker 1988, for reviews, and Comittee of the American Neurological Association, 1989), though they are the basis of present and presumably future therapeutic approaches, will not be discussed since they have little or no bearing on the feasibility and outcome of surgery.

II. Gliomas in Brain: Local Conditions for Surgery

Surgeons are concerned with a mechanical approach to lesions which can be localized anatomically. A tumor is "operable" if it can be removed totally without harm to surrounding structures. Brain gliomas do not metastasize, hence only local control is required. The feasibility and therapeutic value of surgery depends only on the surgical anatomy of the lesion and how it fits within the surgical anatomy of the brain.

1. Surgical Anatomy of Gliomas

The first requirement for a tumor to be extirpated by surgery is that it should offer a clearcut, identifiable delineation from normal tissue, the classical "cleavage plane".

The surgeon's appreciation of the topographic anatomy of a glioma is at first sight often rather optimistic (Ciric 1987, Guyot 1987). Most hemispheric gliomas appear as circumscribed lesions enlarging and swelling one, two or three gyri, limited by the arachnoid of adjacent structures and/or with a distinct cleavage plane from the edematous white matter. This

plane is rarely as evident as the one which limits a metastatic tumor but it allows a real dissection of the bulk of tumor. The color and consistency of the surrounding brain is sufficiently different to mark a recognizable limit. Most of the time these boundaries are lost at some point at the periphery of the tumor, especially at its deepest pole where the tumor seems to blend with the adjacent white matter. This zone often appears to be the original root of the lesion, in contact with or not far from the periventricular region, in keeping with a number of observations suggesting that most gliomas arise from the subependymal plate, an area in which more than elsewhere, dividing cells could be susceptible to carcinogenic influences (Lewis 1968, Hopewell *et al.* 1975, Vick *et al.* 1977).

Unfortunately pathological findings are quite different. A limited number of anatomical studies has addressed the problem of the topographic organization of gliomas. The relatively ancient studies of Scherer are still highly informative. Scherer reviewed the autopsies of 120 cases of cerebral glioma in which coronal sections were examined, including the whole tumor and surrounding tissue, from one pole of the brain to the other (Scherer 1940: 1 and 2). The main conclusions are as follows:

The only type of glioma which often shows a pure expansive type, without infiltration of the adjacent brain are the ependymomas. All other varieties of glioma have an infiltrative rather than an expansive mode of growth.

In about 30% of these cases a narrow regular zone of infiltration surrounds the tumoral tissue. This is observed in piloid astrocytomas, most of the oligodendrogliomas and some glioblastomas (medulloblastomas and cerebellar astrocytomas in the posterior fossa have a similar feature).

In 60% a large zone of infiltration exceeds the homogeneous tumoral tissue involving more than one lobe and, in $^1/_3$ of the cases, the other side of the brain.

Among these, 35% appear macroscopically as clearly defined tumors but microscopic examination reveals a far-reaching extension of tumoral cells along fiber bundles suggesting secondary infiltration. Based on cell kinetic studies, it is thought that cells that migrate into normal tissue may well be the most viable and have the highest capacity for proliferation (Levin 1976). More than half the glioblastomas and some rare oligodendrogliomas are of this type.

Another 25%, including all astrocytomas and some glioblastomas, seem to be primarily diffuse lesions producing little destruction of nervous tissue but an enlargement of brain structures often difficult to distinguish from simple edema and recognizable as tumor only because degenerative changes such as microcystic transformation are commonly encountered.

Finally, about 10% of all gliomas are primarily multicentric, this being often recognized only through extensive microscopic study (concerning

multicentricity, slightly lower figures have been published more recently (Schieffer *et al.* 1978, Hochberg *et al.* 1980).

These findings have been repeatedly confirmed by subsequent studies (Maxwell 1946, Matsukado *et al.* 1961). Burger *et al.* (1988) in a series of 15 untreated glioblastomas which come to autopsy, recently stressed the same basic features: some glioblastomas are relatively well circumscribed, but most of them involve large areas of the brain, have an irregular asymmetrical shape and send out tongues and spikes of active cells along fiber pathways such as the corpus callosum or optic radiations. Gliomas are rarely confined within one lobe of the brain; very often they cross the midline. Moreover, considering the possibility of intraarterial chemotherapy Burger noted that only 3 of the 15 cases were localized unilaterally in the distribution of only one major artery.

One can argue that these studies on autopsy material are not relevant to lesions at the time of surgery, but in fact, in vivo studies using stereotaxic techniques have lead to very similar results (Daumas-Duport and Szikla 1981, Kelly *et al.* 1986, Kelly *et al.* 1987, Daumas-Duport and Scheithauer 1987) hence the macroscopic limits of the lesion that appear to the neurosurgeon are in most cases well within the histological limits found by the pathologist.

2. Surgical Anatomy of the Brain

The second general requirement for operability is that the lesion can be approached and removed without unacceptable damage to functionally important structures. Early bold neurosurgeons experienced, and sometimes accepted, functional disasters. Warned by that experience, our neurosurgical training was tempered by strict limitations and taboos. The brain is divided into silent areas in which a surgical approach and resection are acceptable, and eloquent areas or deep regions, in which surgery is forbidden or considered extremely hazardous (Mullan 1975). Certainly these interdictions are still relevant but should be revised and more finely tuned. The resection of tumor tissue in itself will not produce a deficit. Functional hazards come from damage to neighboring structures and such damage is dramatically reduced by the conditions of modern surgery and anesthesia. We operate on a slack brain, under magnification or a microscope and with corticosteroid treatment. An ultrasonic aspirator is routinely used and we need little or no retraction. We carefully avoid the sacrifice of any veins or arteries. There remains, however, the problem of the brain tissue itself. Concerning the cortex, our geography of eloquent brain regions is largely based on the unique experience of stimulation during surgery for epileptic disorders gathered by Penfield and his group (Penfield and Jasper 1954, Penfield and Roberts 1959) and more recently enriched by Ojemann (Ojemann 1979, Ojemann and Dodrill 1985). It is generally assumed that the

resection of a cortical area from which stimulation elicits a given response will be followed by a corresponding deficit. In fact, except for some anecdotal observations (Ojemann 1979), we lack precise studies supporting this assumption. Mere extrapolation from the field of epilepsy into tumor surgery is debatable. Changes in the functional organization of cortical fields in contact with or infiltrated by a slowly growing tumor are totally unknown.

In recent years many efforts have been devoted to improve the safety of tumor resection in functional areas by mapping the brain during surgery (vide infra). Even in the absence of such sophisticated procedures, it is common experience that extensive tumor resection, with postoperative CT scan control (Ciric *et al.* 1987) is possible in eloquent brain areas with no postoperative deterioration but rather with an improvement of neurological status. In fact, essentially the same results are achieved within and outside the so-called "functional" area. It is certainly wise to keep in mind the particular risks linked to some areas of the cortex. However, this risk is perhaps much more threatening underneath the cortex within the white matter bundles, internal capsule, optic radiation, etc., which are often displaced by the mass effect of the tumor and displaced again during the surgical removal of the tumor bulk.

Under the conditions of modern neurosurgery, the functional risk in the majority of cases is more limited and more controllable than usually thought. However, this risk persists, particularly deep in the brain. Given their tendency to infiltrate surrounding structures and the imperative necessity to preserve these structures, gliomas may be resectable but in the vast majority of cases are not amenable to complete extirpation.

3. Rationale for "Incomplete" Surgery

These conclusions were more or less anticipated from the very beginning of neurosurgery. After the first (Bennett and Godlee 1884) and subsequent surgical attempts to remove gliomas, even in Cushing's time (Cushing 1909), it was clear that the aim could not be to cure these tumors. The goal was, in fact, to relieve symptoms, particularly those related to the mass effect of the lesions. That was the time of "decompressive surgery" (for historical perspective see Garfield 1980). We will see below that this somewhat mechanistic goal is still appropriate even though the use of steroids has dramatically changed the life-threatening effects of intracranial masses and consequently the heroic atmosphere and real danger of tumor surgery in the recent past.

It is our feeling that the immediate relief of symptoms, a goal that in most patients can be achieved, remains a valuable justification for surgery and perhaps its only undeniable effect. However, neurosurgeons have be-

come more and more aware of the increasing basic knowledge in the biology of these tumors, glioma surgery has been accorded more-sophisticated ambitions and more-biological goals; decompressive surgery became "cytoreductive surgery". The aim of cytoreduction is not to cure the patient but to achieve an essential first step in a multimodality treatment by removing as many neoplastic cells as possible. The often-quoted paradigm in cancer surgery adjusted to brain tumors (Levin 1976, Shapiro 1982) is as follows: given an initial tumor burden of 5×10^{10} cells (50 g), a subtotal or "total" surgical resection might remove 90% of the tumor and leave between 5×10^9 and 1×10^9 cells. Radiotherapy (RT) might kill two logs and chemotherapy (ChT) again two logs of cells leaving 1×10^5 cells to be killed by the body's immune mechanisms. We know that the last steps of this program are not achieved because the biological conditions in brain tissue and the biological profile of gliomas are such that, on the one hand, chemotherapy has only a limited action allowing the remaining tumor to grow faster than the drug can act and, on the other hand, the natural immune system and the immunoreagents produced so far, are even less effective.

Thus the biological goal of cytoreduction is essentially to optimize the tissue conditions to increase the effectiveness of radiotherapy by:

1) removing necrotic tumor tissue which is likely to cause major edema due to the continuous liberation of toxic molecules into the surrounding brain (necrosis cannot be evacuated, the brain being devoid of lymphatics). If RT or ChT should kill cells without removing debris, a serious worsening of symptoms could occur (Takakura and Sano 1972, Kumar *et al.* 1974);

2) removing the bulk of tumor tissue with population of cells resistant to RT and ChT because they are hypoxic and not actively dividing;

3) altering tumor kinetics. It is likely that, following resection, cells kept quiescent and metabolically depressed by overcrowding are recruited into the active pool and enter a phase of growth making them more susceptible to RT and/or ChT. Kinetic studies by Hoshino (Hoshino *et al.* 1972, 1975, Hoshino 1984) led to the conclusion that, in malignant gliomas, these movements are very active even after a partial removal and the benefit is very temporary. Well-differentiated gliomas on the contrary are believed to have only limited exchanges between quiescent and proliferating pools of cells and resection should give place to slow growth. The larger the resection, the longer the time taken by the tumor to regain its original volume.

III. Gliomas in Patients: Prognosis of the Disease

Since it is known in advance that surgery is not curative, its value in a given patient, how much it can prolong life and/or alleviate suffering, should be evaluated with a clear awareness of the probable natural history of the

disease in this same patient, for what length of survival and with what quality of life is it compatible. We believe that a reliable evaluation of the prognosis is the fundamental basis for therapeutic intervention.

Concerning the prognosis of gliomas, three facts stand out from the huge body of clinical literature accumulated in recent years. First, the prognosis, though generally bad, is highly variable. Second, it depends much more on the disease itself than on the treatments we employ to oppose its course. Third, to a certain exent the prognosis is predictable: a number of biological, clinical and radiological variables have been recognized which are significantly correlated with various prognostic end points. This section will review the many variables considered as "predictive factors" that have to be examined in the patient and taken into account when setting his treatment strategy (Weir 1973, Hildebrand and Brihaye 1975, Maire *et al.* 1981, Byar *et al.* 1983, Cohadon *et al.* 1985).

1. Histological Factors of Prognosis

As in other fields of oncology, the most time-honored clue to prognosis is the histological appearance of the tumor itself. A number of conventional histological and/or cytological features have long been associated with malignancy. The association and accumulation of such features in one given case may lead to a diagnosis of greater or less malignancy, a "grading" which should yield a straightforward insight into the future of the patient (Burger 1985).

For clinicians, histological grading of tumors is a long-used and conv enient means of classifying patients into prognostic groups in order to assess the natural history of the disease and the value of therapies. But in fact, it is more than that, for there is a strong belief among surgeons that pathologists have access to the very nature of the lesion, that they are able to unveil unequivocal "Truth" about it, a "Truth" that functions as a sentence of life or death, the grade simply meaning more or less life expectancy. Pathologists are more modest. Nevertheless they have made great efforts to produce an ideal braintumor classification and grading system that both reflects their own theoretical interests and is usable for practical purposes by clinicians (Bailey and Cushing 1926, Kernohan *et al.* 1949, Zülch 1956, Jellinger 1978). Tooth (1912) with the National Hospital specimens, was the first to demonstrate a correlation between prognosis and histological features. Bailey, together with Cushing (1926), proposed the degree of cellular differentiation as an index of prognosis. The classification of Kernohan (1949) proposed 4 grades of malignancy for astrocytomas, oligodendriogliomas, ependymomas, glioblastomas being assimilated to grade IV astrocytomas. Kernohan grading is based upon seemingly objective criteria—number of mitoses, percent of undifferentiated cells,

spreading of necrosis, vascular proliferation, degree of cellular pleomorphism—but it was soon apparent (Kernohan and Sayre 1952) that differences between grade III and IV were unclear and that the survival rates for grades II and III were almost the same. Moreover, recent attempts have failed to confirm the prognostic value of Kernohan grade III and IV distinctions (Nelson *et al.* 1983). Zülch thoroughly discussed the limitations of grading tumors but still proposed a four-grade system which, at least for intermediate grade III and grade IV, does not fit within the Kernohan system (Zülch 1956). In the WHO classification of brain tumors that he supervised, Zülch (1979) again used this four-grade system. It in turn has been criticized (Gulotta 1981) and has not in fact gained general acceptance. Confronted with these difficulties in organizing a clearcut grading system, there is a tendency among therapists either to rely on a simplified grading or to search for single discrete histological features, the presence or absence of which would define distinct prognostic groups. A three-tiered diagnostic system was initially proposed by Ringhertz (1950). It has been widely used (Rubinstein 1972, Russel and Rubinstein 1977) and its practical value confirmed by large scale therapeutic trials undertaken since 1965 by the brain-tumor study group (BTSG) of the National Cancer Institute USA (Byar *et al.* 1983, Walker *et al.* 1976, 1978, 1979, 1980). This system describe three groups of tumors: astrocytomas (A), often called low-grade astrocytomas (LGA), anaplastic astrocytomas (AA) and glioblastomas (GB) separated by simple criteria. Essentially the difference between A and AA is based on the presence in the latter of one or more histological features of anaplasia (Fulling and Garcia 1985, Nelson *et al.* 1985), mitotic activity, nuclear pleomorphism, cellular density, vascular endothelial proliferation, secondary structures. The difference between AA and GB is based on the presence in the latter of areas of necrosis among the neoplastic cells (Nelson *et al.* 1983, Burger *et al.* 1985).

Further attempts at refining this three-grade classification on the basis of supplementary specific histological features have been attempted. In the group of AA, the degree of vascular endothelial proliferation and elevated mitotic rates (more than 1 mitosis per 10 microscopic fields ($\times$ 400)) were clearly related to prognosis (Fulling and Garcia 1985). The degree of cellularity and cytologic pleomorphism were not of similar value. In the GB group, the presence of giant cells has been found to be associated with a longer survival (Burger and Wollmer 1980). In another study the presence of lymphocytic infiltration was correlated with a longer evolution (Brooks *et al.* 1978, Palma *et al.* 1978). This was confirmed in our own patients, but contradictory findings have also been reported (Schiffer *et al.* 1979, Burger and Wollmer 1980, Gulotta 1981). More generally, cytologic or histologic features considered to represent higher degrees of differentiation, microcystic changes and recognizable fibrillary astrocytes, were associated

with better prognosis whereas the reverse was true if a homogeneous population of small anaplastic cells was found (Burger and Green 1987). The biological aggressiveness of these anaplastic cells has been well documented in an autopsy study (Giangaspero and Burger 1983).

In the same line several groups have tried to characterize more subtle indicators of tumor biology likely to forecast clinical aggressiveness. A cell-kinetics approach is possible by measuring the labeling index in neoplastic tissue samples obtained in vivo by biopsy after injection of tritiated thymidine (Hoshino 1984). A reliable correlation between the labeling index and prognosis was found (Hoshino *et al.* 1975, Broggi *et al.* 1988) but criticized and not confirmed in another study (Bookwalter *et al.* 1986). Assessing the metabolic rate of the tumor with PET scan measurements of glucose utilization has demonstrated an inverse correlation between median survival time (MST) and the level of glucose metabolism (Patronas *et al.* 1985). The identification of proliferating cells with monoclonal antibodies has also yielded encouraging results (Zuber *et al.* 1988). These studies, despite their considerable interest, have not yet led to current clinical applications.

2. Nonhistological Factors of Prognosis

The statistical analysis of large series of patients has identified a number of heterogeneous variables highly correlated with prognosis. These "prognostic factors" (Hildebrand and Brihaye 1975, Byar *et al.* 1983) may concern the host, the tumor, the host-tumor relationship and therapeutic modalities. Their knowledge give a phenomenological, not an explanatory description of prognosis. We know very little about the mechanisms through which each factors bears a predictive value and, of course, the predictive value of a given factor should not be confused with its possible causative role. Certain prognostic factors are probably also risk factors acting as determinants of the course, whereas, others are simple markers with no direct role in the progress of the disease. The analysis of prognostic factors is of paramount interest. On the one hand, they allow to adjust treatment to the predicted future of an individual patient. On the other hand, the influence of some of these factors is so great when compared with the influence of therapies that they have to be taken into account when forming homogeneous groups for assessing treatment differences in large series of patients.

a) Clinical Findings

It is generally accepted that whatever the group of tumors under consideration, the age of the patient is always a potent variable inversely correlated with the length of survival or other prognostic end points. This is not to be confused with the fact that the incidence of various types of

glioma is dependent upon the age of the subject (Scanlon and Taylor 1979). For example in the Tohoku brain-tumor registry in the elderly the incidence of A, AA and GB was 5%, 29.4% and 35.5% respectively whereas in the 0–9-year-old group, the incidence of the same tumors was 23.3%, 5.9% and 2.9% (Katakura and Yoshimoto 1988).

In AA and GB, the influence of age on prognosis has been stressed by many authors (Jelsma and Bully 1969, Scanlon and Taylor 1979, Walker *et al.* 1980; European Organization for Research and Treatment of Cancer, 1981; Maire *et al.* 1981, Salcman *et al.* 1982, Cohadon *et al.* 1985, Burger and Green 1987, Coffey *et al.* 1988). In studies from the BTSG (Walker *et al.* 1980, Byar *et al.* 1983) the ratio of the death rate (number of deaths divided by the total number of patient-months of follow up) for patients of 45–54, 55–64 and over 65 compared to that of patients under 45 was 1.75, 2.5 and 3.5, respectively. Even adjusted to each histological type, age remains in all series the strongest indicator of survival. In GB, advanced age was found to be correlated with a number of histological variables associated with a poor prognosis (for example, a lesser degree of cellular differentiation) but statistical analysis demonstrated that none of these variables could account for the effect of age on prognosis (Burger and Green 1987). Similar findings have been reported in clinical studies considering such variables as performance status or duration of symptoms (Byar *et al.* 1983, Cohadon *et al.* 1985). In 461 cases of LGA at the Mayo Clinic (Laws *et al.* 1984) the age of the patients at the time of surgery was by far the most important variable in predicting length of survival. In another study (Piepmeyer 1987) of 60 cases, MST is reported to be 8.47 years before, and 4.85 years after the age of 40.

Another clinical trait which has been repeatedly found to be of high prognostic significance is the functional status of the patient at the time of diagnosis currently assessed through the Karnofsky score (KS) (Karnofsky *et al.* 1949), (Walker *et al.* 1980, Gilbert *et al.* 1981, Maire *et al.* 1981, Byar *et al.* 1983, Cohadon *et al.* 1985). In the BTSG study there was an inverse correlation between death rate and KS at diagnosis. The ratio of death rate for highest and lowest score being roughly 3 which is comparable to the 3.5 ratio found between older and younger age categories (Byar *et al.* 1983). Similar findings have been reported by different authors (Gilbert *et al.* 1981, Maire *et al.* 1981, Cohadon *et al.* 1985).

The length of the preoperative symptomatic period of the disease has also consistently been found related to prognosis (Burger and Wollmer 1980, Scott and Gilbert 1980, Walker *et al.* 1980). In BTSG studies, patients with a duration of symptoms greater than 6 months have a mean death rate half that of those with duration of symptoms less than 6 months. In another study (Takeuchi and Hoshino 1977) an approximately linear relationship between the length of preoperative and survival periods was

found. A history of epilepsy is also related to a better prognosis (Scott and Gilbert 1980, Walker *et al.* 1980).

b) Neuroradiological Findings

CT scan discloses a number of tumor traits which, taken together, provide a considerable amount of prognostic information. First are those features which are in fact an indirect approach to pathology (Butler *et al.* 1978, Lilja *et al.* 1981, Rich *et al.* 1985). Even if CT images cannot provide a histological diagnosis, supposing that the lesion under consideration is a glioma, its CT appearance, particularly the presence or absence of contrast enhancement, bears a very strong relationship with malignancy. It has even been claimed that CT is likely to yield a more reliable prognosis than histology since it is less subject to sampling errors (Marks and Gaddo 1977). CT allows an estimation of the tumor volume which has been found negatively correlated with MST (Cohadon *et al.* 1985). Similar findings have been published concerning only the volume of the contrast-enhanced part of the tumor in malignant gliomas (Levin *et al.* 1980). However, the relationship between lesion size and course was not confirmed in another study (Reeves and Marks 1979). Other CT scan findings such as the presence of cysts or calcification (Takeuchi and Hoschino 1977) or the extent of the low density area surrounding the enhanced part (Levin *et al.* 1980) have been found correlated to a prolonged survival time. Postoperative CT scan has also been considered of prognostic value. The disappearance of contrast-enhanced areas being a favorable sign which could, indirectly, assess the extent of the resection (Murovic *et al.* 1986).

3. Multivariate Analyis

Up to the present, each factor has been studied and the degree of correlation with MST or other prognostic end points separately evaluated with very simple statistical tests. It is also possible to assess the relative influence of groups of factors acting together using multivariate analysis with a method of adjustment, usually Cox's regression model (Cox 1972, Peto and Peto 1972). When many different prognostic factors are analyzed in large series of patients using this multivariate analysis, a stepwise classification of these factors can be obtained and can recognize which among them provide more information concerning the prognosis. In the study of the BTSG (Walker *et al.* 1980) four individual variables were found with $p < 0{,}00001$, age at randomization, duration of symptoms, performance status (KS) and histopathological category (GB versus other malignant gliomas). In a series of 192 gliomas studied in our clinic (Cohadon *et al.* 1985) age and performance status were found again with $p < 0{,}00001$. Although other variables, and particularly histological grade, when ana-

lyzed individually were strongly associated with prognosis, they bring no added predictive value to the association of age and performance status. These results can be explained by the interactions between factors; there is for example, a highly significant correlation between histological group, age and performance status. Age as a predictive factor is highly redundant with other predictive factors and in a sense bears the cumulative prognostic value of all of them.

The high predictive value of such simple clinical features as age and KS is of considerable clinical relevance. It allows the constitution of risks group with comparable life expectancy and may yield in one given patient at the bed side an approach to individual prognosis (Pro-Cox test (Cohadon *et al.* 1985)) with some ground of probability.

IV. Results and Modalities of Surgery

Obviously when proposing an operation, we must know what results in terms of both survival time and quality of life during this time can reasonably be expected following surgery. Then, aware of the fact that complete resection is generally impossible, we have to decide how far we intend to go. How can we plan and how can we assess an optimal resection, is it feasible and realistic to try to extend it. Finally, given the limitations, cost and expected benefits of this surgery, the question arises as to whether or not we have any alternative solutions of equivalent value to propose.

1. Results of Surgery in Terms of Duration of Life

Looking at the results of surgery in terms of survival time, the first point under consideration is the operative mortality. This has dramatically changed over the years from 40% in the earliest reports to approximately 25% in the 1965–70 periods to less than 5% at the present time. It was reported as less than 2% in Salcman's and Kaplan's study in 1986 (Salcman and Kaplan 1986), and 0% in recent small series (Ciric *et al.* 1987). The mortality rate in any surgery is first a reflection of the selection of patients operated upon and also a reflection of general surgical risks, (i.e., thromboembolic, infectious complications etc.) which still exist, at least in our clinic. We can assume that at present with reasonable patient selection, glioma resection is in general low-risk surgery with, in large series, a mortality rate lower than 3%.

There are few studies available assessing the benefit of surgery alone without complementary RT. Salcman, summing the results of six such studies grouping 349 cases, gives a MST of 4 months (Salcman 1980). In fact, with the exception of very rare cases of LGA curable by surgery alone, all such patients receive RT so that the available survival data concerns a

combined surgery-plus-RT treatment (Rutten *et al.* 1981, Garcia *et al.* 1985) and, in recent years, most of the time a multimodality treatment with the addition of various drugs. (Walker *et al.* 1976, Walker *et al.* 1978, European Organization for Research and Treatment of Cancer 1981, Kristiansen *et al.* 1981, Levin *et al.* 1985, etc.).

Figure 1 a–c (reproduced from Rougier (1989) presents a compilation of data from some relatively recent reports with calculated standard deviations. For GB the MST after standard treatment is 9–11 months, with a survival rate of 2% at 3 years and 0% at 5 years. In fact, whatever the therapeutic strategy, survival curves closely approach 0 after 24 months. For AA, the MST is around 42 months with 35 to 45% of patients still alive at 5 years. Similar results are reported by Takakura with postsurgical treatment utilizing either RT or RT plus ACNU ChT, the MST was 13 and 34 months for GB and grade III A (AA), respectively (Takakura *et al.* 1986).

Data are much more heterogeneous for LGA and recent reports lack long-term results. Laws gives an MST of 4.5 years and notes that "during the first 5 years after surgery there exists a constant risk of death. After 10 to 15 years the survivors seem to have a life expectancy comparable to that of the general population" (Laws *et al.* 1984). Similar findings are reported in the Japanese serie with a favorable prognosis for those cases surviving for 5 years (Kitahara 1988). Piepmeyer on 60 cases observed during 1975–1985 gives an MST between 5 and 10 years according to variables such as age, presence of a cyst, enhancement on CT scan etc. (Piepmeyer 1987).

2. Functional Results

Both the functional hazards and functional outcome of surgery clearly depend on the selection of patients operated upon according to the location

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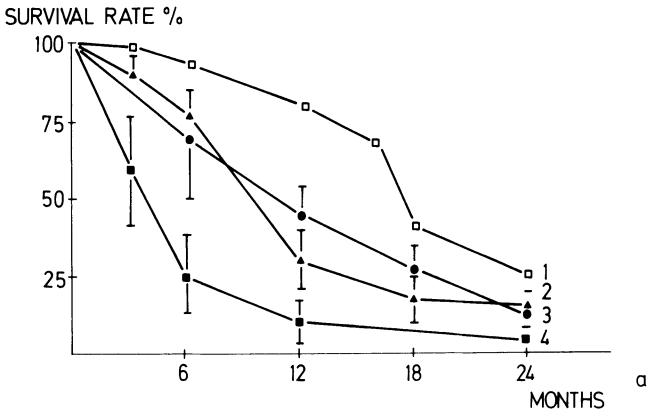
Fig. 1. Compilation of data from the literature with calculated standard deviation concerning various therapeutic modalities from Rougier 1989: Gliomes de la lignée astrocytaire. In: Tumeurs du système nerveux et de ses enveloppes, F. Cohadon (ed). 1 vol. Flammarion Médecine-Sciences, pp 291–301. a) Concerning glioblastomas: *1* Open square (Neuwelt *et al.* 1986) Surgery + RT + ChT after BBB opening. *2* Black triangle (Salcman *et al.* 1982): Surgery + RT + ChT. *3* Black circle (Salcman *et al.* 1982): Surgery + RT. *4* Black square (Taveras *et al.* 1962, Rougier *et al.* 1981). b) Concerning anaplastic astrocytomas: *1* Black square (Garcia and Fulling, 1979, Fulling and Garcia, 1985): Surgery + RT. *2* Open circle (Chang *et al.* 1983, Burger *et al.* 1985): Surgery + RT + ChT. c) Concerning low grade astrocytomas: *1* Open square (Laws *et al.* 1984): Surgery with or without RT. *2* Black triangle: (Fazekas 1977, Sheline 1977, Rutten *et al.* 1981, Laws 1984): Surgery + RT. *3* Black circle: (Fazekas 1977): total resection. *4* Black square (Sheline 1977): Partial resection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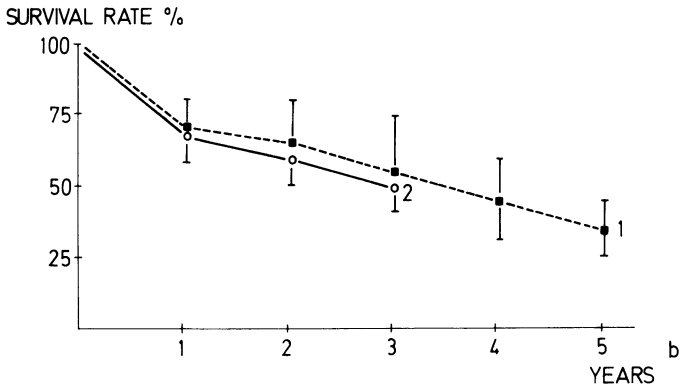
SURVIVAL RATE %
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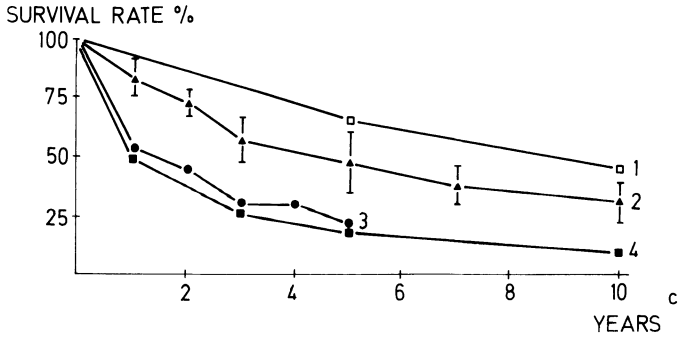
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of their tumor. Generally, we completely share the opinion that surgery relieves preexisting neurological symptoms and rarely creates new ones (Frankel and German 1958, Taveras *et al.* 1962, Ransohoff and Lieberman 1978, Shapiro 1982, Ransohoff 1983, Ammirati *et al.* 1987).

The traditional goal of internal decompression is still in order since neurosurgeons are still referred quite a number of malignant-glioma patients suffering from mass effect, elevated ICP and brain shift. The alleviation of focal loss of function and disturbances of higher integrative activities often depends on the relief of mass effect. Even in eloquent brain areas good functional results can be achieved such as those reported by Ciric (Ciric *et al.* 1987) in which an improved or stable postoperative neurological status was observed in 97% of the patients having undergone total resection. These good immediate surgical results mostly benefit patients with malignant gliomas (Hochberg and Pruitt 1980, Shapiro 1982); patient capable of self care (KS 80) will maintain their level of function for most of their remaining lifespan. Hochberg analyzed a series in terms of quality of survival of 74 patients treated by surgery plus RT and ChT (Hochberg *et al.* 1979). This series is a good example of what is generally achieved with or without ChT and irrespective of the drug used. Most patients underwent a clear improvement of function following surgery plus RT and maintained the same level of function for an average of 8 months. During this period 62% of patients had a better level of function than before the operation, 40% had some occupational activity and 75% were capable of self care. Afterwards a decline ensued. In this group the immediate postoperative level of performance is the best indicator of both the level of performance that would be maintained afterwards and of the duration of this remission period. Patients with a 90% postoperative functional level maintain an average of 85% for 18 months, whereas with 70% postoperative functional level, they will remain at an average level of 55% for only 9 months. Very similar results have been recently published (Trojanoski *et al.* 1989). In our clinic the postoperative course of GB was investigated in a series of 50 consecutive cases. Living conditions were evaluated using the KS. In parallel a scoring system was developed to evaluate neuropsycho-emotional problems. The quality of mood, sleep, sexuality, intrafamilial relationship, level of activity and compliance to treatment were separately given a value on appropriate scales and cummulated. Scores on both scales (KS and this one) were highly correlated and remained so throughout the course. A score over 80 in the immediate postoperative period remains at this same level until 2.5 ± 1 months before death. At that time, neuropsychological and neurological functions deteriorate rapidly. Interrogation of both patients and family showed that brain glioma is not considered to be an especially painful or debilitating disease. Surprisingly, at variance with what we know in the field of head injuries,

gliomas are rarely felt by the patient and family as a menace to the "self" or to the mind.

3. Extent of Surgery

It is a general principle in cancer surgery that complete resection is preferable to partial removal or simple biopsy. Dandy (1921) already felt that radical excision would improve results. This seems to be confirmed by a number of reports in the literature (Stage and Stein 1974, Hildebrand and Brihaye 1975, Byar *et al.* 1983, Ciric *et al.* 1987) claiming that on the whole patients live longer and better after subtotal resection than after partial surgery. Most of these studies however should be interpreted with caution since the extent of surgery is related to other variables such as the location and invasiveness of the tumor which have a strong bearing on both survival and functional results.

Concerning the GB and AA group, data from one of the BTSG studies (Byar *et al.* 1983) dividing surgical resection into biopsy only, subtotal resection and total resection, total resection plus lobectomy, indicates a doubling of the death rate for patients with biopsy as compared to patients with lobectomy, subtotal or total resection falling in between. In the study by Shingai for GB (Shingai and Kanno 1988), the MST was 3 months for nonoperated cases, 5 for partial extirpation and 14 for total extirpation. In the same study for AA, the MST was 10 months for partial extirpation, 16 months for the unoperated group, 36 months for subtotal and 74 months for total extirpation. The authors concluded that total extirpation prolongs life for 9 to 11 weeks in GB and for 5 years in AA. Unfortunately in this report, the functional status during survival is not considered. One recent study by Ammirati *et al.*, specifically looks into this problem. In a consecutive series of 31 malignant gliomas (21 GB, 10 AA), 19 patients underwent gross total removal and 12 a partial resection, this being assessed by early postoperative enhanced CT scan. The group with gross total resection lived longer (90 versus 43 weeks of MST) and much better with an independent status (KS $\geqslant$ 80) preserved for 185 versus 12.5 weeks (Ammirati *et al.* 1987). Similar results presumably concerning the same group of patients were reported previously by these authors (Ciric *et al.* 1987). The difference between the two groups is impressive with a high degree of statistical significance despite the small number of patients.

Concerning low grade astrocytomas (LGA) relatively few studies (Fazekas 1977, Laws *et al.* 1984, Kitahara 1988) are available. In the study at the Mayo Clinic, Laws (Laws *et al.* 1984) showed that total removal versus subtotal resection or biopsy is associated with a much higher survival rate at 5 years. From the survival curve presented, one can derive an MST of 3 years after subtotal resection (404 cases) against 8.5 years after total resection (57 cases). Data from the Japanese brain-tumors registry as quoted

by Hoshino (1984) in a population of 1454 LGA gives a surprisingly precise correlation between the magnitude of resection and the 5-year survival rate.

4. Brain/Tumor Limits

Since the results of surgery are clearly dependent on the extent of resection one should seek in all cases total or near total removal of the lesion. There is no place in modern neurosurgery for a deliberate partial resection, that is both useless and dangerous. If only a pathological diagnosis is wanted stereotactic biopsy is a safe and reliable procedure. To evaluate the feasibility of subtotal removal we should be able to know in advance the topographical extension of the tumor in the brain space and the situation of important functional structures around it. To achieve a subtotal removal once the flap is turned we need again to identify tumoral limits and to spare functional elements.

a) Images of the Tumor

Modern neuroimaging techniques provide an amazing source of topographical information that can be used in vivo. Correlation between CT density pattern and histological findings were studied in the late seventies but only recently were precise spatial adjustments between both sets of data critically assessed on autopsy material (Burger 1988) and in vivo (Kelly *et al.* 1987). For high grade gliomas the contrast enhanced parts of CT scan images corresponded to highly cellular tumoral tissue and/or massive infiltration of neoplastic cells together with neovascularization, the central hypodense area often surrounded by the enhanced ring corresponded to necrotic tissue. The peripheral hypodense area did not surround the entire lesion. In about half the cases infiltrative cells were found far beyond the limit of hypodensity. The current practice of evaluating the outer border of a glioma 2 to 3 centimeters from the enhanced margins is unreliable. Neoplastic elements following the white matter bundles are simply not visible on CT. For low grade lesions hypodense images at CT are even more difficult to interpret: they correspond either to densely cellular neoplasm or to infiltrative cells and/or peritumoral edema. In most cases, neoplastic cells were found far beyond the hypodense area. However a well circumscribed hypodense area with a sharp gradient of density at the periphery corresponds to dense neoplasm as seen in pilocytic astrocytoma, oligodendroglioma and some LGA, but not to diffuse infiltration of more or less functional tissue. Unfortunately NMR imaging is not better (Kelly *et al.* 1987). Tumoral tissue as well as peripheral infiltration and edema indistinctly lengthen T_1 and even more T_2. Neoplastic cells are found in T_1 and T_2 normal areas as well. Finally one can reliably consider that the contrast enhanced image on CT and/or the annular enhanced pattern

around a hypodense central area represents the massive part of high grade gliomas. It is more hazardous to claim that the central part of a purely hypodense image on CT represents the central bulk of a low grade tumor, and nothing can be inferred from a low grade density image with poor density gradients, an outer margin indistinctly fading into the surrounding brain tissue. Even with such limitations the abnormal patterns disclosed at CT and/or NMR are in practice, the only guide for our resections. The goal is to remove the image and the disappearance of the image on post-operative control CT scan will be taken as a proof that the goal has been achieved (Murovic *et al.* 1986, Ciric *et al.* 1987).

b) Maps of the Brain

To fully utilize these topographical informations, it is necessary that the surgeon should be able to match the spatial arrangement of the tumor displayed by imaging techniques with the functional brain and ultimately with the actual brain he exposes at surgery. For tumors located in silent brain areas we need only to project the pathological image on the surface of the scalp in order to correctly trace the skin incision. With a little attention this is usually achieved without problem. In case of tumors located in eloquent areas or in the depth of the brain, the indications for surgery, and at surgery the progress of the resection, may require much more precise representation of the topographical situation.

For this purpose, a number of groups in this country routinely use stereotactic maps of the brain in which all the relevant information is introduced. When the operative indication has to be discussed because possible functional problems are anticipated, a stereotactic investigation is carried out before undertaking open surgery. Stereotactic methodology, particularly the biorthogonal approach developed by Talairach, allow the superimposition of unmagnified, undistorted neuroradiologic data and yield AP and lateral views of the brain in actual size. On these documents we can represent the statistical projections, derived from an appropriate atlas of key structures like the pyramidal tract or optic radiation in their normal anatomical situation (Talairach and Szikla 1967), even though we know that they are likely to be more or less displaced. This methodology was originally developed to plan depth electrode investigations and corticectomies for epileptic disorders, but it was also used for tumor surgery before the coming of the CT scan (Pecker *et al.* 1979). At that time, the tumor limits were inferred approximately and drawn from angiographic or ventriculographic changes. Obviously the transposition of CT scan data to these stereotactic representations of the brain was of considerable interest (Bergström and Greitz 1976, Cohadon *et al.* 1977, 1978). To achieve this goal we proposed an appropriate technique which needs only very simple

equipment and is still routinely in use in our clinic (Cohadon *et al.* 1979). NMR data can be transposed in the same way.

Eventually, a full map is produced in which images of various types and origin are superimposed. In our experience the contribution of such maps is decisive when considering indications. They are even more useful if surgery is decided upon, to plan and to carry out a resection which will proceed following a succession of identifiable anatomical landmarks such as gyri interfaces, characteristic loops of vessels, ventricular wall etc. This application of stereotactic methodology in the field of tumor surgery, though sometimes quite demanding, is always rewarding and inspiring. Future developments are conceivable like the introduction of PET scan data allowing a new type of functional mapping based on the detection of focal increase in cerebral blood flow following neuronal activation (Fox *et al.* 1987). Similar approaches, most of the time only to target stereotactic biopsies on deep seated lesions have been developed. More sophisticated methods and more expensive equipment, with recordings of CT scan and NMR in stereotactic conditions, the use of computers to match data of various origins and to calculate trajectories are currently in use in a number of neurosurgical groups (Apuzzo and Sabshin 1983, Heilbrun *et al.* 1984, Apuzzo *et al.* 1987). A modern evolution of stereotaxic technique to laser resection of deep seated tumors has been developed (Kelly *et al.* 1985, Kelly *et al.* 1986) and is described in this volume by Kelly.

c) Tumor Limits—Position of Vital Structures

With or without a map to direct his progress the surgeon still needs to recognize the ground. In many cases, there is no major problem in identifying tumor tissue by its macroscopic appearance and consistency and in superficial lesions, the outer margin of the tumor bulk is relatively easy to follow. However, at some point or another the limits are blurred. Several attempts to improve our discrimination of those limits by the intraoperative use of tumoral markers particularly fluorescein (Murray 1982) and radiophosphorus (Reinhart 1989) have been reported. In their present state of development these techniques do not seem to be of real help.

Attempts to identify functional structures have been more successfull. A number of electrophysiological techniques have been investigated which allow intraoperative functional mapping of the cortex. Following, the pioneer work of Penfield and Boldrey (1937) electrical stimulation in awake patients has been used particularly for the location of language and recent verbal memory (Ojeman 1979, Ojeman and Dodrill 1985, Black and Ronner 1987). Evoked potential monitoring under normal anesthesia is generally preferred for localization of auditory and especially somatosensory cortex (Gregory and Goldring 1984, King and Schell 1987, Wood *et al.* 1988).

Several authors claim that electrophysiological monitoring increases the safety of the operation and allows more aggressive resections (Ojeman 1979, Ojeman and Dodrill 1985, Black and Ronner 1987). The feasibility and accuracy of these techniques, as far as the cortex is concerned, is well established, nevertheless, like any other intraoperative refinement, they are time consuming and critical assessment of their practical value is difficult. In fact, despite some convinced reports, intraoperative monitoring has not gained a wide acceptance in the field of tumors.

Our policy is to resect those areas which are clearly tumorous or densely infiltrated as they can be identified visually under magnification if necessary. This is a safe method which very rarely produces only mild temporary functional deficit. CT scan control demonstrates that the mass effect disappears and that the enhanced part of the tumor has been removed. It is quite possible that a detailed mapping would allow the resection of some more milligrams of tumor. The question is whether these few milligrams change the value of inevitably incomplete surgery and change the effectiveness of RT.

5. Is There any Credible Alternative to Surgery?

Considering the dismal prognosis of the disease whatever the chosen therapeutic approach, a number of authors have questioned the value, and even the legitimacy, of surgery as a first step claiming that surgery being palliative, an equivalent palliation could be achieved with biopsy followed by radiotherapy, the patient being spared a major open procedure. For example, Punt in 1984, in a detailed, though at times incomplete and one-sided review, produced arguments which clearly demonstrated the poor achievements of surgery. However, nothing was said of the achievements of RT without previous surgery.

Very few studies are available in the literature on the effect of radiotherapy alone in malignant gliomas. Taveras *et al.* (1962) reported an MST of 6 months, Fix (1966) obtained 31% of survivors at 1 year. Pecker (Pecker *et al.* 1981) compared an MST of 8.6 months after biopsy plus RT to 7.4 months after partial resection plus RT and 10.4 months with subtotal resection plus RT. In our own patients (Rougier *et al.* 1981), we found an MST of 4 months for GB following RT versus 15 months following surgery plus RT and chemotherapy. For AA the corresponding figures were 12 versus 34 months. Unfortunately, such studies are likely to reflect an evident selection bias, the poor prognostic group receiving RT. More recently Coffey's group (Coffey *et al.* 1988) reported on a series of 91 consecutive patients with GB (64) and AA (27) confirmed by stereotactic biopsy and treated by RT. The overall results were compared and did not differ significantly from those of the large historical series of surgically treated patients compiled by Salcman (1980). Moreover, 15 of the 91 patients were

operated upon (12 after and 3 before RT) without a demonstrable supplementary effect. The authors conclude that biopsy plus RT is a rational treatment strategy at least for patients with deep or midline malignant tumors or lobar tumors in critical areas. Undoubtedly, this study is representative of a trend among oncologists and deserves consideration. However, as in similar reports, the small number of patients and the absence of a real control group limits the usefulness of such conclusions. In our view they cannot challenge the huge body of data recommending surgery in spite of its recognized limitations. As far as we know, no randomized-control study comparing the results of RT alone versus surgery + RT has ever been undertaken.

a) Interstitial Radiotherapy

The effectiveness of radiotherapy in treating brain tumors is beyond doubt. Moreover, there exists a dose-effect relationship: groups of patients receiving 50, 55 or 60 Gy by conventional RT demonstrated stepwise increments of survival time (Walker *et al.* 1979). If it were possible to deliver much higher doses to the tumor with a minimum irradiation of the surrounding brain, one could achieve a tumor destruction comparable to surgical resection. Such is the goal of interstitial radiotherapy and, more recently, of stereotactic external radiosurgery.

The stereotactic implantation of an isotope (Talairach *et al.* 1954, Szikla 1979, Bernstein and Gutin 1981) directly into the core of the tumor, according to the inverse square law and tissue attenuation, provides the optimal geometrical conditions for treating the lesion while sparing normal tissue. Beside this is a low dose-rate irradiation with well-documented radiobiological advantages over standard procedures with high dose rate and fractionation. The technique has been used by a number of groups as an alternative to surgery to treat deep seated tumors (Cooperative Study of the Stereotactic French Group, 1979, Gutin *et al.* 1984, Mundinger and Weigel 1984, Szikla *et al.* 1984, Roberts *et al.* 1986, Mundinger 1986, 1988). For these implantations, ^{125}I though very expensive, tends to be preferred to ^{192}Ir or ^{198}Au for its higher relative biological effectiveness and easier radiation protection (Jani *et al.* 1987).

In France, a combined interstitial and external irradiation protocol is generally in use (Cooperative Study of the Stereotactic French Group, 1979). In 1984, we reported on a series of 43 small (under 3.5 cm in diameter) gliomas considered inoperable, treated by temporary implantation of ^{192}Ir (full tumor dose no less than 70 Gy) plus a second target volume 2 cm around the tumor with no less than 40 Gy at the periphery. The results for GB (13 cases) with a MST of 7 months were disappointing. Conversely, an MST of 5 years for AA (12 cases) and a 65% survival at 5 years for LGA (18 cases), was comparable to results achieved by surgery plus external

radiotherapy in operable tumors (Rougier *et al.* 1984). These results for LGA were further confirmed in 1987 in a follow-up evaluation of the same series with no statistical difference in MST between operated and implanted LGA (Lagarde 1987).

b) Stereotactic Radiosurgery

Another means of delivering localized high doses of radiation with a precision comparable to that of the surgeon has been in use in Sweden for quite a long time (Leksell 1951, 1971). With the development of neuroimaging and computer techniques, various types of external stereotactic radiotherapy are currently being developed (Backlund 1979, Betti and Derecinsky 1983, Colombo *et al.* 1985, Kjelberg and Abe 1988, Winston and Lutz 1988, Lunsford *et al.* 1989). The very name "gamma knife" given to the 60 sources of 201 Co radiation developed in Sweden clearly indicates that the aim of these techniques is to achieve results comparable to those of surgery. In the field of gliomas, there is very little experience available in the literature. As with any other technique aimed at a spatially localized target, this one will have to face the fact that gliomas are not spatially localized.

V. The Decision to Operate

Like any decision in medicine, this one needs first combined consideration of the body of pertinent scientific data and clinical experience that we have summarized in the precedent sections, and the unique collection of facts, clinical history, neuroradiological and biological findings, psychological and sociological characteristics, gathered in the patient. Thus we should be able to evaluate the operability of the patient, the operability of the lesion and moreover, to recognize the probable outcome of various therapeutic strategies, to judge the utility of each one of them for the patient, and to make, eventually, an optimal decision.

1. Gathering Relevant Data

a) *Operability of the patient:* Preoperative evaluation of the general condition of and operative risks to the patient is mandatory, paying specific attention to cardiovascular, renal and pulmonary function as well as any history of metabolic, coronary or thromboembolic disease. The relevant laboratory investigations are routinely obtained. In our experience, under the conditions of modern neuroanesthesia, it is very rare that surgery is refused for such general problems.

b) *Operability of the tumor:* CT and NMR data bring all the necessary information concerning the location of the tumor, its size, its apparent

limitation, surrounding edema and mass effect. These data are sufficient for an initial appreciation of operability. Tumor invading the other side of the brain, the hypothalamic area or the upper brain stem are refused. As previously stated if the tumor is encroaching on a highly functional area and/or if its resection is likely to present functional risks, a stereotactic study is required in order to base the indications on precise anatomical data.

c) *Prognosis of the disease:* The most potent factors in prognosis are age and functional status, simple clinical information immediately available at the bedside. Thus modern medicine has rediscovered through considerable statistical effort what has been known since the time of Hippocrates, namely that inspection of the patient provides an important insight into the prognosis. At this point one adds the experience of the doctor who always brings nuances and sometimes different appreciations. He catches at a glance a number of variables not studied in statistics, variables that perhaps he could not analyze in detail but that nevertheless have prognostic significance. To take but one example, the depressed feelings, decreased general interest in life so frequently encountered in patients harboring malignant gliomas is, in our experience, an important pejorative sign.

Crucial information is still necessary; we need the histological diagnosis of the lesion. If the decision is *to operate* upon the patient whatever the possible diagnosis, the surgical specimen will allow pathological examination. If the decision is rather *not to operate* we cannot take the risk of overlooking and referring for RT a benign process such as an abscess, a vascular or inflammatory lesion, or even a meningioma. Imaging techniques do allow to a certain extent the diagnosis of glioma including fairly reliable indication of grade but cannot replace microscopic examination. In 1979, Kendall *et al.*, reported 6.5% false-positive and 6.5% false-negative diagnosis of glioma by CT. We found very similar results during the same period. With increasing experience the percentages of false positives and false negatives have been reduced. The true positive rate has been recently estimated at 0.92 for CT. The coming of NMR will perhaps allow a more accurate detection, but it will not provide a better classification of pathology. The estimated true positive rate of NMR for brain tumors in general was estimated at 0.81 in the same study (Haughton *et al.* 1986). Thus an increasing number of groups consider that certainty as to the tumor's pathologic nature is mandatory before a nonsurgical and sometimes a surgical decision. This explains the increasing use of tumor biopsy.

d) *Pathology of the tumor: stereotactic biopsy*. A number of techniques of tumor biopsy have been developed in recent years. It is our opinion that only stereotactic biopsy fulfils the necessary requirements for both safety and accuracy. We reject free-hand biopsies or pseudo-stereotactic techniques. Various methods are in use to utilize directly or indirectly CT scan

and/or NMR images under stereotaxic conditions (Cohadon *et al.* 1977, Gildenberg 1983, Thomas *et al.* 1986, Sedan *et al.* 1987); adjuvant techniques can be used to increase the accuracy of the approach (Brown *et al.* 1984) or to assess the limits of the tumor and the best place for sampling the tissue (Benabid *et al.* 1978, Rougier *et al.* 1982, Tasker 1985).

In published series (Ostertag *et al.* 1980, Lobato *et al.* 1982, Benabid *et al.* 1985, Kelly *et al.* 1987) a precise pathological diagnosis has been attained in 90 to 97% of the cases with a low mortality (0 to 2.3%) and low morbidity rate (0 to 7%).

Since 1978 we have performed in this clinic, over 1,000 biopsies with no mortality, 5 cases of serious neurological problems and transient neurological deficit or reversible aggravation of a previous deficit in 8 to 10% of patients. It is our opinion that biopsy may provide crucial information at an acceptable risk. However, biopsy is not supposed to provide a full accurate pathological diagnosis (Benabid *et al.* 1985, Chandrasoma *et al.* 1989). We simply ask questions with immediate clinical relevance. Our first question is whether or not this lesion is a tumor. We need to be certain that such diagnosis as abcess or ischaemic or inflammatory lesions are ruled out. The correct answer is presumably obtained in all cases. The second question is what is the nature of the tumor. Again we need to rule out meningioma (very rarely) and more often to recognize nonglial tumors such as a primary lymphoma or metastasis which should benefit from different therapeutic approaches. Again a correct answer is generally obtained. The third question is what is the grade of the glial tumor. Quite often the answer can leave some doubts. The small piece that is sampled is not representative of the whole tumor (Thomas *et al.* 1985) and the multiplication of trajectories and samples obviously would increase the risks of the procedure. The grade of the tumor is easily underestimated by a limited biopsy. In our practice what we expect from the biopsy is first, the diagnosis of tumor and second, the diagnosis of glial tumor. For an evaluation of the malignancy of that tumor, the pattern of enhanced CT scans, the age of the patient and the clinical history sometimes rectify an over-optimistic pathological diagnosis.

2. Assigning Probabilities of Outcome

Now, knowing from clinical examination the main determinants of prognosis and from neuroradiological data and/or pathological diagnosis with a high probability the nature and grade of the lesion, we can refer to our experience and/or to the literature which offers objective references. For any given factor or set of clinical and neuroradiological variables defined in the patient, an easily accessible collection of published data can yield a probable prognosis. Some groups maintain their own data bank

and, though fully aware of its limitations and various biases, are inclined to consult it when seeking indications for a new case. The probabilities of various outcomes can thus be assigned to an individual patient. For example, in our data bank a 60-year-old patient with a KS less than 80, treated with surgery plus RT has 1 chance in 2 of surviving longer than 12 months. We can refine this prediction if we know in addition the grading of his tumor. If it is a LGA he has 1 chance in 2 of surviving more than 19 months; only more than 11 months if it is a GB.

When assigning probabilities of outcome to a given patient, we have to keep in mind the exact meaning of probabilities. Figures like median or mean survival time reflect the behavior of large groups of cases. They are extremely useful to organize our scientific knowledge and to judge our therapies but they are applicable to an individual only at a given—measurable—risk of error. When we consider a large number of cases to produce a statistical picture, we neglect individual traits. By the same token when we apply a statistic to individuals we cannot expect to meet their specific traits.

Concerning assignation of probabilities in reference to a data bank, another problem is that sometimes we lack relevant data. In GB and to a lesser degree in AA, the biological behavior of the tumor is fairly predictable as is, therefore the course of the disease. The prevalence being relatively high and the life expectancy limited, it is easy to gather large numbers of observations in a short period of time and many publications with very similar results are at hand in the literature. The situation is quite different in LGA for which there does not exist at the present time a single study with a sufficient follow-up of a group of patients diagnozed, treated and postoperatively examined by modern means. Moreover, the group of abnormal intracerebral growths designated as LGA is extremely heterogeneous, from small limited resectable masses to large infiltrative lesions spread over half of the brain or more. For some of these lesions the prognosis is virtually unknown.

3. Assigning Utilities of Outcome

When proposing a treatment we assess its utility for the patient in question. If several strategies are contemplated, we should be able to attribute a value to the particular outcome which is likely to follow each one of them. The value attributed will be compared with the cost of the corresponding strategy. Cost plus value then defines a series of situations among which the doctor, patient and family can express preferences and make choices (Kassirer 1976). Ideally all information concerning possible strategies and probable outcomes, once clear in the doctor's mind, should be explained in intelligible and supportable terms to the patient and his

family who in turn would express preferences and dictate the ultimate decision. In the field of brain tumors the common experience is in fact, that the doctor has to make the decision and to take into account an overall appreciation of the situation including non-medical, namely psychological, psychosociological and economically relevant, parameters.

4. Strategies and Choices

In this chapter we will present the management of patients harboring gliomas at the present time in our clinic. We will make no effort to prove that this management is the best and we are aware of the fact that it reflects in part our own philosophy, our own technical programmes, and the facilities at our disposal. Suffice it to say that our results fall within the range of published results from series of various origins including some, in which patients were submitted all along their survival time to heavy and expensive multimodality treatments. To give but two examples of our preferences concerning GB: we believe that the burden and risk of major open surgery is not justifiable if it would add only very few months to the patients' enjoyable life; we believe that a few weeks of supplementary life and a slightly higher percentage of survivors at 1 year do not balance the burden of sequential BCNU chemotherapy following postoperative RT. Such statements are matters of opinion and are sometimes modified in our own group when facing particular situations.

a) Defining Strategies

As explained in the preceding section, we consider that once the positive diagnosis of supratentorial glioma is established, a surgical resection as complete as possible is generally the best available initial treatment in order to relieve symptoms and to prepare for other therapies. However, this surgical resection is not always feasible and we have to consider alternative approaches. In practice the strategies we can propose are as follows:

a) Direct open surgery with the prospect of a macroscopically complete resection is proposed when it is technically possible without major risks, that is, for most cases of lobar tumors with an apparent limitation of the image on CT.

b) In some cases this same type of surgical resection would be the best choice but the localization of the tumor renders it hazardous. We propose as a first step stereotactic investigation which will precisely evaluate the functional risks and allow an appropriate planning of the resection. This applies to most superficial tumors within or in the vicinity of eloquent brain areas or tumors at a depth of a few centimeters, accessible after opening a sulcus.

c) For tumors located in the depth of the hemisphere, not directly

accessible through a simple transcortical or transventricular approach, we do not have the facilities for a stereotactically guided resection. We propose a stereotactically guided irradiation, the diagnosis of glioma being previously confirmed by biopsy. Until recently, interstitial radio-isotope implantation was used followed by an external supplementary dose of RT. Only tumors under 3.5 cm in diameter were considered suitable for this programme. Stereotactic multibeam RT now available in our clinic tends to replace interstitial RT for this type of lesion. For larger tumors, the advantages of interstitial RT are questionable and conventional external RT is preferred.

d) For patients not eligible for the preceding 3 programmes, conventional RT is proposed after histological confirmation of the nature of the lesion. This applies to patients presenting with one or, usually, several of the following features: a large, deep and/or bilateral tumor and/or poor prognostic factors and/or great immediate surgical risks.

e) Lastly, in some patients nothing specific will be attempted against the tumor itself only supportive treatment or treatment of certain consequences of the tumor, elevated ICP and/or epileptic fits.

b) What Treatment for what Patient?

Though the age and functional status are the best predictors and have a considerable impact on the decision, the presumed histological diagnosis remains a major determinant of the indications.

Presumed GB and AA: If the presumed diagnosis in GB or AA, the first clue to the decision is age and KS, age over 70 and KS below 70 being the usual break point. With age over 70 and KS below 70, only supportive care with corticoids and sometimes glycerol is proposed. With age and KS under 70 or KS and age over 70, concentrated irradiation is proposed (2 series of 1.8 Gy in 2 sessions of 3 days separated by a rest period of 3–4 weeks (Constans and Schlienger 1975). With good predictive factors, particularly a KS either normal or likely to be normalized following surgery, surgery is the first choice. Operability is discussed after CT and NMR. If no functional problems are in view, direct open surgery is preferred. The pathological diagnosis of glioma being confirmed, in most cases the patient will then be given conventional RT. With such a policy, we accept that at surgery a nongliomatous lesion can sometimes be found. If functional problems are anticipated, a stereotactic study is undertaken in order to evaluate the chances and probable difficulties of a resection. Usually a biopsy sample is taken in the same session and its results may modify the decision toward open surgery. In cases of deep-seated tumors, stereotactic RT or conventional external RT are preferred according to the tumor size.

Presumed LGA: If the presumed diagnosis is LGA, the indications for surgery are in our view, much more difficult to establish since there is not

enough relevant data in the literature, most published series concerning either extremely heterogeneous groups of tumors often gathered over many years, or very selected groups with particular problems. When there are unfavorable main prognostic factors, age and KS, our attitude is the same as that proposed earlier for GB and AA. The real problem occurs with the surgical indication in young or middle-aged patients in good condition in whom the diagnosis is raised following recent symptoms, often late-onset epilepsy. We know that some of these tumors may remain quiescent for years. Before the CT scan and NMR period, we frequently operated upon cases of LGA, or LGA transformed into AA, in patients with a history of several decades of seizures. Nowadays, a single seizure quite commonly leads to CT and NMR diagnosis of a brain lesion very likely to be an LGA. In such patients there is considerable doubt whether the outcome of any surgery will be better than the spontaneous evolution. There is even a distinct possibility that resection could change the kinetics of the cell populations in an unfavorable and uncontrollable direction. Cerebrospinal fluid seeding during surgery is also a potential danger (Batzdorf and Gold 1974, Nishio *et al.* 1982). We recommend immediate open surgery only if we are reasonably certain to achieve a complete resection. This is uncommon, and arises only in well-delimited lesions in noneloquent brain areas or pilocytic cystic A in young patients (Palma and Guidetti 1985). In most cases, before adopting an active attitude, we need to be certain that the tumor growth represents a real impending menace to the function and/or life of the patient. Careful clinical observation and CT scan control twice a year constitutes a sufficient follow-up. Only antiepileptic drugs are administered. We do not advocate immediate surgery because we can not assume that its long term results would be better than the spontaneous course. We do not advocate biopsy plus external RT either, particularly in young people, and particularly on or near the midline structures, since we fear the possible distant devastating neuropsychological effects of RT in cases of long survival (Hochberg and Slotonick 1980).

If, and only if, the growth of the tumor is clearly established the managements proposed for LGA are the same as those for AA or GB, either plain surgery, or stereotaxic investigation plus open surgery, or biopsy plus stereotaxic irradiation according to the size, limitation and localization of the lesion.

VI. Special Problems

1. Oligodendrogliomas

Oligodendrogliomas represent 5 to 7% (Russel and Rubinstein 1977) of cerebral gliomas. Their biological behavior is not very different from the behaviour of astrocytomas. Nevertheless, some special features are

important when discussing their surgical treatment (Neumann *et al.* 1978, Ludwig *et al.* 1986, Lindegaard *et al.* 1987).

Macroscopically oligodendrogliomas occur as large tumors often in the frontal region with an important mass effect and little edema. Surgical resection is easy most of the time, with a good cleavage plane and little bleeding. In fact, they are just as infiltrative as astrocytomas. Mortality and morbidity rate are rather low. Kernohan thought that the histological appearance of oligodendrogliomas had no bearing on prognosis and that grading these tumors was difficult and clinically irrelevant. This opinion has been shared and seemingly confirmed in the literature (Earnest *et al.* 1950, Paillas and Grisoli 1982, Morsk *et al.* 1985). Accordingly, survival duration following surgery is given for the whole group of oligodendrogliomas. An MST around 35 months with 25–31% of patients surviving at 10 years, is usually quoted (Constans *et al.* 1989). At variance with the astrocytoma group, age does not seem to have a strong negative effect on prognosis. Only recently Smith *et al.* (1983) reviewing 323 cases from the Armed Forces Institute of Pathology proposed a four-grade system from A to D very similar to the one long used for astrocytomas. Tumour grade is correlated with the patient's age and has a strong influence on survival. The mean survival times are 173, 72, 85 and 15 months for grades A, B, C and D respectively and 4 years survival of 71, 45, 43 and 0%. Most patients are given radiotherapy in addition to surgery though this is not proposed systemically since an apparent "total" resection is more often supposed to be achieved, particularly in the frontal region. Since the post-operative course of these patients is often long and, most of the time, symptom free, when recurrence occurs the operation is often repeated again with good results. A number of patients have been operated upon more than twice. Recently, a short series of recurrent oligodendrogliomas with clinically aggressive behavior and pathological features of high malignancy was reported with a good response to combined chemotherapy (Cairncross and MacDonald 1988). This possibility, not often documented concerning oligodendrogliomas, should be considered following reoperation. The prognosis of oligodendrogliomas is, on the whole, far better than that of astrocytic tumors. Finally, for neurosurgeons oligodendrogliomas appear as true gliomas, but rather indolent in nature and more amenable to surgery.

2. Ependymomas

Ependymomas account for 5 to 6% of gliomas (Goutelle and Fischer 1977). Among intracranial ependymomas 50 to 60% are supratentorial in location (Goutelle and Fischer 1977, Lejeune *et al.* 1987). These tumors occur in the vicinity of the ventricle but may behave either as a purely extraventricular growth, particularly in childhood (Zülch 1956), or less

often as an intraventricular tumor with an infiltrative site of insertion in the ventricular wall. The situation of many supratentorial ependymomas in the depth of the hemisphere in or around the third ventricular wall probably accounts for a relatively high operative mortality (12 to 30%, (Kricheff *et al.* 1964, Goutelle and Fischer 1977)) even in recent statistics (17%, (Lejeune *et al.* 1987)).

Though ependymomas are held by some to be theoretically amenable to total extirpation, in many cases resection is incomplete and this seems to have no influence on survival (Pierre Kahn *et al.* 1983, Salazar *et al.* 1983). Indeed, the rapidity of recurrence is much more dependent of the modality of the RT (Lejeune *et al.* 1987, Pierre Kahn *et al.* 1983, Salazar *et al.* 1983). The prognosis is better in childhood with an MST of 37 months (Salazar *et al.* 1983) to 48 months (Lejeune *et al.* 1987) versus 18 (Salazar *et al.* 1983) to 24 in adults. The percentage of 5-year survivors ranged from 30 to 70% in recent studies (Lejeune *et al.* 1987). The predictive interest of histological grading remains controversial (Kernohan and Fletcher-Kernohan 1937) according to Kernohan. Low-grade tumors have been reported to have an MST of more than 4 years versus less than 2 years for high-grade ones with both less recurrence in situ and less CSF seeding. This has not been confirmed by other series (Kricheff *et al.* 1964, Pierre Kahn *et al.* 1983).

On the whole supratentorial ependymomas appear as rather difficult tumors from the surgeon's point of view. Resection is always necessary, particularly due to the high percentage of cases with life threatening intracranial hypertension, but resection is often incomplete and operative risks are rather high.

3. Surgery for Recurrent Gliomas

Unfortunately, the recurrence of a glioma sooner or later following the initial treatment, is to be expected in the majority of LGA and in all AA and GB. Unless the patient's overall condition and/or evidence of multilocated or extensive growth of the tumor rules out further active therapy, reoperation is often contemplated. Though such circumstances are common in neurosurgical practice, few studies have assessed the value of surgical resection of recurring gliomas (Müller *et al.* 1977 1 and 2, Afra *et al.* 1978).

a) Low-grade Astrocytomas

Pool and Kamrin (1968), one of the first to address this problem mention that reoperation for gliomas was common practice in the early days of neurosurgery—one of Cushing's patients was operated upon 6 times. A review of the available literature (22 cases) and of his own series (30 cases) led him to conclude that surgery was the best treatment for these patients

since 57% of them were improved, 44% for one year or longer. The prognostic factors for survival were the same as for the first operation (this series comprised 8 cases of cerebellar astrocytoma and 8 oligodendrogliomas, which fared among the best). Afra *et al.* (1978) presented a series of 121 patients reoperated upon with the primary tumor being, in 57 cases, grade I and, in 64 cases, grade II astrocytomas or oligodendrogliomas. In two thirds of the cases, recurrent tumors were found of increased malignancy. The results of reoperation were poor with a high mortality rate and a survival time exceeding one year in only 18 grade I and 14 grade II patients. There are no clearcut differences in prognosis according to either histological grade at first or second operation or interval between first surgery and recurrence. In the report from the Mayo Clinic surgery for recurrence is mentioned with no further comment. Transformation of an initial low-grade tumor into a malignant one was found in half the cases (Laws *et al.* 1984).

b) Glioblastomas and Anaplastic Astrocytomas

The results of reoperation are again poor in a series of 24 patients with GB or AA reported by Young *et al.* (1981). The MST was 14 weeks and only 5 patients survived 6 months or longer. The interval between the first and second operation and the performance score at the time of recurrence were the best predictors of survival.

Salcman *et al.* (1982), presented an interesting consecutive, prospective series of 76 cases with 67 GBM and 17 AA, in which a second operation was systematically considered and actually carried out in 60 cases. There was no operative mortality and minimal morbidity. A median additional survival of 37 weeks with a 2-year survival rate of 25% are impressive results attributed by the authors to operative refinements and an aggressive multimodality treatment added to surgery. The length of survival following reoperation was independent of histology, patient's age, performance status, and time interval between the two operations. Moser (1988) published a series of 17 cases of reoperation for glioma relapse. Six patients with LGA and 7 with AA were alive without evidence of tumor progression after 31 and 29 months of postoperative follow-up, respectively. Three of 4 GBM died 5, 12 and 17 months after reoperation. There was no mortality and all survivors maintained a 95% performance rate. These surprising results are likely to reflect selection bias as pointed out by the authors: the mean age was 17 for LGA and 27 for AA and, in most of the cases, the first operation had clearly been very partial.

Recently, two reports from different institutions (Ammirati *et al.* 1987, Harsh *et al.* 1987) appeared simultaneously dealing respectively with 55 and 70 consecutive patients reoperated for malignant gliomas. In one study (Ammirati *et al.* 1987), the MST was 36 weeks for GBM and 61 weeks for

AA with a mortality rate of 1.4% and morbidity rate of 16%. Preoperative functional status and extent of resection were the best predictors of survival. KS improved in 45% of patients. In the second study (Harsh *et al.* 1987), the MST was 36 weeks for GB and 88 weeks for AA, but functional improvement was noted in very few patients (5% for GBM, 10% for AA). KS ratings above 70 were maintained for 10 weeks in GB and 83 weeks in AA. In both studies the selection criteria of patients for reoperation were not included and, in both studies, ChT was added in most cases. The results of these reports are relatively close and are probably representative of what reoperation can achieve at the present time.

These and other reports have demonstrated that reoperation for recurrent malignant glioma is feasible and can prolong life with an acceptable functional status. It is our policy to reoperate patients under the age of 60 when they have survived the first operation for one year or more in good functional condition and when the recurrent tumor causes mass effect and is reasonably accessible. Following reoperation, these patients are given BCNU chemotherapy as well.

VII. Conclusions

Surgery is not and can never be a completely appropriate solution for brain gliomas because surgery aims at localized lesions and gliomas are in general poorly localized. This very basic fact, well known but often overlooked, should remain the basis of our management of patients. Whatever, the sophistication of our surgical or ancillary armamentarium, whatever the resolution and various modalities of our functional monitoring, gliomas will continue to recur within 2 centimeters of our resection limits because there are hidden active neoplasic cells. In the face of this biological evidence, many recent achievements may appear naive though technically impressive.

On the other hand, surgery is still and presumably for a long time, will be an important step in the treatment of gliomas. It is unlikely that we will improve the early detection of brain tumors: in this country approximately two thirds of the patients referred to neurosurgeons with a likely diagnosis of glioma have had CT scan within 1 week of the first symptom and already harbor lesions several centimeters in diameter. In such cases surgery is useful to relieve mass effects promptly and evacuate toxic debris.

Such surgery, being useful but only palliative, should remain circumspect and reasonable. It is our opinion that it should not employ highly expensive and, in the long run, illusory technical means, and that it should not be undertaken if its predictable outcome is just to give to the patient a few more weeks of life in poor functional condition.

It is unlikely that substantial therapeutic progress will come with or without surgery from new combinations of old and new modalities of RT (Hochberg *et al.* 1981) old and new drugs, together with some modern

adjuvants (Winter *et al.* 1985) as in most of the protocols now available in North America and recently listed (Kelly 1989). Hopefully, a solution for the cure of gliomas will come rather from progress in molecular biology which may create highly targetted agents, able to reach and kill each and every neoplastic cell.

VIII. Annex: Financial Cost of Gliomas

To our knowledge very few studies are available concerning the financial cost of gliomas. In 1980, the radiotherapy department of the Besançon regional hospital (Schraub and Altwegg 1980) published a comparative study on the cost of treatments in various cancers (Table 1). Only the first set of treatments following diagnosis was considered. The cost of surgery accounted for only one fourth of the total price. Glioma surgery was more expensive than surgery for breast, colic or laryngeal cancer, but less than for esophagus or lung cancer. At the same time, we conducted a retrospective study of a small randomized group of malignant glioma treated in our department (14 cases). The cost of the whole course of the disease until death was estimated. The cost of the first set of treatments was very similar to that in Besançon and accounted for approximately two third of the total cost of the disease. One day in the life of a patient surviving with a malignant glioma and cared for normally until his death cost the community 375 FF (254–734).

These figures, if representative of the cost of a reasonably good management of patients do not rank the gliomas among expensive diseases in modern medicine.

Table 1 a. *Cost of the First Set of Treatments in Malignant Glioma*

Diagnosis	9,224	(5,241–15,231)
Surgery	22,072	(16,789–41,079)
Radiotherapy	6,360	(4,119–28.149)
Chemotherapy	40,770	(40,272–45,612)
	78,428	(66,423–130,073)

Table 1 b. *Cost of Surgery in Other Cancers*

Breast	11,959	(9,446–16,816)
Lung	65,231	(33,778–127,647)
Larynx	16,693	
Esophagus	26,673	(19,940–32,020)
Colon	16,561	(10,808–27,088)

Costs expressed in French Francs, 1980.

Table 2. *Global Cost of Glioma Treatment from Diagnosis to Death in 14 Cases of GB*

Survival time	4–>22 months
Surgery 10 cases	(+ 3 reoperations (for recurrence)
Interstitial irradiation	1
External radiotherapy	12
Chemotherapy	14
Total costs from diagnosis to death mean	121,360 (45,000–247,000)
Total costs per month of survival mean	11,262 (7,625–22,024)

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