
Sponsored by the
European Association of Neurosurgical Societies

Advances
and Technical Standards
in Neurosurgery

Vol. 25



Springer-Verlag Wien GmbH

With 54 partly coloured Figures


Originally published by Springer-Verlag Wien New York in 1999
Softcover reprint of the hardcover 1st edition 1999
Library of Congress Catalogue Card Number 74-10499

Typesetting: Asco Trade Typesetting Ltd., Hong Kong

Graphic design: Ecke Bonk



Printed on acid-free and chlorine-free bleached paper

SPIN: 10704305

ISSN 0095-4829

ISBN 978-3-7091-7318-3 ISBN 978-3-7091-6412-9 (eBook)
DOI 10.1007/978-3-7091-6412-9

## Preface

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

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

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

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

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

In the second part of each volume, we publish detailed descriptions of standard operative procedures and in depth reviews of established knowledge in all aspects of neurosurgery, furnished by experienced clinicians. This part is intended primarily to assist young neurosurgeons in their postgraduate training. However, we are convinced that it will also be useful to experienced, fully trained neurosurgeons.

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

*The Editors*

# Contents



## A. Advances

## B. Technical Standards

**Listed in Index Medicus**

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# A. Advances

# Treatment of Diseases of the Central Nervous System Using Encapsulated Cells

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With 4 Figures

## Contents



## Introduction

The use of neuroactive substances as therapeutic agents represents a major focus of today's neurobiology. The delivery of these substances to the CNS is however complicated by several factors including low oral and transdermal availability and short half-lives (Battler *et al.* 1993). The blood brain barrier (BBB) further prevents the passage of most molecules from the circulation to the brain tissue (Poduslo and Curran 1996). To reach the CNS, these molecules have therefore to be directly injected into the brain with an adequate delivery system, such as a pump. This method is however of limited use for long term applications due to the instability of the thera-

peutic molecules (Penn *et al.* 1997) and the risk of infection linked to the need for repeated refilling. Implantation of cells that have been genetically modified to release therapeutic molecules represents an alternative that can circumvent the above mentioned limitations. The cells can be implanted in specific targets allowing the localized continuous release of bioactive molecules. This approach has been used successfully in various models of neurodegenerative diseases. This technique is however limited by the immune rejection in case of non autologous sources and potential tumor formation with the use of cell lines (Jaeger 1985) preventing clinical applications. One solution to these problems is the technology of encapsulation. The transplanted cells are surrounded by a selectively permeable biocompatible membrane, preventing the dissemination of the cells as well as immune rejection.

## Brain and Immunity

The CNS is classically described as an immunoprivileged site. These properties are linked to the presence of the blood-brain-barrier (Poduslo and Curran 1996), the low expression of major histocompatibility complex proteins (MHC) (Hart and Fabre 1981), the absence of lymph drainage and the exclusion of lymphocytes. However, in pathological conditions, activated lymphocytes are able to pass the BBB and microglia present antigens in an MHC I and II environment (Gehrmann *et al.* 1995). Allografts have been reported to be capable of survival for extended periods of time when transplanted into the CNS (Blomer *et al.* 1996, Horellou and Mallet 1997). However, xenografts are usually rapidly rejected (Bjorklund *et al.* 1982, Uchida *et al.* 1989, Aebischer *et al.* 1991, Horellou *et al.* 1991, Sloan *et al.* 1991). Improved survival has been shown following long-term immunosuppression with either cyclosporin A or FK 506 (Brundin *et al.* 1986, Ortega *et al.* 1992, Schueler *et al.* 1995). However, immunosuppressive treatments can result in many unwanted side effects. Moreover, in the CNS, neural grafts are rapidly rejected if the recipient of the transplant has been challenged to donor antigens (Widner and Brundin, 1988, Sloan *et al.* 1991).

## Encapsulation of Cells

To avoid the problems of immune rejection and tumor formation associated with transplantation of cellular grafts, our group has devised a method for physically separating cells from the host brain tissue (Aebischer *et al.* 1991). This physical barrier consists in a semipermeable membrane with a controlled pore size. A molecular weight cut-off in the range of 50 Kd is typically used. This cut-off allows the inward diffusion of nutrients and the outward diffusion of the secreted bioactive factors. Components of

the immune system are however, for the most part, too large to diffuse into the capsule. Direct cell to cell contact between the host immune system and the grafted cells is therefore prevented (Fig. 1). The capsule can be implanted at any site in the host brain using classical stereotaxic methods. Subarachnoid implantation can be achieved using a minimally invasive surgical implantation under local anesthesia (Buchser *et al.* 1996). In case of severe unwanted side effects, the device can be retrieved. Moreover, two additional safety mechanisms are incorporated to ensure the elimination of the implanted cells in case of capsule breakage. First, the immunogenicity of xenogeneic cells will lead to rejection of the cells even in immunoprivileged sites if they are not protected by an immunoisolating membrane (Bjorklund *et al.* 1982; Uchida *et al.* 1989, Aebischer *et al.* 1991, Horellou *et al.* 1991, Sloan *et al.* 1991). Second, the herpes simplex virus thymidine kinase suicide gene (TK) is incorporated into the engineered cell lines. Oral intake of the antimicrobial drug ganciclovir will activate this gene and eliminate selectively the cells expressing TK.

Two types of capsules can be distinguished. Microcapsules consist in a selectively permeable membrane formed of two oppositively charged polyelectrolytes, usually alginate and polylysine, surrounding small cell clusters (Lim and Sun 1980, Winn *et al.* 1991). These membranes present however several disadvantages including poor mechanical stability, lack of retrievability and potential blocking of CSF circulation with resulting intracranial hypertension (Aebischer *et al.* 1993). Macroencapsulation describes selectively permeable thermoplastics shaped in hollow fibers and filled with cell suspensions (Aebischer *et al.* 1991, Aebischer and Lysaght 1995). The diameter of these hollow fibers is in the range of 300 to 500 $\mu$m to allow the appropriate availability of nutrients to cells located in the middle of the device. Optimal biocompatibility and minimal inflammatory response is obtained by fine tuning the chemical composition of the membrane and the surface morphology. The composition of the matrix has to be adapted empirically for each cell line and will depend upon their phenotype and growth characteristics (Zielinski and Aebischer 1994). Hydrogel based matrices are typically being used.

Cell lines can be engineered by classical methods (Sambrook *et al.* 1989) and cloned by limited dilution. Clonal cell lines can be selected for optimal parameters, including secretion of the desired therapeutic factor, stability of secretion over time, *in vitro* and *in vivo* survival of the cell line within the capsule. Practically, clonal cells are amplified to generate master cell banks, which are in turn amplified for the constitution of working cell banks. These banks should ensure homogeneity and reproducibility in the preparation of the devices. Those cell lines are checked for the absence of pathogens such as bacteria, viruses, yeast or fungi prior to their use (Aebischer *et al.* 1996). These cell lines are also tested for the absence of

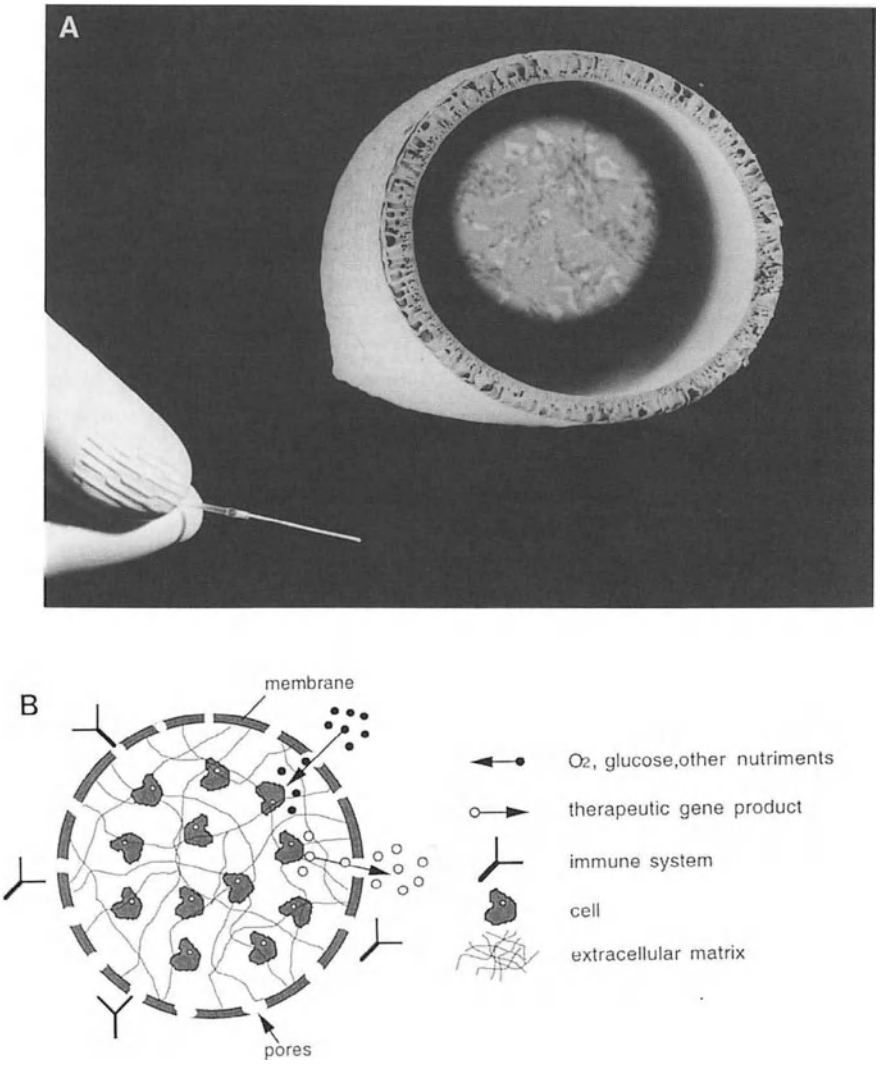


Fig. 1. (A) Montage illustrating the concept of encapsulation: cells are surrounded by a double skin PAN-PVC selectively permeable membrane as used in clinical protocols. On the lower left side, a surgeon is holding a 2 cm device by it's silicone catheter. (B) Principle of immunoisolation by encapsulation: genetically modified cells are embedded in a hydrogel based matrix. The pores of the membrane allow the diffusion of nutrients and bioactive cell products. The membrane prevents the diffusion of xenogeneic molecules and the destruction of the cells by the host immune system. Adapted from Handbook of experimental pharmacology: neurotrophic factors, Hefti FF (ed) Springer

tumorigenicity and toxicity as assessed by injection of unencapsulated cells into small animals. The feasibility of this approach has been shown in numerous animal studies and in two clinical trials as described in the following sections.

## Chromaffin Cells for Pain Relief

Pain is a major problem for many patients suffering from cancer. The management of chronic pain remains a challenge for the clinician with current available treatments. Indeed ten to thirty percent of those patients cannot be adequately relieved with current therapies (Portenoy 1993). Opioids, although very potent on the short term, are often limited in their long term use by side effects such as tolerance and a relative inability to treat persistent pain syndromes (Puntillo *et al.* 1997). Attempts have been made to chronically deliver analgesic substances in the epidural or intrathecal space using drug pumps. However the requirements for refilling, maintenance, cost and the risk of infection limit their widespread application. Cells secreting analgesic factors represent therefore an elegant approach to circumvent the above mentioned limitations.

Chromaffin cells are the neuroendocrine cells of the adrenal medulla and paraganglia (Unsicker and Krieglstein 1996). They have been shown to release numerous analgesic substances including catecholamines, enkephalins, endorphins, neurotensin, and somatostatin (Livett *et al.* 1981; Verhofstad *et al.* 1989). Catecholamines and opiates have been shown to exert potent analgesic effects when released epidurally or intrathecally (Yaksh and Reddy 1981, Ossipov *et al.* 1997). Chromaffin cells also secrete several neurotrophic factors including transforming growth factor $\beta$, fibroblast growth factor and ciliary neurotrophic factor (Unsicker 1993, Unsicker and Krieglstein 1996). These factors might exert direct antinociceptive effects (Siuciak *et al.* 1994) or reduce transynaptic neuronal degeneration in the spinal cord (Hama *et al.* 1996).

Isolation techniques of chromaffin cells have been well described for various species including humans (Pollard *et al.* 1984, Sagen *et al.* 1993, Sagen *et al.* 1995). An important advantage of these cells is that they can be isolated and purified in extremely high numbers (Unsicker and Krieglstein, 1996). For example bovine chromaffin cells can be obtained with a purity of approximately 95%. The easy accessibility and great yield of the latter make them the ideal donor source for large scale applications.

### *Chromaffin Cells in Animal Models*

Allografts of chromaffin cells have been shown to exert behavioral improvements in acute nociceptive tests such as the paw pinch, hot plate and

tail flick test (Sagen *et al.* 1986a). These antinociceptive effects have been linked to the simultaneous release of opioid peptides and catecholamines. This was corroborated by the possible attenuation of the effect by the α-adrenergic antagonist phentolamine and the opiate antagonist naloxone (Sagen *et al.* 1986b, Hama and Sagen 1994).

Grafts of chromaffin cells were also shown to be effective in several models of chronic pain. One of these, the Bennett model (1988), consists in loosely ligating the sciatic nerve unilaterally with chromic catgut sutures, which induces a chronic constriction injury lasting 7–9 weeks. This induces pain behaviors closely resembling clinical neuropathic pain syndromes like allodynia and hyperalgesia. Chromaffin cells implanted intrathecally have been shown to be able to reduce hyperalgesia induced by a noxious thermal stimulus, whereas touch evoked-allodynia and spontaneous pain appeared only partially reduced (Hama and Sagen 1993). These results were confirmed by Vaquero *et al.* (1991) who showed reduction in pain responses to subcutaneous injection of formaline up to 2 months after the implantation of adrenal medullary tissue in the subarachnoid space. In a model of axotomy, the usually observed autotomy (self-injury of the denervated limb) is reduced in animals transplanted with adrenal grafts (Ginzburg and Seltzer, 1990). In a model of central pain induced by ischemic spinal cord injury, bovine chromaffin cells implanted in the lumbar subarachnoid space were shown to abolish mechanical allodynia and to reduce the pain induced by cold (Yu *et al.* 1998). However, survival of the xenografted adrenal cells was considerably decreased 8 weeks following implantation, and immunosuppression is required to achieve longer survival periods of the grafts.

To circumvent the problem of immune rejection, the use of encapsulated chromaffin cells was tested in different models of pain. For instance, encapsulated bovine chromaffin cells implanted in the lumbar subarachnoid space of rats suffering from a chronic constrictive lesion of the sciatic nerve are able to reduce signs of spontaneous pain as well as pain induced by mechanical non-nociceptive stimulations (Décosterd *et al.* 1998).

### *Chromaffin Cells in Clinical Studies*

Based on the numerous encouraging results of chromaffin cells for the treatment of pain in animal models, several clinical trials were initiated. Winnie *et al.* (1993) reported improvements in 4 out of 5 immunosuppressed patients suffering from terminal cancer following cadaver-sourced adrenal allograft isolates. This approach is however limited by the low number of potential donors. Moreover, xenogeneic chromaffin cells have showed poor survival and low basal expression of catecholamines when transplanted directly as graft donor cells (Freed *et al.* 1990, Kordower *et*

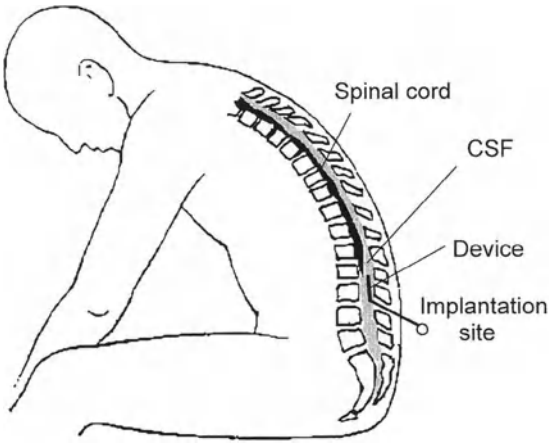


Fig. 2. Schematic representation of the implantation site of the device. Adapted from handbook of experimental pharmacology: neurotrophic factors, Hefti FF (ed) Springer

*al.* 1990). Although drug immunosuppression is able to extend survival of these grafts (Schueler *et al.* 1995), these treatments do show many untoward side effects that limit their widespread use.

To circumvent these problems, our group evaluated the feasibility of transplanting encapsulated bovine chromaffin cells in patients suffering from intractable chronic cancer pain. A phase I trial was conducted in 7 patients suffering from intractable chronic pain due to end stage cancer or unrelieved neurogenic pain. The patients were implanted with a device that accommodates the few million cells necessary for achieving therapeutic effects. These devices had been previously tested for biocompatibility, and retrievability in various animal models (Joseph *et al.* 1994). Briefly, chromaffin cells derived from the adrenal gland of young calves were purified and cultured for 3 days to allow screening for pathogens. These cells were then loaded into a 5 cm long selectively permeable polyacrylonitrile/polyvinyl chloride (PAN-PVC) hollow fiber connected to a silicone catheter. These devices were analyzed before implantation for secretion of catecholamines. Implantation procedure was generally uncomplicated and recovery was uneventful except for transitory headaches (Figs. 2, 3). The patients were scored for potential alleviation of pain by the VAS and the McGill pain score. Intake of conventional drugs was monitored as well. All patients ($n = 4$) receiving morphine before implantation were able to reduce their dosage. Five patients felt a significant reduction in pain as assessed by the McGill pain score, suggesting that this cell therapy might be beneficial in the treatment of chronic intractable pain (Aebischer *et al.*

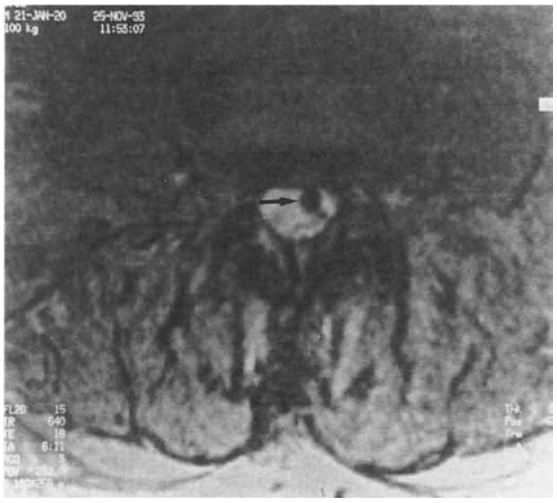

Fig. 3. Magnetic resonance image showing the subarachnoid position of the device. Horizontal section of L2 vertebra. Oversignaling (arrow) of the titanium connector exaggerates device size. With permission from anesthesiology

1994, Buchser *et al.* 1996). All implants were recovered after implantation periods ranging from 41 to 176 days. Macroscopically, the implants appeared free of fibrous adhesions. Histological and biochemical analyses of the explants confirmed the viability of the implanted cells and their ability to release catecholamines. This study confirmed the long-term feasibility of implanting immunoisolated xenogeneic cells in the CSF of patients. The design of the implant allowed uneventful recovery of the implants. However the positive effects observed must be taken with caution due to the low number of subjects and the lack of adequate controls. A double blind phase II study was therefore initiated to confirm the promising preliminary results. Data from this clinical trial are currently being evaluated.

## Neurotrophic Factors in Neurodegenerative Diseases

Neurotrophic factors (NF) are small soluble proteins that are necessary for maturation, differentiation, maintenance, survival and repair of neurons (Levi-Montalcini 1987, Snider and Johnson 1989). In the absence of trophic support the neurons shrink or die. In the event of axonal lesion, regenerating axons are stimulated by the upregulation of NF production (Meyer *et al.* 1992, Curtis *et al.* 1993, Curtis *et al.* 1994). Although none of the neurodegenerative diseases has, to date, been linked to a deficit of a particular neurotrophic factor, they might create a favorable environment

for the neurons and therefore slow down the degenerative process. In diseases characterized by a slow degeneration they may even be able to promote regeneration of the system. The above mentioned characteristics have made NF strong candidates for the treatment of many different neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's or Huntington's disease.

### *Amyotrophic Lateral Sclerosis*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting primarily lower and upper motoneurons (Tandan and Bradley 1985a). It shows a prevalence of 5 /100000. Typically, it affects patients between 30 and 70 years of age and leads to paralysis and death in 2 to 5 years after diagnosis. The etiology still remains largely unknown, although oxidative stress and excitotoxicity have been implied (Tandan and Bradley 1985b). There is currently no treatment available for this disease. Pathologically, motoneurons are vacuolized and present important accumulation of neurofilaments in the perikaryon and the proximal axonal compartment (Tandan and Bradley 1985a).

### *Models of Amyotrophic Lateral Sclerosis*

*In vitro*, motoneurons have been shown to respond to a variety of NF, including ciliary neurotrophic factor (CNTF), brain derived nerve factor (BDNF), neurotrophin-3 (NT-3), neurotrophin 4/5 (NT4/5) and glial derived neurotrophic factor (GDNF). *In vivo*, these factors have all been shown to rescue neonatal facial motoneurons from axotomy induced cell death (Sendtner *et al.* 1990, Sendtner *et al.* 1992a, Yan *et al.* 1992, Yan *et al.* 1995). CNTF has been shown to slow down the degeneration of motoneurons in different rodent models of ALS including the wobbler (Mitsumoto *et al.* 1994) and pmn-pmn mouse (Sendtner *et al.* 1992b). Sagot *et al.* (1995), using encapsulated baby hamster kidney cells genetically modified to release CNTF implanted subcutaneously were able to show that CNTF was able to delay the progression of the disease, to improve motor function and to increase survival time by 40% in pmn-pmn mice. Histological counts confirmed a reduction in the loss of facial motoneurons and phrenic nerve myelinated axons.

### *Clinical Trials in ALS*

These encouraging results prompted the initiation of clinical trials in ALS patients. Two phase I/II trials involved subcutaneous injections of up to 60 $\mu$g/kg human CNTF 3 times a week (ALS CNTF treatment study (ACTS)

Study group, 1996) or daily injections of 5 $\mu$g CNTF in the highest dose (Miller *et al.* 1996b). Clinical scores and survival were however not modified between treated and untreated patients. Moreover, at the higher doses, systemic administration of CNTF had to be discontinued due to severe side effects. Those included dry cough, weight loss, acute phase response and fever (Miller *et al.* 1996a). They have been attributed to the widespread distribution of CNTF receptors located outside the CNS (Fantuzzi *et al.* 1995). Intrathecal delivery of CNTF by means of a mechanical pump has been evaluated by Penn *et al.* (Penn *et al.* 1997) in a phase I trial. This technology is however hampered by the short half-life of CNTF in solution.

Based on extensive experience with various animal models, our group has performed a phase I clinical trial using the encapsulation technology (Aebischer *et al.* 1996). This approach allowed the continuous delivery of CNTF directly into the CSF, increasing the delivery to the motoneurons and preventing the activation of CNTF receptors located outside the CNS. Prior to human applications, the safety and feasibility of the approach were tested in a sheep model, presenting a similar size of the spinal cord than humans (Joseph *et al.* 1994). The implant devices consisted in 5 cm long polyether sulfone (PES) hollow fibers connected to a silicone catheter to allow manipulation and retrieval. These capsules were seeded with baby hamster kidney cells genetically modified to secrete human CNTF.

Twelve ALS patients were enrolled in this initial open label study. Patients accepted for this trial had to be in the early stage of the disease with a forced vital capacity (FVC) greater than 75%. Exclusion criteria were enrollment in other clinical trials for ALS or other medical illnesses. All patients were implanted with a first device for a period of approximately 3 months. The devices were then explanted and replaced by a new one. Evolution of the disease was assessed every month using the forced vital capacity, the Tufts Quantitative Neuromuscular Evolution (Andres *et al.* 1986) and Norris scale (Norris *et al.* 1974). Patients were also closely monitored for the onset of adverse side effects. Laboratory examinations included monthly plasma measurements of fibrinogen, C reactive protein, sedimentation rate, WBC total and differential count. Serum and CSF CNTF levels were also evaluated regularly.

The devices were well tolerated by all patients and no limiting side effects were reported. All patients examined showed an absence of measurable CNTF in their CSF prior to implantation. This level raised to detectable levels in the order of nanograms following implantation. Simultaneous measurements of lumbar and cervical CNTF showed that the cervical concentration was 14.6% of the lumbar level of CNTF, confirming that the whole spinal cord is exposed to the neurotrophic factor after lumbar subarachnoid implantation of the capsule. Preliminary evaluations

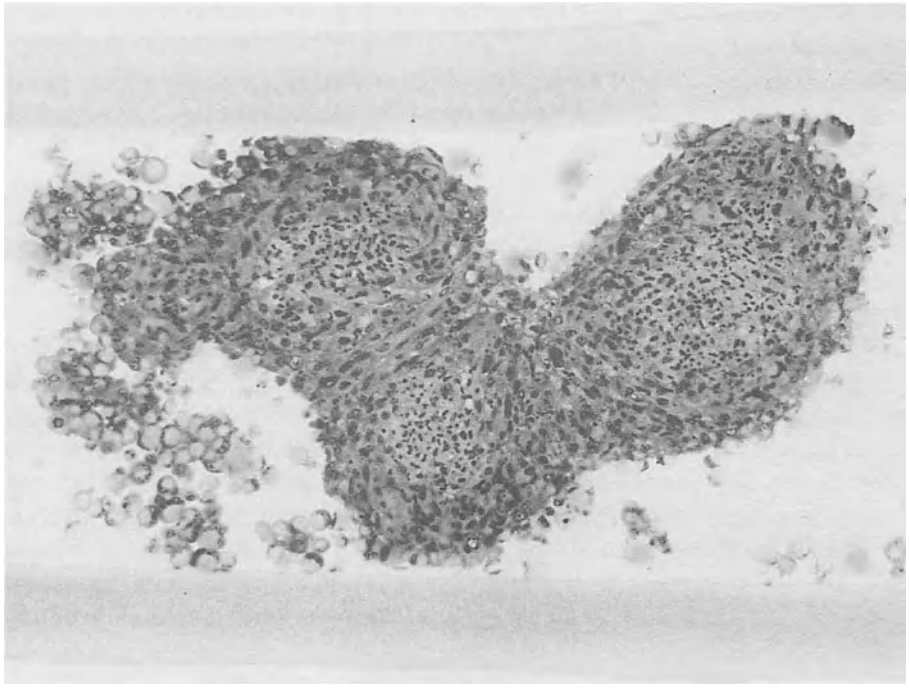

Fig. 4. Longitudinal section of an explanted capsule from a patient involved in the phase I ALS clinical. Viable BHK cells genetically modified to secrete hCNTF can be seen 17 weeks post implantation (hematoxylin and eosin). With permission from nature medicine

of the clinical scores indicate that the disease continues to progress. However, the small number of patients involved in the study complicates the assessment of a potential slowing down of the neurodegenerative process. All explanted devices were intact following retrieval and were shown to secrete CNTF as measured by ELISA. Histological examination of the device showed viable BHK cells within every device (Fig. 4).

To obviate the variations of secretion from one capsule to another observed with BHK cells, a different cell type is being investigated. Myoblasts present the advantage that they can be cultivated and extended in large amounts. However once loaded in the device, they can be differentiated into post mitotic myotubes, which will stop to divide. These cells are currently being tested in a small phase I clinical trial.

## Future Approaches

The two clinical studies described above have confirmed that the transplantation of xenogeneic cells in the subarachnoid space is possible using a

semipermeable device. This technology has been shown to be appropriate for clinical use. The next step with this technology will be to evaluate intracerebral implantation of these devices. Huntington's disease and Parkinson's disease constitute privileged targets. Preliminary studies conducted in rodents and non human primates have shown promising results.

Huntington's disease is an autosomal dominant disorder characterized by cognitive impairments, behavioral abnormalities and involuntary choreiform movements (Gusella and MacDonald 1995). The disorder has been linked to an expansion of CAG repeats in the huntingtin gene that induce the selective degeneration of striatal neurons (The Huntington's Disease Collaborative Research Group, 1993). The excitotoxic drugs quinolinic acid and NP-3, are able to mimic clinical and histological features of this disease when injected in the striatum. Encapsulated BHK fibroblasts genetically engineered to secrete human CNTF were able to reduce the extent of acute striatal damage produced by quinolinic acid and improved motor functions of rats when implanted in the lateral ventricle (Emerich *et al.* 1996). In a similar neuroprotection model in cynomologous monkeys, CNTF releasing implants were able to reduce the extent of striatal damage on different cell populations including GABAergic, cholinergic and NADPH diaphorase-positive neurons (Emerich *et al.* 1997). In a model of chronic lesion induced by NP-3, Mittoux *et al.* (1998) showed improved motor and cognitive functions.

GDNF, a member of the transforming growth factor $\beta$ family, has been found to exert potent trophic activities on both dopaminergic (Lin *et al.* 1993) and motoneurons (Zurn *et al.* 1994). It appears therefore as an attractive candidate for the treatment of Parkinson's disease. Encapsulated cells releasing GDNF were also able to prevent the degeneration of dopaminergic cell bodies of the substantia nigra and reduced the drug induced rotation behavior following a medial forebrain axotomy in a rodent model of PD (Tseng *et al.* 1997). In baboons chronically intoxicated with MPTP, the same encapsulated cell line was able to induce reinnervation of the striatum and was associated with significant behavioral improvements (Palfi *et al.* 1998).

We believe that these encouraging results in animal models of Parkinson's and Huntington's disease justify the initiation of clinical trials with this technology.

## Conclusion

The two clinical trials conducted by our group have shown that implants containing genetically modified xenogeneic cell lines is achievable in patients using a selectively permeable membrane. An important advantage of this technology is that there is no need for systemic immunosuppression.

The encapsulation approach can overcome many of the problems associated with the systemic administration of therapeutic molecules since: 1) the molecules are secreted directly in the CNS; 2) there is no need for repeated injections which limits the risks of infection; 3) stability of the therapeutic proteins is warranted by fresh *in situ* synthesis; 4) the implantation of the devices has been shown to be minimally invasive and has not been associated with any significant side effects. Moreover the safety of the procedure is enhanced by the possibility to retrieve the implant at any time. In case of breakage of the device, the host immune system is able to reject the xenogeneic cells even in immunoprivileged sites like the brain. Moreover the addition of a suicide gene should allow the selective destruction of the genetically modified cells.

## Acknowledgments

The authors thank Isabelle Décosterd and Jean-Marc Joseph for their help and comments. A. F. H. is sponsored by a grant from the Roche Research Foundation MD-Ph.D. program.

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# Intracranial Endoscopy

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With 3 Figures

## Contents



## Summary

Since 1910, when Lespinasse [73] in Chicago was the first surgeon to use an endoscopic device for the treatment of a neurologic disease, various methods of endoscopy have evolved into accepted diagnostic and therapeutic adjuncts of modern neurosurgery.

Nevertheless, until recently technical shortcomings of the available endoscopes have prevented the widespread use of neuroendoscopy. However, now, at the end of the 20th century, endoscopes can be regarded as some of the most important instruments for the development of microneurosurgery into the 3rd millennium.

The aim of this review of intracranial endoscopy in neurosurgery, which admittedly might not be completely objective in the authors' personal assessment of various endoscopic techniques, is first to depict the historical evolution of neuroendoscopy, second to describe the technical equipment used in intracranial endoscopic neurosurgery, third to characterize the most frequent endoscopic methods in brain surgery, and fourth to indicate how neuroendoscopy might develop in the near future.

It will be shown that this ongoing evolutionary process in neuroendoscopy was only possible with the mutual influence of improved diagnostic techniques, increased microanatomical knowledge, refined neurosurgical instrumentation—especially the introduction of the surgical microscope, and endoscopic diagnostic and therapeutic strategies.

## Introduction

At the end of the 20th century, various neuroendoscopic techniques have evolved into accepted surgical methods for diagnostics and therapy in neurosurgery.

Three tendencies of endoscopic surgical techniques in neurosurgery can be characterized, and these are:

1. Neuroendoscopy as a distinct surgical procedure, e.g. endoscopic treatment of the carpal tunnel syndrome or endoscopic third ventriculostomy.
2. Neuroendoscopy with the use of endoscopes as the main surgical instruments (= endoscope-guided microsurgery), e.g. endoscopic syringostomy of septated hydromyelia or endoscopic fenestration of intracranial arachnoid cysts.
3. Neuroendoscopy with the use of endoscopes as additional optical instruments to reduce intraoperative retraction during microsurgical procedures (= endoscope-assisted microsurgery), e.g. endoscope-assisted microsurgical clipping of aneurysms or endoscope-assisted intracranial tumor surgery.

According to the organization of the human nervous system the entity of these endoscopic techniques in neurosurgery can be subdivided into endoscopic peripheral nerve surgery, endoscopic spinal surgery, and endoscopic brain surgery.

Endoscopic peripheral nerve surgery includes the treatment of median nerve compression syndromes and methods for thoracoscopic sympathectomy and vagotomy.

Endoscopic spinal surgery includes a variety of intramedullary proce-

dures, of intradural extramedullary as well as of extradural procedures. Endoscopic spinal surgery can be carried out via anterior, lateral or dorsal approaches to almost all levels of the cervical, thoracic, lumbar and sacral spine.

Endoscopic brain surgery includes distinct endoscopic procedures through burrhole trephinations, endoscope-guided procedures through burrhole trephinations, and endoscope-assisted procedures through craniotomies or craniectomies. Endoscopic brain surgery can be carried out in the ventricular system, in brain tissue, in the subarachnoid space, and in the sella. Endoscopic brain surgery has indications in hydrocephalus surgery, intracranial and skull base tumor surgery, cerebral aneurysm surgery, and in microvascular decompression of cranial nerves.

It is obvious that all these various forms of neuroendoscopic surgery cannot be carried as routine procedures in acceptable numbers leading to an acceptable experience in a single department. It seems unreasonable to assess and criticize surgical methods one is not familiar with. Therefore, the authors of this review, being experienced with a broad spectrum but not with all of the above mentioned neuroendoscopic strategies, would like to discuss in detail only those intracranial procedures which are performed in their own department in acceptable numbers.

## Historical Perspective of Neuroendoscopy

The evolution of neuroendoscopy started about 100 years ago at a time when the first traces of modern neurosurgery emerged from the huge field of general surgery. The surgical instruments at that time were not designed for neurosurgical operations, and therefore at a relatively early stage it was regarded as necessary to invent techniques and to use instruments which helped to reduce the surgical trauma during operative treatment of neurologic diseases. Thus, in 1910, Lespinasse [73] was the first surgeon who successfully used a burrhole trephination in combination with an endoscope, in fact an urethroscope, to treat two children with hydrocephalus. With this endoscopic approach to the lateral ventricles he was able to perform a kind of choroid plexus coagulation. At least one of the two children survived this first endoscopic choroid plexus coagulation for several years.

It was exactly then that Harvey Cushing [19] invented new techniques suitably applied in neurosurgery for the control of intraoperative bleeding. It turned out shortly afterwards that these new techniques for careful hemostasis led to an enormous improvement in the clinical outcome of neurosurgical patients. It was also at that time, in 1911, that Jacobaeus [61] reported on the first clinical experiences with two other endoscopic methods, laparoscopy and thoracoscopy, which two decades later were refined by Kalk [64] and which, by the end of the 20th century should revolutionize the treatment modalities for a number of surgical fields like

abdominal surgery, thoracic surgery, vascular surgery, urology and gynecology. Endoscopic thoracoscopy was also the fundamental principle used by Wittmoser [137] for his pioneering clinical work on thoracoscopic sympathectomy and vagotomy.

In 1918, radiographic techniques for the diagnosis of hydrocephalus and its etiology were introduced into neurosurgery by Walter Dandy [20, 21]. With the help of air injection and fluoroscopy of the ventricle system he was able to demonstrate the dilated ventricles preoperatively and to verify some causes of occlusive hydrocephalus. Dandy was also the first neurosurgeon to perform choroid plexus extirpation for the treatment of hydrocephalus [22], but as he was not very successful with this technique he abandoned it after a short time.

The low success rate of choroid plexus extirpation prompted Mixter [87] in 1923 to combine ventriculoscopy as a diagnostic procedure with ventriculocisternostomy or third ventriculostomy. He was the first surgeon to perform third ventriculostomy as an endoscopic therapeutic method.

However, this new treatment of occlusive hydrocephalus with the help of endoscopes at that time was only possible due to the improvement of diagnostic techniques which occurred a few years earlier, the progress of neurosurgically relevant microanatomical and physiological knowledge, and advances with neurosurgical techniques and instruments like the above mentioned techniques for hemostasis.

A further milestone in neurosurgical diagnostics was passed in 1927, when Moniz [88] described the technique of cerebral angiography (which he called "arterial encephalography"); initially it was performed for the localization of intracranial tumors. This method was refined by Seldinger [125] more than 25 years later with a catheter replacement technique of the needle in percutaneous angiography; cerebral angiography still represents one of the most important diagnostic techniques in neurosurgery.

In addition, the discovery of fundamental physiological principles of capillary perfusion and capillary permeability by Landis [71] in 1934 began to influence surgical and especially neurosurgical operative strategies and thus may have changed the preference for large scale approaches in favour of operative techniques with less iatrogenic tissue traumatization.

It can be regarded as a fact that the introduction of cerebral angiography and of pneumencephalography as well as the increase in basic physiological knowledge also had an impact on the endoscopic treatment of hydrocephalus in the 1930's and 1950's as reported by Putnam [106] and Scarff [120, 121, 122]. With cerebral angiography and pneumencephalography as diagnostic means it was possible to visualize the choroid plexus of hydrocephalic patients preoperatively and to determine sectors in the lamina terminalis and in the tuber cinereum for the safe fenestration of the third ventricle in occlusive hydrocephalus.

For several decades the endoscopic treatment of hydrocephalic problems remained the only indication for the use of endoscopes in neurosurgery, but endoscopic hydrocephalus surgery lost its significance with the advent of ventriculoperitoneal and ventriculoatrial shunt methods.

Due to further advances of microanatomical and radiographic knowledge of the skull base and the subarachnoid cisterns [70, 76], and due to improved neurosurgical instruments for micropreparation and hemostasis [14, 69, 77] in the 1950's and 1960's, there was an increasing tendency in neurosurgery to attack lesions involving the skull base and the basal subarachnoid cisterns. Unlike the ventricular system and the brain surface itself these locations provided only narrow working spaces in close vicinity to important structures, and a number of neurosurgeons worldwide started to develop microsurgical techniques and introduced the surgical microscope into neurosurgery [10, 18, 27, 68, 69, 72, 77, 102, 103, 107–110, 127, 128, 130, 136, 139, 140, 142].

This most important instrument of today's neurosurgery allowed for better coaxial viewing, better illumination of the surgical field, better assistance and teaching of the residents. At the time when the first operations with surgical microscopes were made in neurosurgery, neurosurgeons were also introducing rigid and flexible endoscopes into microneurosurgery. Ogata *et al.* [91] in 1965 developed a rigid neuroendoscope ("encephaloscope") and Fukushima [35, 37] was the first neurosurgeon to make use of flexible endoscopes ("ventriculo-fiberscopes") for endoscopic biopsy of intraventricular tumors. These first experiences with improved intraoperative viewing provided by endoscopes and especially by microscopes induced an enormous interest in microsurgical anatomy of the peripheral and central nervous system [70, 76, 105, 108, 109, 110, 141]. In the 1970's and early 1980's the surgical microscope became the most important instrument in neurosurgery and, together with new developments in diagnostic techniques like the introduction of computed tomography and magnetic resonance imaging, it allowed for the treatment of more complicated neurological diseases with a better outcome.

In addition, during that time, further important developments in neuroendoscopy as well as in stereotaxy were achieved, e.g. the technique of endoscopic evacuation of intracerebral hematomas [8, 9], stereotactic aspiration of colloid cysts of the third ventricle with and without endoscopic control [13, 26, 96, 145], stereotactic guided microsurgery of cerebral lesions [28], endoscopic biopsy of intraventricular tumors [35, 39], further refinements of the technique of endoscopic third ventriculostomy [42, 134], fenestration of intraventricular cysts with flexible steerable endoscopes and argon lasers [103], to mention only a few.

However, quite soon some neurosurgeons realized that the intraoperative use of the surgical microscope alone had its limitations, especially

when it came to side viewing properties and to the depiction of small yet important details in deep-seated intracranial spaces. One solution of this problem was seen in extending the approaches [48, 81, 124, 133], another solution was the application of mirror systems to inspect hidden corners of the surgical field as suggested by Sugita *et al.* [128] in 1975. The third and, in our opinion, the most elegant possibility to solve the problem of insufficient intraoperative control of intracranial hidden corners was proposed by Prott [105] in 1974 when he performed endoscopic cisternoscopy of the cerebellopontine angle, by Apuzzo *et al.* [6] in 1977 when they introduced the so-called side-viewing telescope for intracranial applications during open microsurgery, and by Oppel [94] in 1981 when he applied intraoperative endoscopy during procedures in the cerebellopontine angle to enlarge the visual field of the surgical microscope in the course of tumor exstirpation in the cerebellopontine angle and in the course of microvascular decompression. All of these three studies can be regarded as the initiation of endoscope-assisted microneurosurgery, which, along with other neuroendoscopic techniques, experienced a revival in the 1990's [17, 33, 40, 78, 82, 84, 90, 100, 101, 131, 132]. This ongoing revival of neuroendoscopy seems to be due to further improved endoscopic technical equipment and also to an enormous progress in computer-based diagnostic and neurosurgical technologies [7].

It is obvious that the increasing numbers of clinical procedures using neuroendoscopy recently induced an increasing interest not only in microsurgical anatomy but also in endoscope-specific neuroanatomy [36, 39, 65, 78, 84, 90, 92, 97, 100, 105]. Everyone performing neuroendoscopic procedures realizes quite soon that the knowledge of neuroanatomy has to be expanded, because the dimensions and the topography of intracranial and spinal structures as seen through the endoscope may appear very different from the same structures seen through a surgical microscope. In the 1970's Apuzzo *et al.* [6], Fukushima [36], and Prott [105] described the endoscopic anatomy of the cerebellopontine angle, and these studies were of importance for endoscope-assisted microsurgery performed in this intracranial area. Just recently, in the 1990's, Karakhan [65], McKennan [84], O'Donoghue and O'Flynn [90], Oka *et al.* [92], and Perneczky *et al.* [97] published a number of important studies on endoscopic neuroanatomy and endoscopic topography of various intracranial regions like the ventricle system, the subarachnoid space of the anterior, middle, and posterior cranial fossa as well as parts of the skull base.

## Endoscopic Equipment for Neurosurgery

The endoscopic equipment used for neurosurgical procedures consists of rigid and flexible endoscopes, trocars for the coaxial guidance of the scopes

and instruments, various instruments for grasping, cutting, and hemostasis, fixation devices for the scopes or the trocars, light sources, and equipment for viewing and documentation of the endoscopic images.

### *Endoscopes*

A variety of endoscopes for virtually every kind of practical use in neurosurgical intracranial procedures is available today.

The scopes are divided into two main groupes, rigid endoscopes and flexible endoscopes. Rigid endoscopes are also called lensscopes while flexible endoscopes are usually constructed as fiberscopes.

Rigid endoscopes or lensscopes are built of three main components: the lens system itself, an integrated illumination glass fiber, and a steel alloy shaft incorporating these elements.

In modern rigid endoscopes the lens system is usually composed of a serial array of different lenses, the objective lens or front lens at the distal tip of the instrument, the relay system consisting of a varying number of rod lenses, and the ocular lens at the ocular or eyepiece. The rod lens system, invented by Hopkins and therefore also called the Hopkins system, provides a picture with excellent quality of contrast, brightness, and colour. As this system is composed of rather long and thin lenses the major shortcoming of the rod lensscopes is their remarkable fragility.

The main advantages of rigid lensscopes are endoscopic images of high quality regarding resolution and colours. In addition, they are focussable to varying object distances, the rigid shaft can be easily controlled as it will never bend in a blind corner, and they can be safely sterilized in an autoclave at 134 °C.

Rigid endoscopes are available with diameters of 1.2 to 12 mm and with shaft lengths of 60 to 400 mm. The shafts may be straight or angled at 90°. The latter endoscopes are very useful for endoscope-assisted microsurgical procedures as the eyepiece of such angled endoscopes does not obscure the visual field of the surgical microscope. Endoscopes with diameters of 2 to 6 mm and with lengths of 100 to 250 mm are most frequently used for intracranial neuroendoscopy.

The front lens of rigid endoscopes can be constructed with prisms of different degrees of inclination, 0°, 30°, 70°, and 110°. This leads to 0°-, 30°-, 70°-, and 110° lensscopes with corresponding viewing angles. 0°-scopes allow for a straight forward view, 30°-scopes for a side forward view, 70°-scopes for a side view, and 110°-scopes for a backward view.

Rigid lensscopes can be used for almost all intracranial endoscopic or endoscope-assisted procedures, but they cannot be used to move around corners which might be sensitive neural or vascular structures within the operating field.

This seems to be the main advantage of flexible endoscopes which are also called fiberscopes because of their construction of glass fiber bundles integrated into a plastic tube. The inner filling with several thousand glass fibers serves as a light transmission system towards the tip of the endoscope and, at the same time, as an image transmission system towards the proximal end of the scope. The image arriving at the proximal part is observed through an eyepiece.

There are two different image fiber systems, the bundle fiber type and the multicore fiber type. The bundle fiber type is composed of a huge number of glass fibers fixed in identical arrangements at the distal and the proximal end of the endoscope while in the intermediate section the fibers are only loosely arranged. Due to this loose arrangement of fibers in the intermediate section the bundle fiber type endoscope provides a high degree of flexibility. In contrast, the multicore fiber type is composed of glass fibers fused over the entire length of the endoscope. This method of glass fiber arrangement reduces the production costs, allows for small bundles with a high number of fibers, thus an improved image quality, but, as a disadvantage, decreases the flexibility of the instrument as well. Flexible endoscopes may be constructed as instruments with passively bendable shafts or as fiberscopes with steerable tips. The steering of the tip should, in our opinion, better be called active bending of the distal end of the endoscope. In these "steerable" endoscopes the distal section of the instruments retains a number of tiny hinges which are moved by fine wires connected to a fingerpiece at the proximal end of the scope. The length of the distal bending section of these endoscopes usually ranges between 12 and 35 mm depending on the outer diameter of the scope.

The number of glass fibers determines the number of picture elements to be acquired with a flexible endoscope. The number of picture elements therefore is the limiting factor for the resolution of the image at the eyepiece. As a corollary, larger diameters of fiberscopes allow for more glass fibers inside and provide for a better resolution of the endoscopic image. For example, about 1.000 to 10.000 fibers can be packed into fiberscopes with outer diameters of up to 4 mm whereas 10.000 to 100.000 fibers require diameters of up to 15 mm. Regarding these diameters it is clear that the number of picture elements of most neuroendoscopes ranges between 1.000 and 10.000.

The disadvantages of flexible scopes are that they have a resolution worse than the rigid ones, that they are not focussable, and that they cannot be autoclaved but must be gas-sterilized, which allows for only a limited number of sterilization cycles.

Thus rigid endoscopes are preferable whenever this is possible. Especially for endoscope-assisted microneurosurgery it is recommended to apply rigid endoscopes as only the shaft of rigid instruments can be posi-

tioned and fixed precisely in the operating field. For this purpose we use rod lensscopes as well as fiberscopes with a curved rigid steel shaft which may be used as dissectors and therefore are called "viewing dissectors".

Principally because of their superior image quality, we use lensscopes with 4 mm outer diameter, a shaft length of 160 mm, viewing directions of 0°, 30° and 70°, and an image angle of 90°. Whatever neuroendoscopic procedure is being carried out, it is strongly recommended to start the endoscopic part with a 0° lensscope for straight forward viewing. This facilitates the intraoperative orientation within the intracranial anatomy. In a second step, in order to look around corners, 30° or 70° lenses may be used, but the application of these latter scopes requires a careful control of the tip of the instrument and its shaft which should be guided through a trocar or under the surgical microscope, because, especially with the 70° lens, the viewing sector is outside of the axis of insertion.

### *Instruments Used During Endoscopic Procedures*

When performing neuroendoscopic procedures like third ventriculostomy it is important to use trocars together with the lenses. These trocars enable the coaxial insertion of the lensscope and of microinstruments without touching the surrounding brain tissue. The types and forms of trocars are numerous. Usually, in neuroendoscopy, their outer diameter ranges between 4 and 7 mm depending on the number of channels inside. For third venticulostomy, a trocar system with at least four channels should be the minimum, one channel for the lensscope, one for the instruments, one for irrigation, and one for the outflow of the irrigation solution and drainage of cerebrospinal fluid. The trocar, when occupied by the channel obturators, should have a blunt tip to prevent laceration of vessels within the brain tissue during insertion.

Further instruments for neuroendoscopic procedures are micro scissors with sharp and blunt tips, biopsy forceps, grasping forceps, and Fogarty balloon catheters of varying diameters.

Hemostasis during neuroendoscopic procedures can be achieved by continuous irrigation with Ringer solution, by inflation of the Fogarty balloon catheter in vicinity of the oozing, and with bipolar or monopolar electrodes. The monopolar electrodes may have various shapes like hook electrodes or sharp and blunt needle electrodes.

The most important instrument for the application of endoscopy is the light source connected to the endoscope via a glass fiber light cable. Usually, the light source is a halogen metal vapor arc lamp, filtered to exclude the hot infrared spectrum, and transmitted towards the endoscope via a glass fiber light cable 350 cm in length, which should be sterilizable in an autoclave at 134 °C. The light intensity necessary to illuminate the

intracranial surgical site may be set manually, but, in addition, the light intensity of most of the modern cold light sources can be controlled via a direct video signal system operating within the cold light source for optimum light intensity.

### *Fixation Devices for Neuroendoscopes*

In order to fix safely the trocars and endoscopes intracranially during neuroendoscopic procedures it is of the utmost importance to use strong fixation devices. There are several ways to achieve safe fixation:

In the course of stereotactic guided neuroendoscopic operations the trocars together with the endoscopes can be fixed with special adapters to the stereotactic frame.

Another fixation method for neuroendoscopes is the use of a combination of two Leyla retractor arms.

Recently, with the revival of neuroendoscopic techniques, special flexible support arms which allow for precise 3D positioning and fixation of the endoscope and the attached chip camera in any required position have been constructed. These strong support arms are connected via adapters to the side rail of the operating table. The fixation of such support arms can be achieved mechanically or pneumatically.

Most fixation elements have at their disposal various adapters for the different endoscopes and trocars.

### *Equipment for Observation and Documentation of Endoscopic Images*

To look through the ocular of the neuroendoscope with the naked eye should never be attempted because of the disturbance of sterile conditions and because of ergonomic problems. Efficient working with a neuroendoscope, whether it is a flexible scope or a lensscope, is impossible without a video system. Thus, the observation of the endoscopic image during the procedure with video equipment is absolutely necessary. In addition, the documentation of neuroendoscopic operations is strongly recommended, to improve the learning experience for the surgeon, and to meet the need to teach and train residents. Adequate documentation can be achieved with videotaping or with printing.

The video equipment for neuroendoscopy consists of special endoscope video camera heads attached to the endoscope ocular via a patent stopper device. This camera head is connected to the camera control unit through a camera cable. Although the camera head and the camera cable usually may be gas sterilized, frequent sterilization with gas reduces the lifespan and the quality of the camera. Therefore draping of the camera head and the camera cable with a sterile plastic cover sheet is preferred.

All modern CCD video cameras for endoscopy provide digital image

processing which is suitable for videotaping as well as for videoprinting. For most neuroendoscopic procedures 1-chip-cameras are sufficient, especially when fiberscopes are used. For special neuroendocopic tasks with the necessity for precise colour separation 3-chip-cameras are available which separately digitalize the red, green, and blue components of the video signal. However, the use of 3-chip-cameras only makes sense with high quality lensscopes but not with fiberscopes. Naturally, PAL-, SECAM-, and NTSC-versions of most video cameras are available for worldwide use of video equipment in neuroendoscopy.

The video signal from the camera is transmitted to the video tape recorder, which should at least be of super-VHS-quality, and from there to at least two video monitors, one for the surgeon and another one for the assistant and the nurse, for permanent observation of the intracranial surgical site. The monitors should be placed in front of the surgeon and the assistant for ergonomic working facilities.

For endoscope-assisted microneurosurgery with parallel use of endoscopes and the surgical microscope there are several possibilities to observe both microscopic and endoscopic images. The endoscope video signal may be transmitted to a video monitor as described above. Alternatively, it may be transmitted to an LCD-screen mounted directly beside the surgeon's microscope eyepieces, as suggested by Taneda *et al.* [131] in 1995. A third alternative to observe both microscopic and endoscopic images at the same time is to use a commercially available twin video system (Storz Company, Tuttlingen, Germany) which allows for a picture-in-picture viewing mode of endoscopy and surgical microscopy. Other solutions for parallel viewing of endoscopic and microscopic sequences like head-mounted LCD-screen glasses or display of endoscopic images into the microscope oculars are only in an experimental stage and are currently not available for routine endoscope-assisted procedures.

For digital image documentation the video signal from the CCD-camera can also be used. Digital image storage of the video signal is possible with virtually all personal computers equipped with commercial video cards. The digital images obtained in the single frame mode can be edited with special software to improve the image quality, to enhance contrast, and to produce photographic prints for the medical record as well as slides for professional presentation and scientific publications. Documentation of endoscopic images for the medical record can also be achieved with a video-colour-printer fed with signals from the video tape recorder.

## Surgical Techniques and Indications of Intracranial Neuroendoscopy

The surgical techniques for intracranial neuroendoscopy can be divided into three groups:

1. Distinct neuroendoscopic techniques with the use of scopes, endoscopic trocars, and endoscopic instruments alone introduced through regular burr-hole trephinations.
2. Neurosurgical techniques with the endoscope as the main instrument for viewing, but with usual microinstruments inserted along with the endoscope.
3. Endoscope-assisted microneurosurgery with the microscope as the main viewing instrument and the endoscope as an additional optical aid in the course of the surgical procedure.

While neuroendoscopy currently covers almost the entire spectrum of intracranial surgery with the exception of functional neurosurgery, i.e. hydrocephalus surgery, tumor surgery, and cerebrovascular surgery, each of these various applications of endoscopy is recommended for special indications. As mentioned earlier, neuroendoscopic techniques can be used for procedures in ventricular surgery, intraparenchymal surgery, subarachnoid space surgery, and skull base surgery.

Endoscopic techniques for intracranial surgery with special systems developed for well-defined indications are applied in third ventriculostomy [16, 38, 41, 42, 87, 121, 134], in endoscopic pellucidotomy [16], in endoscopic evacuation of third ventricle colloid and parasite cysts [24, 74, 89, 96], in endoscopic fenestration of suprasellar arachnoid cysts [15, 23, 46, 104, 116, 119, 123] and multichambered hydrocephalus [16, 75], in endoscopic treatment of aqueductal stenosis [37, 93], in endoscope-guided placement of ventricular shunts [79], in endoscopic evacuation of intracerebral and intraventricular hematomas [9, 16], in endoscopic treatment of intracranial tumors [1, 11, 35, 39, 46, 47, 59, 138, 145], and in the expanding field of endoscope-assisted microneurosurgery [6, 17, 33, 36, 40, 63, 78, 82, 84, 90, 94, 101, 105, 113, 131, 132, 133].

When regarding the numbers of publications concerning the above-mentioned distinct intracranial neuroendoscopic procedures, it is obvious that there are a few well-defined indications which are generally accepted and performed in many centers and, in contrast, a large number of less well-defined indications confined to special cases and performed in only a few centers.

### *Endoscopic Third Ventriculostomy and Endoscopic Pellucidotomy*

Third ventriculostomy or third ventriculocisternostomy is one of the most important intracranial neuroendoscopic procedures, with a long history. After an era of routine implantation of ventriculoperitoneal and ventriculoatrial shunts in communicating and non-communicating hydrocephalus of any kind of etiology, today endoscopic third ventriculostomy can be regarded as the treatment of choice for a number of forms of non-

communicating hydrocephalus. Endoscopic third ventriculostomy has experienced a renaissance since the late 1980's. This is due mainly to three factors: 1. Newly developed endoscopic systems with sophisticated video equipment designed for ventricular surgery have been introduced into the market. 2. The preoperative diagnostic techniques have been much improved with the advent of magnetic resonance imaging including magnetic resonance-based cerebrospinal fluid flow studies, which is an extremely important means for the diagnosis of non-communicating hydrocephalus. 3. The unsatisfactory long-term experience with relatively high failure and infection rates of shunt systems. There is agreement that endoscopic third ventriculostomy is indicated for the treatment of all acute and chronic forms of non-communicating hydrocephalus. If the entire neurosurgical team of a center is experienced in this minimally invasive surgical technique, endoscopic third ventriculostomy may be performed not only in elective cases but also in emergency situations requiring a few minutes for the whole procedure. Endoscopic third ventriculostomy is indicated for all cases with clinical and radiographic (CCT or MRI) findings of non-communicating hydrocephalus. This comprises a number of non-communicating hydrocephalus types with stenosis or closure of the aqueduct as well as cerebrospinal fluid pathway obstructions within the fourth ventricle including the apertures of the fourth ventricle. Not only the imbalance between the size of the upper three ventricles and the fourth ventricle is important for the diagnosis of occlusive hydrocephalus. The bulging of the third ventricle floor towards the diaphragma sellae, the prepontine cistern, and the basilar artery tip is a reliable sign of obstructive hydrocephalus and may serve reliably to exclude supratentorial brain atrophy, which is the most important differential diagnosis of non-communicating hydrocephalus. This downward bulging of the third ventricle floor usually is nicely seen in sagittal MRI studies, and therefore sufficient MRI diagnostics including MR cerebrospinal fluid flow studies are recommended for preoperative planning in elective and urgent but not in emergency cases of non-communicating hydrocephalus.

Endoscopic third ventriculostomy can most often be carried out as a free-hand procedure as the frontal horn of the lateral ventricle, the foramen of Monro, and the third ventricle are usually wide enough to allow navigation down to the tuber cinereum. Stereotactic planning of endoscopic third ventriculostomy may sometimes be necessary in cases with a narrow foramen of Monro, in cases with scarring at the floor of the third ventricle when the typical landmarks are not clearly visible, or in cases with deformed lateral ventricles.

At the beginning of the procedure the patient's head must be fixed as once the scope has passed the foramen of Monro, any head movement may seriously damage the fornix, the veins or the plexus at this level. The

external landmark on the skull for burr-hole trephination is the coronal suture about 2 to 2.5 cm from the midline. The exact position of the burr-hole can easily be determined using coronal and sagittal MR images with a straight line drawn from the imaginary burr-hole through the foramen of Monro down to the imaginary stoma at the floor of the third ventricle. Following the trephination and opening of the dura the frontal horn of the lateral ventricle is punctured with a Cushing needle, and after withdrawal of the needle the same trajectory is followed with the endoscope trocar. Under endoscopic view and continuous irrigation the ventriculoscope is then navigated through the foramen of Monro leaving the typical landmarks like choroid plexus, thalamostriate vein, septal vein, fornix, and caudate nucleus untouched. The tip of the ventriculoscope is then fixed in front of the tuber cinereum, where between the infundibular recess rostrally and the mamillary bodies caudally the thinned-out floor of the third ventricle is usually transparent enough to give a view to the basilar tip, the P1-segments of the posterior cerebral arteries, the posterior communicating arteries, the prepontine cistern, and the posterior clinoid processes. The stoma is made between the infundibular recess and the mamillary bodies rostrally to the basilar tip in order not to injure the thalamoperforating arteries emerging in a dorsocraniolateral direction from the basilar artery and the posterior cerebral arteries. In most cases the stoma is performed with a Fogarthy balloon catheter. The tip of the catheter is punctured through the third ventricle floor, and the small stoma is then dilated with the inflated balloon. After the stoma has been created the tip of the ventriculoscope is navigated down into the prepontine cistern in between the basilar trunk and the clivus in order to carefully observe the basal subarachnoid cisterns for existing membranes sometimes impairing the CSF flow through the stoma. If such membranes exist they are opened in the same fashion with the balloon catheter.

In shunt-dependent patients with a functioning shunt, who should become shunt-free following third ventriculostomy, it is important to ligate the shunt 2 to 3 days after the procedure to prevent the closure of the stoma. Functioning shunts frequently induce closure of the stoma as they reduce the CSF flow through the stoma. If the ligature of the shunt is well tolerated over a period of about 3 months and if, in addition, MR imaging flow studies carried out 2 to 3 months after third ventriculostomy and shunt ligature demonstrate good patency of the stoma and a reduction in the size of the ventricles, the shunt can be removed.

Endoscopic pellucidotomy is carried out in the same way as third ventriculostomy. Endoscopic pellucidotomy is indicated in virtually all forms of acute or chronic unilateral obliteration of the foramen of Monro with unilateral dilatation of a lateral ventricle and clinical signs of raised intracranial pressure. Unlike third ventriculostomy, the position of the burr-

hole is chosen about 4 cm from the midline at the coronal suture, but should not be too far lateral, in order not to injure the ipsilateral head of the caudate nucleus when puncturing the frontal horn of the lateral ventricle with the ventriculoscope trocar. Under endoscopic view the ventriculoscope is navigated through the frontal horn down to the septum pellucidum. Here the stoma is made into the septum at a position where no veins run. Usually, this position can be nicely determined under endoscopic view. Like in third ventriculostomy a balloon catheter is used to puncture the septum. At this point the utmost care must be taken not to penetrate the lateral wall of the non-dilated frontal horn of the contralateral ventricle.

The methods of endoscopic third ventriculostomy and endoscopic pellucidotomy as presented above may be modified according to the personal experience of the neurosurgeon. Stereotactic methods, whether frame-based or frameless, laser techniques, ultrasound-guided techniques, or various techniques of neuronavigation may be used in conjunction with endoscopic third ventriculostomy [16, 38, 41, 42, 87, 121, 134]. To learn more about these additive methods it is recommended to study the pertinent literature. However, assessment of the results of endoscopic third ventriculostomy has become controversial. Clinical and radiographic signs of improvement after third ventriculostomy have been extensively discussed in the literature. In our experience it is usually sufficient to see clinical improvement, i.e. disappearance of signs and symptoms of raised intracranial pressure. Radiographic signs such as CSF flow at the level of the stoma, reduction of the width of the third ventricle, or reduction of the dilation of the lateral ventricles are secondary for the judgement of improvement. If a patient after third ventriculostomy is free of symptoms, but the stoma is not clearly depicted or the dilated ventricles do not show a reduction in size in postoperative MR imaging studies, we do not repeat the ventriculostomy. The only indication for repeat ventriculostomy is lack of clinical improvement.

### *Endoscopic Evacuation of Third Ventricle Colloid Cysts*

The neurosurgical treatment of colloid cysts of the third ventricle has been controversial for many years [2, 13, 16, 24, 26, 46, 74, 80, 89, 96]. Shunting procedures, open microsurgical resection [2, 74], stereotactic aspiration [13], endoscopic evacuation [24], or combinations of these techniques [26, 46, 74, 80, 96] have been advocated as the best treatment modalities for these lesions. Although it has been reported [74] that endoscopic evacuation provides better short-term postoperative results than microsurgical transcallosal resection, it seems that none of these techniques alone is the treatment of choice. There are too many variables that influence the post-

operative long-term results like the size of the cyst as well as the size of the ventricular system, the viscosity of the colloid cyst content, the age and clinical condition of the patient, and mainly the experience of the neurosurgeon. Recently, this has been shown in a consecutive 12-year series compiled by Mathiesen *et al.* [80].

For this reason we do not recommend endoscopic evacuation as the one and only surgical procedure for third ventricle colloid cysts. Usually, in cases with dilated lateral ventricles and signs of elevated intracranial pressure the subarachnoid space of the interhemispheric fissure is very narrow. Thus, the interhemispheric transcallosal approach is deemed to be traumatic in cases with dilated lateral ventricles. In such cases we start with an endoscopic transcortical transventricular approach through a small craniotomy 3 cm in diameter, and we navigate the ventriculoscope down to the foramen of Monro where the wall of the colloid cyst is always visible through the endoscope. There the cyst may be coagulated, punctured with a sharp needle and aspirated under endoscopic control. In our opinion, it is rarely feasable to aspirate the whole cyst content and to remove the cyst wall through the working channel of the ventriculoscope. Usually, parts of the colloid remain stuck to the cyst wall which itself is often firmly attached to the roof of the third ventricle and to the choroid plexus. Pure endoscopic removal of such attached elements is not recommended as this action may induce too much trauma and a number of complications.

Therefore, if the cyst is not easily aspirated through the ventriculoscope, we use the surgical microscope via a small 1.5 cm corticotomy and resect the cyst microsurgically. The microsurgical interhemispheric transcallosal approach is used in cases with a narrow ventricle system and thus with a wide subarachnoid space in the interhemispheric cistern which gives good access to the corpus callosum. In cases where we start with a microsurgical approach the endoscope is used in the course of the procedure when parts of the cyst wall extend into hidden posterior corners of the third ventricle, and therefore such an endoscopic procedure may be designated endoscope-assisted microsurgery.

### *Endoscopic Fenestration of Arachnoid Cysts*

As with the treatment of third ventricle colloid cysts there is also continuing discussion of the best surgical treatment of intracranial arachnoid cysts [15, 16, 23, 39, 40, 104, 116, 119, 123]. Apart from shunting arachnoid cysts, which in our opinion should be avoided because of frequent shunt complications, the microsurgical therapy of these cysts has been a standard procedure since the early 1960's with Liljequist's detailed description of the subarachnoid spaces at the base of the brain. However, developing endoscopic techniques and other technical capabilities in the 1980's and 1990's

induced a number of neurosurgeons [15, 23, 104, 116, 119, 123] to use these endoscopic techniques for the fenestration of intracranial arachnoid cysts at various locations. Although for well-defined subgroups of intracranial arachnoid cysts endoscopic surgery may be the therapy of choice, there are some concerns about the regular application of pure endoscopic interventions for any arachnoid cyst. One concern is that arachnoid cysts frequently have quite tough membranes, and thus, during an exclusive endoscopic procedure, the available microinstruments applied through the working channel of the endoscope may not be adequate to open the membranes wide enough or to resect parts of the cyst wall. If the membranes are not fenestrated sufficiently this would induce an early closure of the cyst.

In our experience especially the arachnoid cysts located in the temporal region and in the posterior fossa have rather tough membranes. This may be caused by a more densely packed arachnoid trabecular network in some intracranial areas like in the region of Liljequist's membrane being one of the most well-known intracranial arachnoid structures, but also in the vicinity of the carotid cisterns or in the quadrigeminal cistern, which is usually closed dorsally with a tough whitish arachnoid layer. All these dense arachnoid layers are frequently encountered during microsurgical procedures such as in the course of an infratentorial supracerebellar approach to the pineal region [127], even if there is no arachnoid cyst.

Suprasellar arachnoid cysts, especially when they extend into the ventricular system, are different from this as they frequently, but not always, present with thin walls which may be easily opened with endoscopic microinstruments.

Recently, it has been shown nicely with endoscopic methods by Santamarta *et al.* [119] and by Schroeder *et al.* [123] that many if not all symptomatic intracranial arachnoid cysts present with a slit-valve mechanism, where the slit-valve allows inflow of cerebrospinal fluid into the cyst during one cardiac cycle thus supporting the growth of an untreated symptomatic arachnoid cyst.

In conclusion, the following regimen is recommended for symptomatic intracranial arachnoid cysts, whatever the presentation:

The first preoperative investigation is an MR imaging flow study, which in a number of cases demonstrates non-communication of the cyst with the subarachnoid space. In well-selected cases with contradictory or unclear MR imaging findings cranial CT cisternography may be very helpful to determine the amount and time course of contrast medium enhanced cerebrospinal fluid communicating with the cyst.

The aim of surgery is to restore the communication of the arachnoid cyst content with the cerebrospinal fluid within the subarachnoid space of the cisterns or within the ventricles. This means that as much as possible of the cyst wall should be fenestrated or even resected.

According to recent studies [15, 119, 123] and to our personal experience most suprasellar arachnoid cysts bulging into the ventricular system are eligible for exclusive endoscopic fenestration. Therefore, in suprasellar arachnoid cysts endoscopic fenestration may turn out as the treatment of choice, but long term results are still needed. In all other cases with temporal cysts or with cysts in the posterior fossa in which the cyst walls extend from the inner table of the vault down to the subarachnoid cisterns, a combined microsurgical endoscopic procedure is advised. In these cases we start with a burrhole over the area where the cyst wall reaches the vault. After opening of the dura and of the parietal cyst membrane a ventriculoscope retaining 2 to 3 working channels is introduced into the cyst under continuous irrigation. The ventriculoscope is advanced down to the visceral part of the membrane where usually typical anatomical landmarks like cranial nerves or arteries of the circle of Willis are seen shimmering through the visceral cyst membrane. If testing with a balloon catheter or endoscopic microscissors inserted through the working channels of the scope demonstrates tough, rigid cyst walls which do not allow for sufficient endoscopic fenestration, the burr-hole is enlarged to a small 2 cm craniotomy. Under the surgical microscope the visceral membrane is then fenestrated or partially resected as widely as possible, creating arachnoid windows in between the cranial nerves, the arteries, and bridging veins at the base of the brain with standard microsurgical instruments. Before finishing, the endoscope can conveniently be used to inspect the created windows for small additional membranes in the depth of the surgical site, which are sometimes not clearly visible with the surgical microscope. These deeper membranes may then be fenestrated with standard microscissors or diamond knives through the craniotomy under endoscopic control.

Thus, most surgical procedures for intracranial arachnoid cysts are started as endoscopic interventions, but in their course require the additional use of the surgical microscope. Nevertheless, the combination of the surgical microscope and the endoscope in arachnoid cyst surgery is extremely useful.

### *Endoscopic Evacuation of Intracranial Hematomas*

An array of techniques for endoscopic evacuation of intracranial hematomas has been described over more than a decade [9, 11, 39, 44, 65]. Although they seem to be easy to apply with the appropriate endoscopic instruments not all these endoscopic techniques for hematoma evacuation have gained widespread general acceptance, and this is mainly due to the clinical presentation. Most acute intracranial extracerebral hematomas, whether acute epidural or acute subdural, present as emergency cases with clinical signs of raised intracranial pressure and rapid neurological deterio-

ration. For virtually all epidural and acute subdural hematomas immediate removal via a large craniotomy is the treatment of choice. For this purpose usually a quick emergency team and a good craniotome are sufficient, and detailed preoperative planning or a surgical microscope are not necessary. The surgical factors of primary importance for the prognosis of patients with acute epidural or subdural hematomas are the time interval from diagnosis to surgery, an adequate craniotomy, and an accurate hemostasis including dura holding stitches before closure to prevent a recurrence of the hematoma. Therefore endoscopes in the surgical treatment of acute epidural and subdural hematomas strictly have to be refused—we never use them in such cases; none of the important steps mentioned above can be achieved with endoscopes of any kind.

With acute intracerebral or intraventricular hematomas things are different. For the correct surgical treatment of intracerebral or intraventricular hematomas a detailed preoperative planning and the intraoperative use of the surgical microscope is necessary. Usually, microsurgical removal of the hematoma under the microscope is sufficient. However, in a few selected cases with intraventicular hematomas filling out all compartments of one lateral ventricle, i.e. frontal, temporal, and occipital horn, or in cases with hematocephalus and consecutive hydrocephalic dilation of the ventricles the intraoperative use of an endoscope in addition to the microscope can help to remove hidden parts of the clot which may not be visible through the microscope. For this purpose, after partial evacuation of the hematoma under the microscope, an endoscope is introduced into the hematoma cavity or into the lateral ventricle, and suction and washing out of remaining clots is completed under endoscopic control.

Exclusive endoscopic evacuation of intracerebral hematomas has been advocated by Auer *et al.* [9], but this method has not achieved broad acceptance. Nevertheless, in the hands of an experienced neurosurgeon with extensive endoscopic training, endoscopic evacuation of intracerebral hematomas in circumscribed cases may be a good alternative to conventional microsurgical removal. It is important to mention that good irrigation of the cavity is needed for endoscopic hematoma removal, because blood sticking to the front lens of the scope will abolish visual control and orientation.

Hellwig and Bauer [46], in 1992, described a neuroendoscopic technique to assist evacuation of multi-loculated chronic subdural hematomas with a flexible endoscope via a single burr-hole trephination. We have used this technique in a number of cases with encouraging results. After opening of the dura and of the parietal layer of the chronic subdural hematoma the first cavity is irrigated until water-clear solution is washed out. Then a flexible endoscope is introduced into the cleared cavity and advanced towards the membranes enclosing the second and any further loculi of the

chronic subdural hematoma. The membranes are perforated with the tip of the endoscope itself or with microinstruments or a balloon catheter. Care should be taken not to injure the cortical surface with uncontrolled movements of the flexible endoscope shaft and to irrigate thoroughly. The endoscope may also be used to control the introduction and the position of the subdural drainage before closure of the wound. We would like to stress that this endoscopic technique is not indicated for chronic subdural hematomas with a single cavity.

### *Endoscopic Treatment of Intracranial Tumors*

Treatment of brain tumors with endoscopes as the main surgical instruments is described extensively in a number of publications [1, 11, 12, 35, 37, 46, 47, 59, 63, 93, 113, 115, 145]. To date, endoscopic treatment of intracranial tumors is mainly restricted to endoscopic fenestration of tumor cysts, endoscopic therapy of tumor-associated occlusive hydrocephalus, and endoscopic sampling of tumor biopsies. Other than with some very recent thoracoscopic methods to remove spinal tumors and to stabilize the thoracic vertebral column [25, 114, 115] intracranial neuroendoscopy is not applicable to remove or even to reduce the size of the vast majority of intracranial tumors. This is due to the fact that today there is not a single instrument which could be applied through the working channel of available endoscopes and which would remove tumor masses within reasonable margins of time and safety.

Nevertheless, especially in diagnostic interventions for intracranial tumors affecting the ventricular system, i.e. those infiltrating the ventricular ependyma or those bulging into the ventricles, endoscopes have become popular adjuncts of stereotaxy and open surgery. The techniques for endoscopy-guided sampling of biopsies are manifold including free-hand, frame-based and frame-less stereotactic procedures. Flexible and rigid endoscopes have been used to take biopsies from intraventricular tumors or to fenestrate cystic lesions. Fukushima [35] described a fiberendoscopic transventricular technique to biopsy intraventricular tumors and to perform aqueductoplasty of the mesencephalic aqueduct. Abdullah and Caemaert [1] reported on the endoscopic treatment of three patients with craniopharyngioma using rigid lensscopes. Hellwig *et al.* [46, 47] and Zamorano *et al.* [145] combined stereotactic biopsies of ventricular tumors or tumors affecting the cranial midline with endoscopic supervision of the sampling process. Benabid *et al.* [12] proposed a robotic system for endoscopic biopsy of intracranial tumors.

Although there are numerous reports on endoscopic treatment of intracranial tumors, these endosurgical techniques require well-defined indications and they are not easy to carry out. Much neuroendoscopic experience

is necessary to navigate an endoscope towards the tumor with precision, to take adequate biopsy samples, and to perform sufficient hemostasis.

In our opinion the indications for endoscopic tumor biopsies are rare for those tumors involving the lateral ventricles and the fourth ventricle. For lateral ventricle tumors, usually microsurgical exposure and subtotal or total removal are more effective but not much more invasive than taking biopsies. The same is true for fourth ventricle tumors which, in addition, quite frequently obliterate the cerebrospinal fluid outflow at the apertures of the fourth ventricle. Therefore, microsurgical removal of lateral ventricle lesions or fourth ventricle tumors is thought to be superior to endoscopic biopsy sampling.

With tumors affecting the confines of the third ventricle or bulging from the suprasellar space upwards into the third ventricle things may be different. For a number of patients with such lesions it seems to be beneficial to take tumor biopsy samples under endoscopic control, whether freehand or guided by stereotaxy, to verify the diagnosis and to continue the treatment with non-surgical methods such as radiation. Entering the third ventricle with an endoscope seems to be less invasive than most microsurgical approaches to this complex area. In addition, in patients with noncommunicating hydrocephalus and neoplastic lesions of the posterior part of the third ventricle occluding the aqueduct, not only tumor biopsy samples may be taken under endoscopic control, but endoscopic third ventriculostomy can also be performed in one session. Unless a flexible steerable fiberscope is used for this purpose, advancing a ventriculoscope through the foramen of Monro as well as reaching the tumor in the posterior part of the third ventricle and the floor of the third ventricle in between the infundibular recess and the corpora mamillaria in one session mostly requires the application of a second burr-hole trephination. In these situations one burr-hole for endoscopic third ventriculostomy is placed at the coronal suture, and the second burr-hole for endoscopic biopsy from the posterior part of the third ventricle is placed in the frontal bone about 3 to 5 cm precoronal, based on careful preoperative calculations and with the help of frame-based or frame-less stereotaxy.

### *Endoscope-Assisted Microneurosurgery*

Endoscope-assisted microsurgery makes use of the combined application of two important instruments for intraoperative observation of microanatomical details, the surgical microscope and the endoscope. Usually, endoscope-assisted microsurgery is carried out as a standard microsurgical procedure with the surgical microscope. During the procedure, one or more rigid endoscopes are used to achieve the following important goals: reduction of brain retraction, inspection of hidden corners, and depiction

of microanatomical details which are not precisely visible in the zoomed and thus light-reduced beam of the microscope.

## Significance of Reduction of Intraoperative Traumatization

Since Landis [71] in his pioneering work in 1934 described the physiological range of capillary pressure, it has been shown in a number of studies [3, 4, 5, 31, 34, 45, 49, 86, 100, 126, 129, 135, 143] and has become a widely accepted fact that brain retraction exceeding certain limits causes significant intraoperative trauma to brain tissue and may have adverse effects and sometimes may cause permanent neurologic deficits.

This adverse effect of retraction of superficial brain structures in mainly due to a significant impairment of capillary perfusion and venous outflow leading to a severe reduction of regional cerebral blood flow, especially if cortical veins and/or bridging veins are sacrificed [5, 29, 30, 31, 66, 126, 129, 144]. The preservation of bridging and cortical veins in the vicinity of the brain retraction area is of the utmost importance for the prevention of local venous infarction within the cortex compressed by the brain retractor. Clinical studies [3, 4, 129, 135, 143] have repeatedly demonstrated that even in routine microsurgical procedures with standard head positions and in patients with normal intracranial pressure regional brain retraction pressures usually exceed 20 mmHg (2.66 kPa), especially when only a single retractor is applied and when deep-seated processes are exposed. It is obvious that future microsurgical interventions should aim at a reduction of such high retraction pressures which can lead to local areas of cortical infarction. In addition, it has been shown that the careful choice of the adequate surgical approach permits a significant reduction of retraction of cranial nerves and arteries at the base of the brain.

Thus, to minimize brain retraction and intraoperative trauma various methods [5, 34, 45, 48, 66, 81, 95, 100, 124, 126, 128, 129, 135, 142] have been proposed, e.g. application of special medications and anaesthetic techniques to achieve brain relaxation, special brain retractor systems to reduce the danger of ischemic brain injury, special intraoperative techniques with recommendations for head positioning, cerebrospinal fluid diversion, use of mirror systems, and preservation of bridging veins, as well as special surgical approaches including contralateral approaches to aneurysms of the anterior circulation, trans-third ventricular approaches to high-riding basilar tip aneurysms, and extended approaches through structures of the skull base of the anterior, middle and posterior cranial fossa.

Although most of these methods have their indications in special situations and cases, in our opinion, an elegant and quite simple method that permits a significant reduction of brain retractor application is represented by the intraoperative use of endoscopes. This technique, called "endoscope-

assisted microneurosurgery" is applicable to virtually all microsurgical intracranial interventions involving exposure of preformed spaces like the ventricular system, the sella, and especially the subarachnoid space of the basal cisterns.

## Endoscope-Assisted Tumor Surgery

Endoscope-assisted surgery may be performed in microsurgical approaches to virtually all complex tumours encountered in the ventricles, in the brain parenchyma, in the subarachnoid space including the neighbouring skull base structures, and in the sella [6, 17, 33, 40, 63, 78, 82, 84, 94, 100, 101, 105, 113, 132]. Recently, in a series of 50 patients undergoing transnasal, transsphenoidal surgery, it has been shown that for tumors involving the sella, the suprasellar area, and the upper clivus, endoscope-assisted microsurgery may have advantages over conventional transsphenoidal surgery [63], but long-term results of this rather new technique are still lacking. Although there is a widespread range of possible indications for endoscope-assisted tumor microsurgery [6, 17, 33, 40, 82, 100, 101], this technique, which has been first described in the 1970's by Apuzzo *et al.* [6] and by Prott [105], was primarily used for posterior fossa microsurgery, especially for tumors located in the cerebellopontine angle extending into the internal auditory meatus [84, 94, 105, 118, 132]. Our personal experience with endoscope-assisted microsurgical removal of intracranial tumors comprises more than 200 complex cases of intraventricular lesions, and tumors arising from the skull base or involving important skull base structures.

The technique of endoscope-assisted microsurgery for tumors takes advantage of the space-occupying effect of the lesions. Usually, a space for the endoscope can be created within the tumor cavity or the neighboring cerebrospinal fluid spaces, whether ventricles or subarachnoid space of the basal cisterns, by partial tumor removal under conventional microscopic control. Thus, together with carefully planned positioning of the patient and an adequate craniotomy or craniectomy, in many patients the retraction of nervous or vascular structures to observe and to extirpate the tumor remnants may be markedly reduced or even completely avoided during tumor removal. Endoscopic observation of all hidden angles after completion of tumor extirpation and before closure of the wound may also confirm complete removal of extensive lesions. It is well-known that sometimes this confirmation of total tumor removal is not possible with the surgical microscope alone.

In conventional approaches to tumors affecting skull base structures of the middle and posterior cranial fossae, extensive bone drilling is usually inevitable, to expose and manipulate the tumor and to avoid retraction of the temporal lobe or the cerebellum. However, this extensive bone drilling

may compromise microanatomical structures in close vicinity or within the skull base like, for example, the vestibular system, the carotid artery, the cavernous sinus, and a number of cranial nerves. In such situations intraoperative endoscopy significantly helps to reduce the extent of bone removal, the extent of brain retraction, and the risk to skull base structures. In patients with midline lesions extending far to both sides of the brain stem endoscope-assisted microsurgery may allow removal of the entire lesion in a single unilateral procedure, thus avoiding a second surgical intervention.

Skull base tumors extending into the suprasellar space or into the ventricular system may be approached via subfrontal, subtemporal or transcortical transventricular routes. These approaches, when carried out with conventional microsurgery, quite frequently require significant retraction of the frontal or temporal lobe or, in the case of transcortical approaches, an extended corticotomy may be necessary. During endoscope-assisted microsurgery in most cases the longitudinal diameter of the corticotomies can be reduced to about 1.5 cm. The space created after partial removal of the tumors usually permits excellent navigation of the endoscope under microscopic control down into the surgical site within the lateral ventricles, the third ventricle, the suprasellar, premesencephalic, and prepontine subarachnoid cisterns as well as the upper clivus, the posterior clinoid processes, and the sella turcica.

## Endoscope-Assisted Aneurysm Surgery

Endoscope-assisted microsurgery for intracranial aneurysms is used for direct surgical approaches to deep-seated aneurysms of the posterior circulation (Fig. 1) and large or giant aneurysms of the anterior and posterior circulation. The technique of endoscope-assisted aneurysm microsurgery may be used for incidental aneurysms as well as for aneurysms presenting with subarachnoid hemorrhage.

In aneurysm surgery endoscopes are useful instruments in addition to the conventional microsurgical techniques for two main reasons:

1. Endoscopes help to reduce the retraction and manipulation of superficial nervous or vascular structures when approaching deep-seated or large aneurysms, a fact which is especially important for patients with a fresh subarachnoid hemorrhage who quite frequently have an extremely irritable cortical surface and basal arteries developing vasospasm after the slightest touch.
2. Endoscopes, better than other instruments like mirrors, permit the intraoperative observation of the close vicinity of the aneurysms, e.g. the borders of the aneurysm neck, the perforators at the back side of the lesions, neighbouring cranial nerves, the clip position during or after clipping, and the patency of the neighbouring vessels.

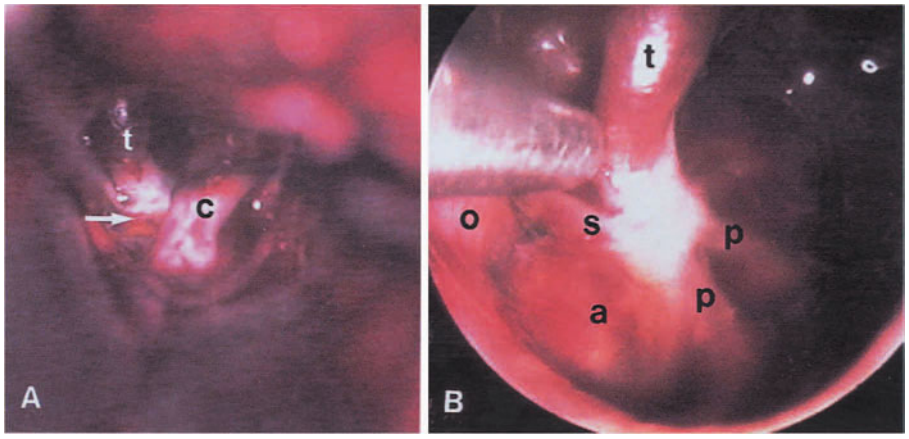


Fig. 1. Microscopic and endoscopic photograph after microsurgical exposure of a basilar tip aneurysm arising between the origin of the left superior cerebellar artery and the left posterior cerebral artery in a 43-year-old female with acute subarachnoid hemorrhage. (A) Microsurgical exposure of the basilar aneurysm via a left supraorbital subfrontal approach. The median part of the left Sylvian fissure has been opened giving access to a small optocarotid window, the carotid artery (*c*), and a rather large retrocarotid window. After opening of Liljequist's membrane, careful irrigation of the subarachnoid space, suction of subarachnoid hemorrhage clots, the basilar trunk (*t*), the basilar tip, and the yellowish neck of the aneurysm (white arrow) are visible through the retrocarotid window. Although using high-quality surgical microscopes, in such deep-seated locations the light power of the microscope beam sometimes is not sufficient to depict all microanatomical details which may be important to close the aneurysm and to spare the patency of neighboring vessels. (B) Endoscopic photograph using a 4 mm 0° lensscope demonstrating the additional information which may be gained with the endoscope-assisted microsurgical technique. The endoscope has been introduced into the small optocarotid window under microscopic control. The front lens of the scope has passed the optic nerve and the carotid artery, and the scope is fixed in front of the basilar tip which appears whitish because of light scattering from the endoscope. The shaft of the endoscope in between the optic nerve and the carotid artery remains under control of the surgical microscope. The rather large retrocarotid window may now be used to work under endoscopic control with suction instruments, dissectors, and aneurysm clips. A suction instrument pointing towards the basilar trunk (*t*) appears in the upper left quarter of the photograph. The origin of both posterior cerebral arteries (*p, p*) dissappearing in the hemorrhagic cerebrospinal fluid of the prepontine cistern, the origin of the left superior cerebellar artery (*s*), as well as the neck and a part of the fundus of the thin-walled basilar aneurysm are clearly visible with the endoscope. In addition, the left oculomotor nerve (*o*) is depicted below the suction instrument in between the superior cerebellar artery and the aneurysm. All this information is acquired without any retraction or manipulation of superficial nervous or vascular structures

Unlike in endoscope-assisted microsurgery for intracranial tumors, the endoscopes in aneurysm surgery can only be advanced through the anatomically preformed subarachnoid spaces of the basal cisterns as there is no cavity which can be created by partial removal of the lesion. Therefore

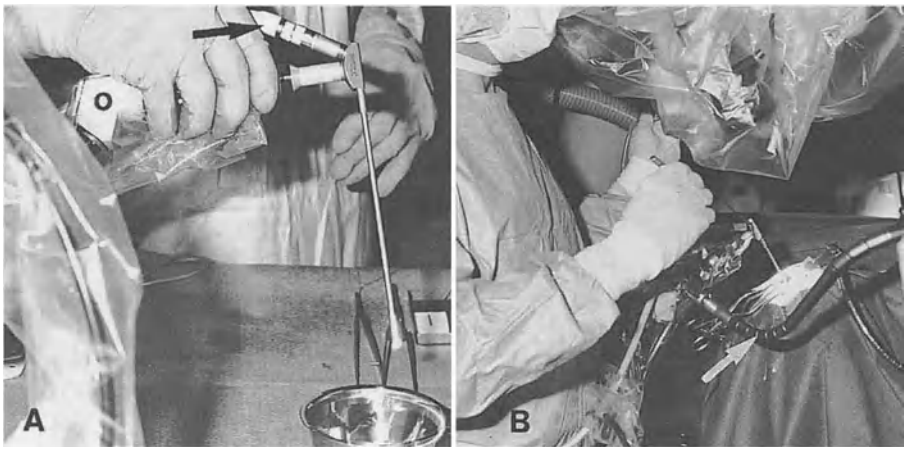


Fig. 2. (A) Photograph showing the intraoperative assembly of a 90° angled lensscope used for endoscope-assisted microsurgery. Due to the fact that the light cable (arrow) and the camera ocular (*o*) are mounted to the side of the endoscope shaft they do not obscure the microscopic visual field. The camera cable which is seen on the left side of the photograph is draped with a sterile plastic cover sheet. (B) Photograph of an endoscope-assisted microsurgical procedure demonstrating the intraoperative use of the endoscope shown in (A). The scope has been introduced into the surgical site under microscopic control. A strong Leyla-like support arm (white arrow) attached to the operating table is used to securely fix the endoscope in the desired intracranial position. Using this support arm permits convenient bimanual work with microinstruments under optical control either of the microscope or the endoscope

in endoscope-assisted aneurysm surgery it is important, especially in cases presenting with subarachnoid hemorrhage, to carefully dissect the arachnoid layers and to wash out the blood clots from the cisterns. Together with an exact positioning of the patient's head this accurate clearance of the arachnoid space allows the surgeon to access, to dissect, and to clip most aneurysms under combined endoscopic and microscopic control without major retraction of the brain.

Usually an endoscope is navigated under microscopic control into the surgical field only when additional optical control exceeding that of the microscope is desirable (Fig. 2). This control may encompass precise visualisation of the aneurysm neck, the parent vessel, the vicinity of the aneurysms, or the advancing clip blades. Without an endoscope such situations quite frequently require additional retraction of superficial or neighboring structures or additonal, time-consuming removal of bony parts of the skull base.

In addition to the detailed depiction of the individual microanatomy in the vicinity of the aneurysms intraoperative endoscopy may also be helpful during and after the clipping process. Sometimes the opening clip applicator or the clip itself, even though specially designed clip application systems are used [99], may obscure the surgical field in the microscope beam during clip application. An endoscope with its front lens fixed near the neck of the aneurysm permits a continuous and detailed observation of the advancing and closing clip blades. In such a situation, the additional use of an endoscope may help to achieve complete closure of the aneurysm neck, to preserve the patency of the parent vessel, to spare perforating arteries from clipping, and to minimize retraction of neighboring cranial nerves.

Detailed preoperative planning is mandatory for all cerebral aneurysm patients eligible for microsurgical treatment. Usually, in emergency cases a preoperative computed tomography scan is sufficient to demonstrate the width of the subarachnoid cistern which form the microsurgical routes to the aneurysms. During the computed tomography session a CT angiography with 3D reconstruction may deliver information about the aneurysm itself, but this new technique does not replace conventional cerebral angiography for the precise diagnosis of intracranial aneurysms. Thus, conventional cerebral angiography is obligatory for preoperative planning. Especially for patients with incidental aneurysms preoperative MR imaging studies are performed to gain as much information as possible about the anatomy of the subarachnoid windows in between cranial nerves, vascular structures, and brain surface giving access to the aneurysms. These anatomical windows framed by sensitive structures are of utmost importance for the performance of endoscope-assisted microsurgery for cerebral aneurysms.

## Endoscope-Assisted Microvascular Decompression

Endoscope-assisted microvascular decompression of cranial nerves in the posterior fossa is performed for the treatment of trigeminal neuralgia, hemifacial spasm, glossophayngeal neuralgia, and complex compression syndromes due to dolichovertebral or dolichobasilar arteries. Microvascular decompressions today are routine procedures through small craniotomies or craniectomies with a low surgical morbidity. Therefore, the question may arise whether there is an indication at all for the intraoperative use of endoscopes. Indeed, most microvascular decompressions may be performed without the endoscope-assisted technique. However, the complex compression syndromes of more than one cranial nerve in a single patient due to dolichovertebral or dolichobasilar arterial loops may be treated in a safer fashion with the intraoperative application of endoscopes.

Quite often the dolichoarterial loops depict a close contact to the brain stem, and brisk mobilisation of these large vessels may do harm to small perforators supplying the medulla oblongata and the pons. In such situations endoscopes better than mirrors allow for safe and careful observation of the back side of these large vessels without any retraction, a manoeuvre which is not possible with the surgical microscope alone.

In addition, cases with recurrent symptoms requiring reoperation are eligible for endoscope-assisted microvascular decompression. Sometimes an endoscope positioned with its front lens in the vicinity of the nerve entry zone will disclose a second arterial loop that was unseen during the first operation with the surgical microscope alone.

To reduce second look surgery due to hidden arterial loops it is our policy to plan all microvascular decompression procedures as endoscope-assisted microsurgical interventions, not only for the complex compression syndromes and for second look operations, but also for the "simple" microvascular compression syndromes. In addition to enhanced safety, simple cases of endoscope-assisted microvascular decompression provide good training for the more difficult and complex cases.

## Possible Future Development of Intracranial Neuroendoscopy

The revival of neuroendoscopy during the last decade of this century with many new possibilities due to improved diagnostic techniques and high-technology endoscopic instruments gives us an indication of the possible development of this almost 100-years-old neurosurgical technique in the near future. In our opinion, the genuine era especially of intracranial endoscopy in neurosurgery is just at its start. Other surgical specialties like abdominal surgery, orthopedic surgery, urology, gynecology, and otolaryngology are more advanced in endoscopic techniques [111]. Many of these specialties have determined precise indications for the use of endoscopy in well-defined diseases and, in addition, they are able to work with complex endosurgical systems.

Neurosurgery is just at the beginning of this process, and the subspecialty of spinal surgery within our field seems to be in the forefront of the development of new endosurgical techniques. Percutaneous endoscopic discectomy, when properly indicated, is already an established minimally invasive procedure [83], with long-term outcomes comparable with conventional microsurgical nucleotomy, whereas the new technique of neuroendoscopic treatment of septated syringomyelia [60] has still to prove its place in the surgical therapy of idiopathic, tumor-associated, postinflammatory, and posttraumatic hydromyelia. Very recently, anterior thoracoscopic approaches to the thoracic spine have been described by Dickman

and Mican [25] for multilevel anterior discectomies and anterior interbody fusion as well as by Rosenthal *et al.* [115] for thoracoscopic microsurgical removal of tumorous lesions, anterior decompression and subsequent stabilization of the spine.

Most of these endoscopic treatment modalities in spine surgery and other surgical specialties make use of multiportal approaches, which are necessary for the introduction of the scope and various instruments at the same time. Intracranial microsurgery and endoscopy have for a long time been domains of uniportal approaches exclusively on the same side as the lesion or, in midline processes, on the side of the non-dominant hemisphere. However, this traditional concept of uniportal and ipsilateral approaches, whether microsurgical, endoscopic, or combined, may be revised in favour of biportal and contralateral approaches for well-defined indications [32, 34, 62, 95].

In addition, the fast developing field of data processing, microstructure and microsystems technologies, as well as computer hardware and software innovations, will have a significant impact on microneurosurgery in general, but especially on neuroendoscopy in the next decade [7, 12, 43, 67, 85, 98, 117].

Looking into the near future of neuroendoscopy also forces us to face the economic and social problems of the next generation, not only in the so-called 1st world industrialized countries, which have to keep their health care systems in balance, but also in the poor 2nd and 3rd world countries which have enormous problems to establish stable health care systems for the majority of their people. To buy a modern fully equipped surgical microscope is usually easy in industrialized nations, is difficult in 2nd world countries, and is impossible in 3rd world countries. For those companies working in the field of neuroendoscopy this statement should be a warning as generally the financial potential of 2nd and 3rd world nations for the purchase of low-cost articles is underestimated. The more expensive an article the fewer the units that are sold worldwide. To keep the prices for neuroendoscopic systems low means to corroborate the alternation from microscope-based microneurosurgery to endoscope-based microsurgery worldwide. Although being constructed as a high-tech apparatus, to buy and to run a fully equipped neuroendoscopic surgical system today is much less expensive, yet equally effective for a number of indications as compared to the purchase and maintenance of a surgical microscope. Therefore, it will be one significant task of neurosurgeons of the next generation to work out and to broaden the spectrum of indications for endoscopic microneurosurgery, indications which stand the test of time and of neurosurgical expertise in both industrialized nations and developing countries. This will be an important contribution to keep future neurosurgical therapy attractive and, hopefully, affordable for all people.

### *Neuroendoscopy with Neuronavigation and Intraoperative Imaging*

Due to the enormous development of computer technologies with permanent innovations of computer hard- and software and integration of these innovations into robotic and surgical planning systems a variety of diagnostic procedures and neurosurgical operations have been revised during the last decade [12, 38, 43, 59, 67, 85, 117, 138]. However, most of these technical improvements are so new that their real potential in future neurosurgery is difficult to estimate. Nevertheless, a number of developments augur well for the development of neuroendoscopy:

Neuronavigation with application of frameless stereotaxy and intraoperative imaging seems to provide significant future possibities not only for microneurosurgery but especially for neuroendoscopy. Goodman [38] described a magnetic resonance imaging-directed stereotactic technique for endoscopic third ventriculostomy, which may prove useful for those occlusive hydrocephalus patients with deformities of the ventricular system, small interventricular foramina, or scarring on the floor of the third ventricle. To overcome problems with neuronavigation due to intraoperative brain shift very recent developments combine frameless or framebased stereotaxy with intraoperative imaging [43, 67, 117, 138]. Intraoperative imaging using either computed tomography, magnetic resonance imaging or ultrasound devices applied to the use of endoscopes will make the existing neuroendoscopic interventional techniques safer and will open new indications of neuroendoscopy which today still belong to the field of microneurosurgery. Once reliable, not too expensive intraoperative imaging techniques and adequate endoscopic instruments for microsurgery are developed, a number of intracranial microsurgical procedures for vascular, cystic, and neoplastic lesions will be performed exclusively through endoscopes. Thus, in our opinion, conventional microsurgery with the microscope will gradually be replaced by newly created techniques of endosurgery with well-equipped endosurgical systems. Clearly, neurosurgery is not a field where such new techniques are adopted rapidly. Most neurosurgeons were resistant to the introduction of the surgical microscope into microneurosurgery in the 1960's, a process which is comparable with the advent of neuroendoscopes in the 1990's and which will continue for the next 2 to 3 decades.

### *Biportal Endomicrosurgery*

To work out new indications for endoscopy in microneurosurgery implies abandoning some "traditions" of this rather young specialty. One tradition is to enter the skull on the side where the pathology is located, and another tradition is to create a uniportal approach. In contrast to this traditional

concept, it has been shown that some well-defined intracranial vascular lesions may best, i.e. with less intraoperative trauma and with reliable safety, be exposed via contralateral approaches [34, 95]. This concept of a contralateral approach derives from the anatomy of the major arterial vessels of the circle of Willis within the subarachnoid space of the basal cisterns. All those aneurysms arising from the medial wall of the internal carotid artery or those of the basilar tip, of the P1 segment of the posterior cerebral artery, and of the superior cerebellar artery pointing with their dome directly towards the beam of an ipsilaterally placed surgical microscope may better be exposed with less retraction and manipulation of the vessels, aneurysms, and neighboring cranial nerves via a contralateral craniotomy. This contralateral strategy also forms the basis for biportal endoscopic approaches to various intracranial areas, because the inevitable necessity of almost coaxial endoscopic control of the tip of endoscopic instruments and of intracranial anatomy hidden by those instruments is the main disadvantage of uniportal endoscopic procedures.

For most other surgical specialties applying endoscopic procedures such as laparoscopy [61, 64, 111], thoracoscopy [61, 137], and endoscopic joint and spine surgery [25, 83, 114, 115] well-defined bi- or multiportal endoscopic interventions have been established. These bi- or multiportal surgical techniques permit the precise visual control of various instruments inserted through portals and trocars different from that of the endoscope itself.

Very recently, it has been demonstrated by Jallo *et al.* [62] in a clinical study that some intraventricular neuroendoscopic procedures may best be carried out using two working portals, one for the endoscope, and the other one for the instrument trocar. In a preclinical cadaver study Fries and Reisch [32] showed that such biportal endomicrosurgical intracranial interventions are feasible in the subarachnoid space of the basal cisterns as well. They clearly demonstrated that the biportal endomicrosurgical strategy was useful for effective and safe dissection within various subarachnoid cisterns including the olfactory groove, the prechiasmatic cistern, the optic and carotid cisterns, the entire suprasellar and parts of the parasellar area, the pre- and perimesencephalic cisterns, and the prepontine cistern. Thus, biportal intracranial endoscopy presented good exposures of the olfactory nerves, the lamina cribrosa, the optic nerves, the anterolateral aspect of the chiasm, the carotid arteries, the anterior cerebral arteries, the M1 segment of the middle cerebral arteries, the posterior communicating arteries, the oculomotor nerves, the tuberculum sellae, the diaphragma sellae, the pituitary stalk, the posterior clinoid processes, the P1 segment of the posterior cerebral arteries, the basilar tip, the superior cerebellar arteries, the mamillary bodies, and the anterior surface of the mesencephalon and the pons (Fig. 3). These important intracranial structures, frequently affected by

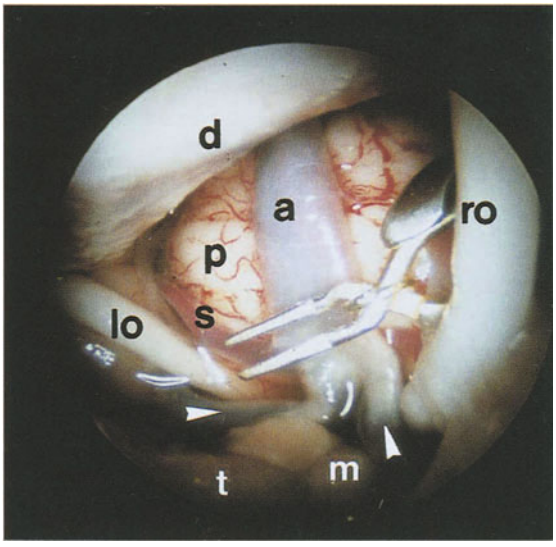


Fig. 3. Endoscopic photograph of a biportal endomicrosurgical cadaveric dissection of the prepontine cistern. A combination of a small right-sided temporal craniotomy to apply conventional aneurysm clips and a right-sided supraorbital burr-hole trephination posterior to the linea temporalis to advance a 4 mm lensscope subfrontally towards the prepontine area has been used. The endoscope has been carefully pushed under visual control through the optocarotid window into the suprasellar space. The arachnoid membranes of the right carotid cistern and Liljequist's membrane have been removed and cerebrospinal fluid from the basal cisterns has been released through the trocar of the endoscope. Then the endoscope has been fixed with a support arm just above the dorsum sellae (*d*) giving an excellent visual impression of the upper clivus and the entire premesencephalic and prepontine space. Under either endoscopic or microscopic control the aneurysm clip could be introduced through the temporal craniotomy below the right temporal lobe. The aneurysm clip, using a conventional clip applicator, has been forwarded to the prepontine cistern just posterior to the right oculomotor nerve (*ro*) and anterior to the basilar artery (*a*). The tip of the aneurysm clip as well as the important microanatomy of this area remain under permanent visual control of the endoscope. Note the tuber cinereum (*t*), which forms part of the floor of the third ventricle and the site of third ventriculostomy, the mamillary bodies (*m*), both posterior cerebral arteries (white arrowheads), the left and right oculomotor nerves (*lo, ro*), the left superior cerebellar artery (*s*), and the anterior surface of the pons covered with a number of small arterial branches, rami ad pontem, arising dorsolaterally from the midbasilar trunk. Using this biportal endomicrosurgical technique permits an optimum control not only of the shaft of the microinstruments but especially of the tip of the microinstruments and the microanatomical structures which, in the course of a uniportal exposure, might be obscured by superficial intracranial structures or the shaft of microinstruments. Thus, most of the biportal endomicrosurgical procedure can be performed without retraction and with a minimum of iatrogenic traumatization. Although two portals are needed for this procedure, biportal intracranial strategies may possibly improve future microneurosurgical strategies

pathologies involving the skull base, cranial nerves, the circle of Willis, and cerebral, mesencephalic or pontine midline structures, may some day in the future be approached with endoscopic techniques, whether uni- or biportal, not only in anatomic specimens but in neurosurgical patients who depend on our efforts to make neurosurgical interventions less traumatic and more effective.

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# Chronic Deep Brain Stimulation for Movement Disorders

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With 13 Figures

## Contents

## Introduction

### *History and Evolution of Methods*

The surgical treatment of movement disorders has evolved continuously over the course of the twentieth century, not only because of technical progress in neurosurgery but also because of improved recognition of the signs and symptoms of these disorders, and because of a progressive refinement of surgical indications, based on a better understanding of the relevant neuroanatomy and pathophysiology.

The earliest neurosurgical interventions for movement disorders were directed against the pyramidal system. Horsley (Horsley, 1890) reported a case of hemiathetosis that improved after partial resection of the motor cortex. Other proposals for the treatment of movement disorders, all of them based on the same idea, included lesions in the internal capsule (subcortical-pyramidotomy) described by Polenov (Polenov, 1928) and by Browder (Browder, 1948); medullary pyramidotomy, described by Putnam (Putnam, 1938), and section of the pyramidal tract via peduncule (pedunculotomy) described by Walker (Walker, 1949) and Guiot (Guiot

*et al.* 1949). Russel Meyers (Meyers, 1940), was the first neurosurgeon to treat movement disorders with lesions of the basal ganglia. These structures included the sub-callosal fibers, the anterior and posterior portions of the anterior limb of the internal capsule, the anterior two thirds of the putamen and globus pallidus, and, lastly, the ansa lenticularis. This last idea was taken up later by Fenelon (Fenelon, 1950) who electrocoagulated the ansa lenticularis with a probe inserted through a frontal burr-hole, rather than using Meyer's, open transventricular approach.. Cooper (Cooper, 1953) accidentally injured the anterior choroidal artery while performing pedunculotomy on a patient with parkinsonian tremor and found that the tremor was greatly reduced afterwards. This artery supplies the globus pallidus, the ansa lenticularis, the ventral lateral nucleus of the thalamus and other sub-cortical structures. According to the previous work of Hassler (Hassler, 1948), this accidental observation was exploited: attention was thus directed to the essential role of the basal ganglia in motor organisation and programming. The introduction of stereotactic techniques, modified from those previously developed by Horsley and Clarke for use in experimental animals, made surgery of the basal ganglia more precise and less destructive. A number of stereotactic atlases were published, including those of Spiegel and Wycis (Spiegel et Wycis, 1952), Schaltenbrand (Schaltenbrand *et al.* 1977), Talairach (Talairach *et al.* 1957), and Delmas (Delmas *et al.* 1959) which provided better definition of the partial coordinates of the motor structures whose functioning might be modified by focal destruction. Various different targets were used: Spiegel and Wycis (Spiegel et Wycis, 1952) reported on antero-dorsal pallidotomy. Riechert and Hassler (Riechert et Hasler, 1962) later reported on the same technique: Leksell, beginning in 1952, proposed changing the target to the ventro-posterior globus pallidus, but he observed that the results of these lesions were unsatisfactory and gradually moved his target to the postero-ventral globus pallidus, from which the ansa lenticularis originates (Svennilson, 1960).

Pallidotomy rarely suppressed tremor completely and was thus nearly forgotten after Hassler and Riechert (Hassler *et al.* 1954) reported the excellent effect of ventro-lateral thalamotomy on tremor. The wide popularity of this last surgical procedure was due, in part, to Cooper who performed it in 8000 cases of movement disorders, including 5000 cases of Parkinson's disease, between 1951 and 1968 (Cooper, 1977). Numerous other series, including those of Riechert (Riechert, 1978), Mundinger (Mundinger, 1966), Gillingham (Gillingham, 1960), Krayenbühl (Krayenbühl *et al.* 1963), and van Manen (van Manen, 1962) yielded success rates of 85–90% against tremor, while the effect on rigidity was less pronounced. Speelman has estimated that 37000 stereotactic operations for Parkinsonian tremor were performed until 1968 (Speelman, 1991), when L-Dopa began to be used in the treatment of parkinson's disease. Over the years, the stereo-

tactic target was generally restricted to the posterior part of the motor area of the lateral thalamus and to the Ventralis Intermedius Nucleus (V.im.) where smaller lesions were performed (Albe-Fessard, 1973; Guiot *et al.* 1967; Hassler R, 1955, Hassler R, 1955b; Hassler *et al.* 1960; Hirai *et al.* 1983; Laitinen 1985; Nagaseki *et al.* 1986; Ohye *et al.* 1975; 1977; 1979; 1979b; 1982; Pollak *et al.* 1993; Siegfried and Blond, 1997; Talairach *et al.* 1950, Talairach *et al.* 1957; Tasker *et al.* 1982; Tasker *et al.* 1987).

Important clinical advances in thalamotomy and major advances in the understanding of thalamic anatomy and physiology came about with the use of intraoperative electrophysiological exploration (macrostimulation, microstimulation and microrecording). An outstanding contribution was made by neurophysiologists (Albe-Fessard *et al.* 1961; 1963) by means of cellular recordings performed through an occipital approach. Recordings in the nucleus ventro-intermedius (V.im.) revealed not only cells firing in response to active or passive movements (kinesthetic cells) but also cells whose activity was synchronous with contralateral tremor (Tremor-generating cells). Somatotopy within the V.im. was also observed. These results led many neurosurgeons to consider the V.im., to be the ideal target for stereotactic lesions in the treatment of tremor (Narabayashi, 1964; Ohye *et al.* 1976; 1979; Tasker *et al.* 1983) and they recommended the use of this target in cases of isolated parkinsonian tremor. A more anterior lesion is necessary in cases of more complex movement disorders involving a cerebellar type disturbance (nucleus ventro-oralis posterior, V.o.p) or associated rigidity (nucleus ventro-oralis anterior, V.o.a.).

Although a spectacular and total suppression of tremor could be obtained in 85 to 90% of operated patients, recurrenes could be observed in about 4% to 20% (Hirai *et al.* 1983) after several weeks or years. Moreover when the lesion size was increased to prevent this recurrence, morbidity such as motor deficit, dystonia, speech disturbance and sensory loss could be observed with a reported frequency of about 25% transitory deficits and 2 to 9% permanent ones (Stellar and Cooper, 1968). In addition, bilateral procedures, although they were reported to be feasible (Matsumoto *et al.* 1984), were often associated with severe neuropsychological deficits, and dysarthria (Matsumoto *et al.* 1979; 1977) and were thus rarely performed as a routine procedure in patients with bilateral disease.

## *Rebirth of Stereotaxy and Development of Chronic Deep Brain Stimulation (CDBS) in the Treatment of Movement Disorders*

### The Transient Decline of Surgical Treatment

The advent of dopatherapy (Cotzias *et al.* 1967), resulting from a tremendous amount of basic research in cathecholamic systems, completely

changed the therapeutic approach of the disease and for decades the surgical treatment of Parkinson's disease and other dyskinesias was practically withdrawn from the therapeutic arsenal. In the 70's, the follow-up of L-Dopa treated patients began to reveal some drawbacks of the substitutive treatment such as intolerance, decreased efficacy or even additive complications such as abnormal involuntary movements, due not only to the evolution of the disease but also to the dopatherapy itself. Then, stereotactic procedures for thalamotomies were once again performed (Andrew *et al.* 1981; Derôme, 1965; Derôme *et al.* 1986; Fox *et al.* 1991; Goldman *et al.* 1992; Narabayashi *et al.* 1984; Siegfried, 1979). In order to avoid surgical complications, accurate localization of the most effective target must be achieved during surgery, using electrophysiological methods: deep brain recordings of electrical activity of neurons in the thalamus (Albe-Fessard *et al.* 1973; 1988; Bertrand *et al.* 1967; Guiot *et al.* 1973; Sem-Jacobsen, 1966; Taren *et al.* 1968) aimed at the recognition of specific discharge patterns in the surrounding structures such as the Ventro-Postero-Lateral (VPL) sensory thalamus in front of which is situated the V.im. target, or inside the Vim target itself (Lenz *et al.* 1988; Ohye *et al.* 1974; Ohye *et al.* 1979; Ohye *et al.* 1984; Pollak *et al.* 1993).

## The Discovery of Electrical Stimulation Effect

During these procedures, it has been shown that electrical stimulation, which was routinely performed to avoid incorrect electrode placement, was able to inhibit completely and immediately both parkinsonian rest and essential postural tremor. However this effect, which was immediately reversible when the stimulation was discontinued, was only obtained at "high" frequency (i.e. at 100 Hz and more) and was not achieved with frequencies below 50 Hz. Microelectrode recordings of neuronal activity in the human thalamus had revealed the presence of burst discharges synchronous with tremor in V.im. These authors observed that stimulation through the same microelectrode at high frequency suppressed parkinsonian rest tremor immediately and electrocoagulation within that area stopped tremor permanently. (Albe-Fessard *et al.* 1961; 1962; 1963; 1988; Guiot *et al.* 1968; 1973; Hassler, 1955, 1955b; Jasper *et al.* 1966; Matsumoto *et al.* 1979/77; Matsumoto *et al.* 1984; Narabayashi, 1989; Ohye *et al.* 1984, 1989; Siegfried, 1986; Taren *et al.* 1968; Tasker *et al.* 1983, 1986; Hirai *et al.* 1983; Tasker, 1986). This effect was used for several years as an intraoperative test for electrode placement.

Neurosurgical interest in deep brain stimulation has been greater in the past few years, since the independent reports of Siegfried (Siegfried, 1986)

and Benabid that thalamic stimulation, using a slightly different target from those previously used, results in a marked and prolonged reduction in tremor. Benabid proposed it as an experimental therapeutic procedure to a patient already thalamectomized on one side and who persistently requested for a contralateral procedure because of the progression of the disease (Benabid *et al.* 1987; 1988). This patient gave his informed consent and the implantation of chronic deep brain stimulation electrode was performed. During surgery as well as during the test period of 10 days following the electrode implantation, the result was excellent and long-lasting and led to a procedure of chronic internalization of a stimulator. A pilot study of long-term high frequency V. im. thalamic stimulation of the treatment of disabling tremor was initiated for patients in whom a second operation contralateral to a previous thalamotomy was under consideration and for those in whom bilateral surgery was advocated (Benabid *et al.* 1988; Benabid *et al.* 1989; Benabid *et al.* 1991; Siegfried, 1992, 1993, 1997). Very encouraging results have been confirmed subsequently in larger series of patients: this technique is now a very feasible neurosurgical procedure and is indicated for other types of dyskinesia, including dystonia of various origins and multiple sclerosis tremor (N'Guyen *et al.* 1993). More recently, akinesia and iatrogenic dyskinesia seem to be relieved by stimulation at other sites: the sub-thalamic nucleus (Benazzouz, 1993; 1995) and the ventro-postero-lateral portion of globus pallidus (Siegfried, 1994).

## Physiological Basis: Mechanisms of Motor Disorders

### *The Basal Ganglia Related System*

#### The Basal Ganglia System

The core of the system is well defined and includes the striatum (with distinct sensorimotor and associative areas), the pallidum (external [GPe] and internal [GPi] parts) and the substantia nigra, pars reticulata (SNr). This core system is connected to other structures, acting as regulators: substantia nigra pars compacta (SNc), subthalamic nucleus (STN), the centro median-parafascicular thalamic complex (C.M.P.f.) and the pedunculopontine tegmental nucleus (PPC). (Percheron *et al.* 1989; 1994; 1996; Flaherty and Graybiel, 1991; 1993; Parent A, 1995). If SNc and STN are obviously implicated in movement disorders, the role of C.M/.P.f. and PPC is not well defined up to now, but their implications in the basal ganglia system have been demonstrated (Nauta et Mehler, 1966).

## The Basal Ganglia Connections

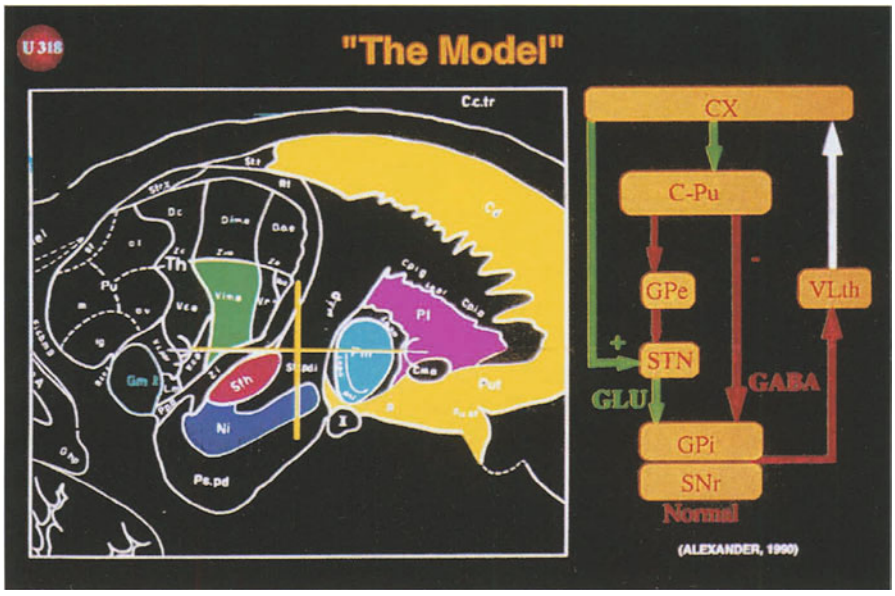
Anatomical components of the basal ganglia have been described at the beginning of the 20th century, but modern tracers methods were needed to demonstrate their main connections. However, data from the current literature support two apparently contradictory hypotheses: 1. that of parallel processing of information suggested by Alexander (Alexander *et al.* 1990). This supposed segregated circuits (limbic, motor, oculomotor, and prefrontal), with specific competence of neural networks for specific information traffic. 2. that of informational convergence to the pallidum (GPi) and confluence to the thalamus, supported by Percheron (1994). This latter hypothesis derived from neuromorphological studies of neuronal connections. The main connections between basal ganglia have been repeatedly recalled, from the well-known schematic diagram of Alexander (1990) (Table 1). These consist in cortical connections to striatum and STN, projecting back to the cortex with different relay in pallidum and SNr (Ilinsky *et al.* 1985; 1987; Jones, 1985). The last relay which is common to all pathways, is the motor thalamic nuclei which display heavy projections to motor, premotor, supplementary motor (SMA) areas. However, this model is open to criticism because the role of pedunculopontine nucleus is not assessed, and the cerebellar afferences and their functions do not appear.

## Thalamic Situation Inside the Basal Ganglia Circuitry

Most circuits involving the basal ganglia are linked with the thalamus. Finally, concordant neuroanatomical data demonstrate that the sensorimotor thalamus is an area concentrating many afferent pathways, before their projections to the cortex (Joffroy *et al.* 1971). This situation probably aims at highly effective information transfer. This could be considered as the most effective highway of neuronal informations, where, in normal condition, no traffic accidental event could occur. This organization seems to be the support of goal-directed, precise, and rapid movements, and allows effective interface between the main 2 systems, namely the motor and the cognitive basal ganglia systems. This interface is necessarily involved in working memory, and motor memory processes (Mogenson *et al.* 1980).

In patients with Parkinson's disease, degeneration of the nigro-striatal pathway induced dopaminergic denervation of the neostriatum. These pathological and biochemical disorders led to a global dysregulation of basal ganglia structures, as shown by both metabolic and electrophysiological studies which emphazise the up-regulation of GPi and its correlates, namely the down-regulation of motor thalamic areas and the

Table 1. *Network Involved in the Pathogenesis of Parkinsonism and Movement Disorders: Simplifed Representation of the Alexander Diagram (Red Lines Represent Inhibitory Pathways, Green Lines Represent Excitatory Pathways)*




*Cx* Cortex; *C-Pu* caudate and putamen; *Gpe* lateral pallidum; *STN* subthalamic nucleua; *Gpi* medial pallidum; *Snr* pars reticulata of the substantia nigra; *VIth* lateralis oralis and intermedial subdivision of the thalamus; *GLU* glutamertergic pathways; *GABA* gabaergic pathways.

failure of the excitatory role of thalamo-cortical projections. However, this model is not adequate for tremor which is a hyperkinetic disorder.

## Thalamic Subdivisions Involved in Motor System

The thalamic subdivisions devoted to sensori-motor control have been a subject of controversy for years. In Percheron's view, this could be related to the confusion in thalamic nomenclature, due to historical opposition between different schools of research on the primate thalamus. For this reason, the subdivisions have been defined by their afferent connections (Percheron *et al.* 1996a, 1996b). This nomenclature seems to be interesting, because it allows to integrate the thalamus subdivisions in the functional diagram of basal ganglia system. However, there is a consensus for the description of three segments in the antero-posterior plane: 1. the pallidal

afferents represent the ventralis lateralis nucleus of neurosurgeons (VL), also called the lateralis oralis territory (LO), 2. the cerebellar afferents represent the V.im. of the neurosurgeons, also called the lateralis intermedius territory (LI), 3. the sensory lemniscal afferents represent the VPL of neurosurgeons, also called lateralis caudalis territory (LC).

The authors debate thereafter on 2 crucial points: 1. Are the human thalamus subdivisions identical to those of the primate? 2. Does V.im. in human receive both spinothalamic and vestibular afferents and what is their respective role in the genesis of tremor?

### The Linkage of the Basal Ganglia System with Cerebellum

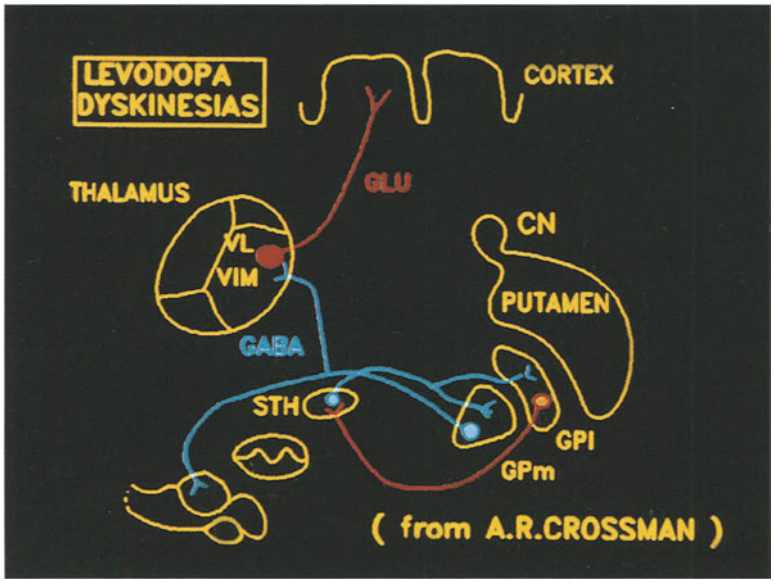
There is little information about involvement of cerebellum in parkinsonism, especially for akinesia and rigidity, but recent studies confirm two important facts: 1. its close connections with the lateral thalamus, 2. its implication in all types of tremor. There is strong evidence confirming that the main afferents to V.im. are axons from the dentate and the red nuclei and other cerebellar nuclei: nuclei fastigii, globosus and emboliformis (Percheron, 1977; 1996; Asanuma *et al.* 1983), and metabolic studies in vivo revealed specific increases of regional cerebral blood flow (rCBF) in deep cerebellar areas in relation with tremor, and decrease rCBF in relation with tremor suppression (Parker *et al.* 1992; Deiber *et al.* 1993). The specific role of small cerebellar nuclei in the pons in the pathogenesis of tremor is uncertain, since there is little evidence of their involvement. Clinical studies failed to demonstrate that rest tremor could occur after either rubral or other cerebellar lesions.

## *Evidence of Basal Ganglia System Dysfunction in Motor Disorders*

### Clinico-Pathological Studies

Parkinsonian symptoms were associated with basal ganglia lesions in the early 20th century, due to the Tretiakoff's thesis (Tretiakoff, 1919), showing nigral depigmentation occurring in cases of either post-encephalitic or idiopathic parkinsonism. The confirmatory studies appeared only 50 years later with the detection of nigro-striatal degeneration. More precise pathological studies showed diffuse lesions spreading to non-dopaminergic cells (Javoy-Agid *et al.* 1984; Gray, 1988). Other hyperkinetic movements have been related to more or less specific lesions in other sites: striatum or thalamus in dystonia (Marsden *et al.* 1985; Lehericy *et al.* 1996), caudate nucleus in chorea, subthalamic nucleus in ballismus (Buruma *et al.* 1986).

Table 2. *Semi-Schematic Representation of Pathways Involved in Levodopa Induced Dyskinesias*




However, no strict relationships exist between symptoms and structures, for example: 1. Thalami from patients with essential tremor never displayed neuropathologic changes, despite obvious neurophysiological abnormalities, 2. Ballismus may occur while STN is spared (Schwarz *et al.* 1960; Caparros-Lefebvre *et al.* 1994a). 3. The levodopa induced AIMs are still partly understood (Table 2). Both types of dyskinesias which may occur simultaneously in the same patient: dystonic and choreic movements are seen successively during the levodopa test. There is a clear relationship between levodopa-induced AIMs and brain dopamine synaptic concentrations, but the specific involvement of one structure has not been proved. Thus we can not assume a relationship of "one lesion-one structure," and neuropathologic reports were only the first stage of knowledge of basal ganglia involvement, and the localizationist theory failed to account for motor disorders.

## Biochemical Overview

Nigro-striatal degeneration, as the cause of Parkinson's disease, remained controversial until dopaminergic depletion was demonstrated in 1960

(Ehringer *et al.* 1960). Early most-mortem studies have shown decreased levels of neurotransmitters in all systems: dopaminergic depletion involving nigro-striatal, and also cortical and limbic dopaminergic projections. Motor symptoms appearance is strictly related to percentage of dopaminergic neurons loss (70%). Cholinergic depletion (in the nucleus basalis and hippocampus) and noradrenergic depletion (in the locus coeruleus and limbic system) seem to be predominating in demented patients. The immunoreactivity for neuropeptides also decreases in most basal ganglia (Agid *et al.* 1989). However, exhaustive description of Parkinson's disease biochemistry, even with sensitive measurements of neurotransmitters, failed to improve understanding of pharmacological conception of the disease, as well as physiological mechanisms. The explanation of this disappointing finding is that there is poor correlation between neurotransmitters depletion and receptors properties, nor therapeutic strategies.

## Experimental Data

MPTP, a neurotoxin repeatedly injected in monkeys, provided a good model of parkinsonism. MPTP-exposed monkeys developed all parkinsonian symptoms, except tremor. This allowed us to define the precise anatomo-physiopathological substrate of akinesia, which is a hyperactivity of GPi, demonstrated by increase of the regional brain uptake of 2-deoxyglucose, associated with decrease uptake in GPe. Simultaneously, STN appears hyperactive (Crossman *et al.* 1985, 1987). This dysregulation of GPi was confirmed by different ways: excessive and non selective neuronal activity in response to passive movements (Filion *et al.* 1988), and modification of neurons arborizations and connections with increased convergence (Percheron *et al.* 1989). The consequences of GPi hyperactivity is an increased activity of thalamo-cortical inhibitory neurons. These results emphazised that there are 3 crucial targets for CDBS: thalamus, GPi and STN.

However, it is poorly understood why bilateral pallidal necrosis after monoxid carbon poisoning or anoxia, also induce akinesia. In the same way, why does pallidotomy (which usually involves GPi) improve both dyskinesias and akinesia?

Drug-induced dyskinesias had been previously provoked by injections of kainic acid, or bicuculline in striatum or pallidum of monkeys (Crossman *et al.* 1984, 1987). If these sometimes mimicked human dyskinesias, they could not be compared with the pathological process of parkinsonism. MPTP monkeys developed levodopa induced AIMs which are much more similar to those of humans. Post mortem ligand-binding studies have clearly demonstrated that the suspected dopaminergic supersensitivity did

indeed appear in relation with these AIMs (Boyce *et al.* 1987). These AIMs are controlled by pallidal stimulation. Interestingly, Aziz *et al.* (1991) showed that MPTP-induced parkinsonism was alleviated by STN lesions, and Benazzouz confirmed the role of STN by electrical stimulation (Benazzouz *et al.* 1993). However, STN lesions induced constant hemiballismus.

## Metabolic Studies

Several studies have reported regional cerebral blood flow and glucose or oxygen metabolism measurements with positron emission tomography (PET), but that type of measurement only assessed the overall level of neuronal metabolic activity. The exploration of dopaminergic function needs specific radio-labelled tracers. The fluorine-18 labelled dopa seems to be an analogue of L-dopa and is recognized by dopaminergic receptors. This is an in-vivo good indicator of nigro-striatal denervation. The lack of selectivity for specific subtypes of dopaminergic receptors do not allow more precise physiopathological studies. However, there are specific patterns of hypofixation: predominant in putamen in PD, involving both putamen and caudate in multiple system atrophy (Otsuka *et al.* 1991; Masuda *et al.* 1991). Metabolic studies which are not a good tool as routine diagnosis test, are useful for the evaluation of physiological effects and CDBS complex effects (Parker *et al.* 1992; Deiber *et al.* 1993). When tremor release is obtained during thalamic stimulation, controlateral SMA and premotor rCBF are reduced, as those of cerebellar nuclei, bilaterally. Interestingly, the results of rCBF modifications during pharmacological stimulation using L-Dopa test are similar to those of thalamic stimulation (Duffau *et al.* 1996). Then, drugs and electrical device could have the same effects.

## Neurophysiological Substratum for Subthalamic Nucleus Stimulation

Hemi or bi-ballism usually occurs after STN lesioning. This can be reproduced by injection of antagonists drugs in the STN. The most impressive symptom is the severe hypotonia, as can be seen after cerebellar lesions to a lesser extent, but the severity of the associated abnormal movements discouraged STN lesioning for akinesia. In contrast, different experiments have suggested that STN is hyperactive in parkinsonism with rigidity (Crossman *et al.* 1985, 1987). STN hyperactivity which is reproduced by GABA antagonist injection (bicuculline) induces excitatory influence to substantia nigra pars reticulata and GPi. The idea that parkinsonian

rigidity could be treated by hypotonia induced by STN inhibition arose from experimental studies in MPTP-monkeys (Aziz *et al.* 1991). STN lesions in MPTP-monkeys induced severe choreic and ballistic dyskinesias, whereas STN stimulation improved motor performance with fewer AIMs (Benazzouz *et al.* 1993).

### Unresolved Problems

Several questions remain unanswered at present:

1. What is the role of structures such as cerebellar cortex and nuclei, and pedunculopontine nucleus in the development of parkinsonian symptoms?
2. Where is the generator of tremor?
3. What is the physiopathology of each type (choreic, and dystonic) of levodopa induced AIMs?
4. Why does inhibition or destruction of pallidum induce either akinesia, or akinesia release?

All of these, like many others, are research topics which have still to be addressed both experimentally and clinically. Among the methods which could contribute to this approach, CDBS appears to be a selective, reversible and powerful tool to aid understanding of basal ganglia dysfunction in human patients.

## Technical Overview of Chronic Deep Brain Stimulation

### *Methods: Stereotactic Procedure*

Since quality and stabilitiy of the results depend primarily on the precision of electrode implantation, every effort must be made to reach the target with maximum accuracy. The procedure can be done in one session, including determination of the target by ventriculography, and implantation in the target of an acute stimulating-recording electrode followed by the chronic Deep Brain Stimulation electrode. However, in order to ensure a more precise location of the ideal target and to avoid an unduly long procedure for the patient, this procedure can be divided into three sessions (Benabid *et al.* 1996). Step I, under general anesthesia, is implantation of titanium screws, which remain in place in order to allow further painless repositioning and positive contrast ventriculography. Stereotactic MRI is performed between step I and II, to help determine the target site and between II and III to check the position of the electrodes; step II is the stereotactic implantation of the electrodes; step III is the test period preceding the internalization of the stimulus generator.

The localization of deep intracerebral structures relies on the prior identification of deep midline structures by positive contrast ventriculography, which is generally performed by direct puncture of the frontal horn of the lateral ventricule (9 cm from nasion, 25 mm from midline) with a 65 mm long Cushing cannula. Placement is confirmed by control X-ray after injection of a 5 ml air bubble. With the use of these landmarks and the air bubble test, none of the reported complications (Cheshire *et al.* 1990; Marks *et al.* 1991) has been observed. 6.5 ml of Iopamiron 200 (Schering) are then injected. X-rays are taken under teleradiological conditions (3.5 m between X-Ray tube and film) in the supine and prone positions. Selective ventriculography is an altenative method, following the statistical localization method of Siegfried (Siegfried *et al.* 1980): a line is drawn from the bregma to the lowest point of the posterior clinoid process and the position of the foramen of Monro on the line is estimated on both frontal and lateral images. A doubly oblique approach to the foramen of Monro then allows selective filling of the third ventricle. The incidence of clinical changes and of anatomic distortion is lower than when "global" ventriculography is used. The anterior (AC) and posterior (PC) commissures and the midline of the third ventricle are used to calculate the coordinates of the V.im., GPi and STN targets from the stereotactic atlases of Schaltenbrand and Bailey and of Talairach (Schaltenbrand *et al.* 1977; Talairach *et al.* 1957). (Figs. 1, 2).

## *Localization of Stereotactic Targets*

### Localization of V.im. Nucleus

#### *Ventriculography*

The coordinates of the nucleus ventrointermedius (V.im) are calculated from the lateral X-Ray according to proportional geometric diagram based on the AC-PC line (Talairach *et al.* 1957; Taren, 1968). The position of the V.im nucleus on lateral projection can be estimated by a parallelogram where the lower side is formed by the second and the third twelfths of the intercommissural line, and the upper side by the fourth and fifth twelfths of line parallel to the intercommissural line and half as high above it as the apex of the thalamus. The estimated position of V.im. on the horizontal axis is 11.5 mm from lateral wall of the third ventricule (Derome *et al.* 1986; Tasker *et al.* 1986) and thus varies with the ventricular width which is typically 6 mm, but may vary from 5 to 9 mm, according to the literature. On the lateral view, electrode target projection is superimposed on the main axis of the V.im nucleus determined as described above. Electrode

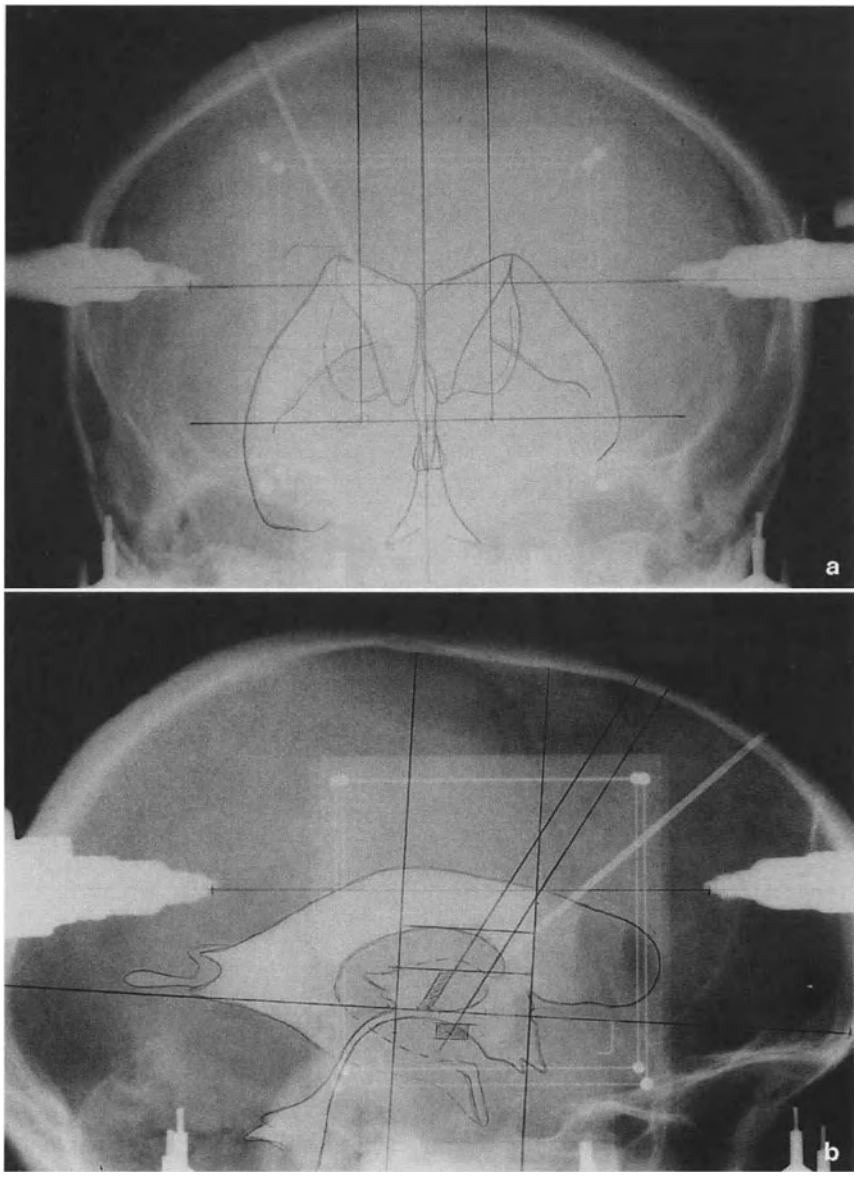



Fig. 1. Ventriculography based determination of the V.im. and STN targets. The significant landmarks, which can be clearly seen, if necessary by taking the X-ray pictures in the recumbent position, are on the lateral view: AC, PC and the top of the thalamus, and on the AP view, the midline of the third ventricle and its lateral walls. Current exploring strategy uses five Ohye electrodes lowered down to the theoretical target. The electrode which provides the optimal results is replaced by the permanent DBS electrode

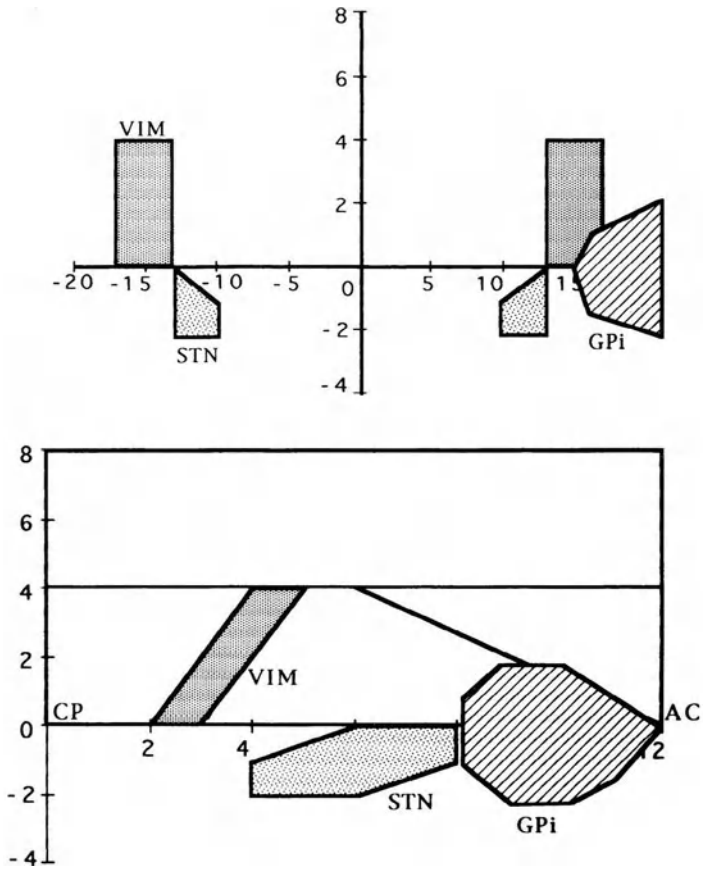



Fig. 2. V.im., STN and GPi targets based on the third ventricle anatomical landmarks. The V.im. target is drawn as follows: On the lateral view (below): a rectangle is constructed with the AC-PC line, as its base whose ends rise perpendicular to the AC-PC line, one at the inner border of AC and the other of PC. The top is a line parallel to the AC-PC line, tangential to the top of the thalamus. A third line, parallel to AC-PC, is drawn at the mid-height of the thalamus. The AC-PC line is divided into 12 parts. The schematic representation of Vim extends from 2/12 to 3/12 on the AC-PC line and from 4/12 to 5/12 on the mid-height line. The Vim area is represented by the resulting parallelogram. On the AP view: the laterality is set at 11.5 mm from the lateral wall of the third ventricle. The STN target is situated below the middle third of AC-PC. On the AP view, the average laterality is 12 mm. The GPi target is situated in the anterior third of AC-PC, from 2/8 of HT above to 2/8 below the AC-PC plane. Laterality extends from 15 to 22 mm from the midline

placement is directed more to the anterior than the posterior border of V.im., in order to minimize or even avoid the spread of current to the ventropostero lateral nucleus of the thalamus (VPl) with its concomittant contralateral paresthesias. On the AP view, the final implantation trajectory of the electrode may be oblique, 6° to 10° from the midline sagittal plane (Lille, Créteil, and some cases in Grenoble) or parasagittal (most of the patients in Grenoble).

In some cases with a predominant action and/or postural tremor, it may be necessary to define the V.o.p nucleus, lying immediately anterior to the V.im.: its location, as given by Taren, is 3 mm above a point 5/12 from the distance of the posterior to the anterior commissure, and 11 mm lateral to the wall of the third ventricule. The ventral oralis anterior nucleus (V.o.a) lies 2.5 mm above the intercommissural line (or on the line from the foramen of Monro to the posterior commissure), 1,5 mm anterior to the midcommissural point and 10 mm lateral to the wall of the third ventricule.

*Magnetic Resonance Imaging (MRI)*

MRI is now an essential tool in the localization of individual anatomic structures. It displays the position of the deep intracerebral landmarks: sagittal images reveal the anterior and posterior commissure and the apex of the thalamus, and coronal images reveal the wall of the third ventricle. These structures provide coordinates in the stereotactic coordinate system (which is defined either by the frame itself, or by its points of attachment to the skull, as in a computerized stereotactic MRI technique). The reference points of the stereotactic atlas are made congruent to the landmarks revealed by MRI by "stretching" or "shrinking" the atlas, if necessary ("anamorphosis," or "warping"). The atlas is then used to obtain the relation of the landmarks to the chosen target structure. The method outlined can be used to localize the globus pallidus, the subthalamic nucleus and the nuclei of the motor thalamus (V.o.a, V.o.p) and V.im. in Hassler's nomenclature, which together constitute the ventral lateral nucleus (VL). Target definition with MRI does, however, require precise alignment of the apparatus to eliminate any inhomogeneity in the magnetic fields; serious distortion may otherwise occur, particularly at the periphery, where the landmarks defining the stereotactic coordinate system are located (marker on the stereotactic frame itself, or at the points of its fixation to the skull) (Rousseau *et al.* 1991). Dormont (Dormont *et al.* 1994) recently showed that the precision of MRI localization for functional neurosurgery can be brought within 1 mm by using precisely controlled magnetic fields and a 256-element matrix for reduction of pixel size. This result confirms and strengthens the conclusions of Kondziolka's comparative studies of the results obtained with CT and MRI (Kondziolka *et al.* 1992).

T1 weighted images are acquired in the sagittal direction, axial sections are taken in planes parallel to the AC-PC line, and coronal sections are taken in planes parallel to the floor of the fourth ventricle which is approximately parallel to the main axis of V.im. or in planes perpendicular to the AC-PC line. These images can be later enlarged to the actual size of the X-ray images obtained by ventriculography, thereby allowing accurate matching of the two sets of morphological data by simple superimposition. MRI does not identify V.im. itself, but helps to determine the lateral boundary of the V.im. nucleus against the neighbouring internal capsule, the actual width of the third ventricle in the AC-PC plane (which is the level of implantation) and the position of the F1-F2 frontal sulcus, which must be avoided in the oblique tracks of the electrodes.

*Electrophysiology*

This provides specific patterns during electrical stimulation (suppression of tremor at 100 to 130 Hz), as well as during extracellular recording of neuronal activity. This method revealed a population of neurons in the V.im. with a high level of baseline activity and selective responses to active and passive contralateral movements. These kinesthesic neurons are located in the ventral two third of the V.im. in a precise somatotopic distribution (Hirai *et al.* 1983; Ohye *et al.* 1977; 1982) and also in the V.o.p. and the most rostral portion of the V.P.l. (Ohye *et al.* 1979; Yoshida *et al.* 1989; Lenz *et al.* 1987). According to these different authors, the optimal target for functional modification by stimulation can found by demonstration of rhythmic cellular activity in the V.i.m. that is synchronized with contralateral tremor (Fig. 3). Such rhythmic activities may perhaps be generators of tremor but one should avoid jumping to conclusions on this matter, as a number of authors, notably Raeva (Raeva *et al.* 1990) have described rhythmic activity in the absence of tremor and more recently, in patients under general anesthesia.

## Localization of the Subthalamic Nucleus

*Ventriculography*

This provides a statistical estimation of the position of STN, with reference to stereotactic atlases (Schaltenbrand *et al.* 1977; Talairach *et al.* 1957). The target coordinates of this structures are: 2 to 7 mm inferior to the midpoint of the bi-commissural line, and 12.5 mm lateral to the midline (Figs. 1, 2). The approach is parallel to the midsagittal plane or oblique, 6 to 10° from the midsagittal plane.

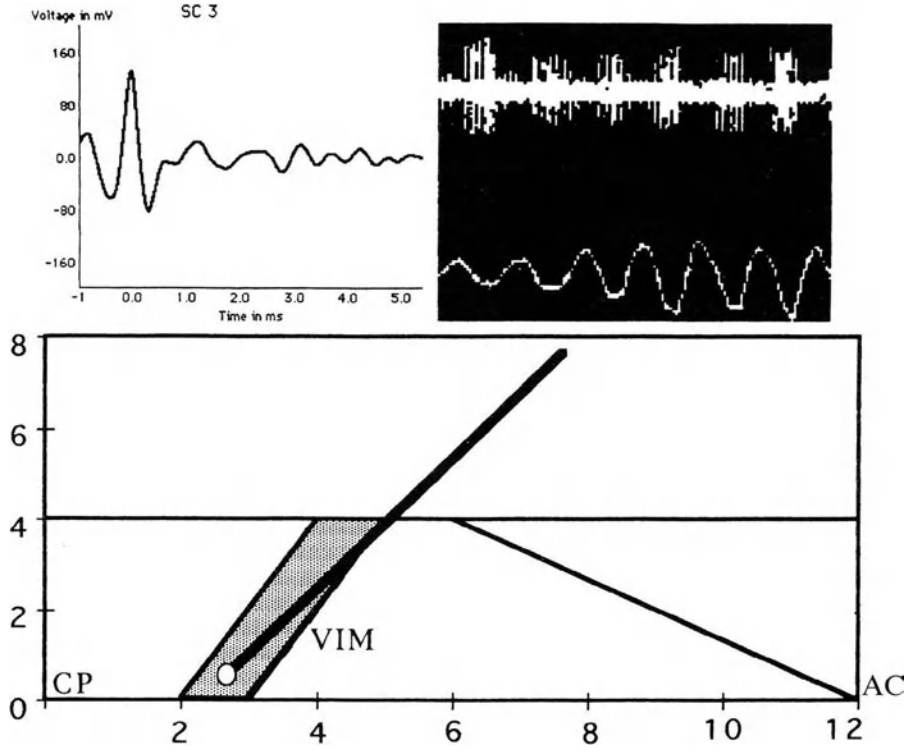



Fig. 3. Typical V.im. cell as recorded with a microelectrode at the bottom of V.im. with bursting rhythmic neuronal activity synchronous with the accelerometric recording of the upper limb tremor

*MRI*

Stereotactic MRI is the key investigation for STN localization. With a special T2 weighted sequence, it is possible to define the STN as an almond-shaped structure, situated 1 to 2 mm anterior to the red-nucleus, 2 to 3 mm superior and slightly lateral to the substantia nigra reticulata, externally limited by the internal capsule, and posterior to the mamillary bodies, allowing precise determination of the coordinates of the centre of this small structure (Fig. 4).

*Electrophysiology*

a) Stimulation. In both V.im. STN and GPi patients, intraoperative stimulation produced an acute response when the stimulating electrode reached the target or its vicinity. STN stimulation induced a recovery of limb aki-

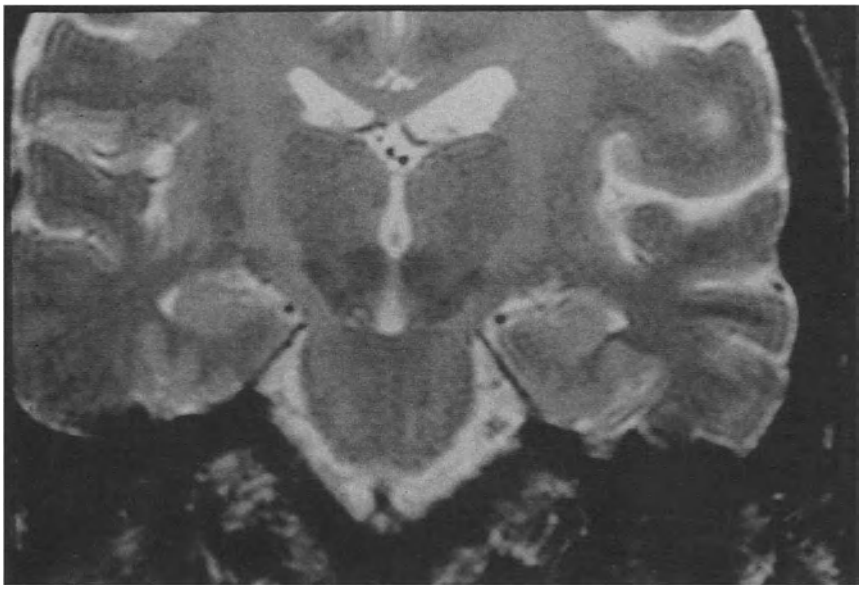


Fig. 4. MRI vizualization of STN (shaded area), Substantia Nigra and Red Nucleus using a "fat shift" T2 weighted sequence on a Philips Gyroscan at 1.5 Tesla

nesia when the patient was in a frozen situation. Motor performance rates were significantly increased, although the reproducibility of this type of assessment was limited, owing to patient fatigue. A very significant decrease in wrist rigidity was in fact the most reliable intraoperative test. Continuous monitoring by the neurologist of passive rigidity during manipulation of the patient's wrist revealed easily detected changes related to effective stimulation.

b) Recording. Multiunit and single unit recordings showed an increase in neuronal firing rate in STN as compared with the surrounding area. This effect was observed regularly at the site where STN is located by MRI and where the best effects on rigidity and akinesia were obtained. The majority of STN cells produce large, asymetrical spikes with a high frequency ($35.2 \pm 8.8$ Hz) firing rate, while another type of biphasic spike fires at a lower rate ($11.1 \pm 2.3$ Hz) which can be changed by passive movements of the limbs and joints. Below the STN level, even larger spikes, very symmetrical, can be recorded, with a lower, irregular firing rate that is unresponsive to stimuli. We attribute these to the substantia nigra which is just below the STN. This last type of cell did not show any observable changes in firing rate during various activities and tests performed during the session.

## Localization of the Gpi (Globus Pallidus, pars interna)

GPi is a larger structure than V.im. or STN and it is necessary to continue interactive clinical and anatomical studies of functional distribution in this structure because there are certainly different functional responses according to the exact side of stimulation.

### *Ventriculography*

According to the atlases, the coordinates of the posterolateral target currently used are as defined by Laitinen: 2 to 3 mm anterior, 20 to 22 mm lateral and 2 to 6 mm inferior to the midpoint of the bi-commissural line.

### *MRI*

Shows nicely the main features of the lenticular complex, using T1 as well as T2 weighted sequences. Inversion recovery turbo spin echo sequences are particularly well suited to show the subdivisions of the globus pallidus and its internal part GPi can be usually distinguished from the external part GPe. On axial sections, GPi usually covers the antero lateral half triangle of a rectangle, the limits of which are 10 to 20 mm lateral, and in the antero posterior direction from the anterior commissure to 10 mm posterior to it, or even to the mid-commissural point (Fig. 2).

### *Electrophysiology*

a) Stimulation. The definitive placement of the electrodes can be determined by location of single unit characteristic GPi activity recordings but also by maximal improvements in controlateral upper limb rigidity and finger tapping with minimal side effects during stimulation. These data are essential although the major indication is made of the abnormal involuntary movements which can not easily be tested in the operation theatre during the long electrophysiological session unless apomorphine test is performed during the same session stimulation.
b) Recording. Depending on the obliquity of the exploring track, characteristic firing patterns, originally described by Hutchinson *et al.* (Hutchinson *et al.* 1994) can be recorded, which allow the surgeon to recognize the GPe, where two types of cells are recorded (low frequency discharge-bursts neurones (LFB: $10.6 \pm 8.9$ Hz) and higher frequency neurones ($60 \pm 36$ Hz) with an irregular pattern and pauses in activity) and the GPi, where neurones are found to be firing at a high rate with a very irregular firing pattern, at $55 \pm 27$ Hz in the external part and at $82 \pm 32$ Hz in the medial part. These three subnuclei are also separated by border cells with a regular firing pattern at about 30 Hz. Below GPi, the adjacent structure which runs

obliquely parallel to the main axis of GPi is the optic tract where light flashes induce evoked potentials and stimulation induces visual phenomena. These electrophysiological patterns have been reported in detail by Hutchinson *et al.* (inson *et al.* 1994).

### *Neurophysiological Explorations*

Since 1987, different methods have been used by the Grenoble team to ensure better investigation of the target area. Initially, the target was defined with the help of a Radionics electrode used for stimulation only. In later patients, this electrode was replaced with a bipolar concentric stimulating recording electrode. However, it soon appeared that geometrical localization of V.im. target was still not adequate. In subsequent patients, two intersecting tracks were used with the same laterality from the midline to achieve correct localization of the best target. The first track (exploratory track), parallel to the midsagittal plane, is aimed at detecting the anterior and posterior limits of V.im., and also at checking the correct laterality. The lateral projection of this track passes through the foramen of Monro and PC. It therefore crosses the inferior half of V.im. and ends in the inferior part of the VPL.

A bipolar concentric stimulating-recording semi-micro-electrode, outer diameter 0.62 mm (kindly provided by C. Ohye or purchased from FHC, Brunswick, ref. 17-300-1 or 20-10-3) is lowered into the thalamus towards the V.im. target through a 2.3 mm diameter burr hole drilled into the skull in the frontal region. The results of this first track guide the placement of the second track (implantation track) towards a correct target, in a plane situated along the anterior edge of V.im. If the first track dictates displacement of the second, this is usually made rostrally. In most cases, including STN and GPi stimulation, the Grenoble team has used another method: a new system has been designed which allows simultaneous introduction of a set of five parallel recording-stimulating electrodes (4 electrodes concentrically disposed around a central one, at 2 mm distance), aimed directly at the theoretical location of the desired target. During progression of this exploring set, electrophysiological procedures are performed. The track which provides the best functional results is chosen for final implantation of the DBS electrode which is inserted in this track, in place of the test electrode. For the Grenoble team, this procedure ensures optimal positioning (Fig. 1). Obviously, the risk of hitting a blood vessel is five time higher with this method than with the previous one but has not been observed in our series. However, a larger area is probed at the same time, increasing the probability of finding the best electrode location. Finally, the chronic electrode is precisely guided and inserted exactly in the track where the best results are observed. This procedure is especially well

suited to small targets, such as the subthalamic nucleus (Limousin *et al.* 1995; Pollak *et al.* 1993a).

A constant current stimulator (WPI Accupulser A310) with an isolation unit (WPI A365R) is used to stimulate structures during the electrode placement procedure, at various sites along the trajectory. The electrode is always used as a cathode. The expected effect of 130 Hz stimulation (in Vim tremor suppression with the lowest (0.2–2 mA) current strength, in STN and in GPI suppression of rigidity and decrease in bradykinesia) is the major criterion in choosing the final placement (Fig. 3). For instance, as the electrode approaches the Vim target, the current intensity threshold necessary to obtain total arrest of the tremor decreases, from more than 10 mA at 20 mm from CP to between 0.1 and 1 mA at the level of Vim, which is reached at about 8 mm from CP. This threshold starts rising again when the electrode leaves Vim to enter the somatosensory nucleus VPL where, simultaneously, increasingly strong paresthesiae are induced, the topography of which is highly indicative of the correct laterality of the track. As shown previously (Guiot *et al.* 1967; 1968; 1973; Tasker *et al.* 1986), paresthesiae in the commissure of the first two fingers are indicative of correct laterality for tremor suppression in the upper limb. Paresthesias elicited in the face would indicate that the track is too medial, while paresthesias in the fifth finger, or even in the leg, would mean that the track should be moved more medially. For each track, comparison between motor and sensory threshold helps to determine the optimal electrode placement (Fig. 5).

Spontaneous as well as evoked multi-unit neuronal activities are also recorded at various sites along the trajectory down to the AC-PC line, using conventionnal preamplifiers (WPI DAM-5A), AC-DC amplifiers (Neurolog NL106), filters (Neurolog NL125), and spike triggers (Neurolog NL201) and processed through a MacLab 4 WPI system and a MacIntosh II CX computer with a 80 Mb hard disk. The pattern recorded depends on the nucleus to be investigated and on the type of electrode used. With a semi-macroelectrode, only multi-unit activity can be recorded: the amplitude of the spikes, described as "neural noise" (Matsumoto *et al.* 1984; Ohye *et al.* 1989) varies along the track and can provide information about the boundaries of the different nuclei. This neural noise is high in Vim and diminishes markedly when the electrode enters the internal capsule. Similar patterns are observed in STN and in GPI (Hutchinson *et al.* 1994). With a microelectrode (FHC Brunswick, ref. 17.300.2), single units are recorded in all three nuclei. The exact position of each stimulating and/or recording site is checked by X-Rays and mapped onto the final operating diagram. This provides a set of data with which the exact location of the chosen nucleus can be mapped, providing a corrected target into which the chronic DBS electrode will be implanted. Shifts of several millimeters between the

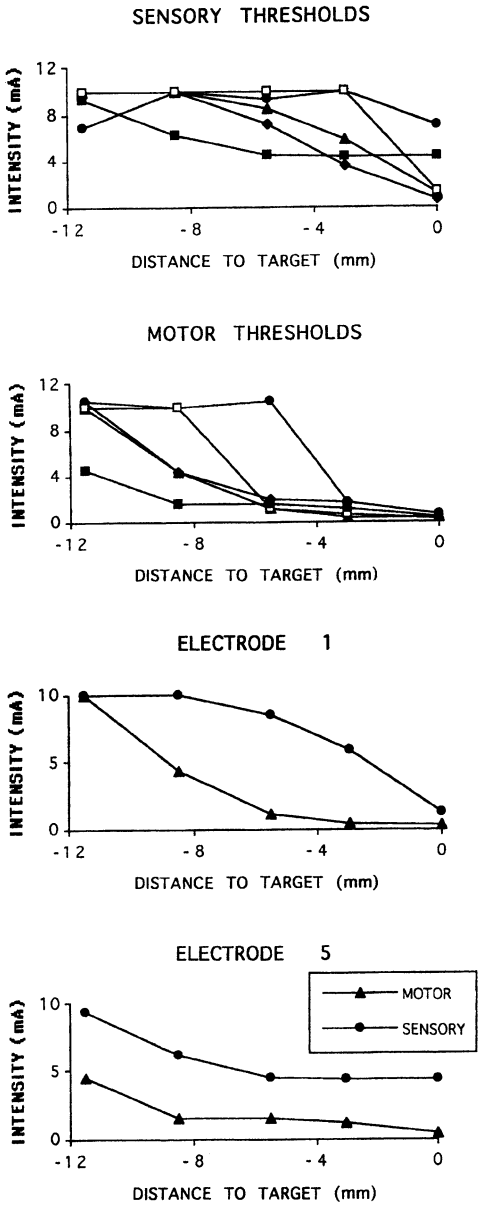



Fig. 5. Changes in threshold currents along the exploring tracks. Along the track down to the target, current threshold for total arrest of tremor (motor) and for elicitation of paresthesias (sensory) are measured for each of the five electrodes (upper charts). The best electrode must provide the lowest motor and the highest sensory thresholds. Electrodes 1 and 5 (lower charts) can be compared: electrode 5 has been chosen due to its low motor thresholds and to its higher sensory thresholds which will induce less sensory side effects

theoretical (ventriculography based) and the corrected (electrophysiology based) targets may be observed, confirming the necessity of the electrophysiological studies for target localization. However, these shifts are rather small, the first localization of the target by the ventriculographic approach being nearly always correct.

### *Chronic Electrode Insertion*

In the three groups (Grenoble, Lille, Créteil) the first electrodes were monopolar (Medtronic SP.5535) with an insulated tip 1.5 mm in diameter, and 4 mm long. The next ones were tetrapolar (Medtronic 3387) with four contacts, 1.5 mm in diameter and 1.5 mm long, separated each by 1.5 mm (for V.im. or GPi stimulation) or 0.5 mm reduced space (Medtronic 3389) for STN stimulation. When control X-Rays confirm the correct final placement, the electrode is fixed to the skull either with a double screw made of titanium, developed by the Straumann Institute (Waldenburg, Switzerland), (Fig. 6). An external screw fits snugly in a 2.5 mm diameter drill hole in the skull and an internal screw holds the electrode. A small plastic valve assures a perfect seal.

Another option is to fix the electrode to the skull by suture anchored in the skull through a short drill hole intersecting the tract hole in a Y shaped pattern. The knot in the suture is then embedded using dental cement (methymethacrylate CMW1). In the two cases, the DBS electrode is connected to its percutaneous extention which traverses the skin in the parietal region. The extra length of wire is folded under the pericranium which is carefully closed as is the skin. When the symptoms are bilateral, the contralateral side is implanted at the same session, following the same procedure.

### *The Post Stereotactic Period*

– An imaging study (CT or MRI) may be performed during this testing period, a few days after implant, to check the position of the electrode and to rule out any possible associated parenchymal lesions (Fig. 7). The Medtronic tetrapolar electrode (3387) is MRI compatible and provides images in which the four contacts can be located precisely by their small magnetic artefact surrounding an area devoid of signal (Fig. 8). The former monopolar electrode (SP 5535), due to its particular metallic composition, had a larger magnetic artefact that prevented good localization of the electrode tip. During the following days, the therapeutic results may be documented with the same series of clinical tests as were performed before surgery. These tests are made with and without stimulation at various parameters in order to determine the best frequency, pulse width, and tem-

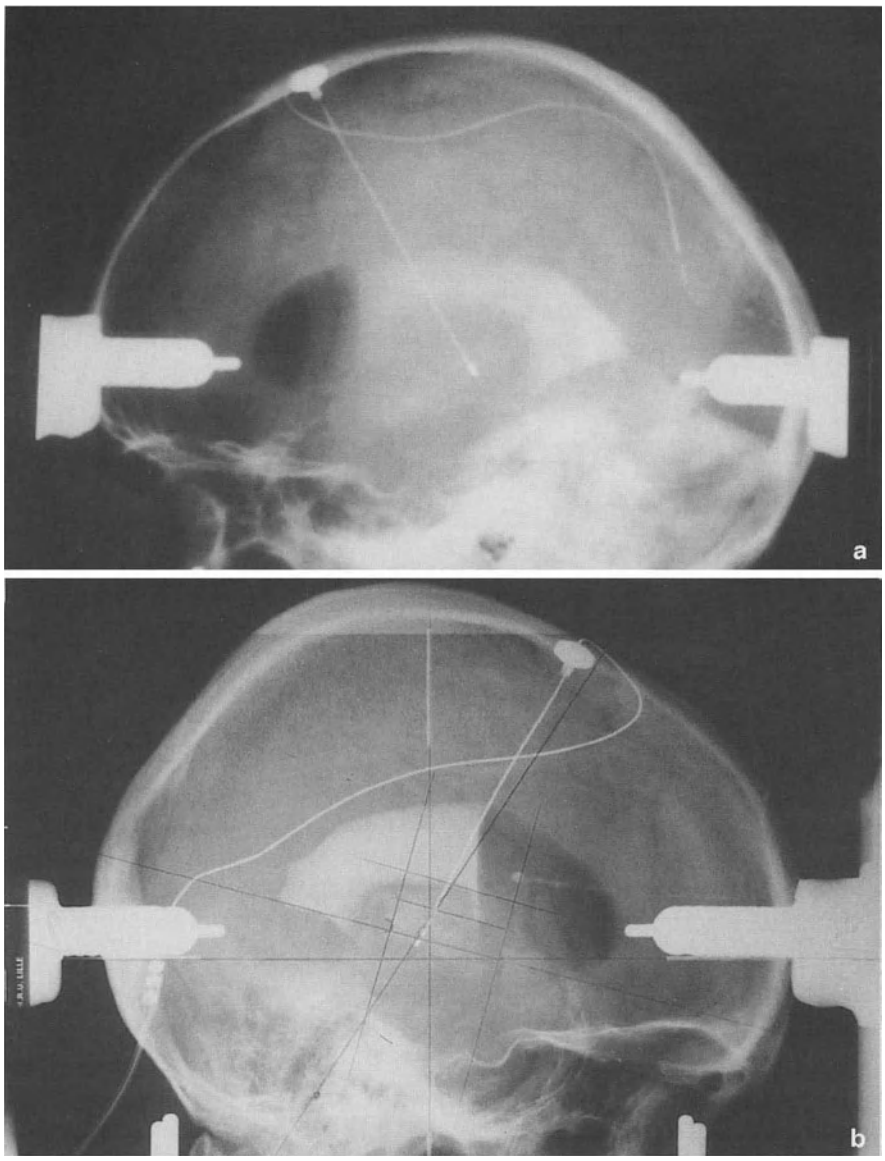



Fig. 6. Final postoperative radiograph. Head is placed in the Talairach'frame. Medtronic monopolar (a) and quadripolar (b) electrode (SP5535 and 3387) fixed to the skull with a Strauman-Avery screw (Siegfried and Blond, 1997)

poral pattern of stimulation. Video recording, neurophysiologic testing, such as accelerometry with and without stimulation, and spectral analysis of the involuntary movement can also be performed.

– When the clinical results are satisfactory, the stimulator is internalized

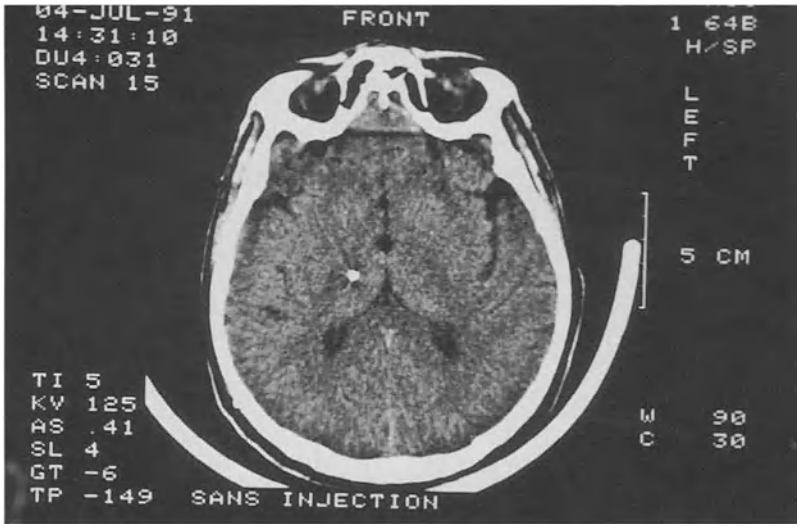



Fig. 7. CT scan control showing the tip of the implanted electrode without parenchymal lesion

within a week of implantation under general anesthesia. Initially, it was radiofrequency mediated (Medtronic) where the pulses are transmitted from an external generator to the implanted receiver through the skin using a coil antenna. This type of stimulator is not really adequate as it allows the patient to modify the stimulation parameters but also to do something wrong and overstimulate himself. The development of implantable, transcutaneously programmable neurologic pacemakers make it possible to implant the anterior stimulation system, and led to the present popularity of intracranial stimulation. The stimulus generator (Medtronic Itrel I or II) is placed in a subcutaneous pocket in the subclavicular area and connected to the distal tip of the electrode via an extension passed subcutaneously up the neck to the cephalic area. Local installation of antibiotics (Rifampycin) is carried out at the level of every surgical wound, making systemic antibiotic therapy generally unnecessary. The neurologic pacemaker is externally programmable using an external programmer consol (Medtronic), allowing the physician to set the frequency (130 to 185 Hz), amplitude (up to 10 volts, usually between 2 to 4 volts), and pulse width (usually 60 or 90 microseconds) independently.

### *Which Target for which Symptom(s)?*

The idea that only one symptom can be controlled by one site of stimulation arose from clinical experience with V.im., since only tremor is

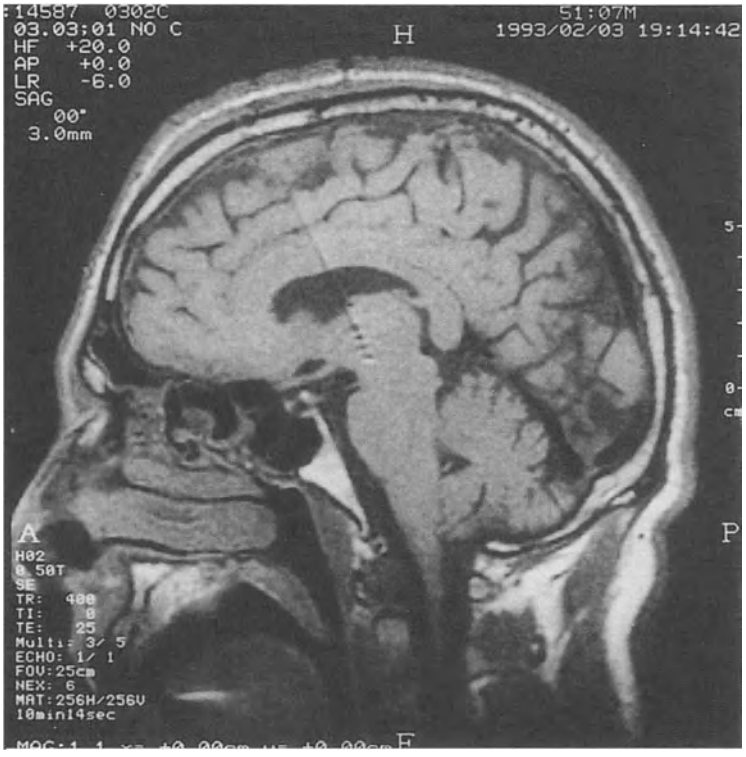



Fig. 8. MRI of the electrode placement after stereotactic implantation, before internalization of the Itrel II stimulator

improved by thalamic stimulation. However, rigidity, akinesia and tremor are probably all improved together by subthalamic stimulation, while iatrogenic dyskinesias may be improved by V.im. stimulation in specific conditions or by GPi stimulation.

## Why is V.im. the Target in Tremor?

The target of implantation is the ventral intermedius nucleus (V.im.) of the thalamus, which for the last years, has also been considered to be the most effective target for thalamotomy in the surgical treatment of movement disorders (Guiot *et al.* 1968; Albe-Fessard, 1961; Nagaseki *et al.* 1986; Ohye *et al.* 1975; Matsumoto *et al.* 1977/79; Matsumoto *et al.* 1984; Ohye *et al.* 1989; Tasker *et al.* 1983; 1986). V.im. has also proven to be a good target for chronic stimulation (Benabid *et al.* 1991; 1996; Blond *et al.* 1991; 1992; Caparros-Lefebvre *et al.* 1992; 1993; 1994). Systematic stimulation during the course of thalamotomies before making the lesions created

spectacular tremor suppression at frequencies higher than 100 Hz. The mechanism of this effect is not yet understood but clinical experience over 9 years has proven it to be effective, but only for tremor.

## Other Targets

Since electrical stimulation is reversible, conservative and does not cause significant tissue destruction, it could have potential applications to other structures of the brain, possibly in other diseases. However, extensive and careful animal experiments are necessary first.

### *Why is STN the Target in Akinesia?*

The two main clinical forms of Parkinson's disease are characterized either by tremor or by akineto-rigid syndrome. Rigidity and akinesia are the most dopamine dependent symptoms and patients with severe akineto-hypertonic forms of Parkinson's disease are therefore most dependent on L-dopa treatment. Past clinical history has obviously demonstrated that STN lesions induce long term hypotonia associated with ballismus, while STN is hyperactive in disorders with rigidity such as Parkinson's disease. STN stimulation has recently been proposed on the basis of previous extensive experimental investigation of the basal ganglia and the resulting concept of the functional connectivity of these structures (Bergman *et al.* 1990; DeLong, 1990). Long term dopa therapy induces motor fluctuations and different patterns of dyskinesia, resulting in highly disabling "on-off" swings which constitute an important therapeutic challenge (Lees, 1989) requiring alternative therapeutic strategies, such as surgical procedures. Destructive stereotactic surgery, such as pallidotomy, (Iacono *et al.* 1995; Laitinen *et al.* 1992; Lozano *et al.* 1995) is currently the most effective procedure for suppressing rigidity and akinesia in Parkinson's disease. Neural grafts could represent an elegant solution, but present results are only moderately satisfactory. Experiments in MPTP-lesioned monkeys have demonstrated that dopaminergic deafferentation induces hyperactivity in STN (Alexander *et al.* 1990; DeLong, 1990) and that destruction of STN suppresses rigidity and akinesia (Aziz *et al.* 1991; Bergman *et al.* 1990) in these animals. Destruction of STN in human patients cannot be considered, due to the high risks of inducing hemiballismus, although a spontaneous hematoma in STN is known sometimes to suppress Parkinsonian signs (Sellal *et al.* 1992). In this condition, the high frequency stimulation could inhibit STN in the same manner as it inhibits the V.im. nucleus for tremor (Benabid *et al.* 1987; 1988, 1989; 1991). This hypothesis was validated by animal experiments which demonstrated that high frequency stimulation of STN in MPTP monkeys rapidly reversed rigidity

and akinesia (Benazzouz *et al.* 1993). This encouraged surgeons to perform STN stimulation in human patients, in whom alleviation of akinesia and rigidity is observed in the operating room (Limousin *et al.* 1995; Pollak *et al.* 1993a).

*Why is GPi the Target in Levodopa Induced Dyskinesia?*

Pallidotomy was frequently used as a treatment of Parkinsonian symptoms several decades ago. Svennilson and Leksell (Svennilson *et al.* 1960) developed it, when different targets in the basal ganglia neuronal network were tried. This method did not appear to be the best surgical solution although its questionnable influence on rigidity led it sometimes to be combined with stereotactic thalamotomy (Blond *et al.* 1987). More recently, Laitinen (Laitinen *et al.* 1992) demonstrated its spectacular effects in most symptoms of Parkinson's disease, confirmed by many series (Fazzini, 1997; Kishore, 1997; Gregory, 1997, Wang, 1997) with practically complete disappearance of iatrogenic dyskinesia on the side opposite the lesions. The revival of pallidotomy is related to the fact that long term treatment with L-Dopa (over few years or more) has led in many patients to the development of rapidly debilitating clinical symptoms that was unknown prior to the use of this drug. The initially successful control of symptoms (primarily rigidity and hypokinesia) may gradually give way to a rapid and unpredictable alternation of severe parkinsonian symptoms, including akinesia and "freezing" with wholly iatrogenic dyskinesia and hyperkinesia. These abnormal involuntary movements in fact constitute an entirely novel disease which explains why this surgical method is now so popular, while it did not receive such a reputation when Leksell was performing it. According to Laitinen (Laitinen *et al.* 1992), ventroposterolateral pallidotomy removes the abnormall hyperactive inhibitory activity of the internal globus pallidus and thus normalizes the function of the pallido-thalamocortical motor control pathways. The neural hyperactivity of the internal globus pallidus, associated with hypoactivity of the external globus pallidus, was also demonstrated by Filion (Filion *et al.* 1991) in monkeys with Parkinsonism induced by MPTP. Differencies in neural activity, between the internal and external globus pallidus, have also been found in humans with Parkinson's disease. Grafton (Grafton *et al.* 1995) showed that the regional cerebral blood flow, measured by position emission tomography (PET) in six patients who had undergone posteroventral pallidotomy, was significantly increased in the ipsilateral supplementary motor area and premotor cortex, but not in the primary motor cortex. All of these findings support the hypothesis that ventroposterolateral pallidotomy removes the hyperactive inhibitory influence of the globus pallidus on the locomotor pathway. Pallidal stimulation, introduced by Siegfried in 1990, is to pallid-

otomy what thalamic stimulation is to thalamotomy: an alternative technique that renders side effects and complications avoidable or reversible and that enables simultaneous, bilateral surgical approaches when necessary. Even so, a unilateral ventroposterolateral pallidal procedure may have small ipsi-lateral benefits in some patients, in addition to its major contralateral effects; many patients clearly have more to gain from bilateral intervention. The results of continuous pallidal stimulation are especially marked by disappearance of severe and very distressing iatrogenic dyskinesia. As for the mechanisms of action reported by Davis (Davis *et al.* 1997) and colleagues concerns the findings of positron emission tomography in patients undergoing pallidal stimulation for Parkinson's disease: there was a strong, stimulation-induced activition of the premotor cortex, similar to that obtained by Grafton in a comparable study of the effect of pallidotomy.

## *Chronic Deep Brain Stimulation for which disease?*

### Parkinson's Disease

Parkinson's Disease is the ideal pathology for which these methods should be developed. The symptoms of this disease are major, unambiguous and rather easy to observe and quantify. Parkinson's disease is characterized by a variable association of three symptoms: tremor, rigidity and akinesia. Rigidity and akinesia are the most dopamine-dependent symptoms and patients with severe akineto-hypertonic forms of Parkinson's disease are dependent on L-dopa treatment. The primary lesion of the disease is also well-known, as well as the cascade of events involved along a well-defined neuronal circuit in the basal ganglia. V.im. has been the object of broad empirical clinical experience in patients, as well as experimental experience in monkeys (Hunter *et al.* 1949). Subthalamic Nucleus, on the contrary, has been well investigated in animals, and its role clearly determined in the physiology of movement disorders, providing a good theoretical basis for human experimental applications.

### Essential Tremor

In Guiot's view, this was the best indication for thalamotomy, since the disease consists only of tremor, which is released by surgery (Guiot *et al.* 1967). However, most authors consider that the efficacy of Vim stimulation is still greater in parkinsonian than in essential tremor. Benabid et Blond observed that proximal tremor, especially involving the shoulder, which is more common in essential tremor, was not as well controlled as distal tremor.

### Dystonia

There are few data available showing improvement of dystonia by Chronic Deep Brain Stimulation. Moreover, dystonia is a feature of a heterogenous range of diseases. Either neurodegenerative primary or secondary dystonia may assume similar patterns of hypertonia, associated or not with hyperkinetic disorders. Then, evaluation of this method should be made in 2 or 3 stages: 1. treatment of focal dystonia due to vascular or traumatic lesions, 2. treatment of well-defined essential dystonia. 3. treatment of unusual disorders when dystonia is the most disabling feature. Siegfried and Blond, in focal dystonia, have obtained good results with stimulation of specific sensory nuclei of the thalamus (these nuclei thus appear to have a role in the organization of movement).

### Other Movements Disorders

Whether other movement disorders, especially those not related to degenerative disorders, may be treated by Chronic Deep Brain Stimulation remains to be clearly defined. The different series are often too small to assess a clear and constant effect of this method on action tremor due to post-traumatic or post-haemorrhagic lesions of the brain stem. Following N'Guyen's publications, Chronic Stimulation of the V.im. seems reasonable in patients with relatively stable multiple sclerosis, who suffered from medically intractable postural volitional dyskinesia, in view of the frequently unsatisfactory results of thalamotomy and its higher rate of functional complications, when used to treat this particularly complex movement disorder (results of the anatomic lesions are already present as part of the disease, and larger therapeutic lesions are required). However, overall assessment of the results of thalamic stimulation in the context of multiple sclerosis is made difficult by the lack of a precise analytic scale and by the complexity of the movement disorder, which is often a combination of postural and intentional dyskinesia with underlying dysmetria, ataxia and spastic paresis.

## Indications and Results

### *Patient Selection*

### V.im. Stimulation

In the three neurosurgical centers, 243 patients have been operated upon since January 1987, including 134 with parkinson's disease, 31 with essential tremors and 67 with various dyskinesias represented essentially by

action tremor of multiple sclerosis (Grenoble: 19; Lille: 11; Créteil: 37). 10 to 50 % of patients were bilaterally implanted, which corresponds to 73 electrodes in Lille and 198 electrodes in Grenoble. 10 to 17% patients had previously undergone unilateral thalamotomy. These patients, who gave their informed consent, were selected on the basis of the severity of their symptoms, the amplitude of tremor, their drug resistance, or intolerance to high doses of drugs and their disability in daily life.

### STN Stimulation

20 cases (18 PD, 2 dystonias) have been implanted since January 1993, 18 of them bilaterally (38 electrodes, the last 15 patients during the same session). These patients, who gave their informed consent, were selected on the basis of the existence of on-off periods, abnormal involuntary movements, and periods of severe akinesia. The resulting disability was evaluated using UPDRS and Hoehn and Yahr scales, duration of akinetic periods over 24 hrs, video recording and surface EMG studies in calibrated tests. Neuropsychological tests were also performed. MRI was normal for each patient. Patients were scheduled for unilateral implantation on the side contralateral to the worst symptoms and later implanted bilaterally. Implantation was always performed bilaterally for STN stimulation for bradykinesia.

### GPi Stimulation

10 cases have been operated since February 1992, 4 of them bilaterally, 2 contralaterally to STN implantation and 2 contralaterally to VIM.

## *Results*

### The Grenoble Experience

*Complications and Side Effects*

– Stimulation of V.im.. V.im. stimulation was well tolerated. No mortality was observed in this series. 3 patients had secondary (24, 25 and 28 months after implantation) scalp ulceration in front of the electrode-to-extension connection. In one patient, this led to the temporary removal of the extension 6 months after implant with replacement 3 months later. In the 2 other patients, the electrode and the extension had to be removed, being successfully reimplanted 4 months later in one of them. One patient with multiple sclerosis developed a small haemorrhage around the tip of the

electrode 3 days after implant, associated with moderate aphasia and slight right hemiparesis which improved within 2 months. At the time of the haemorrhage the tremor, which had been controlled totally by the stimulation, disappeared even with the stimulator turned off and never recurred. Two other patients experienced intracranial microhaematomas which induced a long term thalamotomy-like effect of slight motor neglect which recovered over several weeks. Three other patients had asymptomatic intracranial microhaematomas detected only on routine postoperative CT scan.

Any adverse effects of stimulation were mild and well accepted by the patients because of their relief from tremor and because they disappeared immediately when stimulation was decreased or stopped. These consisted of contralateral paresthesias (9%), limb dystonia (9%), dysequilibrium (7.6%) and dysarthria. Dysarthria affected more often patients who had had previous contralateral thalamotomy (12 out of 23 patients = 51.7 %) than those who were bilaterally stimulated (10 out of 66 patients = 15 %). This suggests that the morbidity rate from dysarthria for V.im. stimulation is lower than that for thalamotomy (Fox *et al.* 1991; Matsumoto *et al.* 1984; Nagaseki *et al.* 1986; Stellar *et al.* 1968). No spontaneous psychological disturbances were reported in our series (Benabid *et al.* 1996). A careful study (frontal lobe function, memory, language and praxis skills) in 9 patients (Caparros-Lefebvre *et al.* 1992) did not detect any neuropsychological impairment before and after V.im. stimulation. Switching on the stimulator suddenly could induce transient but not disabling contralateral paraesthesiae lasting a few seconds. Switching the stimulator off induced transient rebound tremor in about half of the patients without clinical implications but often prevented them from stopping the stimulator at night. However, continuous stimulation induced in some patients (7 out of 20), mainly those with action tremor, a tolerance phenomenon causing a progressive loss of efficacy of the stimulation.

– Stimulation of the subthalamic nucleus. Out of 20 patients (38 electrodes), no mortality, infection, skin problems or general complication were noted. Hemiballismus was never observed, neither during the operating session nor during clinical follow-up. After bilateralization of the second patient, slight facial paralysis, disturbance of verbal memory and impairment of neuropsychological tests consistent with a frontal syndrome were observed, but progressively improved within one month. MRI examination showed hypo T1 and hyper T2 signal disturbance located in the lateral anterior thalamic nuclei above STN, suggesting a local ischemic lesion or oedema following electrode insertion and/or stimulation. The sixth patient developed a large intracerebral hematoma. The bleeding occurred during surgery along the penetrating track, at the supraventricular level, and originated from an arterial branch of the pericallosal territory which was

injured by the exploratory electrode. This had no relationship with STN target by itself. 18 patients were bilaterally implanted, the first two in 2 sessions 4 and 13 months apart respectively, the 16 others in one session. Hemiballismus was never observed during the operating session or during clinical follow-up. After bilateral implantation of the second patient, slight facial paralysis, disturbance of verbal memory and impairment of neuropsychological tests consistent with a frontal syndrome were observed, but these improved progressively over one month. MRI examination showed hypo T1 and hyper T2 signal disturbance located in the lateral anterior thalamic nuclei above STN, suggesting a local ischemic lesion or edema following electrode insertion and/or stimulation.

– Stimulation of GPi (Globus Pallidus, pars interna). Ten patients (14 electrodes) were implanted without mortality nor morbidity. Some of them were slightly drowsy or tired for a few days, which unequivocally seemed to be related to the long surgical procedure under local anesthesia. However, neuropsychological testing failed to show any delayed memory impairment even in the 8 bilaterally implanted patients.

*Benefits*

– V.im. stimulation is mainly effective for tremor. Particularly *parkinsonian rest tremor*. The effect on tremor is scored independently by the neurologist on a 5 point scale (4 = complete disappearance of tremor in all circumstances. 3 = reappearance of a slight tremor on rare occasions, for instance under stress. 2 = moderate benefit. 1 = slight benefit without real improvement in daily life activity. 0 = no benefit at all or worsening of tremor). Immediately after surgery, a microthalamotomy-like effect is responsible for transitory tremor suppression for a few days. During the test period, various combinations of stimulation parameters are evaluated. The best effect with the least side-effects is observed with a pulse width of about 60 microseconds, the lowest possible with the Medtronic Itrel I and II stimulators. The threshold intensity necessary to suppress the tremor totally was investigated for various frequencies of stimulation, the minimum being a plateau from about 100 to 2000 Hz (Fig.1). The stimulators are therefore set at 130 or 185 Hz, the two highest available frequencies on the ITREL I or II. The voltage value is set according to the patient's choice, based on a compromise between benefits and side effects. This voltage increases during the first 6 weeks partly because of a progressive increase of impedance (measurable on the ITREL II) from about 750 to 1000 ohms during the first 4 weeks. The remaining increase may represent habituation of the stimulated structures. The average voltage at latest follow-up is 2.7 volts (range 0.4–5.5 V). A very good result, such as permanent total suppression tremor or only slight reappearance on rare occasions

(scores 3 and 4) was obtained in 71% of the operated sides. More precisely, this major benefit was obtained in 88% of cases with Parkinson's disease, 68% of cases with essential tremor, and 18% of cases related to other causes. In these last cases, the effect was often complete during the first postoperative month but an action component recurred later. Resting tremor is better controlled than action tremor, distal limb tremor better than proximal or axial tremor, and upper limb better than lower limb tremor. In all cases the effect is strictly coincident with the stimulation, without significant delay at onset nor after-effect at cessation of stimulation.

Tremor is the only parkinsonian symptom which can be greatly influenced by V.im. stimulation but this allowed, in one-third of the patients with Parkinson Disease, reduction of L-dopa doses by more than 30%. Rigidity and pain are partly reduced as well as levodopa-induced dyskinesia in this series. Akinesia (Guiot *et al.* 1967) is not modified, apart from the fact that high amplitude tremor prevents semiquantitative assessment of akinesia; when tremor is arrested by stimulation, repetitive movements can be again performed.

Dyskinesias of other origins are much less affected by V.im. stimulation in our series. However, any small improvement may be sufficient to ameliorate the quality of daily living significantly. V.im. stimulation could therefore be considered in these patients on this basis, as has been thalamotomy (Andrew *et al.* 1981; 1984). Movement disorders associated with multiple sclerosis are improved when they consist of postural tremor but not cerebellar tremor.

Dystonia. Thalamotomy has been known for years to have an effect on dystonic movements of various etiologies. The definition of the target area within the thalamus and the suitable size of the lesion remain debated. Thalamic stimulation has been applied in 4 dystonic patients aged 16 to 32, with idiopathic generalized dystonia, accompanied in one by upper limb tremor. One patient had already undergone a thalamotomy contralateral to the stimulated side, while the others underwent simultaneous bilateral thalamic stimulation. The surgical procedure was the same as in patients with tremor except that 2 patients were operated upon under general anaesthesia owing to the extent of their dystonia. Out of a total of 7 stimulated thalami a moderate long-term benefit for contralateral limb dystonia was obtained 4 times; tremor was suppressed in one patient. As in cases of parkinsonian and essential tremors, midline symptoms such as speech, swallowing and gait difficulties, as well as neck, trunk and facial dystonia showed minimal or no improvement. In two cases of familial dystonia however, bronchitis due to inhalation of saliva was suppressed, as well as biting of the lips, and the degree of mouth opening was increased, allowing easier feeding. These two sisters both exhibited dramatic rapid

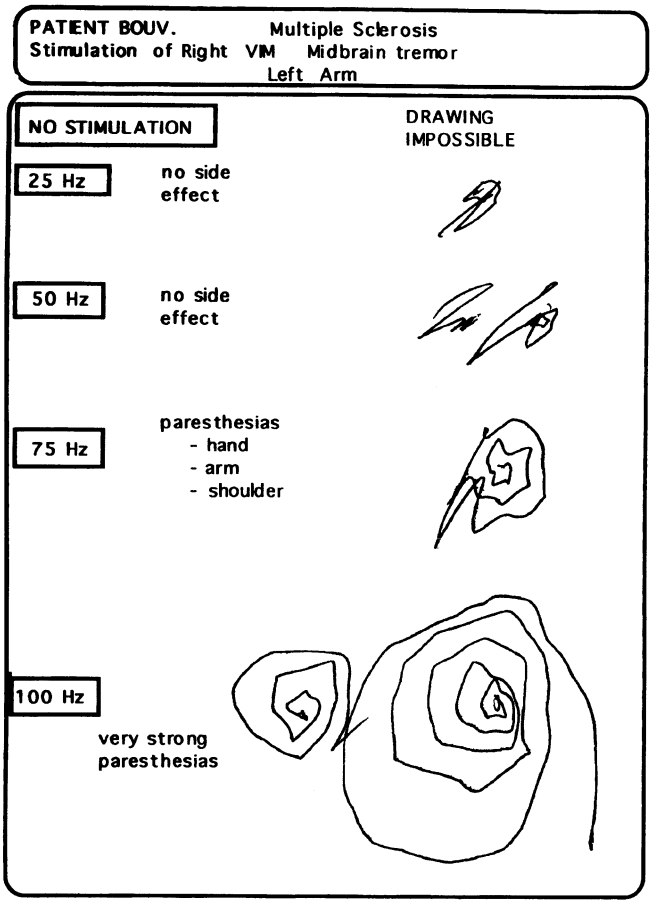



Fig. 9. Frequency dependence of the efficacy of V.im. stimulation on essential tremor: drawing a spiral is improved when frequency increases

worsening of their general status when the generator batteries were depleted, requiring emergency replacement. In these disabling dystonias, the benefit of V.im. stimulation is mainly appreciated by the family and nurses rather than being reflected by the current dystonia scales since it concerns essentially the general status and daily life activities. No adverse effects were noticed. The mean electrical intensity was set higher in these patients than in parkinsonian tremor.

Essential tremor (ET) is also significantly improved by V.im. stimulation during the operation and for the first few months afterwards (Fig. 9). The effect is, however, less stable in time, and in some cases, the tolerance effect may result in total loss of efficacy. The transient effect on the action component of a movement disorder is cause for concern as well as

the rebound effect after stopping stimulation and the development of tolerance. These effects may relate to the mechanism of action, which is still unknown. Similarly, the movement disorders of multiple sclerosis respond differently according to their nosology. The postural component of the tremor is usually well controlled by V.im. stimulation, but the action component near a goal during directed movement is rarely totally suppressed, and cerebellar dysmetria and gait are never improved. In fact, dysmetria may be induced experimentally in parkinsonian patients when the stimulation intensity is increased higher than the level needed for tremor suppression. This may be due to an involvement of cerebellar projection fibers. Finally, and not least, tremor and levodopa-induced AIMs are the only symptoms which can be improved by stimulation. Persistent hemiballismus following vascular ischemia or hemorrhage has recently been reported as being markedly improved by V.im. stimulation (Tsubokawa *et al.* 1995), possibly offering a method for controlling it if it happens after STNs timulation.

Tolerance to V.im. stimulation. Tolerance to V.im. stimulation is of major importance, since it represents a serious drawback of the method which must therefore be resolved. It is noteworthy that tolerance develops with action tremor rather than resting tremor, which most often remains evenly controlled for a long time, even though rebound may be observed when stimulation is stopped. This rebound is, however, limited and tremor returns to the initial level within a rather short time interval, i.e in the order of hours. Tolerance in action tremor is different as it requires an ever increasing stimulation intensity to control the tremor. The resulting current spread involves progressively adjacent structures and therefore induces side effects, such as paresthesias when VPL is reached, which limit the extent to which voltage can be increased in an attempt to secure relief. Tolerance is dose related, and appears mainly in those patients who need high intensities of stimulation even at the outset to stop their tremor. This can be attributed to a less than ideal electrode placement. Tolerance is also worse when patients cannot stop stimulation at night; stimulation holidays, whenever possible, can reverse it.

These aspects suggest a pharmacological basis for tolerance, resembling that observed with opioids. Although no neurotransmitter has been found clearly involved in V.im. function, pharmacological tolerance could happen in other portions of the network. Tolerance might also be due to a fatigue like mechanism, occurring at the level of V.im. neuron membranes, under the effect of chronic stimulation. There is currently no basic neurophysiological knowledge concerning the effects of chronic stimulation on neural structures. Electrical pulses are shaped to balance currents but this might not be long term valid. The effect of alternating polarity pulses, which really balance charge densities, should be studied in order to check

this hypothesis. It should be noted that tolerance to V.im. stimulation is observed in cases of essential tremor where the effect of thalamotomy, when initially satisfactory, is usually reported to be stable (Derome *et al.* 1986; Goldman *et al.* 1992; Guiot *et al.* 1967).

– Only STN stimulation reduces Rigidity and Akinesia. According to our protocol, medical treatment is maintained unchanged during the evaluation period. Patient 1 has been followed up for 36 months. The overall neurological status has improved significantly as well as the quality of daily life activities. The patient's self evaluation scored 35% improvement at 3 months, 60% at 6 months. Freezing occured on average 3 times a day preoperatively, once every 2 weeks postoperatively. Off period dystonia happened 4 times a week preoperatively and disappeared postoperatively. However, there are no significant differences with stimulation on and stimulation off. Increasing the intensity of stimulation above 4 volts induced unpleasant contralateral paresthesias. Patients have been followed for more than 30 months. The clinical changes as well as improvement in quantitative testing are strongly evident when stimulation is turned on and off. Moreover, surface EMG recording of agonist and antagonist muscles of the forearm during passive wrist manipulation show that reflex hyperactivity of the stretched antagonist muscle, which is typical of extrapyramidal rigidity, is almost completely suppressed during STN stimulation, in a way very similar to that observed after apomorphine injection or levodopa administration. The continuous follow-up of these patients (Limousin *et al.* 1995) show an increasing improvement of about 50 % of all symptoms evaluated on the corresponding scales, and a decrease in drug dosage of about 30 to 50%. Patients who before surgery had Levodopa-induced AIMs may exhibit similar complications when STN stimulation is on while they have their regular drug regimen. This tends to diminish with time as drug dosages are progressively decreased. As a general rule, it may be said that STN stimulation provides the patient with a permanent level of improvement equal to his best status during on-periods.

– GPi stimulation abolishes AIMs. Although the electrode placement is guided during the surgical procedure by the effects of GPi stimulation on rigidity and akinesia, AIMs, which cannot be steadily observed during surgery, are strikingly suppressed after surgery, quite often spontaneously for a few days due to a pallidotomy-like effect, and then by continuous GPi stimulation. This allows the patient to continue their regular medication without the disabling side effects of the AIMs. This is clearly a contralateral effect. The effects on akinesia and rigidity are more difficult to assess and seem to be less spectacular than those observed after STN stimulation. However our series is too small and our follow-up too short to allow us to make a definitive statement. Moreover, GPi is a large target and it might be possible that there is a functional spatial distribution,

which would require us to locate precisely the relationship between the subdivisions of the GPi nucleus and the symptoms expected to be influenced. This is supported by Laitinen (Laitinen *et al.* 1992) who claims that the postero ventro lateral part of GPi is the most efficient area, the destruction of which would affect all symptoms almost equally. The answer will come from a long and carefully documented analysis of larger series of patients.

## The Lille Experience

*Stimulation of V.im.*

a) The Surgical procedure differed in some aspects from the one used in Grenoble. General anesthesia was performed in all patients, during the first part of the stereotactic procedure, including fixation of the frame and ventriculography; then, the patients were awakened for the neurophysiological procedure which was limited to stimulation. Recordings were only performed in the first patients. The target is identical but the monopolar or quadripolar electrode is introduced through the frontal lobe from an oblique angle in both sagittal and coronal planes. Once this electrode has been placed at the target and its position has been checked on plain radiography, stimulation is delivered intraoperatively to verify the clinical effects. At the end of the procedure, the electrode is fixed to the skull (a 2.5 mm burr hole) with the double screw described above; just before this is done, a small trough is made in the outer table to receive the head of the screw, so that it will not press on the overlying scalp. The electrode is then connected to an external stimulator through a temporary extension cord exiting the scalp superior to the ear. A plain radiograph is taken at the end of the procedure while the patient is still in the stereotactic frame to provide a final check of the position of the electrode tip and make certain that it has not moved, as even small movement can have serious clinical consequences. The position of the single contact of the monopolar electrode or of each of the contacts of the multipolar electrode is checked in the three-dimensional stereotactic coordinate system. (Blond *et al.* 1992).

b) Patient selection. Forty-five patients (47 implantations) with idiopathic Parkinson's Disease gave their informed consent for thalamic stimulation. In each case, the tremor was debilitating, present for at least 5 hours a day, and refractory to all attemps at medical treatment, including with L-dopa. There were 34 men and 11 women; the mean age was 62 years (range, 43–74 years) and the mean duration of illness was 10 years (3–24 years). Ten of these patients had L-Dopa induced dyskinesia which consisted of chorea in five, dystonia in three, and both chorea and dystonia in two cases. Dis-

tribution of Hoehn and Yahr stages was: stage II: nine patients; stage III: 31 patients; stage IV: five patients. Five patients had previously undergone contralateral thalamotomy.

Eight patients (9 stimulations) with essential tremor, disabling for most activity (writing, eating,...) were selected after they gave informed consent. Two had previously undergone contralateral thalamotomy with excellent results. These series included five men and three women with mean of 36 years (range, 26–48 years). The stimulating electrode was inplanted on the left side in five cases, on the right side in four cases.

The same procedure were performed in 11 patients with relatively stable multiple sclerosis, who suffered from medically intractable postural volitional dyskinesia. Stimulation was performed unilaterally in five patients, bilaterally in six patients. Patients were selected upon clinical criteria including permanent disability during voluntary movements, while patients were still able to have a social or family activities.

c) Results. – Parkinsonian tremor. At mean follow-up interval of 41 months (range, 3–73 months), the results were excellent in 29 cases (total elimination of tremor, except for possible mild tremor under stress) and good in 16 (marked reduction of tremor with functional improvement). Two patients showed only minimal reduction of tremor and no functional benefit on long term follow up.

– Essential tremor. Excellent results (complete disappearance of tremor) were obtained in four cases, while only partial control was obtained in two cases, albeit with marked functional improvement, i.e., the tremor returned only under conditions of fatigue or emotional stress, but then could not be abolished by modifying the stimulation parameters. Two cases were considered failures in the short-term and underwent thalamotomies with excellent results, and one case was a failure in the long-term because an "escape phenomenon".

– Involuntary movements. Due to multiple sclerosis, disappeared completely in eight cases but, in all of these cases, the proximal muscles were only minimally involved in the movement. In six cases, improvement was noted in both proximal and distal components of the involuntary movements, leading to functional improvement in activities of daily life requiring manipulation of objects; these patients thus became able to eat and drink unaided. In 3 patients in whom the proximal muscles were primarily responsible for the involuntary movement, the benefit was small or absent and it was in these cases that the most marked «rebound effect» was seen when the neurologic pacemaker was turned off. One patient who underwent bilateral stimulation had an excellent result accompanied by an improvement in dysarthria and a small improvement in head tremor.

d) Specific effects on iatrogenic dyskinesia. L-Dopa induced dyskinesias were noted prior to surgery in 10 parkinsonian patients. They generally

consisted in choreic peak-dose dyskinesia and dystonic dyskinesia. Among these 10 cases of iatrogenic dyskinesias, chorea was eliminated in all five cases; dystonia was suppressed in two out of three cases, and barely reduced in one; and mixed dystonic and choreiform movements were eliminated in one out of two cases and markedly reduced in the other. The fact that this effect on levopa-induced dyskinesia was observed variably in Grenoble was attributed to some differences in the localization of the electrode tip which could be more anterior, perhaps in the ventral lateral nucleus of the thalamus (VL) since it is introduced in double obliquity in Lille (Caparros-Lefebvre *et al.* 1993). The favorable effect of VL thalamotomy on these iatrogenic dyskinesias had been reported in post-encephalitic parkinsonism (Narabayashi *et al.* 1989), and good results of stimulation for hemiballismus were recently shown (Tsubokawa *et al.* 1995). The area includes VL and V.im., which are the sites of convergence of all neuronal messages of the sensorimotor system. Thus, these are the optimal targets for the relief of different types of abnormal movements, not only tremor. However, the control of both tremor and iatrogenic dyskinesia could require a multipolar electrode or two sites of stimulation.

e) Side effects. There were no perioperative deaths. Three patients died after more than one year, because of stroke or another illness. In one of them, neuropathologic study was performed. One patient developed a chronic subudural hematoma after implantation, most likely because of a tear in a bridging vein resulting from excessive intraoperative loss of cerebro-spinal fluid. A contralateral motor deficit resolved rapidly after evacuation of the hematoma through burr-hole. The other surgical complications consisted of two infections, one at the site of a cutaneous erosion over the extension cord, and the other at the pacemaker site. In these patients, this led to temporary or definitive removal of the electrode. Contralateral persistent dysesthesia occured in six patients and four cases of dystonic posturing of the lower extremity that was present only during stimulation. One patient had mild dysequilibrium during stimulation with a tendency to lateralpulsion. One patient developed dysarthria and slowing of speech with bilateral stimulation; these problems were reversible by stopping stimulation of the dominant thalamus. No motor or visuospatial neglect occurred in any case. A rebound phenomenon occured in 19 patients when the pacemaker stopped functioning, consisting of tremor markedly wider and faster than the initial tremor, sometimes present not only at rest but also in maintained posture and with movement to a given target. After a delay of several minutes to several hours, this rebound-effect subsided and the tremor returned to its initial state.

f) Neuropsychological assessment. This was performed before and after implantation of the thalamic electrode. Mild cognitive disorders were observed prior to thalamic implantation. Neuropsychological testing failed to

reveal intellectual function worsening after implantation except for reverse digit span which was significantly reduced. Intellectual and frontal lobe functions were not damaged by thalamic stimulation. A transient ideomotor slowing was observed in 1 case. Neither dysarthria nor aphasia appeared after thalamic stimulaton. A dysarthria was noted before neurosurgery in 40% of cases but was not worsened after surgery, except in one patient after bilateral stimulation. Significant improvement in the depression score compared with the pre-stimulation state was found in several patients, probably because of the improvement in parkinsonian symptoms (Caparros-Lefebvre *et al.* 1992).

### *Stimulation of Ventro-Postero-Lateral Nucleus of the Thalamus*

Seven patients with focal dystonia were treated with chronic thalamic stimulation. There were three cases of dystonia secondary to ischemic lesions of the thalamo-parietal pathway that were visible on structural imaging. One of these patients also had constant, medically intractable neuropathic pain involving the entire hemibody, but most intense in the dystonic foot. There were two cases of post-traumatic dystonia and two cases in which dystonia appeared in complex neurological context involving other involuntary movements as well.

The first 5 of these 7 patients were treated with stimulation of the ventral-postero-lateral nucleus of the thalamus. This target was chosen because of the experience of Siegfried and Mazars in patients with the Dejerine-Roussy thalamic pain syndrom, whom they treated with chronic stimulation of the VPL at the somatotopic site corresponding to the location of the pain. In the other two patients i.e., those with focal dystonia in the context of other involuntary movements, the VPL-V.im. complex was chosen as the target and a quadripolar electrode was used.

Focal secondary dystonia was greatly improved by stimulation but dystonia related to more diffuse disease was improved only transiently. However, a best analysis of results needs the selection of patients with pure dystonia, not associated with motor deficit nor pyramidal rigidity as it was in one post-traumatic lesion (Sellal *et al.* 1993).

## Comparison of Lille Versus Grenoble Results and Correlation with Electrodes Location

The observation of different effects of stimulation between Lille and Grenoble led us to define the reason why two teams using the same procedure and the same target for deep brain stimulation (DBS) obtained different results on L-Dopa induced dyskinesias, while in both, parkinsonian tremor was improved or totally suppressed. A 10 year experience with DBS in Parkinson's disease now allows comparison between teams' results, and

evaluation of new targets, so long as they use intraoperative ventriculography, as did our two teams (Lille = team A; Grenoble = team B). Both teams aimed at the same target, the ventralis intermedius nucleus of the thalamus (V.im.), but team A observed a clear improvement of choreic peak-dose dyskinesia, while team B did not constantly. We therefore re-examined all teleradioanatomical data of both teams, and compared them with the therapeutic effects. The location of 99 monopolar electrodes of thalamic stimulation applied to treat parkinsonian tremor has been retrospectively measured (team A included 21 patients, 22 electrodes; team B included 52 patients, 74 electrodes). L-Dopa peak-dose dyskinesia were suppressed by DBS in all 9 patients of team A, four of which were severely disabling. Only 8 out of 32 patients from team B experienced a moderate (4) or clear (4) improvement of dyskinesias, while in the remaining 24 patients, dyskinesias were unchanged with and without stimulation. The mean centre of team A's electrodes was on average 2.91 mm deeper, more posterior and medial than team B's ($t = 8.05$; $p < 0.0001$). This does not correspond to the coordinates of the V.im., but seems to be closer to those of the centre median and parafascicularis complex (CM-Pf), according to stereotaxic atlases. Considering only the dyskinetic patients, significant differences were observed in the electrode positions according to the therapeutic effects on L-Dopa dyskinesias, but they were not related to the team membership. Improvement of L-Dopa dyskinesias was significantly associated with deeper and more medial placement of electrodes. The retrospective analysis of DBS cases using comparable methodologies provides important information concerning electrode position and therapeutic outcome. The position of the electrode strongly influences the therapeutic effects of DBS. The results support the hypothesis that patients experiencing an improvement of dyskinesias under DBS are actually stimulated in a structure which is more posterior, more internal and deeper than V.im., very close to CM-Pf. These results are consistent with neuroanatomical and neurophysiological data showing that CM-Pf is included in the motor circuits of the basal ganglia system and shares common afferents with the internal pallidum. This suggests that CM-Pf could be involved specifically in the pathophysiology of L-Dopa peak-dose dyskinesias.

## The Creteil Experience

Thalamic stimulation has been performed in the place of thalamotomy for the *treatment of action tremor of multiple sclerosis*: 37 patients (24 females and 13 males), suffering from multiple sclerosis and presenting a severe action tremor were operated between October 1989 and December 1996. The mean follow-up was 20.8 $\pm$ 16.3 months. The mean age of the patients was 37 $\pm$ 5.1 years. They all suffered from advanced multiple sclerosis with

severe action tremor, refractory to medical treatment. They had suffered from multiple sclerosis for an average of $12.4 \pm 6.$ years, with action tremor for an average of $4.4 \pm 2.9$ years.

The stereotactic procedure is performed under local anesthesia, a 4-contact electrode (Medtronic 3387) being positioned in the nucleus ventralis intermedius of the thalamus (V.im.), identified by ventriculography with reference to Guiot's geometric construction. Initially, a semi-microelectrode 0.4 mm in diameter (USK-100, Single medical, Tokyo, Japan) was positioned in the inferior part of the nucleus, 15 mm lateral to the midline. The position of the semi-microelectrode was considered to be adequate when stimulation clearly reduced the tremor for stimulation intensities less than 1 mA (pulse width: 1 ms, frequency: 100 Hz). The 4-contact chronic stimulation electrode was then inserted. The most distal contact was placed in the target previously located by the microelectrode. After several days of clinical testing, the stimulator (Itrel 2, medtronic) was implanted subcutaneously in the infraclavicular region. In the majority of cases, the stimulator was programmed to deliver stimulation for 12 hours during the day and automatically stop at night.

*Clinical Assessment*

Patients were evaluated before and 1 month after the operation, then every three months. The course of multiple sclerosis was evaluated by EDSS and tremor was evaluated by Webster's score (Webster, 1968). The functional repercussions were evaluated by the patients using a 5-point score (Global disability scale (GDS)): No activity possible (4), major disability (3), marked disability (2), moderate disability (1), normal activities (0). In the last 20 patients, the repercussions of tremor were evaluated by Brown's functional score (Brown *et al.* 1989) and Bain's visual analogic scale (Bain *et al.* 1993). After the operation, the efficacy of stimulation on tremor was evaluated by a global improvement score (0: no effect, 1: satisfactory effect, 2: marked effect).

For the last 20 patients, correlation studies were performed between clinical efficacy of stimulation and presence of a cerebellar syndrome. Adiadochokinesis and dysarthria were recorded as being present (1) or absent (0), and the Stewart Holmes manoeuvre was scored as positive (1) or negative (0). Correlations were performed using Spearman's non-parametric test. Correlations between clinical efficacy of stimulation and history of multiple sclerosis, history of tremor, and initial EDSS score were performed using Pearson's parametric test. The Student t test was used to compare numerical data concerning these patients (Webster, global improvement score, EDSS, functional scale, visual analogue score).

One month after the operation, the efficacy of stimulation of each

contact was evaluated separately during stereotyped positions and manoeuvres of the upper limb: finger-nose movements, arms and forearms extended, arms extended and forearms flexed). Stimulation parameters (intensity, frequency, pulse width) were modified as a function of the best clinical results obtained.

a) Overall results. – Short-term effects on tremor. Three months after the operation, stimulation was effective in 24/37 patients (65%), partially effective in 10/37 patients (27%), and ineffective in 3/37 patients (8%).

– Long-term follow-up of tremor. In the long-term, 21 patients (56.7%) were markedly improved and 8 (21.6%) were more moderately improved. Stimulation was ineffective in 8 patients (21.6%).

Stimulation gradually lost its efficacy in 3 patients with a very good initial result. In one patient, stimulation became totally ineffective, while in 2 others, stimulation remained partially effective. Among the three patients in whom stimulation was never effective, one patient died one year after the operation in a context of progressive deterioration of the disease, and the other two patients did not obtain any improvement despite several unsuccessful attempts to adjust the stimulator.

b) Analytical results. – Webster scale. Global, disability scale. Webster's score and the GDS were significantly improved at the 1-month postoperative review ($p < 0.001$). The difference remained significant at the 3-, 6- and 12-month evaluations.

– Visual analogue scale (Bain). A significant functional improvement of Bain's visual analogue scale was observed at the 1st, 3rd and 6th postoperative months ($p < 0.01$).

– Functional disability scale (Brown). The functional score was significantly improved only at the 1-month postoperative review ($p < 0.01$).

– Correlation with prior status. No correlation was observed between clinical improvement and the preoperative EDSS score or with the history of multiple sclerosis or the history of tremor.

– Correlations with cerebellar signs and topography of tremor. No correlation was observed between clinical improvement and the presence of a cerebellar syndrome.

c) Position of electrodes and clinical result. For the last 20 patients, stimulation was systematically applied to each of the 4 contacts of the electrode in the various positions and manoeuvres of the upper limb.

– Arms and forearms extended. Extension of the arms and forearms locks the shoulder and elbow joints and accentuates tremor of the distal part of the upper limb, but also tremor of the trunk. Tremor appearing in this position was improved in all patients by stimulation of a single contact. Separate stimulation of several other contacts of the same electrode (an average of 3 contacts) also achieved the same result, suggesting a relatively large zone of efficacy.

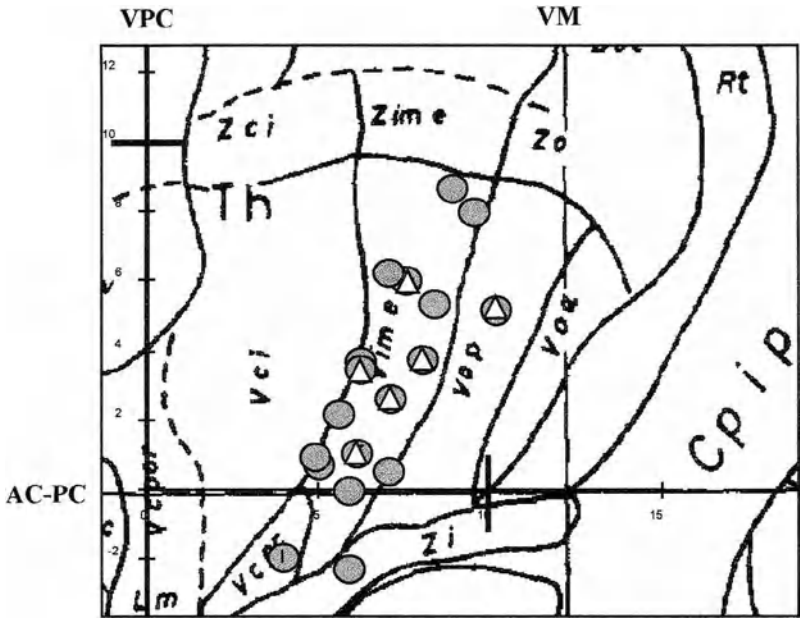



Fig. 10. Effective contact positions on proximal postural tremor (gray circles) and intentional tremor (white triangles), in 6 patients. Lateral view of V.im. (Schaltenbrandt's atlas [22]). *AC* anterior commisure of the third ventricle; *PC* posterior commissure; *VPC* line perpendicular to PC; *VM* line perpendicular to the midpoint of the AC-CP line

– Arms extended and forearms flexed (swordsman's manoeuvre). This position facilitates rotation movement of the arm and flexion-extension of the forearm on the arm and accentuates tremor of the proximal part of the upper limb. Regardless of the contact used, stimulation always remained ineffective in one patient. Stimulation was effective in the other 19 patients. In 6 patients, stimulation was only effective when a well defined contact was used. These contacts were distributed over the entire V.im. (Figs. 10, 11). In 13 patients, the effective zone appeared to be larger, covering several contacts (an average of 2 contacts).

– Finger-nose manoeuvre. This is a complex manoeuvre, as it involves the 2 previous positions and reveals the intentional component of the tremor. Functional improvement, especially the ability to eat, depends on the quality of improvement of the intentional component of the tremor.

Stimulation was ineffective in 4 patients,. In 8 patients, tremor was improved by stimulation of only one contact. In another 8 patients, stimulation was effective by using 2 separate adjacent contacts (average of 1.5 contacts). The zone of efficacy therefore appeared to be relatively limited

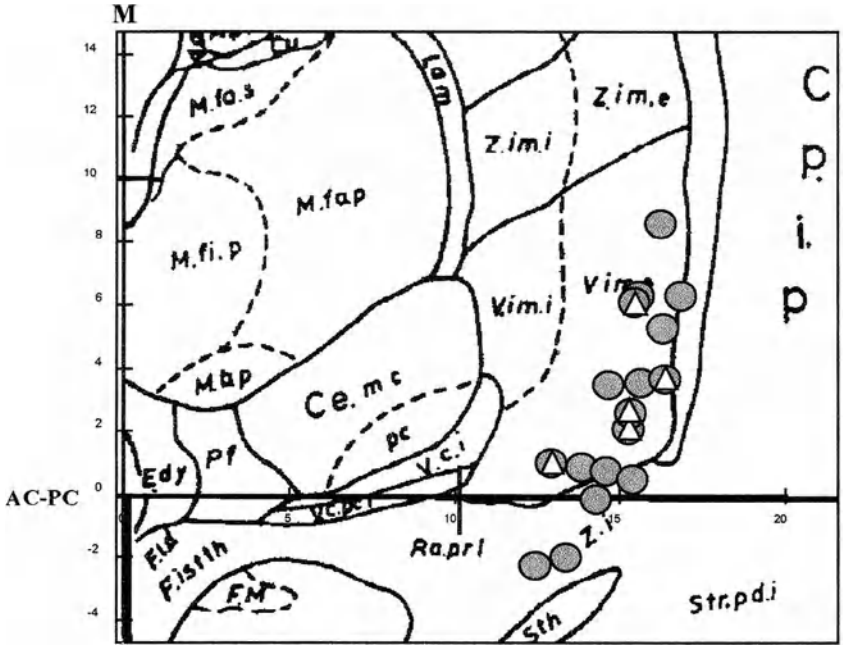



Fig. 11. Same positions as in Fig. 1, AP views; *M* midline

and was preferentially situated in the intermediate part of Vim, close to its lateral border.

– Chronic stimulation parameters. Effective chronic stimulation was unipolar (negative pole on the stimulated contact(s) and positive reference pole) in the majority of cases (34/37 patients), and bipolar (negative pole on the stimulated contact and positive pole on the immediately proximal contact) for 3/37 patients. For these last patients, the bipolar mode was used to minimize stimulation-induced paraesthesiae.

The settings remained stable throughout follow-up in all patients. Improvement of tremor was obtained by stimulation of only one contact in 13 patients, stimulation of two adjacent contacts in 13 patients, and stimulation of three contacts in 2 patients.

The mean intensity of stimulation was 2.26 Volts $\pm 0.05$, the pulse width was 69–90 microseconds and the stimulation frequency was 130 Hz.

Only one patient had to be reoperated to change the stimulator because of flat batteries. A contralateral operation was performed in 5 patients with severe bilateral tremor 4 months to 3 years after the first operation (average one year). Only one of these five patients, operated 4 months after the first operation, was clearly improved. In the other 4 patients contralateral tremor was only partially improved by this second operation.

d) Clinical course of multiple sclerosis. No significant difference was detected between preoperative ($6.6 \pm 0.91$) and postoperative EDSS scores ($6.7 \pm 0.88$). However, for 12/37 patients, a slight increase of the EDSS score (0.5 to 1) was observed 1 month after the operation. This increase was correlated with accentuation of Kurtzke's pyramidal score (Kurtzke, 1983).

Eighteen of the 37 patients had a stable neurological score at the end of follow-up. Three patients were lost to follow-up, one patient died and the neurological score deteriorated in fifteen patients due to progression of the disease, with confinement to bed due to quadriplegia.

e) Complications. Postoperatively, one patient developed an incomplete deficit of the contralateral lower limb to the operation. In 2 patients, gait was transiently altered (for 1 month) after the operation.

One patient developed a subcutaneous infection around the stimulator, which was removed and then replaced 3 months later.

## Discussion

### *Precise Methodology*

#### Clinical Requirements

There are 2 unconditional and invariable rules, which should be applied to every patient before surgery: 1. precise analysis of both disabling symptoms and associated disorders, leading to a clear diagnosis. This usually requires a dynamic collaboration between neurologists and neurosurgeons. 2. precise evaluation of disability and definition of the probability of partial or complete improvement after surgery. This explains the need for specific and validated rating scales of movement disorders such as the globally used UPDRS (Fahn *et al.* 1987; 1988) or in the course of multiple sclerosis, the EDSS (Kurtzke, 1983), the Brown's functional score (Brown *et al.* 1989) or the Bain's visual analogue scale (Bain *et al.* 1993). Videotape recordings before and after surgery are also needed, especially to assess the rebound-effect. When these are not performed, this phenomenon is poorly evaluated and understood, as it was in some studies (Villagra *et al.* 1996).

#### Technical Considerations

Technical aspects. The correlation between the position of the electrode in V.im. and the stimulation-induced effects shows that, generally in rest tremor, the most effective area is situated at the level of the AC-PC line (Fig. 12). Electrodes placed on the anterior border of V.im provide equally

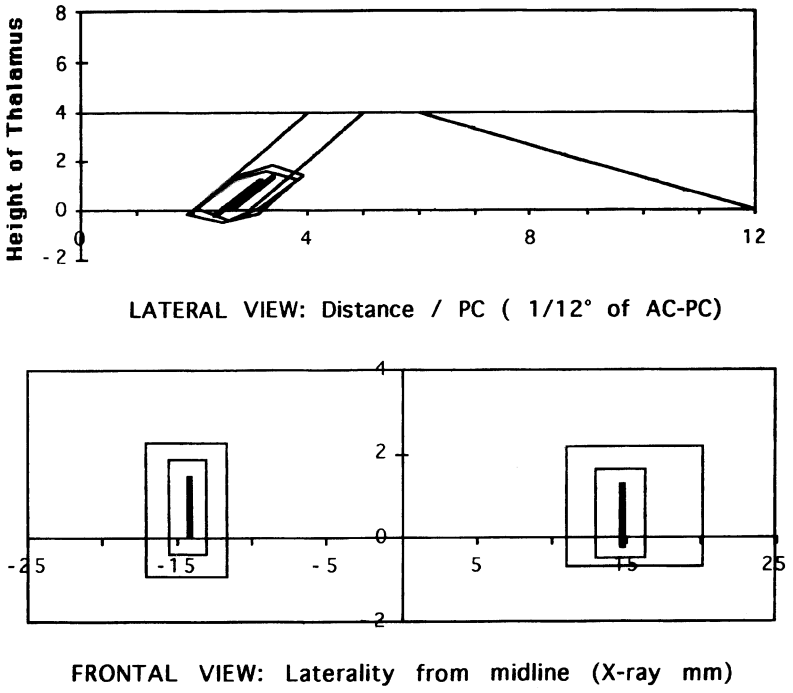



Fig. 12. Computer drawing of the average position of 108 monopolar electrodes represented according to normalized anatomical landmarks. Lateral view: the AC-PC line is divided in 12 parts, the height of the thalamus in 8 parts. AP view: verticality is represented in 1/8 of the height of the thalamus. Laterality is simply expressed in mm from the midline. Average electrode placement is represented by a thick line of the same length while standard deviation area is represented by a polygonal contour on the lateral and AP views. On the AP view, the outer rectangle around the average electrode position represents the extreme deviations

good results with less paresthetic side effects than those situated on the posterior border of V.im. Tetrapolar electrodes clearly show that the lower the contact, the lower the threshold. However, at the same time, the paresthesia threshold is also lowered. The most effective area is obviously the lowest part of V.im, in the AC-PC plane, immediately in front of VPL nucleus (between 2/12 and 3/12 of the AC-PC length ahead of PC). For the action tremor of multiple sclerosis, the use of the tetrapolar electrode was found to be particularly well adapted, as several of these patients required simultaneous stimulaton of two or even three contacts. In this context, the postural component of the tremor is the easiest to control, whereas, the improvement of the intentional component is more difficult to obtain. Laterality is critical and partly indicated by the effects of stimulation (tremor suppression as well as production of paresthesias) recorded during

the exploratory track. It appears that the responsive part of V.im is very close to the internal capsule and that the main part of the nucleus is rather parallel to it. Stereotactic MRI slices taken in the plane of the trajectory show the position of the pyramidal tract and could help in positioning the electrode in an oblique trajectory parallel to the internal capsule. Electrophysiology, as already stressed by Guiot (Albe-Fessard *et al.* 1961; 1962; 1963; 1988; Guiot *et al.* 1973; Hassler *et al.* 1960; Jasper *et al.* 1966; Matsumoto *et al.* 1979/77; Sem-Jacobsen, 1966; Taren *et al.* 1968) is certainly the ultimate method for optimizing the position of the electrode as it has been performed for thalamotomy. Stimulation may identify VPL as well as the pyramidal tract but essentially provides the functional criteria of effectiveness by showing directly, during surgery, to what extent the tremor is suppressed by stimulation and where this can be achieved. Neuronal activity recordings may give additional information which is interesting scientifically in that it may help to understand the mechanism involved. As has already been shown, neurons firing in bursts synchronous with the tremor are recorded in Vim, and thalamotomy at this site provides a very good result (Guiot *et al.* 1973; Hirai *et al.* 1989; Matsumoto *et al.* 1979/77; Ohye *et al.* 1989) as well as stimulation at high frequency. Below this area, neuronal silence is characteristic of the internal capsule and provides the inferior limit for electrode positioning. Similar comments apply to STN and GPI electrode placement.

## Costs

This method is obviously more expensive than thalamotomy. In addition to the stereotaxic procedure, which is almost the same in both methods, V.im stimulation requires electrodes, extension leads, and stimulators. Due to the high frequency at which they are used (130 to 185 Hz), battery life is relatively short. In our experience, the Itrel I has a life span of $29.7 \pm 11.6$ months (min: 17.1, max: 55.5) though some are still active after 64 months. The Itrel II, which we started to implant less than 3 years ago is expected to have 1.5 times the reserve of the Itrel I.

The benefits of stimulation of the subthalamic nucleus are difficult to evaluate as there is currently no alternative procedure with which to compare it since ventro-postero-lateral pallidotomy is still under evaluation. However, the significant decrease in drug dosage which is currently observed in STN patients leads to a reduction in the cost of the procedure, which must be evaluated further.

V.im. stimulation appears to provide a new therapeutic approach in the treatment of parkinsonian tremor, essential tremor and also action tremor of multiple sclerosis. The passage of several years has permitted both definition of the best indications and observation of the long term effects,

among which the appearance of tolerance in some cases needs to be resolved. The slight adverse effects, with the possibility of adjusting them in each patient, as well as their reversibility, the lack of neuropsychological effects during bilateral stimulation, and the possibility of association with previous contralateral thalamotomy, are all strong arguments in favour of this method. A better understanding of the mechanism, optimisation of electrode implantation and stimulation parameters, and even the discovery of new targets (Lozano *et al.* 1995) will further improve the results and probably enlarge the field of application.

## *Chronic Deep Brain Stimulation CDBS Versus Ablative Surgery: Advantages and Drawbacks*

### Thalamotomy

According to some authors (Siegfried *et al.* 1997), with rigorous stereotactic technique, thalamotomy yields excellent results, particularly in cases of typical parkinsonian tremor. Significant morbidity occurred in approximately 1% of the cases, and permanent functional sequelae in approximately 7%. Thus, despite the radical nature of this treatment when compared to the more conservative, reversible technique of stimulation, thalamotomy deserves to retain an important role in the treatment of medically intractable Parkinson's Disease, when the dominant symptom is unilateral tremor. Furthermore, Siegfried (Siegfried, 1980) and Narabayashi (Narabayashi *et al.* 1984) have demonstrated repeatedly that thalamotomy, particularly when centered on the V.o.p.-V.im. complex, not only abolishes tremor but also protects the patient againts iatrogenic dyskinesia secondary to long term treatment with L-dopa. Until unilateral thalamotomy has been compared with unilateral V.im. stimulation by prospective randomized studies, it will remain difficult to make definitive statement about the relative merits and drawbacks of each of these methods. Thalamotomy still has its place, with retricted indications: for young patients with symptoms predominantly unilateral and on the side opposite to the non-dominant hemisphere, this technique could be recommended as the first option. Thalamotomy is less expensive and does not require repeated follow-up and tuning of equipment (Andrews, 1984; Fox *et al.* 1991; Guiot *et al.* 1968; Matsumoto *et al.* 1979/77; Matsumoto *et al.* 1984; Narabayashi, 1989; Siegfried, 1979; 1986; Speelman, 1991; Talairach *et al.* 1949; 1950).

In contrast, V.im. stimulation is more expensive and necessitates frequent return visits (Pollak *et al.* 1993). It is a totally conservative and reversible technique, mandatory when thalamotomy is contraindicated such

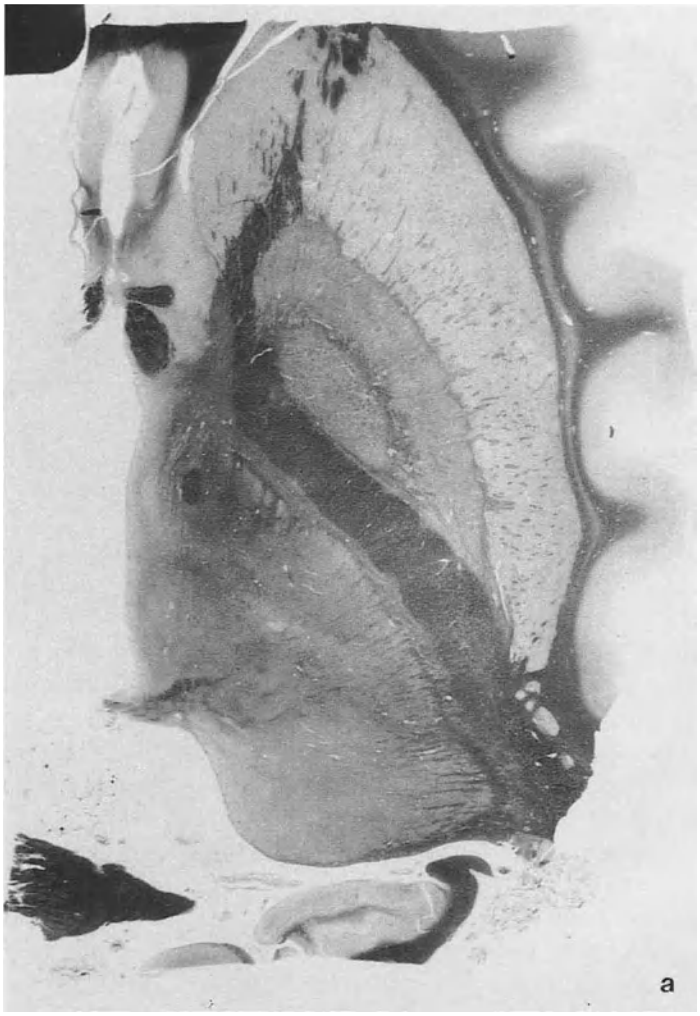



Fig. 13. Section of the thalamus (a) and schematic representation of thalamic subdivisions (b). The arrow showed the electrode track.
*Pal* Lateral pallidum; *PaM* medial pallidum; *LR* lateralis rostralis subdivision of the thalamus (nigral territory); *LO* lateralis oralis subdivision (pallidal territory); *LO* lateralis intermedia subdivision (cerebellar territory); *LC* lateralis caudalis (lemniscal territory); *C* central complex (nucleus centromedianus); *Pu* pulvinar; *PC* posterior commissure; V.im. nucleus ventralis internus (medial part of the cerebellar territory LI)

as in patients who have undergone a previous contralateral thalamotomy or in a patient with bilateral tremor treated by thalamotomy on the non-dominant side, and by stimulation on the other side or by bilateral V.im stimulation. Its known that bilateral thalamotomies, even when they are

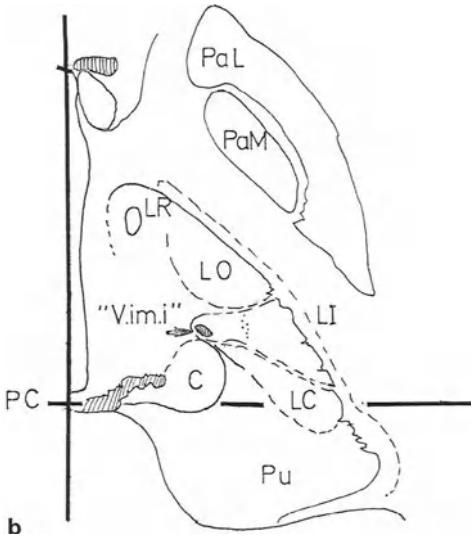



Fig. 13. (*Continued*)

performed in two sessions separated by several months, have a significantly high rate of complications. In comparison, V.im. stimulation has no severe complications, adverse effects are reversed when stimulation intensity is decreased, bilateral procedures do not induce neuropsychological deficits, and recurrences may be controlled to some extent by changing the parameters of stimulation. The slight dysarthria which is observed in only 15% of the bilaterally stimulated patients is also reversible when stimulation is stopped. Long term stimulation does not create a histological lesion, even when tolerance has developed, as shown in a post mortem examination which "demonstrated a small area of gliosis and spongiosis around the electrode track" (Caparros-Lefebvre *et al.* 1994) (Fig. 13).

## Pallidotomy

Since 1987, and especially since Laitinen's publication of 1992, pallidotomy has had a very favorable reception in the United States and elsewhere. The revival of this technique is related to the fact that long term treatment with L-dopa has led, in many patients, to the developement of a rapidly debilitating clinical syndrome characterized by rapid and unpredictable alteration of severe parkinsonian symptoms, including akinesia, freezing, iatrogenic dyskinesia and hyperkinesia. In many series (Fazzini, 1997; Kishore, 1997; Gregory, 1997; Wang, 1997), a lesion in the ventro-

postero-lateral portion of the globus pallidus reduces bradykinesia and suppresses iatrogenic dyskinesia. The incidence of quadrantanopsia, which is the major complication of the method, can be significantly reduced by electrophysiological exploration of the target area. Moreover, improved MRI sequences can obviously provide very accurate localization of the target and also minimize the risks of adverse effects.

The present data, although preliminary, are already significant enough to demonstrate that STN and Gpi stimulation relieve respectively parkinsonian rigidity, akinesia and dyskinesia, and that these effects can be stable with time so that it can be used for permanent treatment of these symptoms. The growing experience, acquired recently by several teams with pallidal stimulation (Siegfried *et al.* 1994), tends to suggest that the indications for pallidal "inhibition" could be met by stimulation rather than by destruction, not least because bilateral procedures will again have less morbidity with stimulation than with lesioning methods (Siegfried et Blond, 1997).

## Neural Transplantation

The experience from Creteil has been particularly well analyzed: the results of fetal mesencephalic transplantation were reported (N' Guyen JP, Keraval Y, Palfi S *et al* (1998) Greffe intrastriatale des neurones dopaminergiques embryonnaires de la Maladie de la Parkinson ) in a series of five patients, all of whom had Hoehn and Yahr scores of 4 or 5, and a partial response to L-Dopa, with adverse side effects. The follow-up period ranged from 3–5 years. The post operative evaluation was performed with timed clinical tests and a self-evaluation, and the antiparkinsonian medical regimen was held constant as long as possible. An improvement in motor performance, mainly on the side opposite the transplant, began shortly after surgery and persisted thereafter. The length of time spent immobile each day decreased by mean of 56% (range, 30–80%). Bilateral transplantation, in one case, resulted in a decrease in periods of immobility, a marked increase in periods of full mobility and a significant reduction of dopa-induced dyskinesia (Siegfried *et al.* 1997). According to the first results obtained by Benabid, the therapeutic effects of STN stimulation on rigidity and akinesia in Parkinson's Disease are so far spectacular, and rather easy to achieve. In this context, indications for STN stimulation seem to be the same as those for neural transplantation. Considering the ethical and technical problems raised by neural transplantation and still not yet resolved, STN stimulation can be offered as a reasonable alternative, as long as neural transplantation has not yielded significantly better results. Similarly, GPi seems to be a good replacement target for stimulation when dyskinesia are involved, especially in cases needing bilateral procedures.

## Why Should Chronic Deep Brain Stimulation be Preferred to Lesion?

Because of its total and immediate reversibility, V.im. stimulation has been attempted in patients presenting with Parkinsonian tremor or essential tremor (Benabid *et al.* 1987). In the same way, other targets have been selected based on their potential effect on different extrapyramidal symptoms without the adverse consequences of lesions: stimulation of the subthalamic nucleus (STN) to treat hypertonia +/− bradykinesia, and more recently of the Globus Pallidus pars interna (GPi) to treat dyskinesia have been tried in a shorter series of patients with significant preliminary results. Bilateral implants of one of these three nuclei can be performed in the same session, due to the low morbidity of the procedure, and without induction of the classical side effects of bilateral thalamotomies (Benabid *et al.* 1988; 1989) or of STN lesions, such as the hemiballismus observed after not only spontaneous hemorrhage but also ischaemia in this area. The excellent results obtained by the V.im. stimulation method justify its use as a first choice for surgical treatment of parkinsonian tremors (Benabid *et al.* 1991). Since electrical stimulation is reversible, not only are its effects on the symptoms more easily observable, but this method may lead to a better understanding of the underlying mechanisms of tremor and other movement disorders (Burleigh *et al.* 1993).

### *What is the Structure Being Stimulated that Arrests Tremor?*

Or is tremor suppression really due to V.im. stimulation? The question arose after the post-mortem study of a patient brain, stimulated for 3 years, with complete suppression of tremor. The neuropathological study showed the electrode tip was located in the most internal and inferior part of V.im., very close to the brachium conjunctivum (cerebellar afferents to V.im.) and also to the Centrum Medianum Parafascicularis (CM-Pf).

Interestingly, the electrode tip was more medial and more ventral than typical lesions of thalamotomy. Thus that stimulation could act by a different mechanism than thalamotomy. Then, the question that emerged from our discussion is whether tremor suppression is due to either V.im. stimulation, or brachium conjunctivum (BC) stimulation, or central complex (CM-Pf) stimulation.

## Is it due to V.im. Stimulation?

For this hypothesis, there are 2 arguments: one is anatomical, one is neurophysiological.

1. The thalamus is a funnel where most motor loops converge after information they have conducted has been less or more modified. To act at

this level may be the best choice, in order to interfere with an abnormal message. However, Marsden and Obeso (Marsden *et al.* 1994) have emphasised the great paradox of thalamic stimulation or lesioning. One could expect that this interference applied to motor messages should have modified simultaneously abnormal and normal motor patterns. If thalamotomy induces motor neglect, there is no evidence that thalamic stimulation modifies voluntary movements.

2. Specific bursts of "tremor" neurons, that pulse synchronously with tremor have been recorded mainly in V.im. (Albe-Fessard *et al.* 1962), but they are also recorded in other different structures, including motor cortex and deep cerebellar nuclei.

## Is it due to Cerebellar Afferent (Namely Brachium Conjunctivum) Stimulation?

For this hypothesis, there are 2 arguments: one clinical, and one metabolic.

1. After a few months of stimulation, about half of the patients experience a rebound-effect when stimulation is stopped, which is a coarse tremor, with semiological resemblance to cerebellar tremor. This could be due to an abnormal cerebellar disinhibition.

2. All metabolic studies have clearly shown that cerebellar activation occurs with tremor of all types: parkinsonian (Parker *et al.* 1992; Deiber *et al.* 1993) essential (Jenkins *et al.* 1993), writing and orthostatic tremor (Wills *et al.* 1996). Despite these studies, it is unclear whether the abnormal cerebellar activation in tremor results from abnormal input, or is due to a primary disorder of the cerebellum.

## Is it due to Central Complex Stimulation?

There is no direct argument for this hypothesis but CM-Pf is a central relay in the basal ganglia pathways. CM-Pf receives afferents from GPi and from the pedunculo-pontine tegmental nucleus (PPN) and is probably involved in the motor circuitry (Fénelon *et al.* 1994). The PPT-CM-Pf connection is a cholinergic pathway, which is inconstantly lesioned in human Parkinson's disease (Agid *et al.* 1989), and is spared in MPTP monkeys who do not display tremor (Herrero *et al.* 1993). This site was the target for Andy's stimulations (Andy, 1980; 1983) in the treatment of various movement disorders. This same site, focussing pallidal and PPN afferents on a small area, could explain how its stimulation may induce the simultaneous control of tremor and dyskinesia.

*Mechanisms of Action*

## Effect of Stimulation on V.im. Cells: Is the Mechanism Augmentive or Suppressive?

a) Neuroaugmentive. The concept of neurostimulation came from observations of analgesic effects achieved when various neural targets were stimulated. This effect was shown to be related to an inhibitory mechanism such as suggested by the gate control theory (Melzack *et al.* 1965); the stimulation acts to reduce pain by reinforcing the inhibitory effects of metenkephalinergic interneurons. This type of stimulation was therefore called neuroaugmentive treatment in contrast to destructive surgical methods.

b) Neurosuppressive. Whatever the mechanism, this deep brain stimulation has neurosuppressive effects on symptoms like pain, tremor and bradykinesia, similar to those obtained by stereotactic lesions, but in a much safer and reversible manner. When considering the rather crude neural events induced during electrical stimulation as compared to the subtle and delicate data processing occuring in neural networks, one may imagine that we are doing nothing but jamming these circuits by overfeeding them with a meaningless flow of inputs. This concept of neural jamming will be further detailed.

There are no currently available data which could provide an explanation for the effect of V.im. stimulation on tremor (Guiot *et al.* 1973; Hassler, 1955; Hirai *et al.* 1983; Ohye *et al.* 1984). The current concepts of neural interactions between the cortex and the nigro-striatal system do not include a clear-cut model of the relationships between dopamine deafferentation and tremor. The Alexander diagram (Alexander *et al.* 1990) provides a theoretical basis for explaining bradykinesia but not for the role of the V.im. nucleus in controlling tremor. The frequency response curve demonstrates the key importance of this parameter. However, the range of frequency is far higher than the range of excitability for cell bodies and corresponds better to that of axons. V.im. destruction by thalamotomy or inactivation by lidocaine injection produces the same effect. Thus, V.im. stimulation does not suppress tremor by means of an excitatory effect.

## The Concept of Jamming

The mechanism of tremor suppression by V.im. stimulation could involve jamming of the neuronal network processing proprioceptive inputs en route from spinal cord to cortex where a reflex response is elicited and conducted to the anterior horn. From the anterior horn, motor nerves trigger a muscular contraction, inducing in turn a proprioceptive input.

Feeding the system with artificial neural noise could deactivate this cyclic phenomenon and stop tremor. Understanding the mechanism of V.im. stimulation-induced tremor suppression is of critical importance. Besides the impact this could have on improving the method and its results, it could contribute to a novel concept in the neurosciences. In addition to excitation and inhibition which are considered as the two main aspects of neural function, a third concept of neuromodulation has been more recently added. One might consider that neuronal networks might also be influenced by a cybernetic process, in which the data processing of a network is based on the recognition of a meaningful input which is then fed into a processing algorithm determined by the network's functional architecture. Eventually, this leads to an output from the network which could in turn elicit a given behaviour. If the network is fed with a foreign additional input, the characteristics of which, principally the frequency, make it similar to blank noise, the network might be unable to distinguish meaningful input from the overall flow of inputs making it incapable of generating the expected behaviour. This is a well known concept in cybernetics and automated systems where high frequency inputs can be used to interrupt the oscillatory behaviour of such systems (Coppe, 1934). This hypothesis is supported by the observation of V.im cells synchronous to tremor (Albe-Fessard *et al.* 1962; Guiot *et al.* 1973; Ohye *et al.* 1975; Matsumoto *et al.* 1979/77; Matsumoto *et al.* 1984; Ohye *et al.* 1989) which exhibit an abnormal hypersynchronization; this may be due to the loss of efficacy of a filter somewhere in the feedback neuronal loop, which could be also desynchronized by high frequency stimulation. Caparros-Lefebvre *et al.* (1994) have proposed a slightly different mechanism involving the cerebellum: in a post-mortem case, they observed that the electrode was in the internal part of V.im. not far from the brachium conjunctivum, which suggests that the cerebellum fibers could transport "an inadequate message that thalamic neurons are unable to understand". This could still fit with the concept of jamming; the involved inputs would be cerebellar rather than proprioceptive.

## Effect of Stimulation on STN Cells

As is the case for V.im., there is currently no clear explanation of the mechanism of action of STN high frequency stimulation. Experimental work in animals has proved that the increased neuronal firing rate of STN cells is responsible for rigidity and akinesia by increasing the inhibitory function of the globus pallidus internus (GPi) (Alexander *et al.* 1990; Aziz *et al.* 1991; Bergman *et al.* 1990). This is probably why pallidotomy relieves these symptoms (Laitinen *et al.* 1992). Animal experiments (Benazzouz *et al.* 1993) and our preliminary (Benazzouz *et al.* 1995) as well as our

current data demonstrate that high frequency stimulation of STN actually inhibits its hyperactivity. Although one may understand what could happen in the neuronal network involved in this mechanism, it is not possible to explain how high frequency stimulation could inhibit the activity of STN cells. It could cause global hyperpolarization of the cell membrane resulting in a loss of excitability, or it could cause jamming of a neuronal loop, as we already suggested in the case of the effects of Vim stimulation on parkinsonian and essential tremor. Actually, little is known about long term stimulation of neural structures and extensive experimental work remains to be done. However, we have recently reported experimental evidence in rats (Benazzouz *et al.* 1993) that high frequency stimulation of STN induces an inhibition in the entopeduncular nucleus (equivalent in rat to the human GPi), in the nucleus reticularis thalami and in the substantia nigra pars reticulata, and an excitation in the globus pallidus (equivalent in rat to the human GPe), and the ventrolateral nucleus of the thalamus. This is frequency-dependent, appears above 60 Hz and is consistent with the basic network of the Alexander's diagram. The mechanism could be a depolarization blockade ending with a shut down of the glutamatergic output of STN cells, as well as a retrograde activation of GPe which would therefore exert a strong inhibitory influence on both STN and GPi. Besides this tentative explanation of the mechanism of STN stimulation, the observation of the STN glutamatergic output shutdown had led us to expect a beneficial effect of this stimulation on the degenerative process underlying the Parkinson's disease. Preliminary experiments have indeed demonstrated that STN destruction by local injection of kainic acid prevents the nigral degeneration of dopaminergic cells following 6-OH-DA injection into the caudate nucleus (Piallat *et al.* 1996).

### Effects of Stimulation on GPi Cells

A similar hypothesis (block of depolarization) could be presented concerning GPi stimulation but we do not for the moment have direct experimental data, other than those in the literature (Alexander *et al.* 1990; Aziz *et al.* 1991; Bergman *et al.* 1990; DeLong, 1990) which set out the basis of the present thinking.

## *The Future of the Method: Long Term Perspectives*

### Do Other Targets Exist?

Due to avoidance of significant tissue destruction and its reversibility, electrical stimulation has potential for application to other brain structures,

in other diseases; however, extensive and careful animal experimentation are necessary before any such applications.

Actually, stimulation of other deep brain structures has been reported to suppress movement disorders (Andy, 1980; Brice *et al.* 1980; Mazars *et al.* 1980; Nashold, 1969) or to induce various effects (Akimoto *et al.* 1956; Alberts *et al.* 1966). If such a concept as neuronal jamming proved to be true, this might mean that other structures (nuclei, cortices or fiber bundles) in the neuronal network could be targeted. The multielectrode electrophysiological approach will be used to investigate structures in close proximity to V.im. and should define more precisely the ideal target. In other areas of the neuronal network, experimental studies should be undertaken. Though the results thus far are quite promising (Limousin *et al.* 1995; Pollak *et al.* 1993a), a larger number of patients must be implanted before a significant statement can be made. The effect of *STN* stimulation on tremor has not yet been sufficiently investigated in humans, but we have observed that the experimental tremor induced in monkeys by lesions of the VTA anterior and lateral to the red nucleus is suppressed by V.im. as well as by STN stimulation. Recently, stimulation of the *motor cortex* has been shown to be of interest in the control of some forms of central pain (Tsubokawa *et al.* 1993). One might expect that stimulation of the motor and premotor cortices at the proper frequency would also alter motor system output and possibly diminish or even suppress tremor. This effect, which has been actually observed by Woolsey (Woolsey *et al.* 1979), could provide a solution to the problem of tolerance although we were not successful in two of our action tremor cases. Recently, N'Guyen *et al.* have reported encouraging results (N'Guyen, 1996).

GPi stimulation, in the same manner as in V.im. and STN, has been considered in view of the results of ventro-posterolateral pallidotomy, initially described by Leksell and then adapted and reintroduced recently by Laitinen (Laitinen *et al.* 1992). Here, as in V.im. and STN, stimulation could replace destructive lesions and provide more adaptability and fewer side effects. We have attempted this in a preliminary study and Siegfried (Siegfried *et al.* 1994) has already reported a series of three patients with satisfactory results. Careful analysis of these approaches will provide interesting new therapeutic orientations.

VPL somatosensory nucleus stimulation has been also reported to stop tremor in pain patients (Mazars *et al.* 1980; Hosobuchi, 1986; Siegfried, 1980). Reports of large series are, however, not available.

## Are there Indications Other than Parkinson's Disease?

Parkinson's disease is the ideal condition in which to apply and develop stimulation therapy. The symptoms of this disease are significant, un-

ambiguous and rather easy to observe and quantify. The primary lesion responsible for the disease is also well-known, as well as the cascade of induced events along a well defined neuronal circuit in the basal ganglia. Surgical experience with V.im. thalamotomies have confirmed this was the best target to alleviate tremor. Then this solid clinical experience in patients, as well as experimentation in monkeys (Ohye *et al.*. 1984) suggested that this was also the best target for stimulation. STN and GPi, on the contrary, have been well investigated in animals, and their role clearly determined in the physiology of movement disorders, providing a good theoretical basis for experimental human applications (Bergman *et al.* 1990; DeLong, 1990). However, the results of STN stimulation can not be compared to lesions which are known to induce severe ballism (Caparros-Lefebvre *et al.* 1994; Schwarz *et al.* 1960). The complex intricate effects of stimulation of a given structure in the brain are rather difficult to rationalise as several feed-back loops and phenomena can be initiated by the process. A detailed analysis of the circuitry and neurochemistry of the involved structures must be made in order to understand what we are doing as well as to establish the rationale of new applications. On the other side however, we must be careful to avoid sterilizing effects of an overconfident theorization, keeping in mind for instance that we just do not know the biological basis of V.im. stimulation, which is however very real and effective.

## Conclusion

V.im. stimulation appears to provide a new therapeutic approach in the treatment of parkinsonian and essential tremors. Experience over 10 years has permitted both definition of the best indications and observation of the long term effects, amongst which the problem of the tolerance that appears in some cases needs resolution. The low incidence of adverse effects, with the possibility of avoiding them by adjusting the parameters of stimulation, the lack of neuropsychological effects during bilateral stimulation, and the possibility of combining stimulation with previous contralateral thalamotomy, are all strong arguments in favour of this method. STN and GPi have now been implanted by several teams for a few years. After a 10 year experience in 3 neurosurgical centers, it is now possible to advocate CDBS in preference to a lesion. A better understanding of the mechanism, optimisation of electrode implantation and stimulation parameters, and even the discovery of new targets, will further improve the results and probably enlarge the field of application. There is no doubt that the application of Deep Brain Stimulation reopens a chapter in the surgical treatment of movement disorders and will help to avoid additional, iatrogenic lesions in an already sick brain.

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*Chronic Deep Brain Stimulation for Movement Disorders*

## Comments

This superb review is a summary of the experience of three French groups that are among the pioneers in the use of neurostimulation for the treatment of movement disorders. Deep brain stimulation with permanently implanted systems is no longer considered merely a second-best alternative to destructive techniques; neurologists in particular, quick to recognize the advantages of a reversible functional alteration, have been important proponents of stimulation. The combined experience reported here is probably the largest in the world, and would be of great importance for this reason alone. A few aspects of this review deserve critical attention, however, and will be discussed in the light of our own personal experience.

1. The relative merits of deep brain stimulation and lesion-making are objectively discussed. Although, as the authors note, no prospective, randomized study has yet compared unilateral thalamotomy with unilateral stimulation of the same nucleus, clinical observation amply demonstrates the superiority of stimulation.

Our own study of the two methods, and their complications, reveals that deep brain stimulation is safer and just as effective, if not more so. When a thalamotomy or campotomy is performed for tremor, the neurosurgeon can indeed observe the disappearance of tremor in the operating room, but not the post-lesional lateropulsion, dystonia, and other phenomena that only appear once the patient is mobilized. Furthermore, the tremor may partially recur a few days after the procedure, when the focal edema around the lesion subsides. A cautious neurosurgeon, attempting to minimize the risk even of minor, transient complications, may make the lesion too small, so that the patient may require a second operation, while a determined attempt to make a sufficiently large lesion carries the risk of a permanent neurologic deficit. Such problems are avoided by deep brain stimulation, in which the parameters can be adjusted in the days after implantation to achieve maximum benefit, and simultaneously avoid unwanted side effects. This decided advantage outweights, in our opinion, the greater expense of stimulation, and the associated risks of infection and hardware failure.

Nonetheless, our experience with over 1500 destructive stereotactic procedures, and more than 300 stimulator implantations, for the treatment of movement disorders shows that lesion-making may still be indicated in certain cases. For young patients undergoing their first neurosurgical treatment, on the non-dominant side, a lesion can bring relief without requiring multiple pacemaker replacements over the ensuing years. Patients who undergo deep brain stimulation with absolutely no unwanted neurologic side effects, and then return for a pacemaker change, can be treated instead with a lesion in the same location, as we have occasionally done. The desired lesion size is chosen on the basis of the stimulation parameters.

2. The selection of the intracerebral target, as the authors properly point out, should be based on the individual patient's symptoms and signs. Only three structures are discussed as possbile targets: the globus pallidus internus, the subthalamic nculeus, and the nucleus ventrointermedius of the thalamus (V.im.). In fact, the options are considerably wider; the V.im. is, indeed, the target "par excellence" for the treatment of tremor, but most Parkinsonian patients also have significant rigidity and hypokinesia. A thalamic lesion or stimulation placed slightly more anterior, in the nucleus ventrooralis posterior (V.o.p.), can improve rigidity as well as tremor, which V.im. stimulation cannot; furthermore, stimulation of the subthalamic region (field $H_1$ of Forel and zona incerta) can improve fine

motor function. The sensory nucleus of the thalamus (VPL) can be used as a target when parkinsonism is accompanied by a sensory deficit, and the nucleus ventro-oralis (V.o.a.) is a further possible target. Among these structures, the globus pallidus internus and the V.o.p. seem to be the best targets for the treatment of iatrogenic, DOPA-induced dyskinesia.

3. The section on indications concerns Parkinson's disease, essential tremor, dystonia, and other movement disorders. The postural volitional dyskinesia of multiple sclerosis is also discussed. In view of the extreme functional disturbance associated with this last disorder, which may lead to total disability and dependence on nursing care, a neurosurgical treatment may be worthwhile even if only a small clinical improvement results. The important findings of the Créteil group are consistent with our own experience. As for post-traumatic tremor, disabling cerebellar tremor, and hemiballism of more than one year's duration, these are also entities where a neurosurgical intervention may be more beneficial than any conservative treatment.

4. Good intraoperative localization of the target is, obviously, critical to the success of the operation. There are many different methods in use. We admire the Grenoble group for the high quality of their operations, which are performed with intensive, timeconsuming technical support. We ourselves, after 35 years of experience, have adopted a more rapid and practical method, which is devoid of stress for the patient, at far lower cost. In the end, the result is what counts.

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# B. Technical Standards

# Recent Advances in the Treatment of Central Nervous System Germ Cell Tumors

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## Contents



## Introduction

Central nervous system (CNS) germ cell tumors (GCT) are rare neoplasms primarily occurring in adolescent and pediatric populations. The age-adjusted incidence rate in the United States is 0.1 per 100,000 person-years. These GCT are, however, more common in far-east Asia than in western countries. The incidences in the United States and Japan account for 0.5% and 3.1% of all primary brain tumors, respectively (CBTRUS 1996, JBTR 1996).

Table 1 shows the WHO histological classification of GCT of the CNS (Kleihues *et al.* 1993). The histopathological entity "germ cell tumor" encompasses a number of histological subtypes including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, mature teratoma, immature teratoma, teratoma with malignant transformation, and mixed germ cell tumors. Furthermore, the mixed germ cell tumors include

Table 1. *WHO Classification of Histology of Central Nervous System Germ Cell Tumors*

| |
|---|
| 1. Germinoma |
| 2. Embryonal carcinoma |
| 3. Yolk sac tumor |
| 4. Choriocarcinoma |
| 5. Teratoma |
| a. immature |
| b. mature |
| c. with malignant transformation |
| 6. Mixed germ cell tumors |
| immature teratoma with germinoma etc. |
| numerous and diverse histological combinations |

numerous and diverse histological combinations such as an immature teratoma with germinoma, an immature teratoma with embryonal carcinoma and so on.

The prognosis for and the responses to adjuvant therapy for these tumors are extremely diverse (Hoffman *et al.* 1991, Horowitz and Hall 1991, Jennings MT *et al.* 1985, Sano 1995). A pure germinoma is a curable neoplasm with a better than 90% 5-year survival rate. In contrast, an embryonal carcinoma is a lethal disease and refractory to ordinary adjuvant therapy. Furthermore, the similarity of the clinical presentation and radiological findings for these tumors makes their management complex. A precise histological diagnosis achieved by surgery greatly influences the results of treatment and is therefore essential to planning the appropriate management of a CNS GCT. An inappropriate diagnosis without histological verification considerably worsens the overall outcome for patients.

Each subcategory is comprised of such rare neoplasms that choosing an appropriate therapeutic regimen is difficult. Selection of radiation therapy in combination with chemotherapy for each type of GCT has been debated. Recently the introduction of chemotherapy has changed the conventional radiation dose and volume; the proper use of chemotherapy may permit dose-reductions in radiotherapy for patients with a germinoma without compromising disease control (Allen *et al.* 1994). Aggressive combination therapy may be necessary to improve the poor survival rate for patients with non-germinomatous malignant GCTs. Neurosurgical care for each GCT should be planned, keeping in mind the precise knowledge available regarding the efficacy of postsurgical adjuvant therapy and the resulting prognosis.

## Diagnosis

Recent advances in MR neuroimaging have allowed us to identify CNS GCT at an extremely early stage and has also enabled a precise delineation of the extent of the disease. However, a definitive diagnosis predicting the histology and possible malignancy cannot be achieved by MRI alone (Fujimaki *et al.* 1994, Sumida *et al.* 1995). To firmly establish an accurate histological diagnosis that will help to determine the extent of adjuvant therapy, surgical resection or biopsy is the first essential step in management of the tumor.

Certain CNS GCTs secrete $\beta$-type human chorionic gonadotropin (HCG-$\beta$) and/or alpha-feto protein (AFP). A preoperative examination of these serum markers has significant value in predicting the prognosis. For example, patients with germinomas producing HCG-$\beta$, which is secreted into the serum and cerebrospinal fluid, generally have poorer outcomes than those with non-secreting pure germinomas. Teratomas with high serum-levels of HCG-$\beta$ and/or AFP may show poorer treatment response than negative teratomas. In addition, an immunohistochemical staining reaction for the human placental alkaline phosphatase (PLAP) is a highly specific marker for germinoma.

Following these diagnostic investigations, management of the tumor should be planned according to the histological and serological malignancy and the extent of the disease. The prognosis for each subtype of GCT is diverse (Jennings *et al.* 1985, Packer *et al.* 1984, Sano 1995, Sawamura 1996, Schild *et al.* 1996a, 1996b, , Shibamoto *et al.* 1994, Shirato *et al.* 1997). We have analyzed the records of 109 patients undergoing treatment for GCT at Hokkaido University Hospital. With a median follow-up duration of over 6 years, the probability of surviving 5 years was better than 90% for patients with a pure germinoma or mature teratoma. The 5-year survival rate in patients with an immature teratoma with or without a germinoma component was approximately 65%. Germinomas producing human chorionic gonadotropin (HCG) showed a significantly higher recurrence rate than non-producing tumors. Patients with GCT that included a highly malignant component, such as an embryonal carcinoma or yolk sac tumor, exhibited a poor prognosis with an approximately 40% chance of 5-year survival.

In selecting a therapeutic regimen, CNS GCT have been traditionally divided into two major groups, that is, germinomas and non-germinomatous GCTs, as a simple extrapolation from gonadal GCT. However, CNS GCT can be grossly divided into at least three categories: namely good, intermediate, and poor prognosis, as shown in Table 2. Solitary germinoma and mature teratoma are curable tumors. Embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma with malignant trans-

Table 2. *Relative Prognosis of Intracranial Germ Cell Tumors*

| |
|---|
| *Good prognosis* |
| solitary pure germinoma |
| mature teratoma |
| *Intermediate prognosis* |
| germinoma with an elevated level of serum HCG-$\beta$ |
| extensive/multifocal germinoma |
| disseminated germinoma |
| immature teratoma |
| mixed germ cell tumors consisting of |
| germinoma with either mature or immature teratoma |
| *Poor prognosis* |
| teratoma with malignant transformation |
| embryonal carcinoma |
| yolk sac tumor |
| choriocarcinoma |
| mixed germ cell tumors including a component of |
| embryonal carcinoma, yolk sac tumor, choriocarcinoma, |
| or other malignant neoplasms such as squamous cell carcinoma |

*HCG* Human chorionic gonadotropin.

formation, and mixed GCT including a component of cancer or sarcoma carry a poor prognosis. Between these good and poor prognosis groups, there are other types of GCT with an intermediate prognosis, such as immature teratoma, mixed germ-cell tumors composed of germinoma with teratoma, disseminated germinoma, multi-focal germinoma, and HCG-$\beta$-producing germinoma.

## Germinomas

### *Surgical Strategy*

Surgical debulking is a part of therapy for intracranial malignant brain tumors such as gliomas. A radical resection of the neoplasm, in general, offers a better prognosis for patients. However, a radical surgical resection of a germinoma carries a certain risk of operative morbidity because germinomas occur in eloquent areas of the brain such as the neurohypophysis, the hypothalamus, or the pineal region (Bruce & Stein 1995, Edwards *et al.* 1988, Hoffman *et al.* 1991, Jennings *et al.* 1985, Wara *et al.* 1979). Since nearly all germinomas are curable with adjuvant therapy, the question arises as to whether germinomas should only be biopsied or if they should be radically removed when possible.

We retrospectively analyzed 29 patients with germinoma who underwent surgery (Sawamura *et al.* 1997). There were 10 solitary pineal, 7 solitary neurohypophyseal/hypothalamic, and 12 multifocal or disseminated tumors. Biopsy was performed in 16 patients (stereotactic 8, transsphenoidal 4, and fronto-temporal craniotomy 4). Partial resection was done in 5 patients (fronto-temporal 3 and occipital transtentorial 2). Gross total resection was achieved in 8 patients with a pineal mass through an occipital transtentorial route. After surgery, 10 patients received radiotherapy alone, and 19 patients were given chemo-radiation therapy. A complete remission was achieved in all patients. The over all tumor-free survival rate was 100% at a median follow-up period of 42 months. There was no significant difference in outcome related to the extent of the surgical resection. Postoperative neurological improvements were seen in only 2 patients, while postoperative transient complications, mainly upgaze palsy, were observed in 6 patients. One patient sustained a slight hemiparesis, thus the surgical morbidity was 3%.

These results indicate that a radical resection of intracranial germinomas offers no benefits over a biopsy. The primary goal of surgery should be to obtain sufficient volume of tumor tissue for histological examination. If there is a strong radiological suspicion of germinoma, a biopsy should be performed. Of course, histopathologic study is handicapped by the small size of specimens, which could not include all components of the tumor if it is a mixed GCT. If there is any suspicion of non-germinomatous GCT, a craniotomy is recommended even for diagnostic surgery. When a peroperative histological diagnosis of pure germinoma is obtained during a craniotomy, no risk should be taken in pursuing the resection.

Germinoma often causes hydrocephalus, which induces headache and vomiting as the initial manifestation of the disease. In order to immediately reduce an increased intracranial pressure, ventricular drainage is recommended. Ventriculo-peritoneal shunting should be avoided because of the potential for peritoneal metastasis (Xu *et al.* 1995). Tumor spreading by way of a shunt occurs infrequently, but it is generally lethal (Edwards *et al.* 1988, Dearnaley *et al.* 1990, Jennings *et al.* 1985, Wolden *et al.* 1995). Gross total or subtotal resection of a pineal mass can resolve the obstructive hydrocephalus. When a patient with obstructive hydrocephalus receives a biopsy, prompt post-biopsy chemotherapy can immediately, usually within several days in our recent experiences, resolve the symptoms of increased intracranial pressure. Germinomas can be remarkably reduced in size either by a single course of chemotherapy or by low-dose radiotherapy (Allen *et al.* 1994, Vijayaraghavan *et al.* 1993, Xu *et al.* 1995). During chemotherapy, ventricular drainage controls the hydrocephalus. As a consequence, the need for the ventriculo-peritoneal shunting operation can be eliminated.

When residual radiographic abnormalities remain after a completion of chemotherapy or radiation therapy, a second-look operation may be feasible. Histologically, germinoma shows the characteristic two-cell pattern which consists of large neoplastic cells and small lymphocytes. In addition to the lymphocytic infiltration, dense granulomatous inflammation is occasionally observed in the tumor tissue. This granulomatous reaction may be pronounced, and some CNS germinomas have been histopathologically misdiagnosed as chronic inflammation (Gotoda *et al.* 1996). The granulomatous component must remain immediately after chemotherapy or radiotherapy, and is usually observed as a residual small enhancing mass on MRI. Balmaceda *et al.* reported that 3 of 9 germinoma patients who underwent a second-look surgery had residual tumor after chemotherapy, and have suggested a second-look operation to avoid unnecessary irradiation or intensified chemotherapy (Balmaceda *et al.* 1996). We, however, do not recommend a second-look surgery for a small residual mass of germinoma which has been firmly diagnosed as a pure germinoma by the first surgery. With a precise histopathological diagnosis, germinomas can exclusively be cured by an appropriate adjuvant therapy including irradiation.

### *Radiation Therapy*

CNS germinoma is an extremely radiosensitive tumor and is curable by radiation alone in approximately 90% of patients (Shirato *et al.* 1997, Wolden *et al.* 1995). During the 1970s and 1980s, most patients with germinoma were irradiated with 50–55 Gy to the local tumor and 30 Gy to the remaining brain and spinal cord. The doses and volume of the radiotherapy, however, are sufficient to cause cognitive retardation, neuroendocrine deficiencies, and spinal shortening (Dearnaley *et al.* 1990, Jenkin *et al.* 1990, Kiltie & Gattamaneni 1993, Sakai *et al.* 1993, Shirato *et al.* 1997). Currently, the main concern is to find the smallest dose which can control the disease and the smallest target volume which will achieve a 100% cure rate. Germinomas tend to be treated with a much lower dose of irradiation applied to a smaller volume than those used with conventional radiotherapy, and an adjuvant chemotherapy is expected to further reduce the dose and volume (Allen *et al.* 1994, Calaminus *et al.* 1994).

The high-risk group for treatment failure or recurrence includes disseminated germinoma, multifocal germinoma and HCG-producing germinoma. An elevated level of serum HCG-$\beta$ at diagnosis is considered to be indicative of a higher risk of recurrence (Balmaceda *et al.* 1996, Sano 1995, Yoshida *et al.* 1993). An elevation of HCG-$\beta$ level during follow-up period after treatment is a sign of tumor relapse. The HCG-producing germinoma may be treated with a more intensive therapeutic protocol than a pure germinoma.

## Radiation Dose

There have been several attempts to determine the impact of dose on survival for patients with germinoma (Fuller *et al.* 1994, Salazar *et al.* 1979). Clinical series reported by Sung, Kersh, Abey, and Dattoli were often referred in review articles when the dose-response relationship is discussed for CNS germinomas (Sung *et al.* 1978, Kersh *et al.* 1988, Abey *et al.* 1981, Dattoli & Newman 1990). However, many biases were involved, such as inclusion of non-biopsied patients and inconsistencies in accuracy of radiographic localization and field size used with similar doses, which were reported by different investigators during different periods. These biases obscured the relationship between dose and patient's outcome. Furthermore, the reported in-field failures of germinoma included relapse of non-germinomatous GCT which were incorrectly diagnosed or histologically unverified before radiotherapy (Matsutani *et al.* 1997, Ono *et al.* 1994, Yoshida *et al.* 1993).

Radiation doses to the primary tumor site of a CNS germinoma have actually been reduced from 50–55 Gy to 40–45 Gy at many institutions (Amendola *et al.* 1984, Schild *et al.* 1996, Shibamoto *et al.* 1994, Shirato *et al.* 1997). It has been shown that the primary lesion of a CNS germinoma can be controlled by 40 Gy in 4 to 5 weeks, providing that the entire part of a given tumor is a pure germinoma and is properly covered by the dose. Furthermore a recent study has suggested that the dose administered to CNS germinoma may be reduced to 30 Gy in 3 to 4 weeks without chemotherapy (Aoyama *et al.* 1997). There is no evidence that the local control of a CNS germinoma requires a higher dose than that of a testicular germinoma, which can be eradicated by doses of 30–35 Gy (Ball *et al.* 1982). The outcomes of patients with CNS germinoma treated with a dose of 30 Gy are comparable to that of patients with testicular germinoma treated with a similar dose (Aoyama *et al.* 1997, Bayens *et al.* 1992). Although, Aydin *et al.* have shown that there was no histopathological residual disease after 18 Gy irradiation for CNS germinomas (Aydin *et al.* 1992), at the present time the efficacy of a dose less than 30 Gy has not been determined.

## Radiation Volume and Techniques

CNS germinomas spread from the primary neurohypophyseal and pineal regions by direct infiltration, or disseminate along the cerebrospinal fluid pathways so that the determination of the target volume for irradiation is a critical issue in achieving a high cure rate. "Multifocal" germinoma is defined as germinoma with multiple lesions involving the pineal gland, hypothalamus, hypophysis, cavernous sinus, optic chiasm, third ventricle

wall, or the anterior half of the lateral ventricle wall, where germinomas preferentially infiltrate. These masses should be distinguished from disseminated germinoma in order to properly choose craniospinal radiotherapy; a multifocal germinoma is a localized disease, whereas a disseminated germinoma represents metastasis. The former may not be indicated for neuraxis irradiation (Allen *et al.* 1994, Hoffman *et al.* 1991, Linstadt *et al.* 1988, Wolden *et al.* 1995).

Brada & Rajan reviewed the literature and have reported that in patients with histologically verified germinoma, the relapse rate with spinal seeding was 13% (18/143) by brain irradiation alone and 5% (3/59) by whole neuroaxial irradiation (Brada & Rajan 1990). These results suggest that whole neuroaxial irradiation was somewhat effective but was not a perfect treatment for preventing CSF seeding. Wolden *et al.* did not give routine prophylactic craniospinal irradiation and obtained a spinal-only failure rate of 2% (Wolden *et al.* 1995). In the CT era, prophylactic craniospinal irradiation has been abolished due to its low efficiency and its significant late adverse effects in young patients (Kiltie and Gattamanei 1995). Several reports have demonstrated that smaller fields of irradiation such as a whole-brain field or a whole-ventricle field may be adequate for a large proportion of patients with germinoma (Ono *et al.* 1994, Shibamoto *et al.* 1994, Wolden *et al.* 1995). However, local field alone has resulted in a higher relapse rate even in the CT era when a precise treatment planning system was not routinely utilized (Aoyama *et al.* 1997).

Precise 3-dimensional treatment planning using a CT simulator and immobilizing devices should be used in whole-ventricle field or smaller field (localized) radiotherapy. CT simulator is composed of a CT scan, a 3-dimensional treatment planning system, and a laser projector of treatment field to the patient's skin (Nagata *et al.* 1994). The treatment volume is determined by CT images, slice by slice, to individually include an enhancing mass and the ventricles. An individualized thermoplastic shell and a head rest can maintain the accuracy of the field. Using the CT simulator, whole-ventricle irradiation alone giving 40 Gy in 20 fractions with planning can sufficiently control intracranial germinomas (Shirato *et al.* 1997). In addition, the development of MRI evaluation at the initiation of radiotherapy has decreased the rate of in-field failures in the last decade.

To reduce the possibility of late adverse effects of the whole-ventricle field irradiation, it appears to be attractive to further reduce or eliminate the radiation volume. Preirradiation chemotherapy has recently been advocated as an adjuvant therapy to decrease the total volume of irradiation (Allen *et al.* 1994). Our recent experience shows that localized irradiation giving 24 Gy in 12 fractions following preirradiation chemotherapy has resulted in 100% local control. The generous local field is defined as the tumor plus approximately a 2-cm margin. Because there is usually no resi-

dual tumor on MRI following a preirradiation chemotherapy, the tumor volume before the chemotherapy is applied for determination of the target volume. The target volume is treated using 2- or 3-field axial technique. Non-coplanar irradiation technique may be applied if the tumor location does not allow involvement of the eyeballs by the axial field arrangement.

Stereotactic irradiation (STI) using a frame for stereotactic surgery and a focused narrow beam, either by linear accelerator or Gamma knife, are emerging as a new irradiation modality of choice for brain lesions. Single fraction STI (or radiosurgery) is of proven value in the treatment of small arteriovenous malformations, radioresistant metastatic tumors, and vestibular schwannomas. However its application for non-biopsied pineal tumors including germinoma must be discouraged. Although radiosurgery, for instance using a 8 Gy single fraction, can actually eradicate a pineal germinoma, an early recurrence will occur around the irradiated area with the steep dose distribution because pineal germinomas infiltrate the posterior thalamus and the midbrain. On the other hand, stereotactic radiotherapy (SRT) with the use of relocatable fixation devices has also been developed as a high-precision technique for fractionated radiotherapy (Brada *et al.* 1994, Shrieve *et al.* 1996). SRT may be integrated into conventional radiotherapy for the treatment of germinoma.

### *Chemotherapy*

Germinomas are highly chemosensitive tumors. Chemotherapeutic agents which have been estimated in previous clinical studies are bleomycin, carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, and vinblastine (Allen *et al.* 1987, 1994, Balmaceda *et al.* 1996, Calaminus *et al.* 1994, Yoshida *et al.* 1993). Chemotherapy alone has usually resulted in a high relapse rate. An international cooperative trial has shown that the probability of surviving 2 years among patients with CNS germinoma which were treated with 4 cycles of carboplatin, etoposide, and bleomycin was 0.84 (95% confidence interval, 0.73 to 0.95) (Balmaceda *et al.* 1996). Strikingly, the relapse rate after this chemotherapy, without irradiation, was 48.8% (22 out of 45 patients). This relapse rate is much worse than those obtained with conventional radiation therapy. Although most of the relapses could be salvaged by irradiation, these results do not allow the use of chemotherapy alone for germinomas.

While efficacy of adjuvant chemotherapy followed by radiotherapy has been investigated, whether this approach will lead to less toxicity in a largely adolescent population enjoying 90% disease control with radiation alone was unclear. (Allen 1991, Allen *et al.* 1987, 1994, Calaminus *et al.* 1994, Ginsberg *et al.* 1981, Goebel *et al.* 1993). Local 45 Gy with craniospinal 30 Gy irradiation after cisplatinum administration was used in a

clinical trial (Goebel *et al.* 1993). This radiation dose and volume, however, is too large because the radiation therapy alone can sufficiently control the disease. In a phase II study, Allen *et al.* planned to give 30.6 Gy local irradiation after chemotherapy using carboplatin, but, consequently, only 4 of the 11 patients were given 30.6 Gy involved-field irradiation, and 5 received 30 Gy craniospinal irradiation with a 20 Gy local boost due to unexpected reasons (Allen *et al.* 1994). If chemotherapy is given with conventional-dose irradiation, it will increase, not decrease, late sequelae (Olshan *et al.* 1992). An European study has suggested that preirradiation chemotherapy followed by 30 to 40 Gy of local irradiation may be adequate for treating pure germinomas without dissemination (Calaminus *et al.* 1994).

Patients who have a complete response (CR) to preirradiation chemotherapy are considered to be tolerant of a significant reduction in radiation doses without a compromise in their long-term survival rate, thereby making possible a reduction in some of late adverse effects (Allen *et al.* 1987). The CR can actually be achieved by certain chemotherapeutic regimens. A regimen using etoposide and cisplatin (EP regimen) for patients with solitary pure germinoma and another regimen adding ifosfamide to the EP regimen (ICE regimen) for patients with other germinomas are currently under investigation by Hokkaido Neurooncology Group (Table 3). The EP regimen consists of cisplatin at 20 mg/m2 and etoposide at 100 mg/m2 given daily for 5 successive days every 4 weeks. The ICE regimen consists of cisplatin at 20 mg/m2, etoposide at 60 mg/m2, and ifosfamide

Table 3. *Outline of the Treatment Protocol of the Hokkaido Neurooncology Group (1992)*

| |
|---|
| 1. *Good prognosis group* |
| EP regimen 3 up to 4 cycles |
| post-chemotherapy localized irradiation; a total dose of 24Gy/12f/3 weeks (no radiotherapy for totally resected mature teratoma) |
| 2. *Intermediate prognosis group* |
| ICE regimen 3 up to 6 cycles |
| post-chemotherapy localized irradiation: a total dose of 24Gy/12f/3 weeks |
| (local irradiation 40Gy/20f/5wks for residual immature teratoma) |
| (craniospinal irradiation 24Gy/12f/3 weeks for dissemination) |
| 3. *Poor prognosis group* |
| ICE regimen 4 up to 6 cycles |
| concurrent irradiation: a total tumor dose of 44–54Gy/27f/7 weeks |
| craniospinal portion 24Gy/12f/3 weeks |
| local boost 20–30Gy/15f/4 weeks |

*EP* Etoposide and cisplatin; *ICE* ifosfamide, cisplatin and etoposide; *f* fractions.

900 mg/m2. Studying more than 20 patients with newly diagnosed CNS germinoma, the overall CR rate within 3 cycles of the preirradiation chemotherapy was 100%. After chemotherapy, 24 Gy irradiation in 12 fractions in 3 weeks applied to the involved field has been enough to achieve a 2-year actuarial relapse-free survival rate of 100%. With a median follow-up duration of 24 months, all patients were alive and free from disease. The dose (24 Gy) used in our study is much lower than the dose previously used in other institutions.

Endocrinologic evaluation of germinoma patients is an important issue because the patient might regain a normal hormonal balance with appropriate treatment. Rappaport has reported that the frequency of growth hormone deficiency was significantly lower in children given cranial doses of 24 Gy or less, but, in contrast, 75% of children treated with 45 Gy showed a sign of growth hormone deficiency (Rappaport & Braunter 1994). A dosage equal to or less than 24 Gy with support of chemotherapy has great advantages in minimizing damage to the developing brain tissue or endocrinological functions. Another advantage of the reduced dose of radiotherapy is the ability to perform craniospinal irradiation without interruption for patients with disseminated disease. In general, patients who received preceding chemotherapy show significant degree of myelosuppression during radiotherapy. However, whole-brain and whole-spinal irradiation can be performed continuously on the same day at least up to 24 Gy. An additional merit of low-dose radiotherapy is the ability to add a second radiotherapy in the event of a recurrence of the disease. An initial treatment utilizing 24 Gy of irradiation leaves another dose of the same magnitude or even larger available for a recurrent germinoma.

Germinomas with multifocal lesions, dissemination, or production of HCG-$\beta$ have a relatively poorer prognosis and a higher recurrence rate than solitary pure germinomas (Allen *et al.* 1994, Dearnaley, 1990, Goebel *et al.* 1993, Hoffman *et al.* 1991, Jennings *et al.* 1985, Sano 1995, Shirato *et al.* 1997, Yoshida *et al.* 1993). For these germinomas, more intensive chemotherapy may be required. Some reports have shown that HCG-secreting germinomas are resistant to an etoposide/cisplatin (EP) regimen and show a higher recurrence rate compared to that of the pure germinoma. Yoshida *et al.* have reported that although the response rate for HCG-secreting germinomas to the EP regimen was very high, the tumor mass regressed much more slowly and the complete response rate was much lower (25%) when compared to that of pure germinoma (77%) (Yoshida *et al.* 1993). Regimens including ifosfamide, cisplatin (or carboplatin), and etoposide have already been shown to be active for refractory or relapsing gonadal GCT (Loehrer *et al.* 1988, Harstrick *et al.* 1991, Schmoll 1989). The regimen including ifosfamide, cisplatin and etoposide can be used as an induction therapy for these potentially refractory germinomas (Table 3).

## Teratomas

Mature teratoma, immature teratoma and teratoma with malignant transformation in the CNS leave patients with good, intermediate, and poor prognoses for survival, respectively. Optimal plan for the neurosurgical management of these lesions is unclear, due in part to their low incidence and to an incomplete understanding of their natural history. Regardless of preoperative diagnosis of the subtypes of teratoma, solitary pineal teratoma is currently the target for total removal. Teratomas in the other regions, in particular neurohypophyseal or hypothalamic lesions, are better partially removed or biopsied to preserve diencephalo-hypophyseal functions.

If total removal of a mature teratoma has been performed, there is no necessity in principle for giving adjuvant therapy (Matsutani *et al.* 1996). However, a tumor which is histologically diagnosed as a mature teratoma might contain a small proportion of germinoma or immature tissue. Relapses after a partial removal of mature teratoma have been reported (Calaminus *et al.* 1994). After a partial resection of a mature teratoma, it may be necessary to give localized-field stereotactic irradiation because mature teratomas have no property of invasion. There is little role of chemotherapy for mature teratomas.

Immature teratomas contain diverse cell lineages that retain an embryonal character and display phenotypic differentiation which may be attributed to the three classic germ layers (Shaffrey *et al.* 1996). In our past series, the 5-year actuarial survival rates for immature teratoma and immature teratoma mixed with germinoma were 63% and 69%, respectively. The recurrence rate after surgery was significantly higher than that of mature teratomas. These results are consistent with those reported by several other authors (Horowitz and Hall 1991, Jennings *et al.* 1985, Sano 1995). Although spontaneous maturation may be a significant aspect of the natural history of intracranial immature teratomas, these tumors do require adjuvant therapy because recurrence will develop even after a gross total resection of the tumor. There has been minimal information available in the literature, however, concerning the response of immature teratomas to chemotherapy (Garre *et al.* 1996). A moderate dose of local irradiation, approximately 40 Gy to the primary site, and cisplatin-based chemotherapy should be given for immature teratomas.

It should be noted that an immature teratoma contains substantially heterogeneous phenotypes which show various responses to adjuvant therapy. Immature teratoma may show a paradoxical response to chemotherapy (Lee *et al.* 1995); when a chemosensitive component of a given tumor is reduced in size, simultaneously the other components such as mature teratoma or chemoresistant tissue increase in size. Rigorous histo-

logical examination of immature teratomas often finds a tiny component of other GCT. An immature teratoma may recur as a different histological subtype of GCT such as germinoma or embryonal carcinoma.

GCT arising in the CNS are occasionally overgrown by cancers of somatic type that are widely assumed to derive from the "malignant transformation" of included teratomatous tissues. These malignant, non-germinal neoplasms are typically chemoresistant, and their emergence is often associated with fatal treatment failure (Freilich *et al.* 1995). Dearnaley *et al.* have reported 12 patients with malignant teratoma (Dearnaley *et al.* 1990); patients were treated with whole neuraxis radiotherapy, giving 50 Gy to the local tumor and 30 Gy to the remaining brain and spinal cord. The overall and cause-specific actuarial 5-year survival rate was 18.2%, and recurrence was confined to the primary site in 6 of 9 patients. In each case the tumor recurred rapidly following an initial partial response. Combined approaches using radical surgery, aggressive radiotherapy, and intensive chemotherapy need to be investigated to improve outcome of patients with teratoma with malignant transformation.

## Highly Malignant Subtypes

GCT including a component with highly malignant histology, such as embryonal carcinoma, yolk sac tumor, squamous cell carcinoma, adenocarcinoma or mesenchymal sarcoma are distressing tumors leaving patients with extremely poor prognosis. For example, prior to 1990, we treated 9 patients with CNS embryonal carcinoma, of whom no patients survived for longer than 2 years after diagnosis. Packer *et al.* also treated 6 patients with embryonal carcinoma using radiation therapy alone or with adjuvant chemotherapy. All patients initially responded to therapy, but only one has survived for longer than 1 year (Packer *et al.* 1984).

Since these tumors are invariably fatal and there is no established effective therapeutic regimen, the selection of therapeutic modes should be directed toward improving the primary response rate, and the late effects of therapy can be at least partially set aside at the present time. For these highly aggressive GCT, more extensive resection may be associated with improved survival, and adjuvant therapy must include multidrug chemotherapy as well as craniospinal axis radiotherapy (Hoffman *et al.* 1991, Schild *et al.* 1996, Wolden *et al.* 1995).

Malignant GCT show a high incidence of subarachnoid dissemination or spinal metastases. Craniospinal radiotherapy with high-dose local boost remains indispensable. The effects of radiotherapy alone, however, have been discouraging (Graziano *et al.* 1987, Jennings *et al.* 1985, Kida *et al.* 1986, Kirkove *et al.* 1991, Senan *et al.* 1991). In addition to conventional

high-dose craniospinal radiotherapy, intensive chemotherapy should be utilized to improve the poor survival rate (Ginsberg *et al.* 1981, Goebel *et al.* 1994, Harstrick *et al.* 1991, Herrman *et al.* 1994, Hoffman *et al.* 1991, Itoyama *et al.* 1990, Loehrer *et al.* 1988, 1989, Motzer *et al.* 1990, Schmoll 1989, Shokry *et al.* 1985). For residual tumors after initial irradiation, stereotactic irradiation may be indicated as a boost technique which can give an additional dose solely to the tumor tissue avoiding excessive dose to the normal brain tissue.

Combination chemotherapy regimens including cisplatin, carboplatin, etoposide, or ifosfamide appear to be a promising approach for highly malignant GCT (Goebel *et al.* 1994, Harstrick *et al.* 1991, Herrman *et al.* 1994, Loehrer *et al.* 1988, 1989, Motzer *et al.* 1990, Schmoll 1989, Wheeler *et al.* 1986). There are striking differences, however, in event-free survival after similar therapy regimens, and at present, there is little evidence to support the role of high-dose chemotherapy in first-line treatment (Calaminus *et al.* 1994). Since 1992, we have also employed a similar regimen including ifosfamide, etoposide, and cisplatin (Table 3) and are obtaining some promising results.

The relatively low success rate of chemotherapy in patients with systemic GCT who have failed to respond to etoposide-cisplatin combinations has led to preliminary evaluations of high-dose chemotherapy based on carboplatin and etoposide with autologous bone marrow transplant or, more recently, peripheral blood stem-cell support. However, the resulting remissions have not been sufficiently sustained and treatment-related death rates remain high (Fields *et al.* 1995, Lotz *et al.* 1995). High-dose chemotherapy followed by autologous stem-cell rescue is to be studied, but only in the salvage setting of patients with relapsed or disseminated nongerminomatous GCT.

## Conclusion

Patients with CNS GCT should have surgical confirmation of tumor histology. Management should be planned according to histological and serological diagnosis, and extent of disease. For solitary or multifocal germinomas, preirradiation chemotherapy followed by reduced-dose irradiation in localized field is suggested. Prophylactic craniospinal or whole-ventricle radiotherapy is not indicated for germinomas. For mature teratomas, complete resection is optimal, which does not require help of radiotherapy. For patients with GCT that include highly malignant histology, efforts to intensify therapy have been undertaken, especially toward exploring the role of chemotherapy.

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# Hypothalamic Gliomas

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With 16 Figures

## Contents



## Introduction

Hypothalamic gliomas are demanding intracranial lesions to deal with. Before the era of CT, a diagnosis of such lesions could be obtained by means of air studies and angiography. However, the diagnosis was only possible when the lesion had become large and clinically evident, and was interfering with the CSF circulation, thus causing hydrocephalus. In smaller lesions, in particular in those located only on one side of the IIIrd

ventricle, the diagnosis was practically impossible since they mostly do not cause endocrinological or neurological disturbances. Histological studies of hypothalamic gliomas in the majority of cases reveal that the tumour is a pilocytic astrocytoma. The pilocytic astrocytoma in this region is a well-circumscribed tumorous lesion which, even when it is large, does not entirely destroy the hypothalamic functional tissue but, instead, mainly displaces and compresses it. The slow growth of pilocytic astrocytomas greatly contributes to the minimal occurrence of the clinical symptoms and signs. Since MRI has become available, the diagnosis of the hypothalamic gliomas has become much easier; however, the slight initial symptoms and signs of the hypothalamic lesions may easily be overlooked for a long time, and so MRI is not undertaken until the tumour has already become large.

Microsurgical techniques are nowadays available and practised in most neurosurgical departments. However, since hypothalamic gliomas do not occur frequently, only limited experience can be gained in operating on such cases in individual centres.

The numerous publications in the relevant literature are not particularly helpful in expanding the useful surgical knowledge, since they deal with the treatment of hypothalamic tumours in the period before the use of CT and adoption of microsurgical techniques. This fact, together with the common belief that an "inoperable" tumour should be irradiated, is the reason why in most cases hypothalamic tumours are not resected completely. Thus the tumour continues to exert pressure against the hypothalamus, and in addition there occur radiotherapy-related sequellae. Under the circumstances, the incomplete tumour resection and additional irradiation are ineffective.

Treatment of hypothalamic glioma has recently changed radically so that nowadays complete and atraumatic microsurgical resection, causing no further neurological deficits, has become the treatment of choice. Radiotherapy and chemotherapy in pilocytic astrocytomas of the hypothalamus are contraindicated. Permanent substitutional hormonal treatment may be necessary in some cases, but in the majority of them normal hypothalamo-hypophyseal reflexes are gradually restored following surgery.

## Anatomy and Physiology of the Hypothalamus

The hypothalamus is a small part of the diencephalon, located on either side of the anterior part of the IIIrd ventricle, its volume being less than 1% of that of the brain. It is connected by the pituitary stalk to the pituitary gland. Posteriorly, the hypothalamus is delimited by the mamillary bodies, and anteriorly it extends to the optic chiasm, the preoptic area and the lamina terminalis. Grossly, the hypothalamus can be divided according to the two directions in which it extends, i.e. the medio-lateral and the antero-

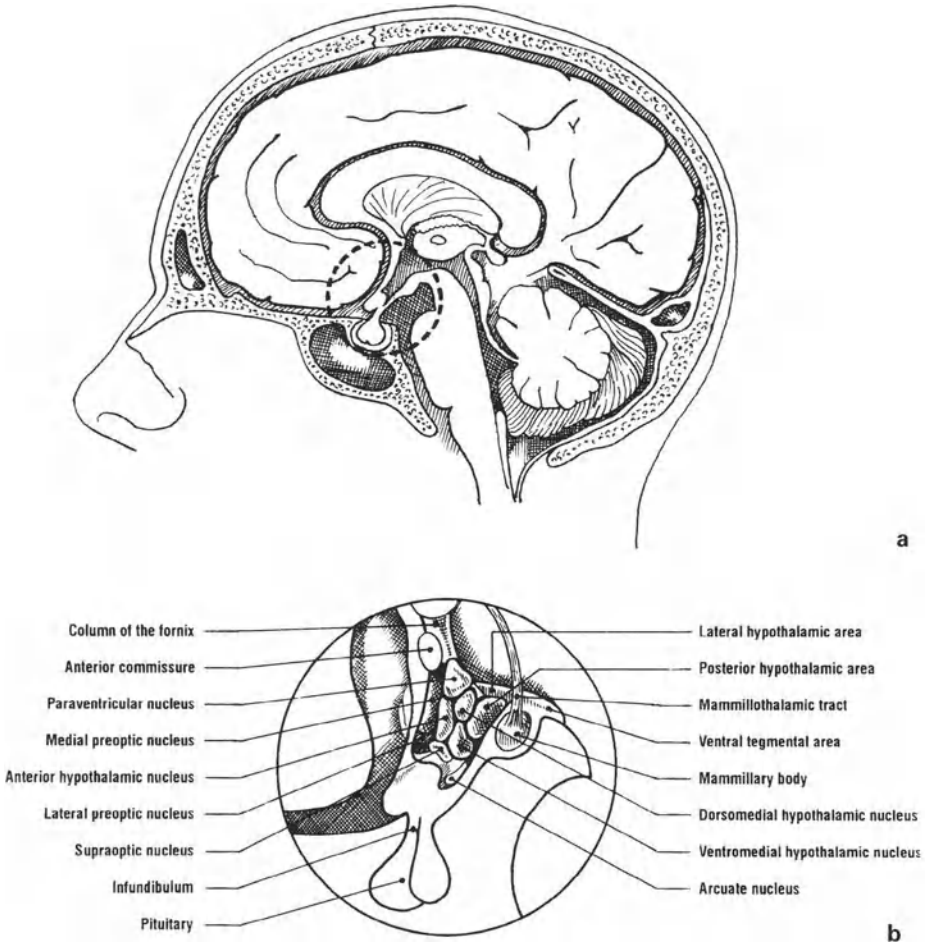


Fig. 1. (a) This schematic drawing of the medial view of the brain with the anterior part of the IIIrd ventricle and the surrounding structures shows (circle) the very centrally positioned small hypothalamic region in comparison with the whole brain. (b) Drawing of the hypothalamic area in the sagittal plane, parallel with the IIIrd ventricle, showing the locations of the hypothalamic nuclei according to the data obtained from experiments on animals as well as on the basis of clinico-pathological cases with hypothalamic tumours causing the individual hypothalamic syndromes

posterior direction. The regions in the medio-lateral direction are the periventricular, the medial and the lateral, while those in the antero-posterior direction are the anterior, the middle and the posterior. The periventricular region borders on the IIIrd ventricle. The basal part of the periventricular region consists of the arcuate nucleus, situated around the floor of the IIIrd ventricle (Figs. 1 and 2). Located in this nucleus (found in lower animals),

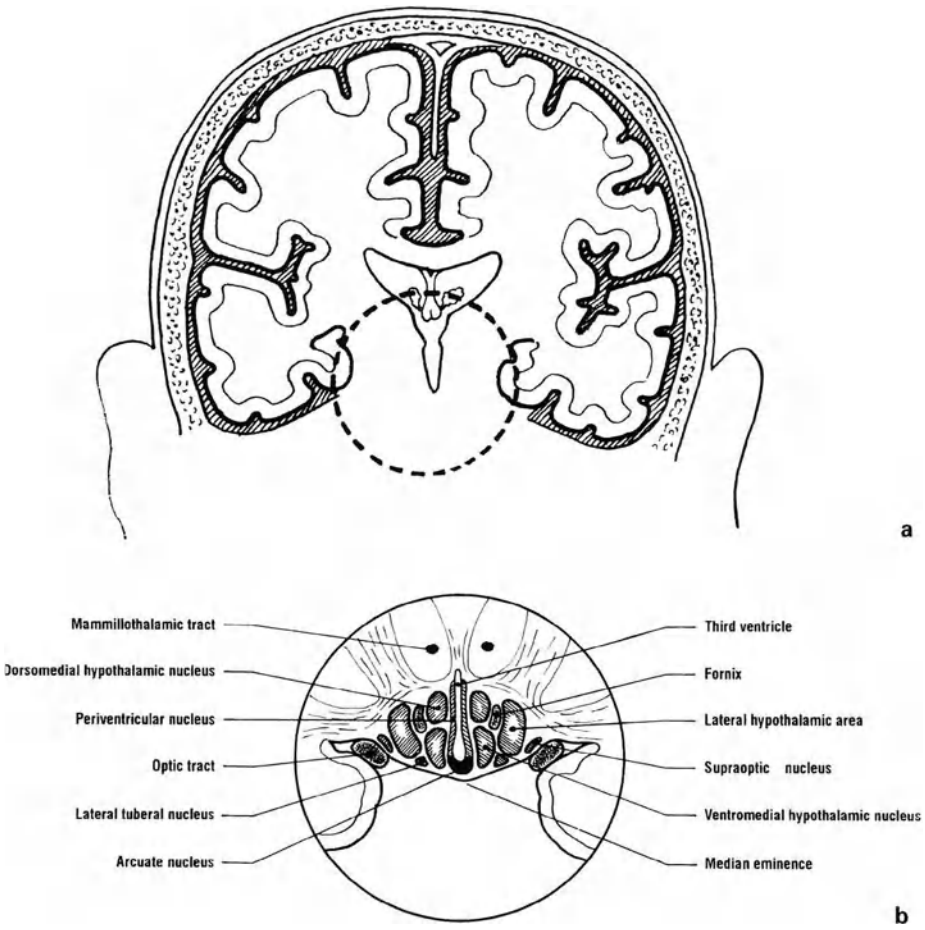


Fig. 2. (a) Drawing of the coronal section of the brain and of the ventricular system at the level of the foramen of Monro, showing the very central position (circle) of the anterior IIIrd ventricle as well as of the hypothalamic region around it. (b) A schematic drawing of the hypothalamic region in the coronal section in the cranio-caudal direction approximately parallel to the direction of the pituitary stalk. Three imaginary regions of the hypothalamus on each side of the IIIrd ventricle, i.e. the paraventricular, the medial and the lateral are shown. The vicinity of the visual apparatus on either side and underneath the hypothalamus explains the effect of a hypothalamic lesion on visual function and vice versa

and in the tuberal nuclei in the basal medial region (found in primates), are the neurons that secrete substances by means of which the hypothalamus exerts control over the release of the hormones of the anterior part of the pituitary gland.

The medial region of the hypothalamus, separated from its lateral

region by the descending columns of the fornix, contains the well-defined nuclei of the hypothalamus: the preoptic and suprachiasmatic nuclei in the anterior region; the dorsomedial and ventromedial nuclei; and the posterior nucleus and mamillary bodies in the posterior region.

The region of the hypothalamus lateral to the fornix is the lateral hypothalamic area. This region projects the longer fibres to the spinal cord and the cortex. Its short fibres form the multisynaptic ascending and descending pathways.

It is characteristic of most fibre systems of the hypothalamus that they are bidirectional. The hypothalamic projections to and from the structures caudal to the hypothalamus are contained in the medial forebrain bundle, the dorsal longitudinal fascicle and the mamillotegmental tract. In relation to the structures cranial to the hypothalamus, the interconnections course by the mamillothalamic tract, stria terminalis and fornix. There are only two exceptions to the bidirection-rule referred to above, i.e. the descending axons of paraventricular and supraoptic neurons (which terminate in the posterior pituitary gland and represent the so-called hypothalamo-hypophyseal tract), and the one-way afferent connections from the retina to the hypothalamus. The suprachiasmatic nucleus, where the latter fibres primarily terminate, is believed to play an important part in the circadian rhythms.

The neurons of the hypothalamus participate in four types of reflexes which depend on the neural and/or humoral output and input: 1. neural input and output; 2. neural input and humoral output; 3. humoral input and neural output; 4. humoral input and output.

It is beyond the scope of this chapter to deal with the interconnections of the hypothalamus with other parts of the brain and the endocrine system in the light of these rather simple four different types of reflexes. It is clear that the regulation of the autonomic nervous system and emotional behaviour, are even more complex reflexes. Likewise, emotional reactions such as fear, anger, pleasure and contentment are also highly complex. Of the same – if not even a higher level of complexity – are the autonomic and endocrine responses integrated at the hypothalamus, which are triggered off by such stimuli as pain and/or pleasure, and which alter the internal state preparing the body for attack, defence or some other adaptive behaviour.

The hypothalamus is the regulator and co-ordinator of all our unconscious and continuing body activity. Its protean function justifies the idea that this small part of the brain represents the centre of centres.

## Hypothalamic Syndromes

Hypothalamic lesions only manifest themselves after they have become large and have damaged the hypothalamus bilaterally. Despite the fact that

ventro-medial lesions of the hypothalamus cause hyperphagia, and lesions of the lateral hypothalamus cause aphaghia and loss of weight, it is still difficult to diagnose a hypothalamic tumour on the basis of clinical manifestations only. Lesions in the anterior hypothalamus cause hyperthermia, obesity, somnolence, fits of rage, and precocious puberty. However, not all these clinical manifestations appear in all patients, nor at the same time, the reason being that the lesion usually grows very slowly and the hypothalamus still functions adequately. Hypothalamic gliomas (pilocytic astrocytomas), while growing, compress and displace the ipsilateral and contralateral hypothalamus. Since the growth of the tumour is very slow, the hypothalamic centres can adapt to the changed relationships and to the coexistence of the benign tumour.

Despite the postulated anatomical nuclei and the physiological centres of the hypothalamus, it is difficult to believe that this simple interpretation of the hypothalamus is completely correct. It is more probable that the dynamic interactions of the cells of the hypothalamus—by means of humoral and neural connections—activate or inhibit the intermediate and distant centres on the basis of qualitative and quantitative changes. However, the concept of hypothalamic centres and syndromes has found support in human case material [4–14, 19, 29, 46, 55, 57].

### *The Ventro-Medial Hypothalamic Syndrome*

This syndrome occurs in patients in whom the so-called "satiety centre" has been destroyed. Such patients require a higher food intake because the lateral "feeding centre" functions normally and is not opposed by the "satiety centre". As the tumour grows further, more hypothalamic functions become affected, which leads on to personal changes and neurological deficits. Such patients require a high caloric intake, and they react with violent rage-like outbursts to any attempt to reduce their food intake. They are emotionally unstable, show uncontrolled rage and aggression, unprovoked laughing and crying, and become withdrawn. Amenorrhea and/or impotence may also be associated.

The hypothalamic control over food intake has also been studied in animals [1, 27].

### *The Lateral Hypothalamic Syndrome*

In cases where the "feeding centre" has been destroyed, aphagia, loss of weight and cachexia occur [56]. This syndrome is very rare and should be separated from anorexia nervosa, which is much more frequent.

### *The Diencephalic Syndrome of Infancy*

This syndrome is characteristic of hypothalamic gliomas involving the anterior hypothalamic area itself, or gliomas involving the region of the chiasm and growing into the anterior hypothalamic region. These patients start losing weight very early between the second and the twelfth month of age; however, they do grow and behave normally [14, 48, 53]. Endocrine studies of these children are remarkably normal.

### *The Anterior Hypothalamic Syndrome*

Lesions in the anterior hypothalamus in late childhood, adolescence and adulthood cause precocious puberty, obesity, somnolence and rage. It is not clear whether the "immature" hypothalamus of infants and younger children, affected by a lesion, responds in a different way to the hypothalamus of adults with lesions at the same location. Most probably the original location of the lesion and its evolution are different in children than in adults; it is also important to know what functions have already been established, and to what extent, when the tumour has reached a critical size at a given location.

All the above-mentioned hypothalamic syndromes may or may not be associated with changes of behaviour due to the extension of tumours in lateral direction(s), affecting the limbic system.

### *Cushing's Ulcer*

This peptic ulcer is located at the greater curvature of the stomach, or at the cardia, or at the pylorus [11, 12, 47, 48]. It occurs in cases of hypothalamic tumourous lesions, as was already reported (11 cases) by Cushing in 1932 [11, 12]. The connection between the posterior hypothalamus and gastric ulceration has also been confirmed by prolonged electrical stimulation of the hypothalamus in experimental animals [37, 38].

### *Diencephalic "Epilepsy"*

This syndrome consists of bursts of autonomic activity producing flushing, hypertension, excessive lacrimation, salivation and sweating. Changes in size of the pupils are followed by Cheyne-Stokes respiration. The initial description of such a "seizure" was given by Penfield in 1929; when the patient died, the autopsy revealed a tumour of the anterior IIIrd ventricle, compressing both sides of the hypothalamus [20, 42, 50].

### *Disorders of Thermoregulation*

This syndrome occurs in lesions of the anterior and posterior hypothalamus [18, 20, 45]. Lesions of the anterior hypothalamus cause hyperthermia, and those in the posterior hypothalamus cause hypothermia.

The well-known clinical syndrome of chronic hypothermia is associated with Wernicke's encephalopathy, where periventricular lesions and lesions of the mamillary bodies were found at autopsy.

### *Disorders of States of Wakefulness*

Two hypothalamic centres have been recognized by neurophysiologists: the wakefulness centre in the posterior hypothalamus and the sleep centre in the anterior hypothalamus. Somnolence is much more frequent than insomnia in hypothalamic tumourous lesions. Experimental animal studies have shown that destruction of the anterior hypothalamic sleep centre leads to insomnia, while destruction in the posterior hypothalamic region leads to hypersomnia [44].

### *Visual Impairment Related to Hypothalamic Lesions*

Most hypothalamic tumours do not cause serious visual problems until they compress the optic chiasm or one or both optic tracts, and/or have become so large that they cause hydrocephalus. On the other hand, optic gliomas – which usually also involve the hypothalamus – may cause a visual field defect well before it is noticed by the patient [26, 28, 30, 39]. The patient, without noticing, may gradually become blind in one eye, or may have homonymous hemianopsia. The latter problem goes all the more unnoticed in very young children.

### *Hydrocephalus Related to Hypothalamic Lesions*

Many clinical manifestations of altered hypothalamic function(s) may not cause any major problems for the patient, until the tumour grows to such a size that the circulation of the CSF is impaired or blocked. When the IIIrd ventricle has been displaced to one side to such an extent that it is occluded in its anterior portion, the ensuing phase is occlusion of one or both foramen/foramina of Monro. This leads to unilateral, or possibly to bilateral hydrocephalus. In addition to the longstanding symptoms and/or signs that the patient has experienced for years, there are now also acute headache, blurring of vision, vomiting and changes of consciousness [21, 33].

## The Diagnostic Procedures

CT and/or MRI are essential in providing and in confirming a diagnosis of a hypothalamic tumour. Since endocrinological tests remain in many cases within normal limits for quite a long time, and since also the clinical manifestations are in many cases not very characteristic, the diagnosis used to be particularly difficult. Before CT and MRI were available it was extremely difficult, in many cases impossible, to diagnose small hypothalamic gliomas. Hydrocephalus was diagnosed either on the basis of characteristic displacement of the arteries or by means of ventriculography. Displacement of the arteries of the anterior segments of the circle of Willis was in certain cases critical in indirect pointing to extensive lesions of the hypothalamus. Despite the fact that visual deficits are always present in gliomas of the optic apparatus, it was difficult to establish the exact location of the lesion. If in the past the visual deficits, endocrinological testing and evaluation of the clinical symptoms led to the diagnosis, prior to the fully developed hydrocephalus; these data nowadays indicate the stage of the disease while the precise location and definition of the tumour are established by CT and MRI.

## Surgical Approaches

When a hypothalamic glioma or a glioma of the visual apparatus has been diagnosed, the question is whether the lesion should be biopsied before open surgery is planned. In large tumours of the region a biopsy is not recommended since such tumours should be excised.

The size and location of the tumour and to a certain degree the associated hydrocephalus dictate the approach to the lesion. The approaches used in hypothalamic glioma surgery are: subfrontal, transcortical-transventricular, pterional, interhemispheric-transcallosal-transventricular and/or a combination of these.

In our series of hypothalamic gliomas the interhemispheric-transcallosal-transventricular approach was used. Only in 5 patients operated on at the beginning of the era of surgery of these tumours at our Department was a combination with the pterional approach used during the same operation.

### *The Interhemispheric-Transcallosal-Transventricular Approach*

The patient is positioned supine. His/her head is fixed in a tripoint Mayfield headrest in a strict posterior-anterior direction, and the neck is slightly flexed (Fig. 3a, b). The head is then shaved along the midline, 7 cm in the antero-posterior direction, the shaved area extending 3 cm on the side of the approach and 2 cm on the contralateral side (Fig. 3b). The skin incision

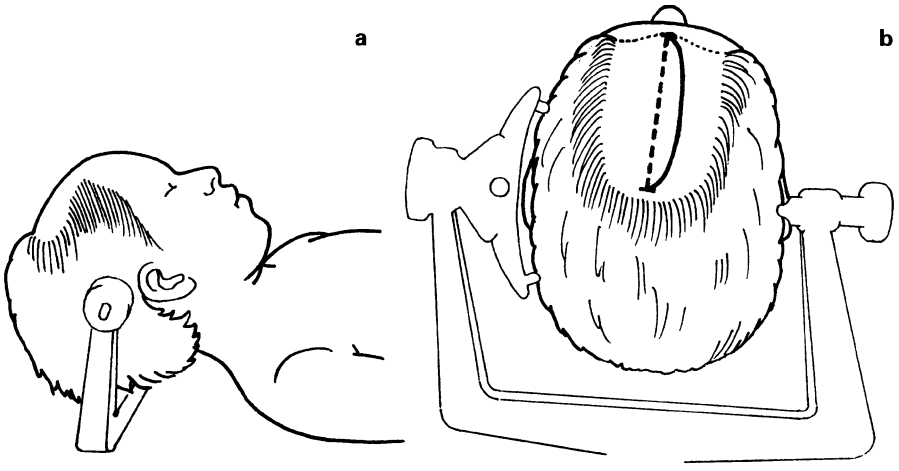


Fig. 3. The positioning of the patient and fixation of the head in the lateral (a) and the postero-anterior view (b) for the interhemispheric-transcallosal-transventricular approach to a hypothalamic lesion. The patient is in a supine flat position with the head slightly elevated at a 10° angulation of the neck. The hair is shaved on either side of the midline, which is marked by a dotted line, and the skin incision line is marked by a full line on the right side of the midline (b)

is made on the side of the approach, and runs parallel to the midline, 1 cm from it, except at the anterior and posterior end where the incision curves to the midline. The bone is exposed asymmetrically in relation to the sagittal bony suture line, so that the exposure is 4 cm large on the side of the approach and 2 cm on the contralateral side. The coronal suture line is visualized on the posterior part of the exposed bone. A single burr hole is made posterior to the coronal suture line and over the sagittal suture line (Fig. 4a). Additional burr holes may be required in elderly patients but in children and younger adults a single burr hole is usually sufficient. The bone flap is cut on each side of the superior sagittal sinus (SSS) and broken away at its most anterior end. The dura on the side of the approach is exposed in an area 2–3 times larger than that exposed on the contralateral side. The dural incision is made on the side of the approach and runs 1.5 to 2 cm lateral to the SSS and parallel to it, except at the anterior and posterior end where it curves to the SSS (Fig. 4b). The dural flap is reflected over the SSS, without any traction. Any major tension of the dural flap over the SSS and/or retraction of the falx and the ipsilateral dural wall of the SSS during surgery may cause the venous flow along the SSS to decrease, and hence cause venous engorgement on the contralateral side of the brain (Fig. 4b). In cases where large bridging veins are present in the area exposed by the opening of the dura, these should not be transected. Dissec-

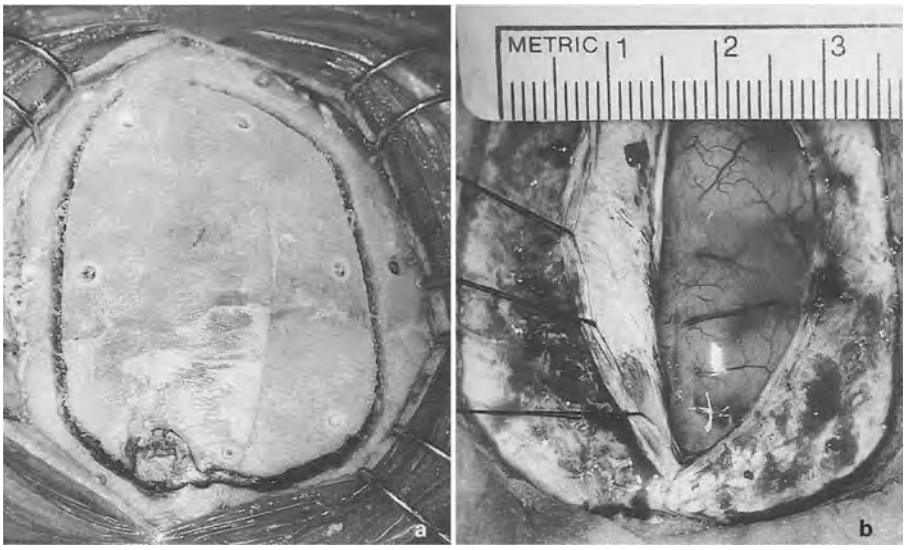


Fig. 4. Photograph of the operative field showing the actual positioning of the single burr hole over the sagittal suture line behind the coronal suture line and the bone cut on either side of the superior sagittal sinus (*SSS*) with a small bridge of bone over the SSS at the anterior end of the bone flap (a). The dural flap is reflected over the SSS to the contralateral side without tension, in order to avoid the narrowing or occlusion of the SSS at the time of surgery. The width of the exposure of the medial border of the cerebral hemisphere is maximally 1.5 cm and is becoming smaller at the anterior and the posterior segments of the dural opening (b)

tion of the veins from the arachnoidal coverings provides the necessary "mobility of the brain" which, during the procedure, should only be displaced by approximately 1.5 to 2 cm laterally from the midline. In cases where dissection of the veins is impossible, the opening of the bone is enlarged either in an anterior or posterior direction, depending on which is free of bridging veins. If sufficient space between the falx and the brain cannot be obtained by this procedure without the risk of damage to the veins, it is necessary to extend the craniotomy to the contralateral side, and to make a dural flap in the same way as on the ipsilateral side. The aforementioned problems with the bridging veins occur rarely because there are in most cases no major draining veins in the frontal lobes, and if small veins are present, one or two may be sacrificed [2, 3, 15, 16, 22, 23, 35, 36, 43, 52, 57]. The frontal lobe is then dissected away from the falx using microforceps and cottonoid pads. Arachnoidal adhesions to the falx should be cut and the frontal lobe gently separated from the falx as well as from the contralateral frontal lobe underneath the falx. Anteriorly and posteriorly, cottonoid pads are placed between the cortex and the falx in order

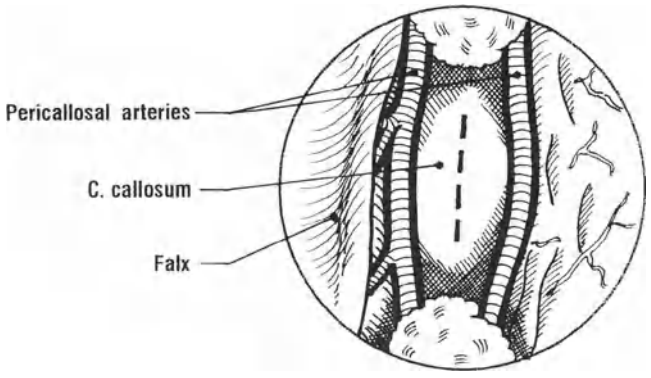


Fig. 5. Completed separation of the cerebral hemisphere on the side of the entry corridor, achieved with gentle dissection and no retraction. The lower end of the falx is on the left and the cerebral hemisphere on the right side. Both pericallosal arteries are gently separated and held apart with two cottonoid pads anteriorly and posteriorly at a distance of approximately 2–3 cm. The incision (dotted line) into the corpus callosum is marked

to gently hold the frontal lobe away from the falx. The calloso-marginal artery is identified on the side of the exposure and, in cases where the falx is small, on the contralateral side as well, and the artery is protected with cottonoid pads. Further dissection of the two frontal lobes is performed until the pericallosal arteries are visualized. The pericallosal arteries are then separated from each other along approximately 3–4 cm of their length. Cottonoid pads are placed between the arteries to keep them separated and to expose the corpus callosum underneath (Fig. 5). Three to four cm long segments of the dissected and separated pericallosal arteries allow – after the corpus callosum has been sectioned – for gentle displacement of the ipsilateral pericallosal artery from the midline in a lateral direction, care being taken not to stretch and/or compress it. When the corpus callosum has been longitudinally cut by 1–1.5 cm, the ipsilateral lateral ventricle is entered and the foramen of Monro is visualized (Fig. 6). The choroid plexus and the thalamostriate vein with its branches along with the septal vein are visualized. In the case of an anatomical variation or irregularity, the septum pellucidum may be perforated and the contralateral lateral ventricle and the foramen of Monro are exposed. Regarding the location of the foramen of Monro, additional tilting of the operative table toward the Trendelenburg or reverse Trendelenburg position and re-adjustment of the head of the microscope may be necessary in order to obtain the optimal viewing angle. If the floor of the frontal horn of the lateral ventricle, anterior to the anterior branch of the thalamostriate vein and lateral to the fornix, does not show any variation, the anterior lateral

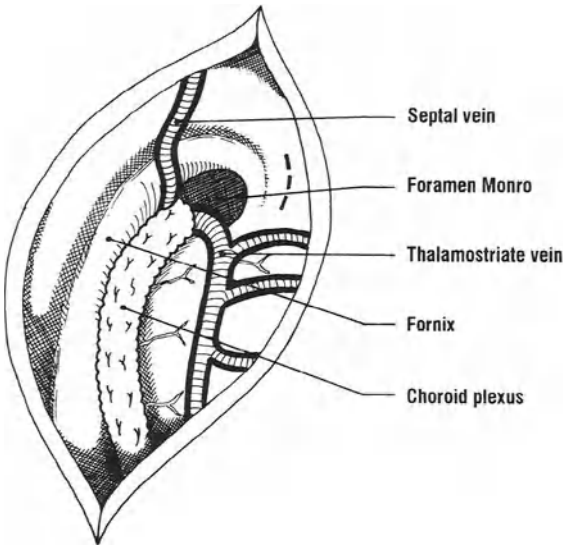


Fig. 6. The drawing illustrates the view into the right lateral ventricle through the interhemispheric transcallosal corridor on the right side of the falx. The individual anatomical structures, which should be preserved intact throughout the surgical procedure, are presented. The dotted line shows the site of the incision into the floor of the lateral ventricle anterior to the anterior branch of the thalamostriate vein and antero-lateral to the course of the fornix

wall of the third ventricle is examined through the foramen of Monro on the ipsilateral side. In most cases the tumour bulges under the floor of the frontal horn of the lateral ventricle, and incision of the ependyma exposes the mass. Gliomas of the hypothalamus are mostly pilocytic astrocytomas of characteristic appearance, and of a greyish colour which is distinctly different from the normal brain tissue. These tumours are, in contrast to optic gliomas, usually solid without cystic component(s). Their vascularity is poor to moderate, so they can be debulked to a large extent by the piecemeal technique without running a risk of injury to any perforating arteries important for the surrounding normal tissue. It is of paramount importance that the fornix should not be retracted and that the vessels on the borders of the tumour, especially on its lateral sides, be preserved. Therefore, tumours should by no means be pulled out or "blindly" resected in large pieces. Only by gradual and careful reduction of the tumour mass – either by means of slight aspiration and assisting cutting or by ultrasonic aspiration – will the surrounding structures remain undamaged. With an appropriate adjustment of the position of the head of the microscope and tilting of the table, the areas in the vicinity of the anterior communicating artery (A. com.) and anterior cerebral artery (part 1) (A.C.A.1)

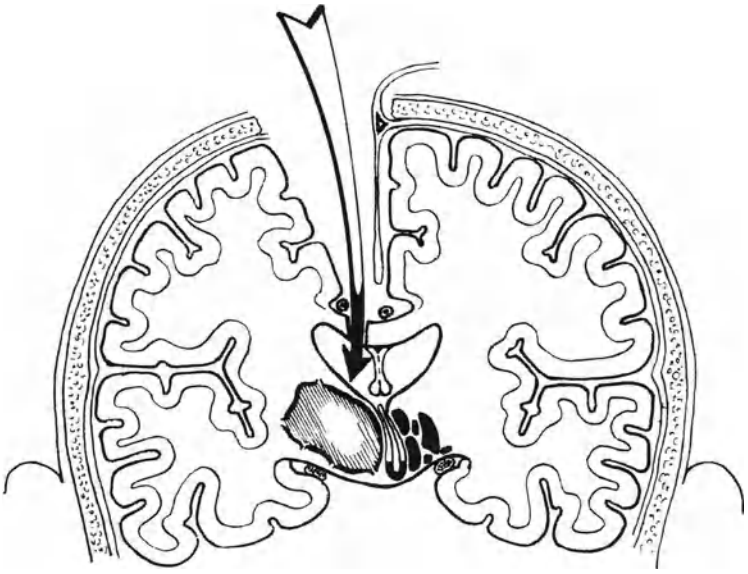

Fig. 7. Approach to a right-sided hypothalamic tumour. The approach is along the falx between the pericallosal arteries through the corpus callosum to the ipsilateral lateral ventricle and then through the floor of the frontal horn of the lateral ventricle to the tumour

on the ipsilateral and contralateral side can be reached, and the tumour deeper and more posteriorly in the brainstem can be reached and completely excised. After removal of the tumour extending into the deeper and posterior parts of the hypothalamus, the bifurcation of the basilar artery and its perforators, and in some cases nerve III on both sides can be visualized.

In tumours mainly located on one side of the IIIrd ventricle the approach used is from the side ipsilateral to the tumour (Fig. 7). If tumours extend around the IIIrd ventricle to the contralateral side, they can in most cases be resected from the ipsilateral side as well; however, in bilateral hypothalamic tumours, a bilateral approach may be necessary in order to avoid retraction of the fornix (Fig. 8). The transseptal approach to the hypothalamus through the septum pellucidum, the contralateral lateral ventricle, and from in front of the first branch of the thalamostriate vein may again require too much retraction of the contralateral fornix (Fig. 9). In optic gliomas originating in the chiasm or in the optic tract and "infiltrating" the hypothalamus, the pterional approach is necessary in addition to the interhemispheric-transcallosal-transventricular approach to enable the resection of the remaining part of the tumour located laterally along the proximal segment of the ACA1 and encasing the perforators

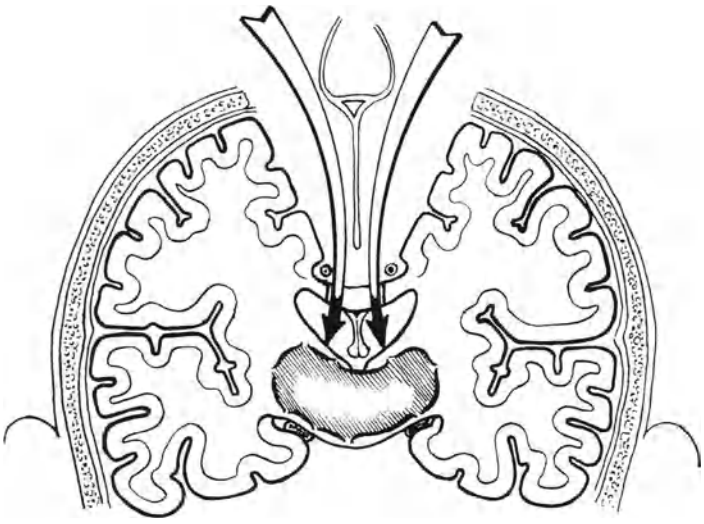

Fig. 8. Approach to a hypothalamic tumour situated mainly on one side of the IIIrd ventricle and extending partially also to the contralateral side around the IIIrd ventricle. This approach is practically the same as that for the hypothalamic tumours located on one side of the IIIrd ventricle. However, when the tumour cannot be completely resected from the contralateral side, another corridor through the septum pelucidum to the contralateral lateral ventricle is used

(lenticulostriate arteries), as well as resection of the tumour extending anteriorly over the chiasm and superiorly into the frontal lobes. An approach to these parts of the tumour through the interhemispheric-transcallosal-transventricular corridor would involve too much retraction of the brain, and very probably cause a lesion of the vasculature. No retraction of the fornices and/or the frontal lobe should be used. "Holding" the brain with bipolar coagulation forceps or with a soft suction tube during the piecemeal resection of the tumour is known as "dynamic retraction" of the brain, and carries much less risk of injury compared to retraction with a spatula, fixed over the brain for a longer period. Equally important as the least possible retraction of the brain is the preservation of all the arteries originating in the anterior part of the circle of Willis, the veins in the lateral ventricle, and/or the veins in the interpeduncular region.

At the end of the operation it is important to examine the IIIrd ventricle for any blood clot which may be occluding the entrance into the Sylvian aqueduct, or any blood clot which may be occluding the foramen of Monro. Any blood in the left and the right lateral ventricles is completely washed out as well. Prior to the dural closure, the subdural space is filled with saline to further ensure that no air remains in the cavities. The dura is sutured in a watertight manner, or, in cases where this is impossible,

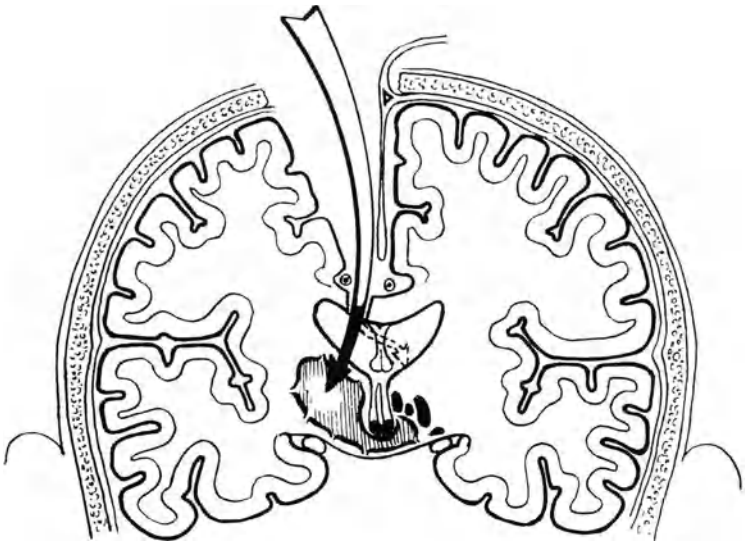

Fig. 9. The interhemispheric-transcallosal-transventricular approach to very large bilateral hypothalamic tumours is shown. This approach is used in order to avoid the retraction of the fornix and to achieve the complete resection of the tumour on each side as well as to ensure the preservation of all the perforators from the anterior portion of the circle of Willis to the normal tissue around the tumour and to ensure hemostasis without damaging the arterial and/or venous structures

two-component fibrin glue is applied along the suture line and over any dural defect from the epidural side. If hemostasis over the dura is complete no epidural drainage is necessary. The bone flap is fixed with separate sutures, and the subcutaneous tissue and the skin are sutured in layers.

## Immediate Postoperative Intensive Care

Children under 12 years of age are transferred from the operating theatre directly into the children's neurosurgical intensive care unit (NICU) where they remain connected to the respirator, if necessary. If they are unable to breathe spontaneously after approximately one hour has elapsed, urgent CT should be performed to rule out a blood clot either in the tumour bed and/or in the ventricles or in the subdural space. If a considerable space-occupying blood clot is seen, it should be removed without delay. However, a large majority of the patients can breathe spontaneously at the conclusion of surgery. They are extubated within the first postoperative hour in the NICU if their conscious level is adequate. In some cases despite the fact that spontaneous respiration is adequate, and oxygen saturation of the arterial blood is normal, the patients remain very sleepy and non re-

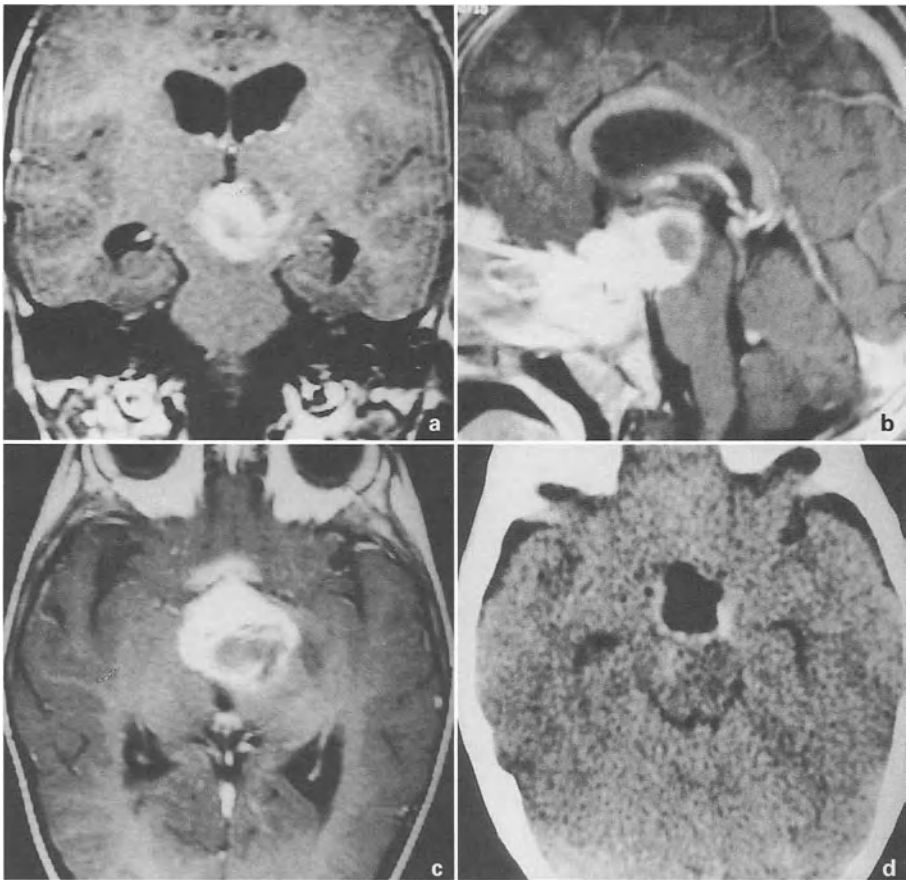


Fig. 10. A 20-month old boy had been sleepy since birth and even more so in the three months before presentation. The boy's clinical condition was close to the diencephalic syndrome. When the boy became more sleepy and started vomiting, the parents asked for an imaging diagnostic work-up. The coronal (a), sagittal (b) and horizontal (c) contrast-enhanced MRI views show a large hypothalamic lesion. The postoperative CT scan performed in the evening of the day of surgery to rule out postoperative hematoma, shows radical removal of the hypothalamic tumour and no hematoma

sponsive, which may be the result of a surgical lesion of the hypothalamus and/or the fornix [25, 31, 32, 40, 44]. To be sure that this is the case and that there is no postoperative blood clot, an immediate CT scan is mandatory. In all other cases postoperative CT is advisable in the evening of the operative day or during the first postoperative day at the latest (Figs. 10, 11). The early CT is an important assurance that there is no blood clot and that the CSF circulation is normal, and at the same time it provides information about the amount of intraventricular air. Postoperatively these

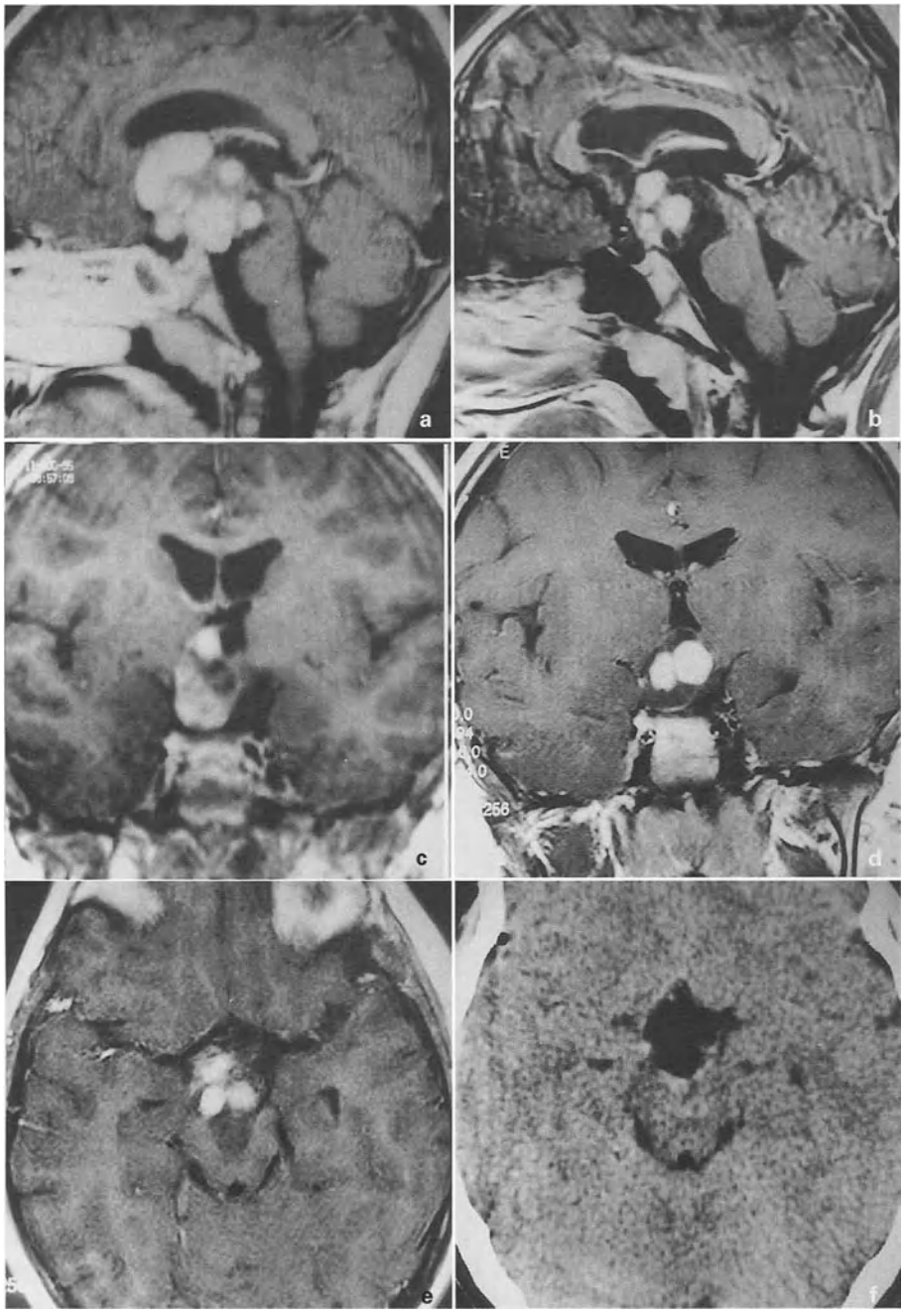

Fig. 11. A pilocytic astrocytoma in a 7-year-old girl, operated on when she was 3. MRI views, sagittal (a) and coronal (c), before the first operation. The recurrent pilocytic astrocytoma 4 years later is shown in MRI films: sagittal (b), coronal (d), and horizontal (e) views. The postoperative CT scan performed in the evening on the day of the second surgery shows complete resection of the recurrent pilocytic astrocytoma and no blood clot (f). Note the size of the corpus callosum section at the first operation (b). Both the first and the second operations were performed in our department

patients may have a slightly elevated body temperature as a consequence of manipulation with the hypothalamic tissue. Such patients may develop the syndrome of inappropriate antidiuretic hormone secretion (SIADH), or the syndrome of cerebral salt wasting (CSW) which will lead to a sodium loss, resulting in hypoosmolarity of serum and hyperosmolarity of urine. More frequently, however, such patients develop diabetes insipidus (DI), and the sodium concentration of their serum may rapidly increase from the normal values to 180 mEq/L or even higher. Such a sharp increase of serum sodium may result in severe complications and also death if it is not promptly corrected. Therefore strict hourly monitoring of fluid balance is mandatory.

Treatment with corticosteroids should be administered in the afternoon, and antiepileptic treatment in the evening of the operative day, and should under no circumstances be postponed until the next day.

In the majority of cases, adult patients operated on for hypothalamic gliomas, or optic gliomas also involving the hypothalamus, are extubated in the operating theatre before being transferred to the NICU. The balance of electrolytes and fluids must be strictly monitored and replacement hormonal treatment must be administered; also, an early CT scan should be performed.

### Later Postoperative Treatment

Most patients operated on for hypothalamic tumours located on one side of the IIIrd ventricle and not extending around it to the other side, do not require any special treatment in the postoperative period, providing that there was no surgical trauma to the surrounding structures nor to the remaining hypothalamus. Many patients, however, after surgery of hypothalamic tumours compressing or destroying one side of the hypothalamus and spreading to the opposite side, do require special care regarding homeostasis. This indeed poses a major problem in patients operated on for large and/or giant hypothalamic tumours involving the entire hypothalamus, either compressing or destroying it. The main concern of intensivists is to treat the electrolyte and fluid imbalance in such patients. The imbalance can occur in the form of DI or in the form of SIADH or CSW syndromes. Treatment of these disorders should be started immediately and requires the supervision of the intensivist in the neurosurgical intensive care unit. Excessive fluctuation of electrolyte values and/or fluids, if not treated promptly, may become irreversible. Medication with corticosteroids and thyroid hormones is easily programmable and should be conducted according to the serum hormone levels. Antiepileptic treatment is given to all patients postoperatively and is programmed individually according to the site of the surgical procedure, location of the tumour, size of the tumour and preoperative presence or absence of epileptic seizures.

Elevated body temperature may occur as a consequence either of damage to the hypothalamus, or of irritation by the breakdown products of the remaining blood clot and tissue debris, or of possible infection. If the elevated body temperature was not present before surgery or immediately after surgery, but occurs one or two days later, a diagnostic work-up should be immediately carried out in order to exclude an infection, and the elevated temperature should not be ascribed too quickly to a central origin. If the abnormal body temperature was already present before surgery and remains the same or becomes slightly more abnormal immediately after surgery, and if the temperature does not suddenly increase from the normal values to very high values several days after surgery, it is more probable that it is a consequence of the hypothalamic damage. Excessive loss of fluids and serum hyperosmolarity, associated with a suddenly and highly elevated body temperature, may cause epileptic seizures which are difficult to treat. In order to avoid misinterpretation of such epileptic seizures as being the consequence of postoperative bleeding in the bed of the tumour, a CT scan is required at an early stage after surgery. In cases of hydrocephalus it is useful to use lumbar drainage, providing that the Sylvian aqueduct and the IIIrd ventricle are free of blood. If this is not the case, an external drain should be inserted into one or to both lateral ventricles. The external drainage may later on be replaced with permanent drainage, if necessary, when the protein content of the CSF has normalised. If a ventriculo-peritoneal (V-P) or ventriculo-atrial (V-A) shunt was inserted prior to surgery, it is left in place, because the patient may need it in the postoperative period. Patients who are drowsy after surgery (a lesion of the fornix) or who show abnormal behaviour and/or even motor disabilities call for more complex postoperative treatment. The family members/parents should be included in neuro-rehabilitation already in the early postoperative period to assist in feeding their child, to encourage their patient to do physical exercises, stimulate their child to be awake and active during the day etc., all of which will restore a normal circadian rhythm much sooner.

As soon as the final histological diagnosis of the tumour is available, the team of physicians including the surgeon who operated on the patient, together with the intensivist/paediatrician, the neurologist, the neuro-oncologist, the neuro-radiotherapist, as well as the patient's family members/parents, should make a decision on complementary treatment and its time frame. If it is decided that radiotherapy (gamma-knife and other) and/or chemotherapy is necessary, it is strongly advisable that this be a continuation of the surgical treatment and not be postponed for too long. The results of the histological examination dictate the necessity for complementary treatment. In pilocytic astrocytomas of the hypothalamus and/or in optic glioma, complementary treatment is not indicated.

## Results

The data for patients treated surgically at our Department are presented in tables I and II. Pilocytic astrocytoma was diagnosed in 47 children between 1 and 12 years of age – representing 76% of the whole series of patients operated on for hypothalamic gliomas. Eighty-three percent had neuro-endocrine deficits in early childhood. Hydrocephalus was present in 23% of cases of the group of pilocytic astrocytomas and in 14% of the whole series of hypothalamic gliomas. Different surgical procedures – shunting in 19%, biopsy in 40%, one open operation in 32%, and two open operations in 17% of cases – and irradiation in 36% of cases had been performed elsewhere in patients with pilocytic astrocytomas before the radical surgery. The patients with oligodendrogliomas in the hypothalamus were all young adults between 18 and 30 years of age. The patients with malignant gliomas of the hypothalamus were in their thirties and forties. Out of the whole series, 70% of patients were treated either medically or surgically, and/or by complementary irradiation as well, before they underwent radical surgical removal of the lesion. In 73% of patients hypothalamic gliomas were resected totally (Figs. 12–15) and in 27% of patients the tumour resection was nearly total. After radical resection of the lesion, benign or malignant, there were no new neuro-endocrine deficits in 42% of patients. In 53% of all patients of the series there were transient new neuro-endocrine symptoms and/or signs which disappeared not later than 3 months following surgery. Only in 5% of cases did additional neuro-endocrine deficits remain permanent. Complementary treatment (irradiation/chemotherapy) was not performed in pilocytic astrocytomas. The overall outcome in this group of 47 patients was excellent. All patients with oligodendrogliomas were irradiated and three of them had chemotherapy in addition. The longest follow-up in patients operated on for hypothalamic oligodendrogliomas has been 7 years, and all these patients are alive. Patients operated on for malignant gliomas of the hypothalamus underwent complementary irradiation and chemotherapy in all cases. All these patients died 2 to 4 years following the treatment.

## Discussion

It is important to evaluate critically the literature about hypothalamic tumours. Only in a small number of publications are intraaxial hypothalamic gliomas not mixed up with other intraaxial hypothalamic tumors and/or intraventricular tumors and, much more frequently, with extraaxial tumours and vascular lesions of the neighbouring structures of the hypothalamus [17, 24, 32–34, 41, 49, 51, 54, 55]. An extra-axial lesion, especially a large craniopharyngioma, a glioma of the visual apparatus, especially an opto-

Table 1.

| Tumors | No. of cases | Symptoms and signs | | Previous treatment | | | | |
|---|---|---|---|---|---|---|---|---|
| | | neuro-endocrine | hydrocephalus | shunt | biopsy | open surgery | | irradiation |
| | | | | | | one | two | |
| Pilocytic astrocytomas | 47 (76%) | 39 (83%) | 11 (23%) | 9 (19%) | 19 (40%) | 15 (32%) | 8 (17%) | 17 (36%) |
| Oligodendrogliomas | 8 (13%) | 6 (75%) | 0 (0%) | 0 (0%) | 2 (25%) | 0 (0%) | 0 (0%) | 3 (38%) |
| Malignant glial tumours | 7 (11%) | 2 (29%) | 3 (43%) | 3 (43%) | 4 (57%) | 1 (14%) | 0 (0%) | 5 (71%) |
| Total | 62 (100%) | 47 (76%) | 14 (23%) | 12 (19%) | 25 (40%) | 16 (26%) | 8 (13%) | 25 (40%) |

Table 2.

| Tumours | No. of cases | Tumour resection | | New neuro-endocrine deficits | | | Complementary treatment | | Died |
|---|---|---|---|---|---|---|---|---|---|
| | | gross-total | total | no. | transient | permanent | irradiation | chemotherapy | |
| Pilocytic astrocytomas | 47 (76%) | 8 (17%) | 39 (83%) | 16 (34%) | 28 (60%) | 3 (6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Oligodendro-gliomas | 8 (13%) | 2 (25%) | 6 (75%) | 5 (63%) | 3 (38%) | 0 (0%) | 8 (100%) | 3 (38%) | 0 (0%) |
| Malignant glial tumours | 7 (11%) | 7 (100%) | 0 (0%) | 5 (71%) | 2 (29%) | 0 (0%) | 7 (100%) | 7 (100%) | 7 (100%) |
| Total | 62 (100%) | 17 (27%) | 45 (73%) | 26 (42%) | 33 (53%) | 3 (5%) | 15 (24%) | 10 (16%) | 7 (11%) |

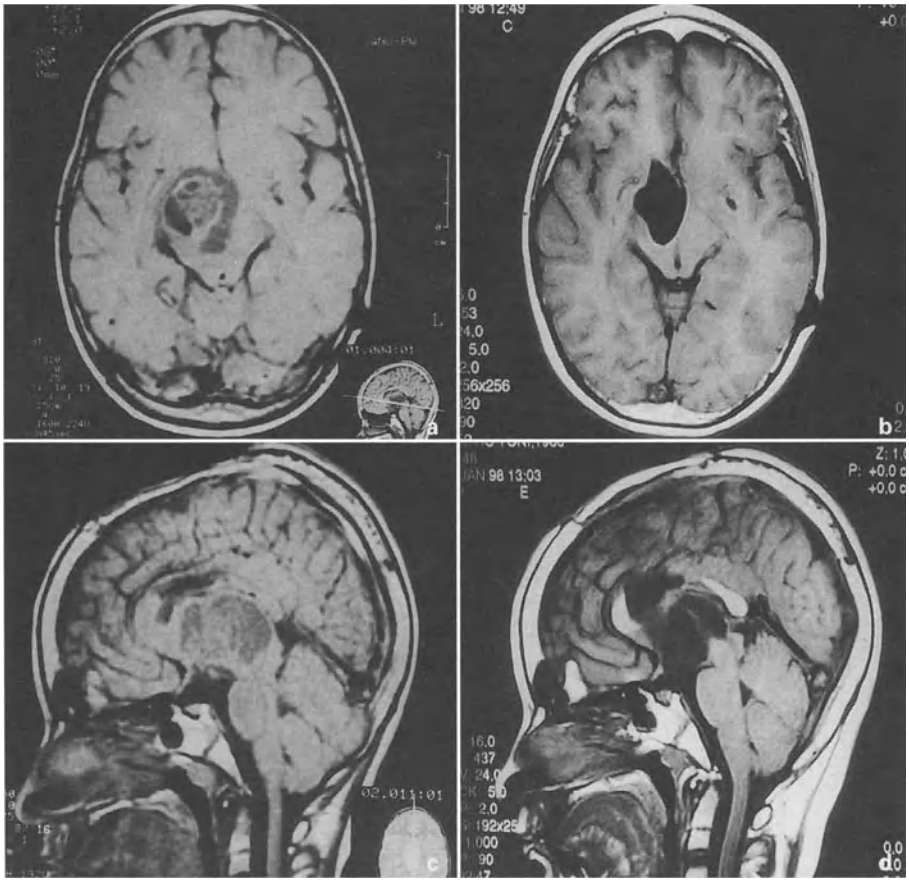

Fig. 12. A 3-year-old boy, operated on twice at another institution. The tumour was classified as inoperable and was irradiated. MRI views, axial (a and b) and sagittal (c and d), show the partially resected hypothalamic lesion (a) and bony and callosal defects following the first two surgeries (c), and the complete resection of the hypothalamic tumour following the third surgery (b and d)

chiasmatic glioma, and/or a carotid-ophthalmic, A.com., A.C.A.1 or basilar tip aneurysm may all cause the same neuro-endocrine disorders as do intraaxial slowly-growing tumours and especially pilocytic astrocytomas. However, surgical approaches to the aforementioned extraaxial lesions are completely different and it is most likely that – if the appropriate approach(es) to any and each of these intraaxial and extraaxial lesions are carried out – the postoperative neuro-endocrine disturbances are going to be very different. Extraaxial tumours, if they have significantly displaced and compressed the hypothalamus on one or both sides, may result in major neuro-endocrine disorders. A non-traumatic approach to and re-

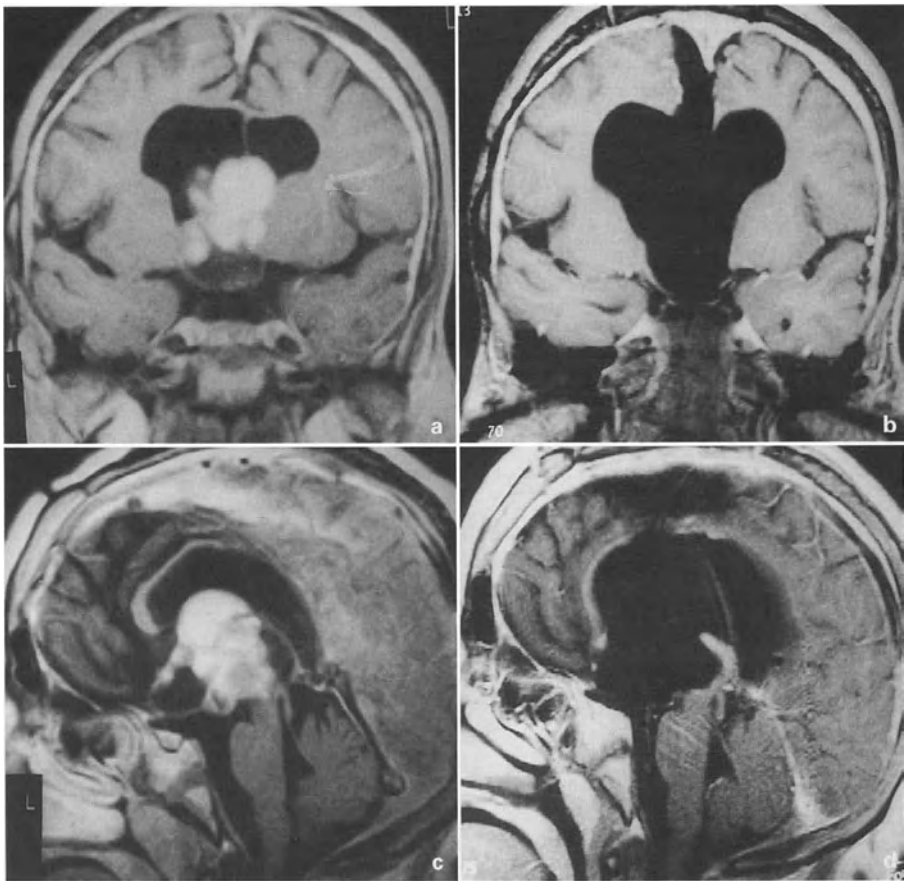


Fig. 13. A large hypothalamic lesion (pilocytic astrocytoma) in a 12-year-old girl, extending into the ventricular system and causing hydrocephalus: MRI contrast enhanced images, coronal (a) and sagittal (c) views. Radical resection of the lesion was achieved, as shown on the postoperative MR images: coronal view (b) and sagittal view (d)

moval of such an intraaxial unilateral or bilateral hypothalamic tumour does not cause new neuro-endocrine deficits after surgery. Endocrine deficits, if present after gross total or total removal of a hypothalamic glioma, usually disappear after 2 to 3 months. The fact that the extraaxial lesions around the hypothalamus cause hypothalamic disturbances means that they have both displaced and compressed the arteries of the anterior part of the circle of Willis (perfusing the hypothalamus) and displaced and compressed the veins, and also compressed the neural tissue of the hypothalamus. Dealing with anatomical situations thus altered is a difficult task for the surgeon; and usually some of these blood vessels are either damaged

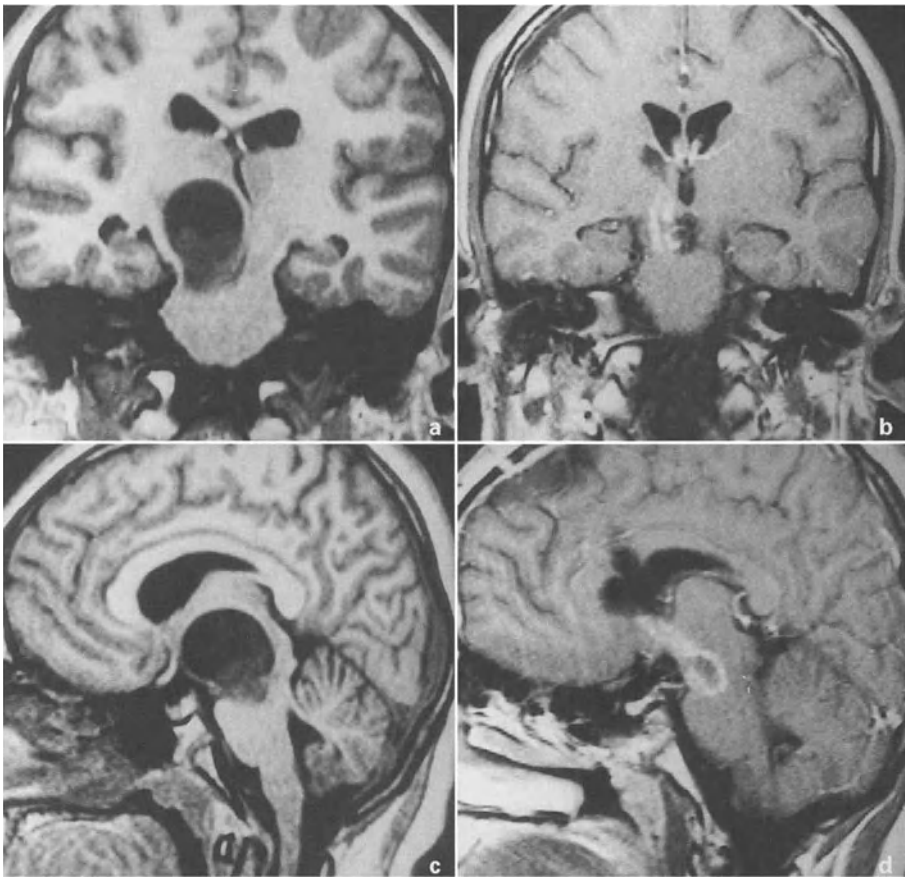


Fig. 14. A large, partially cystic hypothalamic tumour in a 7-year-old boy, on the right side; it was classified as inoperable and irradiation was suggested. Preoperatively the patient had left-sided hemiparesis which completely disappeared within 2 months after surgery. MR images (unenhanced), the only available preoperatively, show the displacement of the IIIrd ventricle, the large cystic portion of the tumour, the solid portion of the tumour in the coronal section (a), the cystic and the solid portions of the tumour in the sagittal section in relation with the brainstem (c), the relation of the cyst and the tumour to the brainstem in the horizontal section (e), and the displacement of the thalamus by the cyst of the tumour in the horizontal section (g). The MRI views, coronal (b), sagittal (d) and horizontal (f and h), show postoperative images corresponding to the preoperative images at the same levels and in the same planes. Due to the complete resection of the lesion and the benign nature of the tumour (pilocytic astrocytoma) no additional treatment was necessary

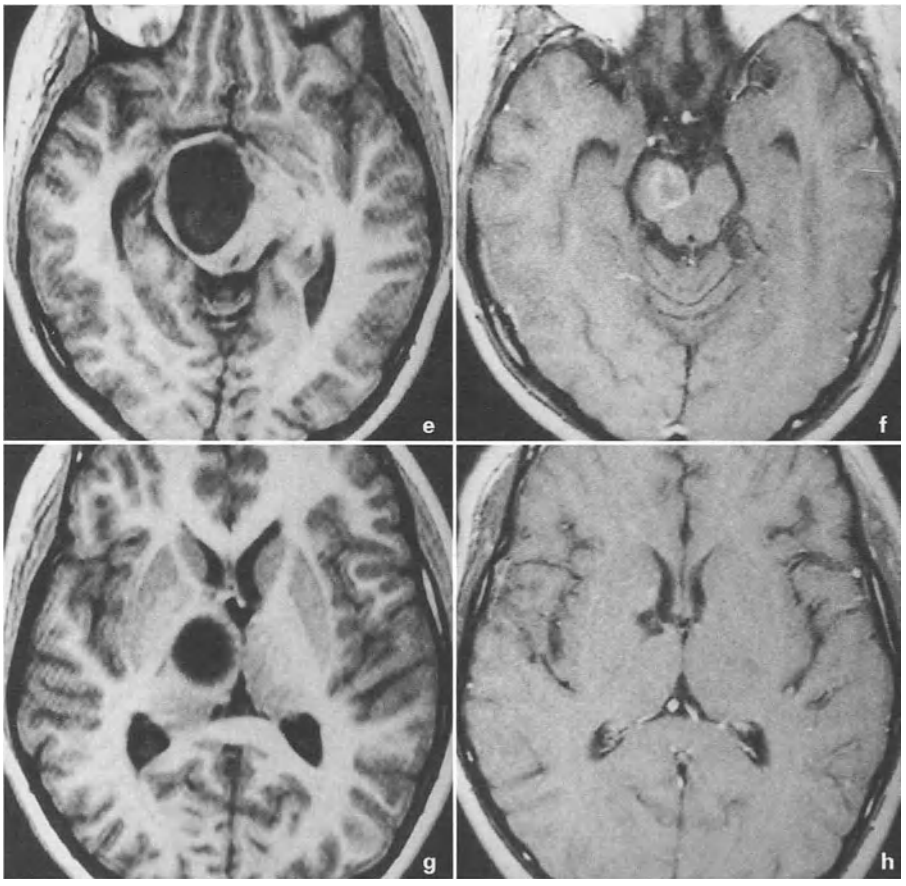


Fig. 14. (continued)

or may react by vasospasm after even gentle manipulation at the time of operation. Any coagulation of arteries or veins in the region may have disastrous consequences for the function of the hypothalamus, visual apparatus, pituitary stalk, and even for the neighbouring neural structures lateral to the hypothalamus. On the other hand, resection of an intraaxial pilocytic astrocytoma of the hypothalamus, which usually displaces the arteries and veins as it expands—providing that the first step of the resection involves debulking of the mass through the most convenient and least traumatizing interhemispheric-transcallosal-transventricular corridor – does not interfere with the blood vessels which provide blood supply to the hypothalamus and the neighbouring structures on the borders of the tumour. Since the tissue of such a pilocytic astrocytoma is different in colour and consistency from the surrounding tissue and does not infiltrate into the

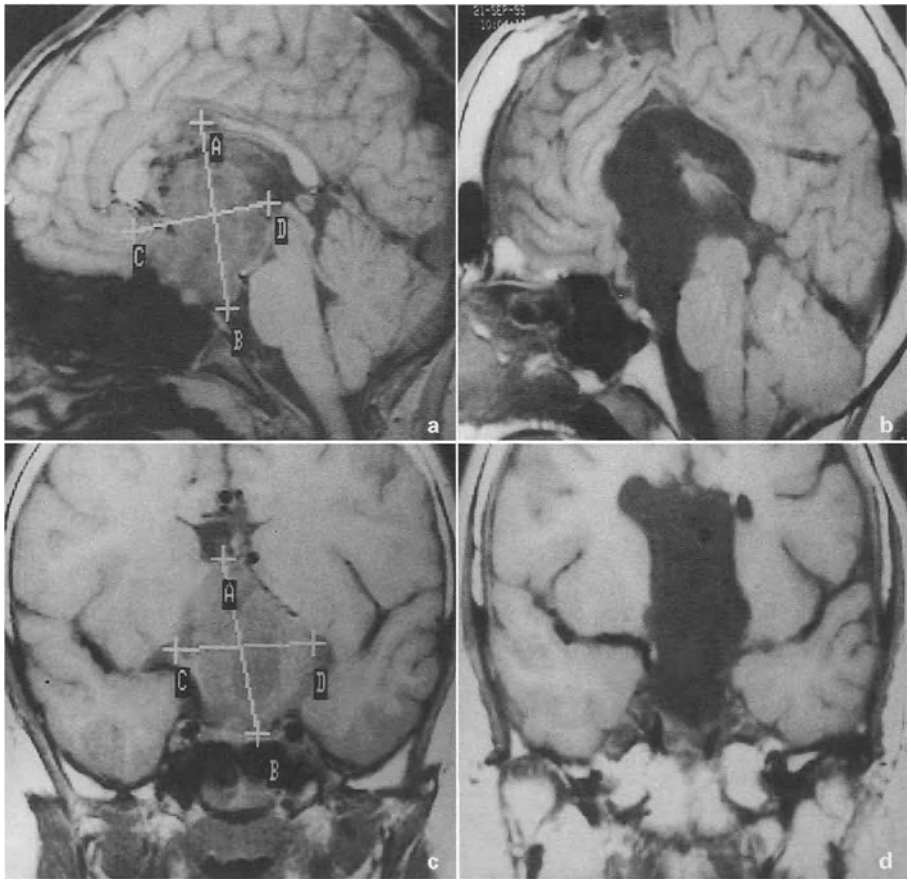


Fig. 15. A hypothalamic pilocytic astrocytoma in a 7-year-old boy, treated in several centres by biopsy, two open surgeries and irradiation, was finally operated on and the tumour was resected completely. MRI views, sagittal (a) and coronal (c) show a large remaining hypothalamic lesion before the last surgery and no tumour after resection, sagittal (b) and coronal (d) views. Note the large lesion of the corpus callosum following previous surgical attempts to resect the tumor (a)

neural structures, it is possible to dissect it gently from the normal brain tissue, and all the vasculature can and should be preserved. If the hypothalamic glioma is not a pilocytic astrocytoma but an oligodendroglioma or a malignant astrocytoma, it is questionable whether complete resection of the lesion is feasible, and if it is, whether it is beneficial for the patient.

In our opinion the only surgical route to intra-axial hypothalamic gliomas which enables total or gross total removal of the tumour without endangering the function of the neural and vascular structures around the tumour, and which preserves all neuro-endocrine functions, is the

interhemispheric-transcallosal-transventricular approach. Similar opinions have also been published elsewhere [57]. In many publications, surgical treatment of hypothalamic gliomas has been described together with the treatment of gliomas of the visual apparatus, and in many others, with treatment of lesions of the thalamus, craniopharyngiomas and other tumours. It cannot be stressed sufficiently how important it is to differentiate between the surgical approaches to the lesions within and around the hypothalamus, bearing in mind that in true hypothalamic gliomas the only appropriate approach is interhemispheric-transcallosal-transventricular on one or both sides; a combination with any other approach is an exception. The opposite holds for all extraaxial lesions, i.e. the optimum approach is in most cases pterional (Fig. 16) or in certain cases subfrontal; in none of these extraaxial lesions is the interhemispheric-transcallosal-transventricular approach sufficient, but it may be used as a complementary approach in some cases.

If one does not have enough experience in treating hypothalamic lesions, one risks forming a wrong opinion on the basis of the relevant literature where one learns that transcortical or transsphenoidal approaches can be used for certain lesions in the hypothalamic region. It is important to understand that the data on the results of surgical treatment of hypothalamic lesions were obtained before, or early on, in the era of microsurgery. One should also carefully evaluate the data on the treatment of giant hypothalamic gliomas, causing hydrocephalus, in which a shunting procedure was performed prior to the attempt at surgical resection of the lesion itself. It is equally important to evaluate data about patients with hypothalamic gliomas (most of them were benign tumours) who underwent a biopsy and irradiation. Such treatment in the past did not remove the underlying cause of neuro-endocrine disturbances, and also added another traumatizing factor (occlusion of small arterial perforators) within the first postoperative year, and it also had a negative rather than a curative effect [17].

Contemporary treatment of hypothalamic pilocytic astrocytomas is total or sub-total resection as the treatment of first choice. Only in cases where the histological examination reveals malignancy of the lesion, should complementary treatment (irradiation and chemotherapy) be added. On the other hand, patients with pilocytic astrocytomas, in whom even only subtotal resection was achieved, should not be irradiated, and surgical removal is again performed when the tumour has grown further, unless the histological picture has changed. In most cases of hypothalamic gliomas biopsy as such is not indicated; however, a frozen section is strongly advisable during open surgery, and the result of the examination dictates the degree of completeness of the excision of the tumour. In most cases, V-P or V-A shunts are not necessary if the tumour has been sub-totally or totally resected and the circulation of the CSF (re)-established. However, in cases

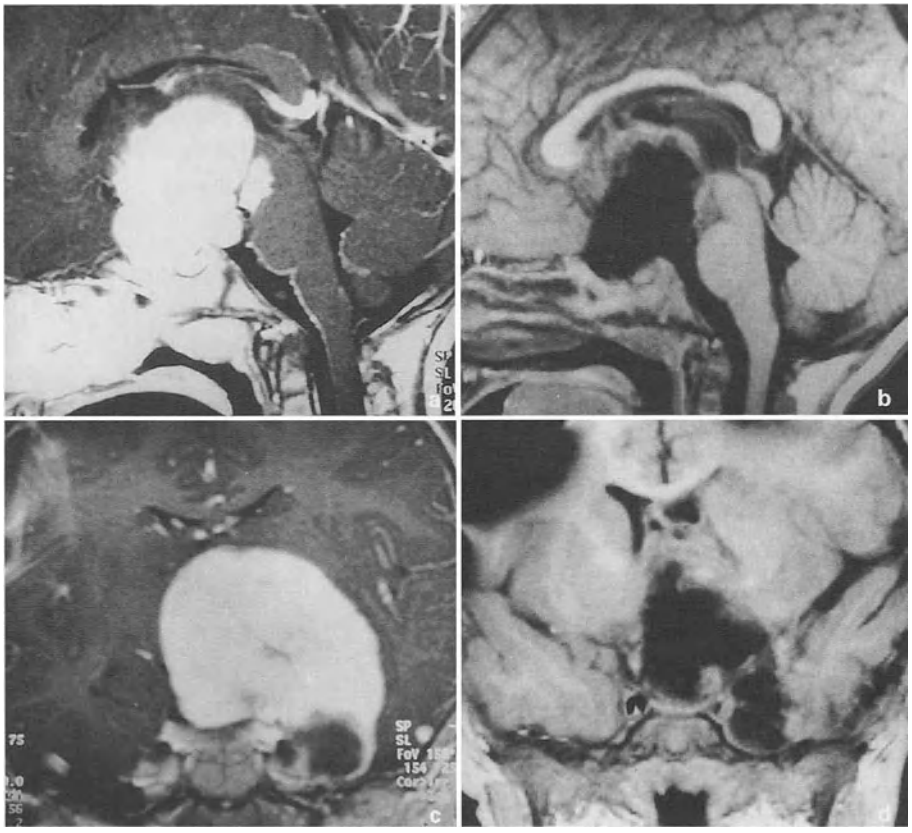


Fig. 16. A large optic glioma in a 3-year-old girl, causing serious visual deficit on the left side and hypothalamic disturbances. Biopsy and two open surgeries were performed, the tumour was declared inoperable and irradiation was planned. At the third surgery the tumour was completely resected and irradiation was not necessary. In the MRI views, sagittal (a) and coronal (c), a large tumour of an unusual shape is seen bulging into the hypothalamic region (a), mainly on the left side; a small defect following two previous operations is seen (c). The postoperative MRI views, sagittal (b) and coronal (d), show complete resection of the tumour and partial preservation of the hypothalamic tissue on either side. This tumour was resected exclusively through a left pterional approach

where V-P or V-A shunts were inserted prior to radical surgery, these shunts are left in place on the occasion of resection of the lesion, and are removed later when MRI has evidenced that the CSF circulation is normal and that both foramina of Monro and the IIIrd ventricle are open.

Since most patients with hypothalamic pilocytic astrocytomas are children under 10 years of age, and a significant number of them require substitutional treatment either at the time of their growth and development or

for the rest of their life, it is mandatory that they remain under supervision by the endocrinologist, pediatrician and neurologist after the acute phase following surgery is over.

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# Surgical Approaches to the Anterior Fossa, and Preservation of Olfaction

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With 18 Figures

## Contents

Access to the anterior cranial fossa is required in numerous neurosurgical pathologies such as traumatic or spontaneous CSF fistulae, as well as in vascular and neoplastic pathologies.

Surgical treatment by intra-cranial approach involving the two olfactory bulbs usually results in anosmia. This handicap, accepted until now by surgeons, appears as an inevitable feature of this surgery. Nevertheless, such a defect is always significant, and may become a true handicap in some fields of activity (perfume makers, cooks ... ) or when alerting smells are necessary (gaz, petrol).

Favorable anatomic conditions are required in order to preserve olfactory function in surgery of the anterior cerebral fossa. This idea led us to conduct a microanatomical study of the olfactory bulb and tracts, with morphological, topographic and vascular survey of these structures.

An original surgical technique for repair of fistulae of the anterior cranial fossa has thus been developed on this basis. This technique, illustrated with a few clinical cases, is applied whenever possible. This anatomic approach to preservation of olfaction in surgery of the anterior cranial fossa can be used for other pathologies, particularly neoplastic and vascular ones.

## Anatomical Study

### Material and Methods

We prepared 15 cadavers with formaldehyde tissu fixation and high pressure intracarotid injection of coloured latex. The olfactory nerve was studied by subarachnoid microdissection under a microscope, so as to leave the arachnoid and pia mater untouched, enabling us to study their architecture and preserving the vascular elements at the surface of the frontal lobe and in the cortical sulci. We analysed the brain, olfactory nerve and cranial base on isolated frozen heads previously injected intra-arterially with coloured latex in sections of the brain and cranium in the sagittal and coronal planes. The meningeal relationship of the olfactory nerve within the cribriform plate were studied histologically under optic microscopy. An ethmoidal block taken from formaldehyde fixated cadavers was dehydrated in graduated alcohols, then embedded in paraffin. 5 $\mu$m sections were stained in HES (hematoxylin-eosin-safran).

### Morphological Study

Situated at the anterior extremity of the tract, the olfactory bulb lies at the bottom of the olfactory groove. Its characteristic shape is usually described in anatomy treaties [64, 84, 98, 10] as:

- Cranially seen, (Fig. 4) the bulb distinguishes itself from the tract by a proximal and sharp widening clearly seen on its medial edge. This aspect appears in 61% of the dissections. The bulb is a progressive enlargement of the olfactory tract for the others.
- Seen from the side, the upper side is concave all the more so in the transversal way when the olfactory groove is deep. The inferior side is marked by the penetration of the olfactory fila. The average dimensions of the bulbs we measured are the same as Schmidt's [102], 8 mm in length, 4 mm in width, and 1.5 mm in height. The olfactory tract is in continuity with the bulb and it settles in the olfactory groove with an ever thinner edge in its proximal part. The average length and width measured are respectively 29 and 2.5 mm.

### Blood Supply

In higher mammals, the telencephalon develops enormously as the bulb and the olfactory tracts diminish in proportion. Vascularisation also undergoes changes.

The results of our dissections on 15 anatomical subjects enable us to

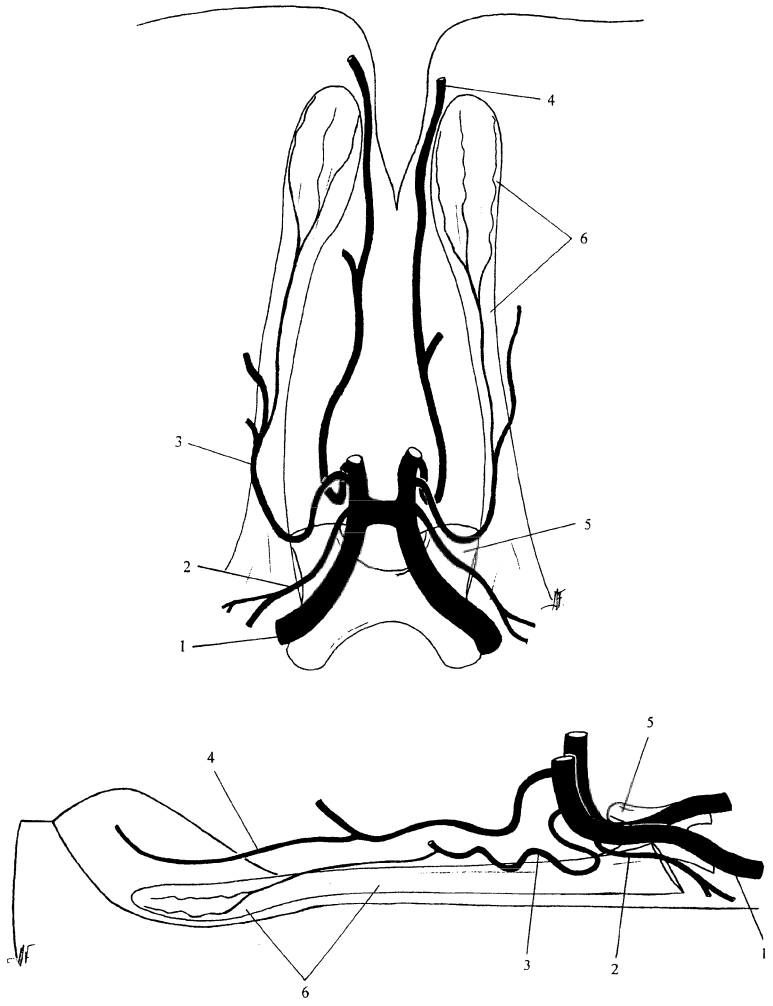


Fig. 1. Groupe I: the olfactory artery is a collateral branch of the anterior cerebral artery (53.3%). Vascularisation of the bulb and olfactory tract, top: upper view, bottom: lateral view

state a precise origin to the perfusion of the bulb and the olfactory tract and its variations. We observed a constant artery situated at the proximal part of the olfactory groove giving terminal branches to the tract and the olfactory bulb. This artery stems from the anterior cerebral artery in its A2 segment in two ways:

- In 16 cases out of 30 (53.3%) it arises from the lateral side of the anterior cerebral artery (Fig. 1), distal to the anterior communicating artery.

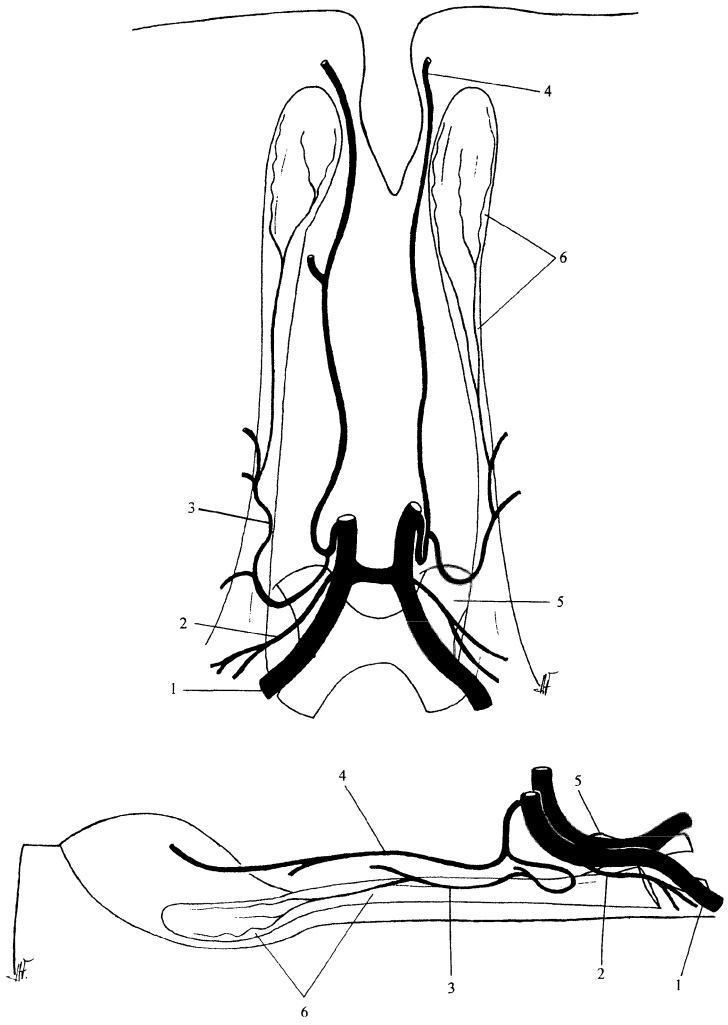


Fig. 2. Groupe II: the olfactory artery is a collateral branch of the medial fronto-basal or medial orbito-frontal artery (46.7%). *1* cerebral anterior artery; *2* long cerebral artery; *3* olfactory artery; *4* medial orbito-frontal artery; *5* optic nerve; *6* bulb and olfactory tract; top: upper view; bottom: lateral view

– In 14 cases out of 30 (46.7%) from a collateral branch of the medial fronto-basal or orbito-frontal artery (Fig. 2). Its initial path regarding the anterior cerebral artery crosses the superior side of the optic nerve and then goes on into the olfactory groove. It gives terminal branches in the direction of the olfactory tract in its first centimeter. A maximum of three terminal branches come in contact with the tract on its medial and lateral sides, and constantly on its superior edge. The other branches are

aimed at the adjacent gyri and in 10 cases out of 30 (33.3%) to the anterior perforated substance. These arteries divide themselves at the level of the bulb to give branches to the superior side, the medial and lateral edges of the bulb.

## Relationship with the Anterior Cranial Fossa

### *The Olfactory Bulb*

It lies on the olfactory grooves. The anterior cranial fossa presents on its medial part a depression limited on both sides by the slopes of the orbital roofs. This region is made of 2 parallel olfactory grooves, lying in sagittal planes and separated by the crista galli. These grooves are quite clear in their anterior part where the bottom of each one is represented by the cribriform plate. The depth and the narrowness of the olfactory grooves depend on the pneumatisation of the ethmoïdal cells and the crista galli (10% of the cases according to Lang). This region is fragile because its thickness is on average of 0.15 mm [1]. The depth of the grooves varies in the anteroposterior direction, it is maximal in its intermediate portion (5.03 mm). This morphology has been described precisely in German papers [57, 59, 60]. The olfactory bulb overlaps only on the posterior third of the cribriform plate. The anterior part is filled with the olfactory fila. This topography was also observed by Foster [30] and by Schmidt [102]. The olfactory bulb is some way off from the dura mater overlapping which makes the top of the anterior extremity of the olfactory grooves: Trolard's anterior olfactory tent. The olfactory fila enter the olfactory bulb after emerging from the holes of the cribriform plate and travelling under the arachnoïd. The results of our dissections enable us to propose a different concept, taking into account the posterior position of the bulb on the cribriform plate (Fig. 3):

- the olfactory fila emerging from the anterior holes have a subarachnoïdal path and end at the ventral extremity of the bulb; the olfactory fila follow a systematized pathway,
- the fila emerging from the foramina in front of the bulb have a shorter subarachnoïdal path. The olfactory fila are surrounded by arachnoïdal prolongations, clearly visible under microscope especially in the anterior part of the cribriform plate. These elements belong to the meningeal sheaths described by Key and Retzius [53] (Fig. 4).

The dura mater makes the peripheral envelope, seen on histological slides after staining. It adheres to the cribriform plate and is continuous with the basal membrane of the nasal cavity. The arachnoïdal diverticulum

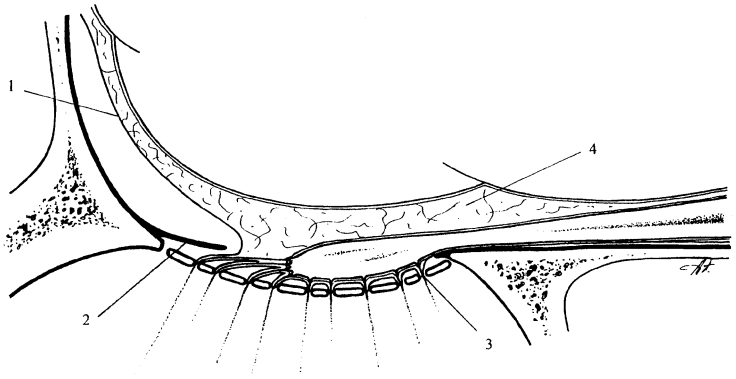


Fig. 3. Sagittal cut of the olfactory cistern. Relationship between the olfactory bulb and the cribriform plate. *1* arachnoïd; *2* anterior olfactory tent; *3* meningeal sheath and olfactory nerve; *4* olfactory cistern

surrounding each olfactory filum appears on histological sections as a perfect funnel. It is composed of a large superior hole communicating with the subarachnoïdal spaces and of an narrow inferior region following the corresponding olfactory filum through a foramen in the cribriform plate. The pia mater is followed by a neurilemma. This arachnoïdal funnel explains the occurrence of rhinorrhea without fracture of the cribriform plate after trauma, due to a shearing effect [87], and spontaneous rhinorrhoeas in case of chronic intracranial hypertension [37, 81].

### *The Olfactory Tract*

The olfactory tracts diverge in a dorsal direction at a 23° angle [102]. Its posterior segment lies on the planum sphenoïdale about 10 mm from the medial line. It crosses the superior side of the optic nerve at the level of its entry to the optic canal.

### *The Cerebral Relationships*

Knowledge of the relationships between the olfactory structures and the inferior side of the frontal lobe has direct relevance to the technique of preservation of olfactory function.

On the inferior side of the frontal lobes, the constant existence of an arachnoïdal cistern containing all the olfactory structures has been shown. Its limits can be clearly stated. When elevating the frontal pole, the anterior extremity of the cistern appears stretched between the inferior side of the frontal lobe and the cribriform plate. It passes under the anterior olfactory

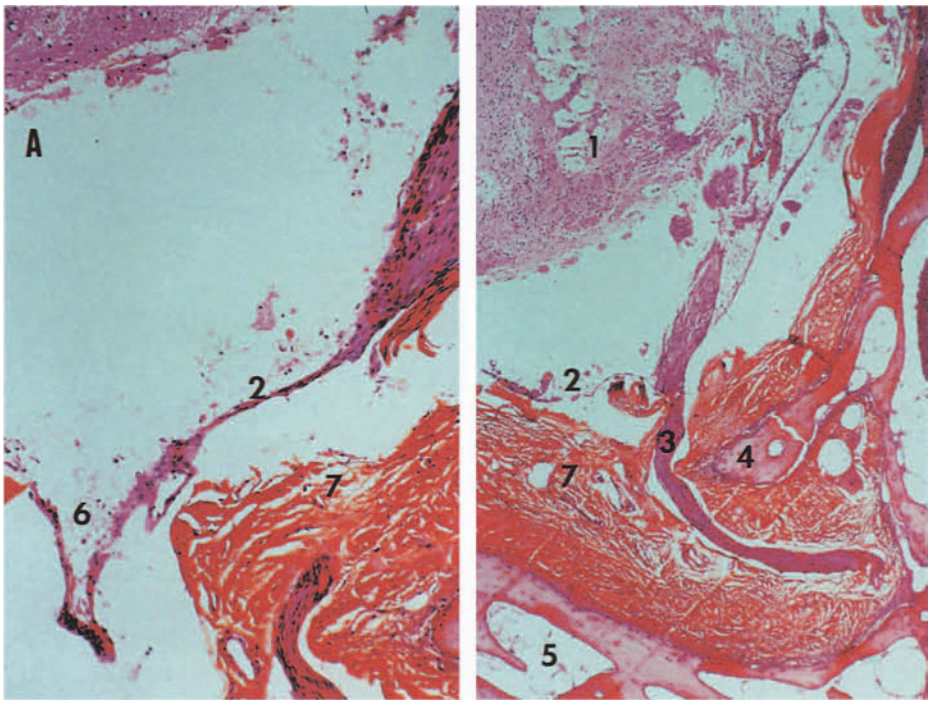


Fig. 4. Anatomical views. (A) Olfactive nerve and osteomenigeal relationships (5 micrometer thick cuts, stained by HES). *1* The olfactory bulb; *2* arachnoid; *3* olfactory fila; *4* cribriform plate; *5* nasal fossa; *6* arachnoidal sheath; *7* dura mater. (B) Relationship between the olfactory bulb and the anterior fossa. *1* Crista galli; *2* cribriform plate; *3* olfactory bulb; *4* olfactory tract. (C) Paramedial sagittal cut and dissection of the olfactory artery (injected with stained latex). *1* Anterior cerebral artery; *2* olfactory artery; *3* terminal branch of the olfactory artery; *4* gyrus rectus; *5* sphenoidal sinus. (D) Frontal cut of the arachnoidal olfactory cistern at the level of the bulb. *1* Olfactory cistern; *2* olfactory bulb; *3* crista galli; *4* gyrus rectus; *5* medial orbitary gyrus

tent and continues with the arachnoïdal prolongations around the olfactory fila (Fig. 4). The inferior wall of the olfactory cistern is made of the arachnoïd which forms a bridge above the ventral part of the bulb and the tract; from the lateral edge of the olfactory sulcus to the medial edge of the gyrus rectus, it adheres to the olfactory structures. On this level, there is in consequence no plane for dissection. On the superior wall of the cistern, the pia mater covers the gyrus rectus and reflects itself in the olfactory sulcus to go on laterally to the medial side of the medial orbital gyrus. On its posterior end, the cistern is open and communicates with the chiasmatic and pericallosal cisterns; there is no arachnoïdal wall between them. The olfactory cistern contains the bulb and the tract, the olfactory artery is located

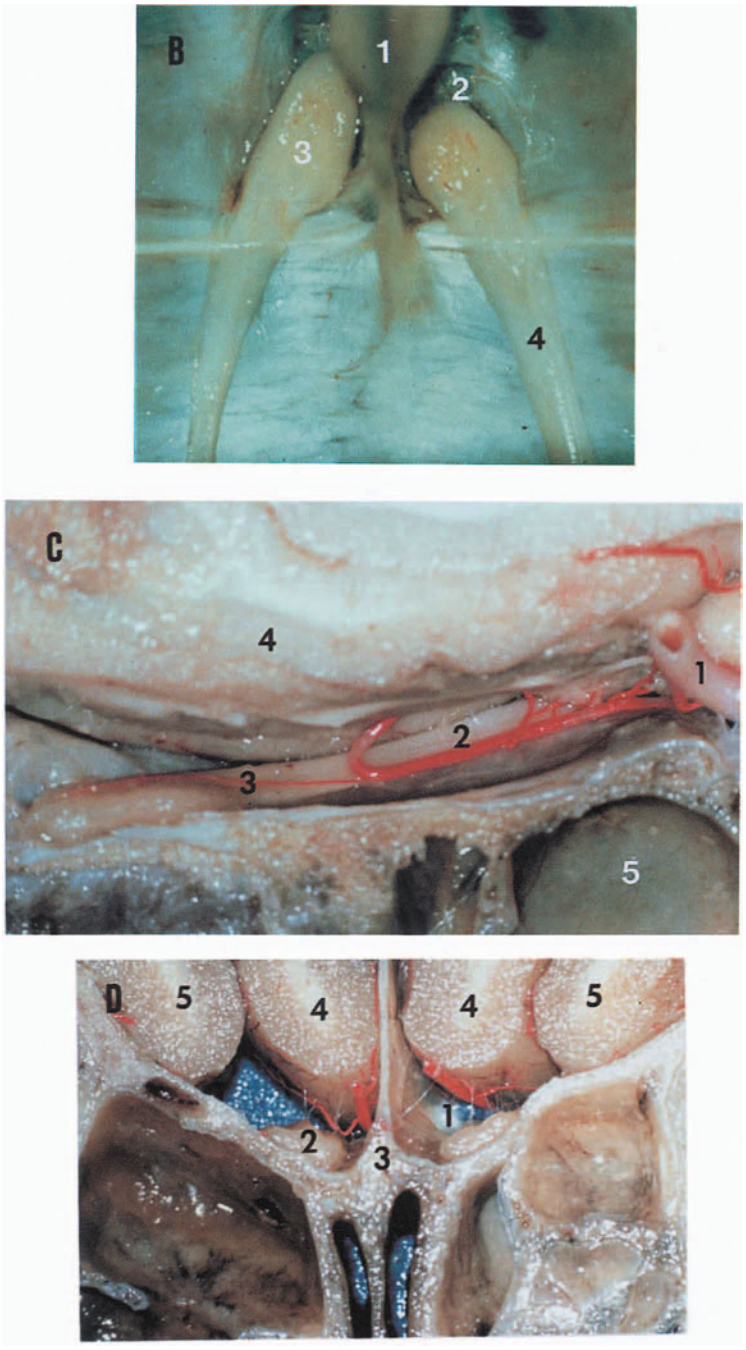


Fig. 4. (*Continued*)

during the first centimeter of the olfactory sulcus ahead of the trigonum olfactorium and gives it terminal branches. The medial frontobasal artery, occupies 14 times out of 30 the medial edge of the cistern and sometimes comes into contact with the medial edge of the bulb to reflect itself in the frontal pole but it doesn't give any collateral branch to the olfactory bulb on its distal path.

In the posterior part, the cistern is reduced to a virtual slit because the tract is located inside the olfactory sulcus. It adhers strongly to it through the arachnoïd. On the medial part of the cistern, the tract frees itself from the sulcus to come to the inferior side of the gyrus rectus. The cistern opens to reach its maximum volume on the superior part of the olfactory bulb. There are arachnoïdal tracts between the superior face of the bulb and the cerebral cortex.

### Conclusion

These results enable us to establish the anatomical basis of the preservation of olfaction during a transfrontal approach of the anterior fossa.

- The constant existence of an arachnoïdal cistern surrounding all the olfactory structures on the inferior face of the frontal lobes gives a microsurgical plane of cleavage.
- It is possible to free the bulb and tract from the inferior face of the frontal lobes when they have their own independant vascularisation. Respect for olfactory function means respect for the olfactory artery. The depth of dissection is measured on average at 45 mm back of the posterior face of the anterior wall of the frontal sinus.
- The olfactory structures are very vulnerable because of the strong attachment of the tract to the frontal lobe by the trigonum olfactorium, and the fragile attachment of the bulb to the cribriform plate by the olfactory nerves and their meningeal sheath. As a consequence, any ill-controlled frontal retraction will provoke avulsion of the olfactory bulb at the level of the cribriform plate.

## Surgical Techniques

We may differentiate the approaches used in pathologies of the anterior cranial fossa according to their direction of access. We make a distinction between:

- Anterior transcranial approaches which give an intracranial view of the fossa.
- Trans facial approaches which display the extracranial side of the anterior fossa through the paranasal sinuses and nasal cavities.

– Craniofacial approaches which perform a combined access through an original approach or by associating the preceding approaches.

Multi-disciplinary cooperation is required (neurosurgeons, maxillofacial surgeons, and head and neck surgeons) to perform these approaches, whether simple or combined.

## *Anterior Transcranial or Superior Approaches*

### The Fontal Transsinusal Approach

Our team use it daily and it is presented here as our basic technique for leak repair.

#### *History*

Frontal craniotomy, isolating an osseous flap only from the anterior wall of the frontal sinus was used initially only to approach the frontal sinus (Schoenbron and Brieger in 1894, cited by Hoffman [45]). It was used by Dandy [15] as a craniectomy, in order to expose and cure CSF fistulae through the posterior wall of the frontal sinus. The trans sinusal approach is presented by Malecki and Powiertowski in 1958 as an approach of the anterior cranial fossa termed "rhino-neurosurgical". It associates a peripheral cutting of the anterior wall of the frontal sinus with the resection of the posterior wall. It is then developed and adapted to the different pathologies of the base, in particular for treatment of the cerebrospinal fluid fistulas. We have used this approach since 1984 according to De Rougemont's method [24]. The microsurgical technique aimed at preserving olfaction during a subfrontal approach of the anterior cranial fossa was described for the first time by Suzuki [118] in the treatment of aneurysms of the anterior communicating artery.

#### *The Approach*

The patient is in the supine position, with external lumbar drainage for the duration of the procedure. It contributes to the relaxation of the brain and avoids traumatic cerebral retraction.

Cutaneous incision following a coronal path is made behind the hairline. The distance between the incision and the hairline must be adapted according to the patient's age, as the hairline recedes of about one centimeter each decade. The depth of the incision must not go beyond the plane of the galea, so as to leave the pericranium intact.

Detachment of the scalp is performed in Merckel's plane, between the galea and the pericranium, thus preserving vascularisation of each of these planes and the innervation of the frontal region. Supraorbital and

supratrochlear branches of the ophthalmic nerve maintain the frontal cutaneous sensitivity. They emerge from the supra-orbital edges, respectively on the level of the frontal and supra-orbital notches, along with supra-orbital and supra-trochlear vessels. They are directed vertically between the subcutaneous cellular tissue and the galea. Laterally, close to the zygomatic processes of the frontal bone, the path of the fronto-temporal branch of the facial nerve is located between the galea and the pericranium and must be scrupulously preserved. Two cm above the supra-orbital edges, the pericranium is incised. Scalp dissection continues under a sub periosteal plane in contact with the frontal bone, so as not to hurt the structures we have already mentioned. It enables us to identify the supra-orbital edges, the naso-maxillo frontal suture, and the origin of the nasal bones. The supra-trochlear and supra-orbital vasculo-nervous pedicles are freed from their grooves or from their foramiena with an osteotome. A graft of pericranium is prepared. This graft can be enlarged towards the parietal region, behind the cutaneous incision if necessary. It may be free or pedicled.

The dimensions of the osseous flap through the frontal sinus depends directly on their volume. During our dissections, the average figures are respectively of 36.8 mm in height (from 34 to 40) and 67 mm in width (from 56 to 78). The inferior landmark of the flap is the nasion, situated usually 3.1 mm above the floor of the frontal sinus [57]. The craniotomy done with an oscillating saw follows the inferior face of the supra-orbital edge up to the lateral limit of the sinus. This limit can be felt with a thin instrument through the osseous incision. The inferior osteotomy is located at the level of the floor of the orbital extension of the frontal sinus (Fig. 5). The superior part of the craniotomy going past the top of the sinus is cut sideways tangentially to the posterior wall, so as to obtain a stability of the flap during reconstruction. This superior osteotomy is arciform, concave towards the bottom, joining the lateral extremities of the inferior osteotomy. The anterior wall of the sinus is freed before by caving in the inter-sinusal and accessory septa.

The sinusal mucosa is very carefully totally removed up to the orifice of the frontonasal canals where it is coagulated. At first, the orifice of the nasofrontal canal is closed by hemostatic sponge. The drilling and coagulation of the totality of the surface of the sinusal cavity is performed, to eliminate microfragments of membrane which could remain and cause local post operative infections, even mucocoeles. Cranialisation of the frontal sinus [67] corresponds to the resection of the posterior wall of the frontal sinus cut peripherally with a drill. This ends the frontal medial trans-sinusal craniotomy. This craniotomy, concerning the anterior and posterior walls of the frontal sinus can be limited to only one side depending on the location of the pathology.

The existence of a small frontal sinus can prevent the realisation of

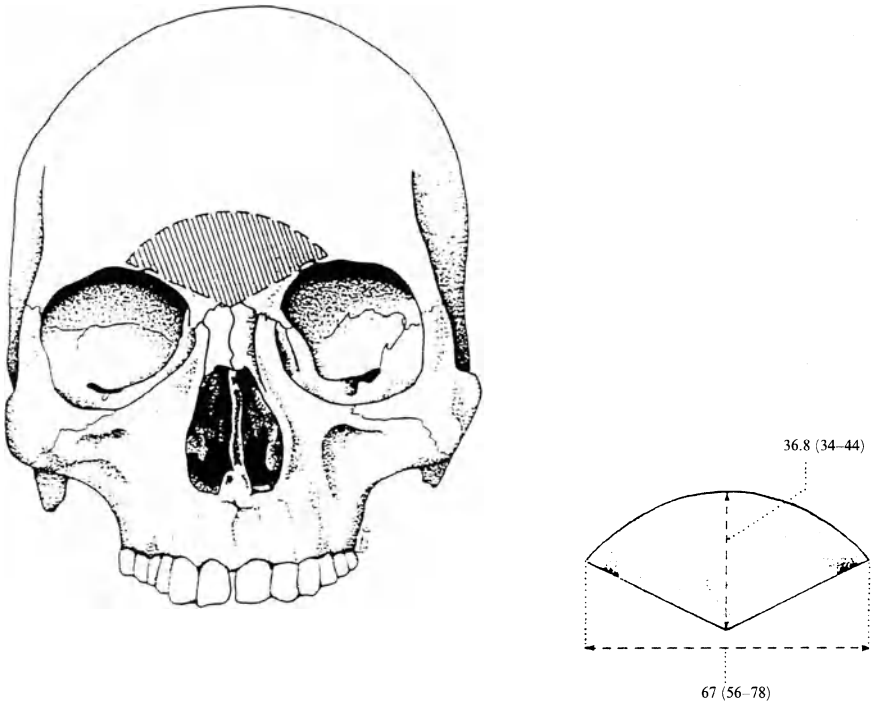


Fig. 5. Trans sinusal craniotomy (average measures in mm)

this craniotomy. Their frequency varies a lot depending on the authors, between 17 and 49.4% [3, 39, 57, 120, 122]. In this case, pneumatisation is limited to the medial orbital process of the frontal bone. The craniotomy is performed so as to obtain a pseudo anterior wall of the frontal sinus, at the expense of the external table and a part of the diploe of the frontal bone. This requires a splitting of the frontoglabellar region with an oscillating saw following the same path as the technique already described. The internal table of the frontal bone is then cut peripherally with a drill, the same way as the posterior wall of the frontal sinus. In case of unilateral hypo-or aplasia, the craniotomy is performed as on a normally developed sinus and enlarged on the hypoplastic side with a craniotome after having detached the dura mater, starting from the controlateral craniotomy.

After opening of the lumbar drainage and under the operating microscope, the dura mater is freed from its medial and anterior insertion by detachment, coagulation, and division of its extension in the foramen caecum. The dural incision is performed transversely as low as possible, at the junction of the frontal and basal part of the dura mater, just above the foramen caecum. The initial part of the superior sagittal sinus is coagulated, sometimes ligatured with unresorbable suture. At this level, the

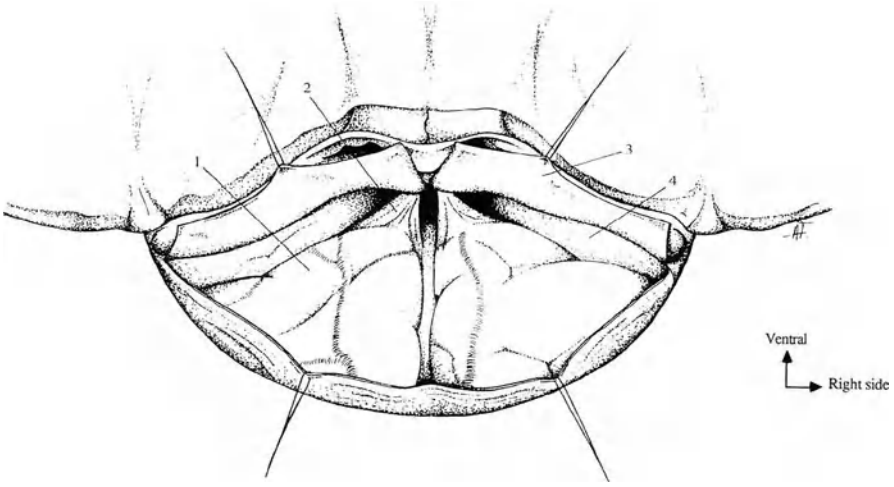


Fig. 6. Intra dural exploration and exposure of the olfactory cisterns. *1* Frontal pole; *2* olfactory cistern; *3* laid back dura mater; *4* orbitary roof

superior sagittal sinus possesses a lumen in only 10% of the cases. In 5 to 6%, there exists an atresia of the anterior part of the sinus, with a proximal end located between 4.5 and 5 cm from the foramen caecum. It is then that appear lateral dural veins, collecting the superficial frontal veins and coming together towards the beginning of the sinus [51]. They are rarely affected by the dural incision. The dural detachment goes on to the lateral aspects and the top of the crista galli, controlling this manœuvre from an intradural view to respect the olfactory grooves. The resection of the crista galli is then possible without danger. The basal insertion of the falx cerebri is cut from the front backwards.

### *The Intradural Exploration*

Respect for the anatomical integrity of the olfactory structures, particularly of the olfactory fila, demands exposure of the anterior skull base through an intradural approach, not through an epidural one. We think this approach is also better suited to the exploration of the base to expose osteodural leaks.

The operative position, the external lumbar drainage of cerebrospinal fluid and the liberation of the anterior dural attachments enable a spontaneous collapse of the frontal lobes backwards and downwards. The use of a retractor is not necessary. The anterior extremity of the olfactory cistern is stretched between the inferior face of the frontal lobes and the cribriform plate (Fig. 6). The opening of the arachnoïdal cistern opens a surgical

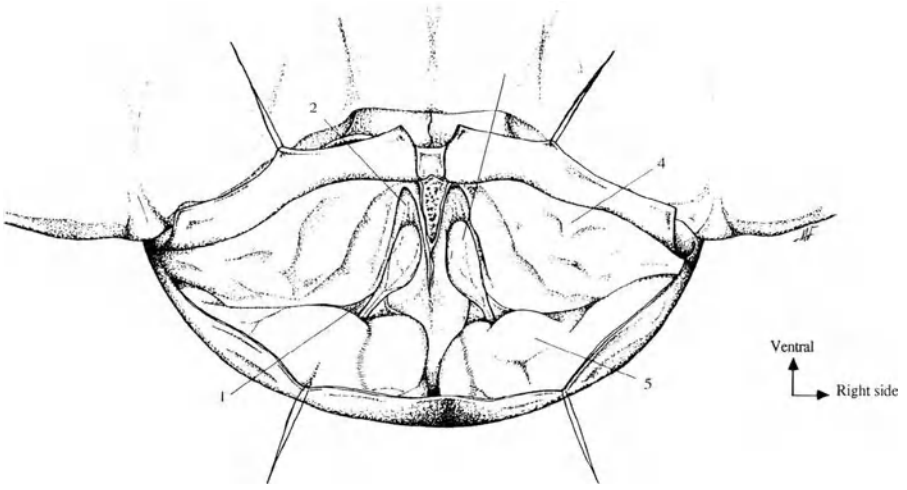


Fig. 7. Opening of the olfactory cisterns and liberation of the bulb and tract of the inferior face of the frontal lobe. *1* Olfactory cistern; *2* cribriform plate; *3* olfactory bulb; *4* orbitary roof; *5* frontal pole

plane of cleavage between the olfactory bulb and the inferior face of the gyrus rectus. The progressive liberation of the bulb and tract is done from front to back, by collapsing the arachnoidal tracts and incising the walls of the cistern on both sides of the olfactory structures. On its posterior part, the plane of cleavage extends between the tract and the medial orbital sulcus (Fig. 7). The depth of the dissection is determined by the presence of the olfactory artery and its terminal branches. At this level, the tract adhers strongly to the sulcus. A posterior extension of the dissection represents a major risk of direct damage to the tract and its vascularisation. The tangential approach at the base and minimal frontal retraction (facilitated by external lumbar drainage) are indispensable for an ad integrum preservation of the olfactory structures. The angle of surgical vision between the olfactory structures and the inferior face of the frontal lobes opens spontaneously, the bulb and the tract remain in contact with the base and the frontal lobes collapse. It establishes a subfrontal working space sufficient to see the leak and repair it. The trans sinusal approach thus gives access to the whole intracranial surface of the anterior skull base, except the postero lateral part, hidden by the relief of the endofrontal eminence. The posterior limit of liberation of the olfactory tract determined by the presence of the olfactory artery projects itself on the base in front of the anterior third of the planum sphenoïdale. Dorsally, the exposure is limited by the olfactory tracts themselves. The frontoethmoidal region is thus totally visible to the

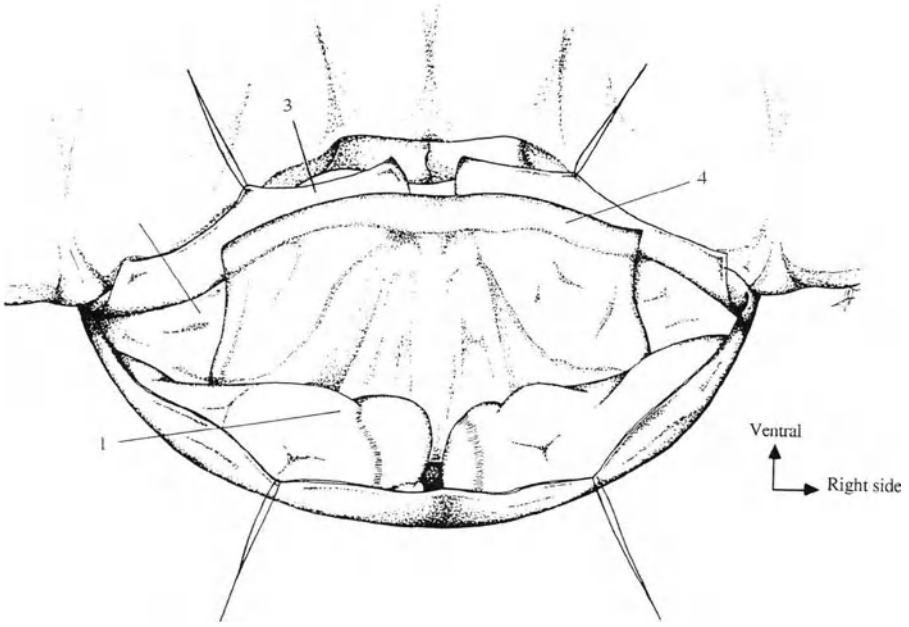


Fig. 8. Transsinusal approach. operative view: *1* Frontal pole; *2* orbitary roof; *3* reclined dura mater; *4* free patch of pericranium

surgeon. The exposure is widened laterally to the medial part of the orbital roofs.

*Reconstruction (Figs. 8 and 9)*

The free patch of pericranium, taken from the frontal region at the beginning of the operation, is slipped in the sub frontal intradural space between the olfactory structures remaining in contact with the dura mater and the base of the frontal lobe. This patch of pericranium is stuck with fibrin sealant. It is largely applied in the space between the patch of pericranium and the dura mater and sheathes the olfactory structures. In the same way, the dura mater is closed by fibrin sealant. The nasofrontal ducts closed by bone grafts taken from the posterior part of the frontal sinus and also by glue. A total quantity of 5 ml is enough. The osseous flap is fixed in its initial position, on the frontal bone by one unabsorbable suture. The scalp is sutured in two planes over a drain. The external lumbar drain is removed at the end of the procedure.

The other anterior frontal approaches are described so that we can study the technical details of exposure, and the pros and cons of each one compared with the transsinus approach already described.

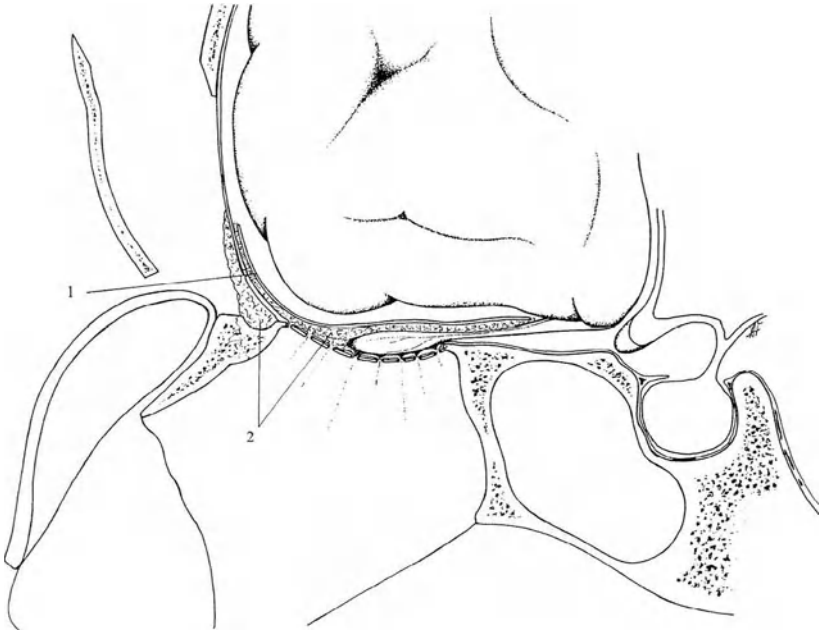


Fig. 9. Technique of base reconstruction: intradural and interolfacto-frontal clogging. *1* Free patch of pericranium; *2* biological glue

## The Suprasinus Transfrontal Approach (Fig. 10)

Uni- or bilateral, it is frequently used as an approach to the anterior cranial fossa. The unilateral flap is usually rectangular, its inferior limit being above the frontal sinus, the volume of which has been checked on radiography. The medial osteotomy gives a safety margin of about 1 to 2 cm from the medial line [8, 119]. Concerning the bilateral flap, special attention is given to the loosening of the sagittal sinus from the internal side of the frontal bone. This is why some perform 2 paramedian burr holes for safe control of the superior sagittal venous sinus. Other authors [90, 107] perform first a unilateral frontal flap, loosen the superior sagittal venous sinus under visual control through a craniotomy, and complete this one by a second controlateral frontal flap. This flap can be pedicled on the temporalis muscle.

The opening of the dura mater transversally to the suprasinusal level is always accompanied by an occlusion of the superior sagittal sinus, the falx cerebri is cut to mobilise the frontal lobes.

Whatever the flap, uni- or bilateral, the approach to the cranial fossa can then be either intra or epidural, with a dissection first between the frontal lobe and the posterior side of the frontal sinus, then truly in contact

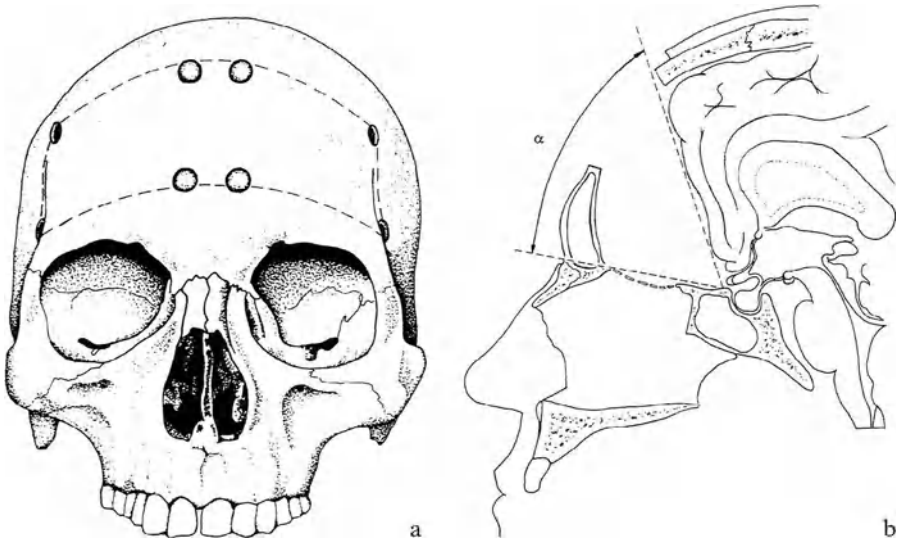


Fig. 10. Suprasinusal transfrontal approach and fronto-basale angle (2)

with the anterior cranial fossa of the skull. The frontobasal angle necessary to reach the fossa requires the retraction of the brain, this angle is on average superior to 30°. Many authors [8, 14, 89, 113, 119] favour immediate polar and basal removal of the frontal lobes, to avoid their contusion and make access to the anterior cranial fossa easier.

## The Frontobasal Approach (Fig. 11)

In 1938, Törmis propsed this approach as an alternative to the preceding one for the treatment of meningiomas of the olfactory grooves. In 1972, Derome [22] described the transbasal extension for this type of craniotomy. The bifrontal craniotomy flap differs from the former one by an anterior osteotomy as low as possible on the level of the orbital edge [22]. Two paramedian holes are drilled on the level of the glabella or by raising the anterior and posterior walls of the frontal sinus [106]. The opening of the frontal sinus is extremely careful, with the removal of the mucosa, the exclusion of the sinusal cavities, and the shutting of the naso-frontal ducts. The operating strategy may then vary:

- Most of the time, priority is given to the intradural dissection [2, 5, 22]; the opening of the nasal sinus cavities and the transbasal extension are performed secondarily.

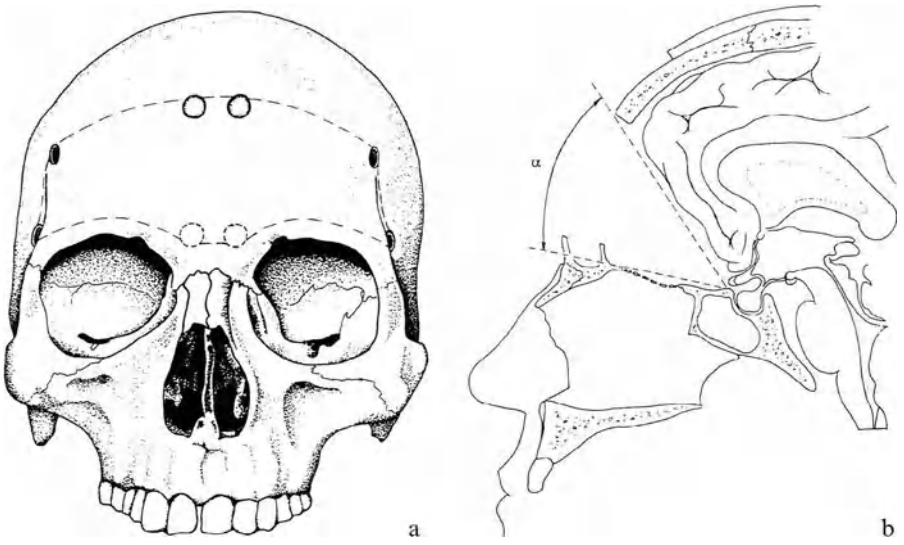


Fig. 11. The fronto-basal approach (a, b)

– Others [106] begin with the transbasal and subfrontal epidural exposure. This approach is used mainly for resections of the cranial fossa enlarged bilaterally to involve the paranasal sinuses, the medial wall of the orbits and the sphenobasilar region, but the shape of the flap gives good control of the olfactory structures if the extension towards a transbasal resection is unnecessary.

## Anterolateral Transcranial Approaches

They must also be mentioned as a complement to the anterior approaches. The pterional and frontopterional approaches give an access which is oblique and tangential to the sphenoidal wing. It is a choice approach for the exposure of the ipsilateral orbital roof and the posterior edge of the anterior cranial fossa (sphenoidal wing, anterior clinoid process, chiasmatic region, which do not have enough control by a strictly anterior approach). The reference is the pterional approach described by Dandy in 1942 [16]; its frontal extension enlarges the subfrontal angle of vision. They may be followed by the resection of a fronto orbital unit. These approaches do not disturb the venous drainage towards the superior sagittal sinus, but the exposure of the olfactory grooves is not sufficient for pathologies concerning them strictly. These approaches are interesting when one wants to reach a strictly unilateral lesion outside and/or behind the olfactory grooves.

The frontal transsinus approach certainly has advantages. It gives access to the median axis of the anterior cranial fossa, minimises the retraction and sacrifice of the frontopolar bridging veins through its tangential approach to the anterior cranial fossa, allows the eventual preservation of olfaction, and the direct access to the anterior cranial fossa gives early control of the vascular pedicles for resection of tumors. Last, it also allows control of the optic nerves and the chiasm as well as of the arterial anterior complex in the midline and beyond the anterior cranial fossa.

### *Transfacial or Inferior Approaches*

There allow a wide access through the paranasal sinuses. The paralateronasal approach described by Moure in 1902 is the technique of reference. These inferior approaches, also called "head and neck surgical" approaches, may be used either single or combined with an upper procedure for pathologies of the anterior cranial fossa. They reach the anterior fossa through its exocranial side, and are very useful for preservation of the olfaction.

### The Paralateronasal Approach (Fig. 12)

The cutaneous incision described by Labayle [55] follows an S shaped path on the nasal pyramid. The subperiosteal exposure is enlarged to the nasal process of the frontal bone, the orbital floor is freed on its anterior part before the infraorbital nerve, and by separating the naso lacrymal duct from its groove. The palpebral ligament is cut and is replaced during reconstruction. The internal wall of the orbit is dissected up to the anterior ethmoidal artery which is clipped and cut. A nasomaxillary osseous flap is cut separating the 2 nasal bones, then transversally following the frontonasal junction and at last loosening the anterior part of the rising branch of the maxilla.

The ethmoidectomy is uni or bilateral, performed using the surgical microscope, and characterised by the fixed resection:

- Of the internal wall of the orbit, while remaining forward of the opening of the posterior ethmoidal duct.
- Of the inter sinus-nasal wall close to the floor of the nasal fossae. The sphenopalatine artery is clipped and severed where it emerges from the sphenopalatine forame. The lacrymonasal duct is cut as low as possible to preserve its ulterior drainage in the nasal fossas.
- Of the whole of the nasal septum in its osseous part.
- Of the plate of the median and superior nasal conchae and the inferior nasal concha.

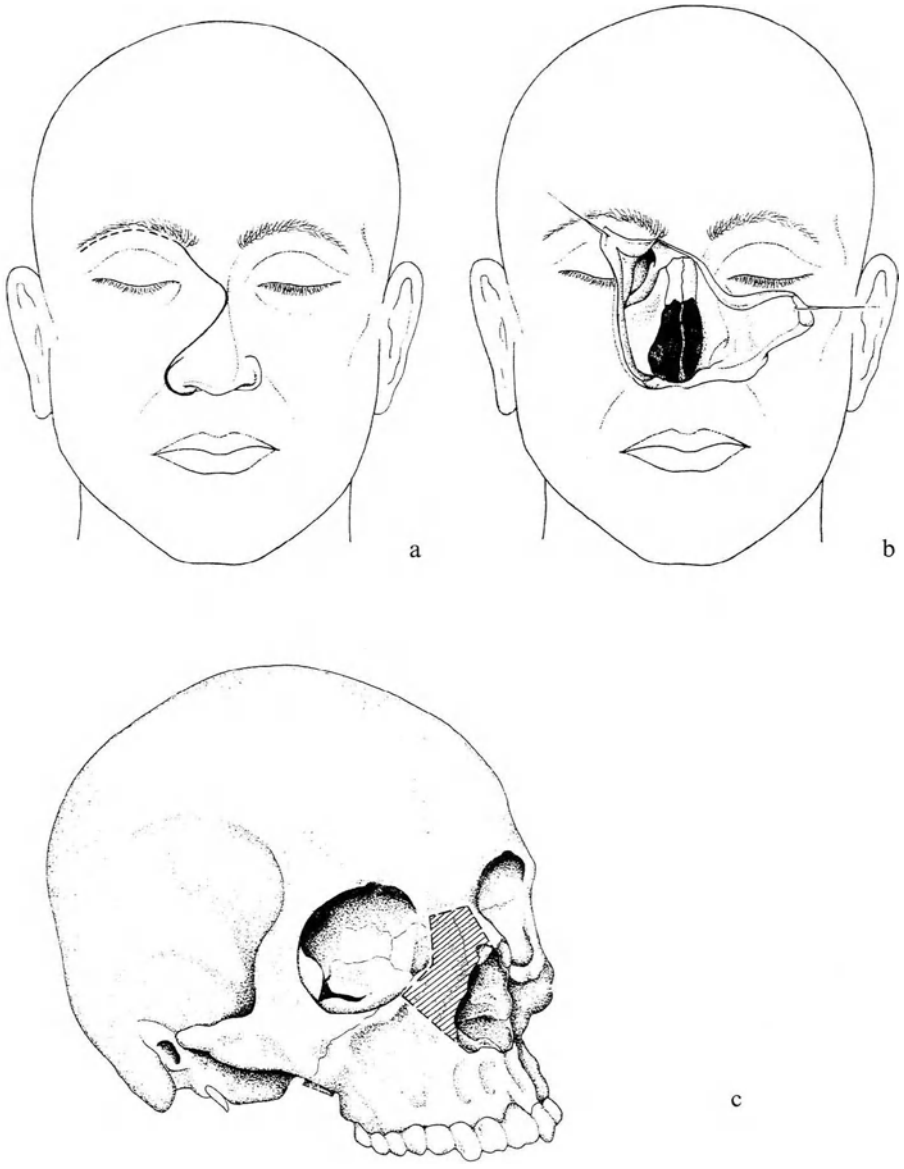


Fig. 12. The paralateronasal approach. (a) Cutaneous incision from Labayle; (b) subcutaneous dissection; (c) the bone flap

– Of the ethmoidal sinuses, always performed from front to back in pieces. On top, we reach the roof of the ethmoidal apparatus and the anterior wall of the sphenoid sinus. The limits are created laterally by the medial side of the orbit, on the back by the anterior wall of the sphenoid sinus, on top the roof of the nasal fossae are exposed on both sides of the septum of the ethmoid, represented by the cribriform plate and the roof of the sphenoethmoidal recess. This allows a careful examination of the exocranial side of the anterior cranial fossa and the treatment of possible fistulaes. Extensions can be performed in any direction, but it is more useful to direct it towards the cavity of the sphenoid sinus. The anterior wall of the sphenoid sinus may then be opened starting from the middle landmark which is the sphenoid rostrum. The opening of the sinus implies the complete removal of the mucosa so as to avoid infection or mucocele. The extension of dissection may reach the pituitary fossa and its content and the middle third of the sphenobasilar area. In fact, some traumatic or tumoral lesions with a more anterior origin may prolong themselves to this more posterior area. But mainly the naso-antro-ethmoidectomy and the opening of the sphenoid sinus unveil the exocranial side of the "nasal" part of the anterior fossa. It extends from the nasofrontal duct to the floor of the pituitary fossa. One must be aware that visual control of the most anterior part of the fossa is more difficult through this approach than for the posterior part. The bone removal allows to reach the dura mater. Samii and Draf [100] enlarge this approach by removal of the floor and of part of the vertical wall of the frontal sinus. But the absence of control on the intradural structures make the removal of lesions with intradural extension more difficult and dangerous.

## The Transethmoidal Approach

Described by Dohlman in 1948 [29], it is proposed for treatment of fistulae of cerebrospinal fluid. The arch shaped cut is made between the eyebrow and the internal canthus of the eye, then one proceeds to an ethmoidectomy and the removal of the middle nasal concha, and the opening of the sphenoid sinus if need be. We then have a unilateral exposure of the fossa on the inferior side of the cribriform plate and the ethmoidal roof. It reveals the osteo-meningeal leaks out with limited exposure [29, 75, 76, 100]. As it is unilateral it respects olfactory function but the area analysed is restricted.

## The Midfacial Degloving Procedure

The transfacial approach called "degloving" and codified by Casson in 1974 [9] is used mainly for treatment of naso-sinus tumors. The incision

is located in the gingivolabial fold according to the Caldwell-Luc approach modified by Denker, which exposes the nasal fossas and the maxillary sinus. The dissection of the soft tissues and particularly the nasal cartilage up to the frontonasal suture. The infra-orbital nerves represent the upper limit of dissection.

The osseous flap corresponds most of the time to that described for the paralateronasal approach. The volume exposed makes access to the antero-superior part of the nasal fossas and the ethmoid more difficult.

## The Transrhinoseptal Approach

This approach was first used for pathology of the pituitary gland. It was introduced by Schoffler in 1907 [104]. It was progressively adopted by most neurosurgeons thanks to the improvements introduced by Hirsch [44], Cushing [13], Guiot [40] and Hardy [42]. It is also of interest for medial and sagittal approaches to the sphenoid including the sphenoid sinus, the pituitary fossa and the superior third of the sphenobasilar area [22].

The approach remains transseptal with subperichondral and subperiosteal dissection through a superior gingivolabial cut. The removal of the osseous wall is performed up to the level of the rostrum sphenoidae; it includes the vomer in its inferior and posterior part. The septal cartilage is dislocated to one side and retracted by one of the valves of Hardy's retractor. The access to the sphenoid sinus is performed under the surgical microscope by the removal of its anterior wall centered on the rostrum and enlarged to use the whole exposure afforded by the retractor.

This narrow approach gives little lateral vision of the moulded structures of the lateral wall of the sphenoid sinus (optic canal, internal carotid artery). As far as pathologies of the anterior cranial fossa are concerned, it is used either alone for procedure centered on the sphenoid sinus (clogging of an osteodural leak) or combined with an anterior trans cranial approach for lesions spreading to the pituitary fossa and the superior part of the sphenobasilar area [22].

## Endoscopic Surgery by the Endonasal Approach

This is not a true transfacial approach but nevertheless is a means of access to the exocranial side of the anterior fossa. Going through the nostril openings, exclusively under endoscopic control, the roof of the nasal fossaes are exposed up to the sphenoethmoidal recess. The ethmoidal roof may be exposed totally through a total ethmoidectomy, or partially through removal limited to the anterior or posterior ethmoid. Examination of the sphenoid sinus may be performed completely through a direct endonasal

approach by enlarging the ostia of the sphenoid sinus or by a transethmoidal approach [91]. Respect for these reliable anatomical landmarks and the use of this technique by a seasonned surgeon allow us to prevent most of the pitfalls (hemorrage, bursting of the orbital wall, direct trauma of the optic nerve or the internal carotid, fistula of cerebrospinal fluid, endonasal synechia) [116]. Rhinosinusal endoscopy under these conditions is a reliable technique. The limited exposure of the anterior cranial fossa through this technique confines its use to very specific indications, specifically CSF fistulaes [79–83]. In these cases it is an interesting alternative to the anterior transcranial or transfacial approaches.

Whatever the chosen approach to the anterior fossa, they all require reconstruction, especially when the dural plane has been opened, which is a problem specific to the treatment of leaks.

Several materials may be used, usually of autologous origin (the fascia lata, muscular tissue, end of the middle nasal concha). None of these elements are vascularised. In our experience, a free subcutaneous fat flap from the abdomen is an excellent tissue for healing. The foremost problem is to maintain this graft, whatever it is, in contact with the roof of the nasal fossaes. We use a Silastic arch, resting on the floor of the nasal fossae. It remains there for 5 to 6 weeks to allow good adherence of the graft which will eventually be covered with epithelium by sprouting of the mucosa of the nasal fossae.

## Advantages and Inconvenients

The inferior approaches, paralateronsal or transfacial, are at risk of specific morbidity. The scabby rhinitis is almost always seen after intervention, and is the consequence of removal of the mucosa. It requires careful and regular cleaning of the operative cavity under endoscopic control if one is to avoid infection and not to hinder reepithelisation. Ephiphora is often for life when it happens post operatively [88] as the consequence of a defect in the reinstallment of the lacrymonasal duct. The osteonecrosis of the naso maxillary flap is seen mainly when the operation is followed by post operative radiotherapy, or when a second surgical procedure is performed after radiotherapy [4]. The unsightly result is a major problem. Fistulae of cerebrospinal fluid occur in some 2% of the cases [31] when tumor removal is performed exclusively through a paralateronasal approach. But this approach is particularly well adapted to lesions of the mid face, and allows among other things the control of endonasal vascular pedicles (anterior ethmoidal arteries and sphenopalatin arteries).

Its complications include anosmia where the olfactory mucosa is removed bilaterally. The exposure of the anterior cranial fossa remains

limited when this approach is need alone, and the risk of a leak may be overlooked during the intervention. There will be visible scar anyway on the nasal pyramid.

### *The Transbasal or Combined Approaches*

These approaches perform a combined approach to the endo and exocranial sides of the anterior cranial fossa. The first craniofacial approach was devised by Dandy [17] in 1941, then Smith in 1954 [112] and Ketcham in 1963 used this approach for tumoral pathology. This surgery never stopped developing with progress of anesthesiology and intensive care and multidisciplinary collaboration between: head and neck surgeons, cranio-facial surgeons, and neurosurgeons. The craniofacial approaches described correspond either to a combined anterior transcranial or transfacial approach, or to a single craniofacial approach.

#### Craniofacial Exposure by the Combined Approach

This combines a paralateronasal approach and an anterior transcranial approach (frontal transsinusal or suprasinusal). It is useful mainly for tumoral surgery, by facilitating removal of the anterior cranial fossa, especially for ethmoidal carcinomas. This concept, developed mainly for tumoral surgery, holds less interest for the technique of preservation of the olfaction, where functional becomes accessory given the prognostic fate of these malignant tumors.

#### Craniofacial Exposure by a Unique Approach

This consists of enlarging a transcranial approach to the superior facial bone with a novel skin incision or a transfrontofacial flap.

#### *The Fronto-Orbital Extension (Fig. 13)*

Cophignon in 1983 enlarged the frontobasal craniotomy by adding osteotomy of a complementary median fronto-orbital unit. Other authors have followed this principle [52, 68, 107], for example, by performs a bifrontal craniotomy followed by a subperiosted stripping up to the frontonasal junction, and intracranially, an epidural loosening [12, 34]. The osteotomy goes on with the cutting of a flap acknowledging the fronto-orbital unit inwards of the supra-orbital nerves, at the frontonasal junction and on the

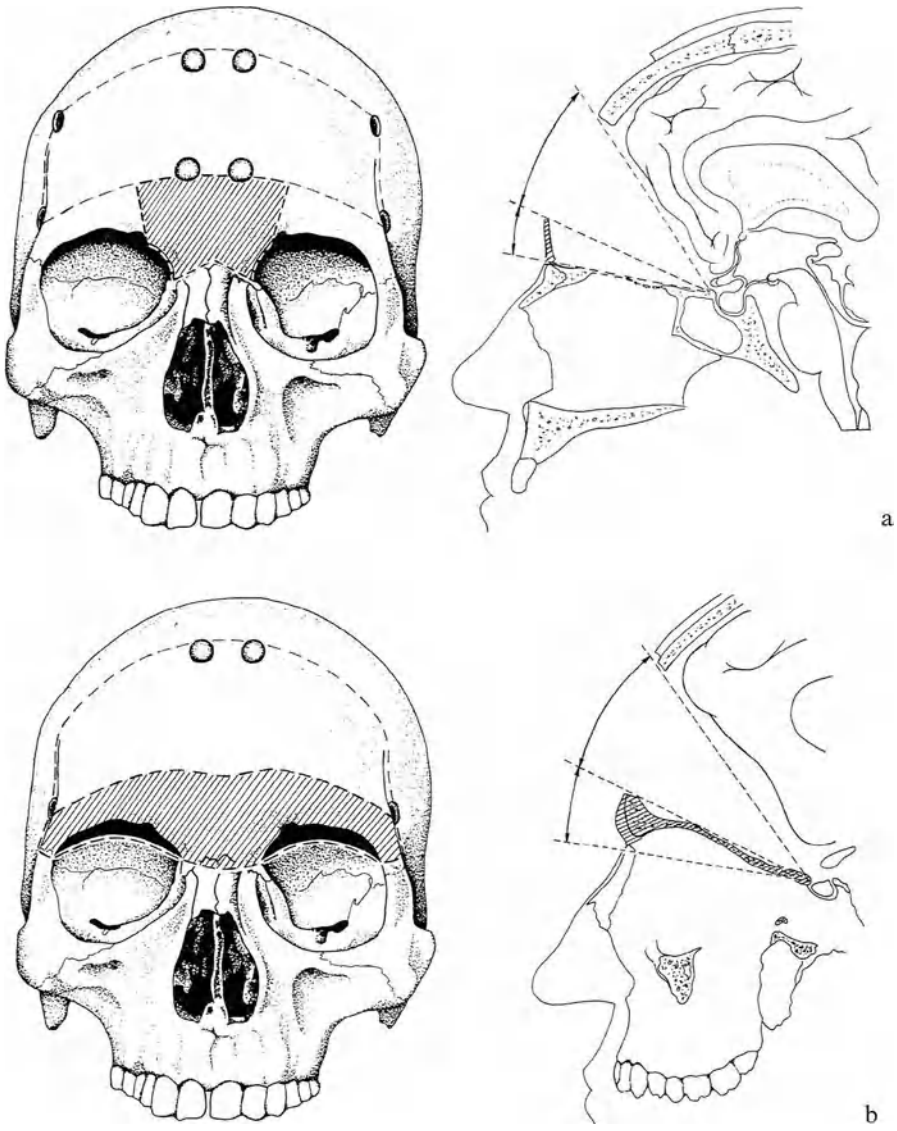


Fig. 13. Frontobasal approach with fronto-orbital unit. (a) From Cophignon; (b) from Sekhar

medial side of the orbits. Initially, the technique is described as taking off the crista galli and the posterior wall of the frontal sinuses. Only the anterior wall of the frontal sinuses will be involved if the olfaction is to be preserved. According to the authors, the width of the osseous unit is adapted to the extent of the lesions. It may reach the zygomatic process of

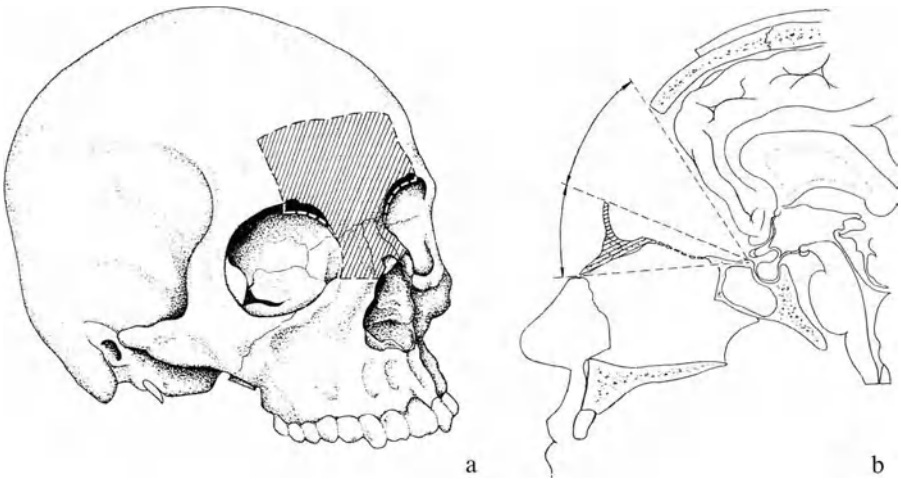


Fig. 14. Fronto-orbitonasal craniotomy from Pinsolle: (a) bone flap; (b) increase of the working angle

the frontal bone on both sides [34, 52, 107]. In most of the descriptions, the posterior osteotomy of the fronto-orbital unit is performed before the crista galli.

This approach allows us to get rid of any anatomical obstacle at the level of the anterior edge of the anterior fossa, which gives a perfectly tangential approach, in the axis of the fossa, thereby reducing frontal retraction. According to our dissections, the angle of vision is increased by an average of 12° and avoids any frontobasal retraction. The loosening of the nasal mucosa recommanded by Derome may be performed through these approaches. A rhinoseptal approach is thus not needed to reach the spheno-orbital area [12].

*The Fronto-Orbitonasal Extension (Fig. 14)*

This is an extension of the preceding technique to include specific bones of the nose. The sub periosted dissection is followed up to the superior edge of the anterior meatus nasi. The fronto-orbito-nasal flap is cut either in one piece with the bifrontal flap [92, 94] or separately [20, 32]. The section of the nasal part is performed before the lacrymal grooves and the osseous flap is reflected after it has been detached from the nasal septum, the lateral cartilage of the nose, and the anterior edge of the fossa. The posterior wall of the frontal sinus is removed. This extension of the fronto-orbital osteotomy to the bones of the nose uncovers simultanesously the endo and exocranial sides of the anterior cranial fossa and constitutes a true craniofacial

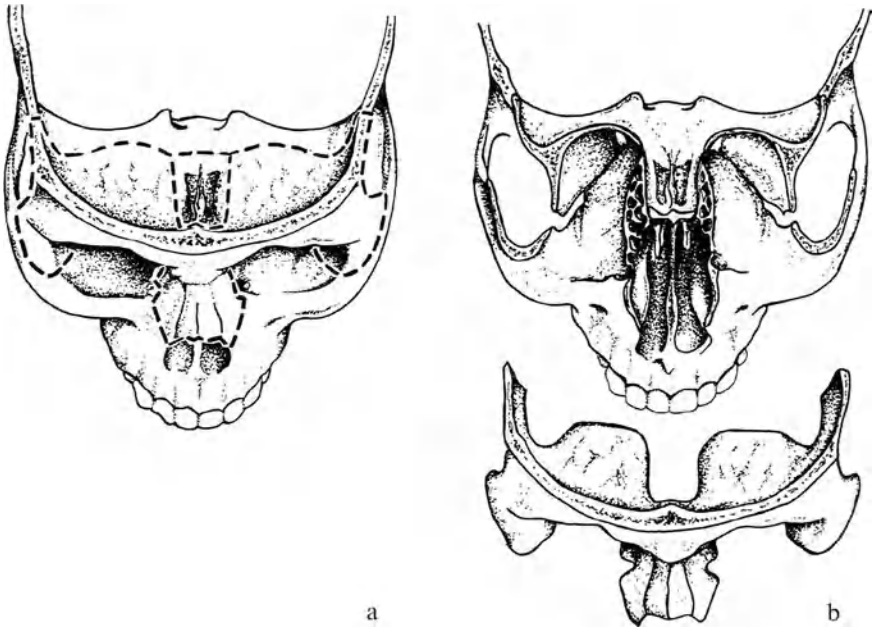


Fig. 15. The fronto-orbito-nasal unit and preservation of the olfaction (from Spetzler) (a, b)

approach. The possibilities of exposure and dissection at the level of the anterior cranial fossa and its floor are equal to that of the frontobasal approach. The originality of this approach is to give direct access to the anterior part of the nasal fossas and the ethmoid. The angle of vision is increased by an average of 17° compared with the frontal transsinusal approach. It removes the dead angle caused by the preservation of the fronto-orbital unit in the combined approach. The association of transbasal and transethmoidal visual control improves the exposure of the sphenobasilar area and of the medial part of the orbits.

At the level of the superior facial area, the visual control is not sufficient beneath the level of the middle nasal concha.

*Preservation of Olfaction (Fig. 15)*

Some authors propose a technique which differs from those we have described.

Spetzler [115] creates a nasal fronto-orbital unit, taking off the orbital roofs and preserving the horizontal plate of the ethmoid and the superior part of the nasal mucosa in continuity with the meningo-encephalic structures. This respect for the olfactory bulb, the olfactory filae, and the con-

tinuity of the dura with the nasal mucosa, ensures preservation of the olfactory function and suppresses the risk of CSF fistulae when there is no dural opening. No reconstruction of the fossa is necessary as the naso-ethmoidal unit takes locks backing place in the center of the anterior cerebral fossa, by embedding itself between the fronto-orbito-nasal unit and the posterior edge of the base (115).

Fujitsu [32] performs an ethmoidectomy from front to back after identifying the fronto-orbito-nasal unit, while preserving anatomical continuity of the functional olfactory unit. Approach to the sphenoidal body is allowed through the lateral dissection of the mucosa of the nasal fossae and by a combined sub mucosal and transseptal approach.

### Advantages and Disadvantages

The combined or transbasal approaches put together the advantages described for the preceding approaches. The extension of the bifrontal craniotomy to the superior facial area gives tangential access to the anterior cranial fossa and avoids frontal retraction. Removed of the fronto-orbito-nasal unit transforms the anterior transcranial approach of the anterior fossa into a true craniofacial approach with possibly transbasal extension. This approach makes possible an "en bloc" resection of naso-ethmoido-sphenoidal tumors [18]. Last, a unique incision is necessary on the scalp. Nevertheless, the trans facial approach remains necessary for carcinological resection of malignant tumors spread to the midface [18, 34, 107] and the length of the operation is considerably increased by the facial osteotomy and its reconstruction.

## *Surgical Techniques: Discussion*

Surgery of the anterior cranial fossa depends on the following problems:
- Accessibility and exposure of the lesions.
- Resection of the tumor or closure of the leak.
- Reconstruction of a waterproof anatomical barrier between the intracranial cavity and the nasosinus cavities of the face.

1. Accessibility and exposure of the lesions.

The frontal transsinus approach represents for us the technique best suited adapted to the exposure of the median area of the anterior fossa and its endocranial relationships. Whatever the size of the frontal sinus, the flap is always possible technically; in cases of agenesia or a small sinus, the osseous dedoubling of the fronto-glabellar bone is possible with the help of an oscillating saw.

The length of the operation including reconstruction is rather short compared with the taking off of a fronto-orbital or fronto-orbitonasal unit. The frontal transsinus flap gives excellent esthetic results. This approach allows strictly tangential access to the anterior cranial fossa. It differs fundamentally from the suprasinus approach where the height of the frontal sinus is an anatomical obstacle which requires significant cerebral retraction, greater by 30° than the preceding one. Working on the anterior cranial fossa is made more difficult by the obliquity imposed by the edge of the frontal sinuses, and it is often necessary to perform an associated trans facial approach for resection of tumors with an extension to the nasal fossa [4, 11, 99, 110, 121]. Thus some authors propose a frontobasal lobectomy to avoid neurological complications due to the retraction. The infectious risk caused by the opening of the frontal sinuses is one reason in favour of the choice of a suprasinus approach, but it is not in fact justified as the number of infections remains low, less than 2% according to Ray [95], 0% for Al-Mefty [1], 1 to 2% in our experience. The infectious risk comes from the closeness to the nasal fossae and their septic content. The rest Mucoceles and intradural abcesses is increased by incomplete resection of the mucosa, the peroperative contamination from the septic nasal fossae is lowered by antiseptic preoperative preparation, and antibioprophylaxis which is used during intervention. Some teams maintain the antibiotic-therapy until the fifth day after surgery.

Concerning the removal of tumors of the anterior cranial fossa, essentially meningiomas of the olfactory grooves, the subfrontal approach uncovers directly their anterobasal insertion and allows initial vascular control of the pedicles of meningeal origin. This vascular "disconnection" will allow a reduction of the volume of the tumor, with less hemorrhage, and improves considerably the surgical procedure. With these lesions, the pedicles coming from the anterior and posterior ethmoidal branches are predominant, and cannot be embolised pre operatively. This frontal transsinus approach is less useful for tumoral lesions located in the orbital area, for which the unilateral frontobasal or frontopterional approach is more convenient. This frontal transsinus approach gives medial and sagittal access which does not suffice to uncover the posterolateral relationships; the inter optical space and the chiasmatic cistern alone can be safely controlled through this approach.

The endocranial and intradural approach is faced with the problem of frontal superficial venous drainage towards the superior sagittal sinus. The bigger the bridging veins, the higher the risk of neurological complications of venous origin. This is correlated with the importance of the drained area. It is made worse when the capacity for frontal superficial venous substitution is weak [123]. The veins involved by the transsinus approach are the frontopolar, medial frontobasal, and anteromedial frontal veins,

belonging to the anterior group of prefrontal veins individualised by Delmas [21]. They are drained by bridging veins into the superior sagittal sinus, more than 2 cm away from the frontal pole [80]. The transvers dural incision when performed as close as possible to the cranial base allows preservation of these veins most of the time. The analysis of the venous phase on the pre operative angiography enables us to evaluate this risk and to reveal the existence of dominant frontopolar bridging veins which exist in 5% of cases [21, 58]. Kanno et Kasama [50] have shown that these are responsible for the occurrence of sub-cortical hemorraghic softening. Last, comitiality and neuropsychological disturbance are linked with direct trauma to the frontal lobes, or with the venous infarction already described.

The exposure of the endocranial side of the anterior cranial fossa involves the sacrifice of the olfactory lobes most of the time. Whenever it is possible, it is recommended to preserve olfaction. Whatever the type of pathology involved, one is advised to try to preserve the olfactory lobes from the beginning of the dissection. Whether it is a success depends on the rest of the procedure. The basis of this technique have been described by Suzuki [118]. The opening of the olfactory cistern allows the freeing of the bulb, then the olfactory tract can be separated from the medial orbital groove while respecting its vascularisation. Surgical cleavage must not go deeper than an average of 45 mm from the back of the anterior wall of the frontal sinus. This requires a tangential access to the cranial fossa.

The paralateronasal approach is part of a combined approach to the endo and exocranial side of the anterior cranial fossa. This is the trans facial approach that we have referred to. For aesthetic reasons, the bilateral sub labial and transnasal approach, known as "degloving" technique may represent an alternative to the paralateronasal approach. Nevertheless it is renowned for the difficult access it gives to the antero superior part of the nasal fossae and the anterior part of the ethmoid [25].

The associated transsinus and paralateronasal approaches are required for large resections of the anterior cranial fossa, especially for surgery of malignant lesion. This resection is centered on the nasal area of the anterior cranial fossa, and for many authors it must be performed "en bloc". The tumoral extension to the bordering areas, to the exocranial level (infratemporal fossa, rhinopharynx) and/or endocranial level (cavernous sinus, superior orbitary fissure, middle cranial fossa) cannot be removed through a unique anterior craniofacial approach: one must resort to the association of these two approaches for extreme malignant lesions [48, 105, 107].

The trans rhino-septal approach and the endoscopic techniques are for focalised lesions and may be an answer to the difficulty of uncovering the posterior part of the nasal area by a superior approach.

The risks of complications linked to a transcranial approach are less-

ened (anosmia, frontal contusion). The exposure of the exocranial side of the medial area by endonasal approach with endoscopic guidance is used to identify and treat CSF fistulae. The rhinoseptal approach is used also for treatment of some fistulae of the anterior cranial fossa that run into the sphenoid sinus. For some, it is the complementary approach to an anterior transcranial approach thanks to its access to the pituitary fossa and to the superior part of the sphenobasilar area [22].

2. The reconstruction of the cranial fossa is an essential part of the procedure.

Operative mortality and morbidity follow poor reconstruction technique [111]. One must respect three fundamental principles: the reconstruction of a waterproof dural floor, the filling in of the dead spaces caused by lesion removal with replacement tissue, and the provision of support for the cranial fossa to avoid meningoceles. The substitute material used must be accepted by the organism and remain stable in the long term.

Pericranium is the material used most often to rebuild the dural plane [33]. The pericranial graft is placed in the subdural space, covering the loss of substance and spreading over the healthy dura mater on the periphery. It is nowadays more often fixed with fibrin sealant than with a suture, experimental studies having shown the reliability of this type of reconstruction [19]. In large defects, it is reinforced by an identical epidural graft. Autologous grafts are made of facia lata and temporal fascia, but in large defects, they have a tendency to frequent necrosis [22]. The dermal graft, well vascularised and waterproof, allows a more reliable duralplasty [22, 117].

For the majority of authors, the rebuilt dural plane is reinforced with pericranium pediculated on the frontal area, covering the whole of the surface of the anterior cranial fossa [34]. It may also be free, as in our experience [22], or made of a dermal graft [4, 22, 86]. It may then be used as a support when no complementary tissue reinforcing the cranial fossa [49, 93, 105, 108, 117], or bring a vascular flap to the bone graft placed at this level [2, 22, 25, 54, 74].

Insertion of tissue to fill the empty part caused by tumoral removal may be done with a bone graft or other tissue. The reconstruction of a bone plane [4, 22, 25, 54, 74] is preferred using autologous graft, cancellous bone taken from the hip joint or a rib being used most of the time [33]. This graft covers the nasal area of the cranial fossa and sometimes the orbital roof.

For some teams [49, 69, 93, 105, 108, 117] it is not necessary to use bone tissue. It reduces the risk of osteonecrosis especially in case of radiotherapy, or of infection (4.8% in Roux's series). In our experience, the use of a free flap of fat from the abdomen allows efficient filling up of the dead spaces, the reinforcement of the watertightness of the pericraniplasty, and acts as a support. A Silastic blade is placed underneath in the nasal fossa,

maintaining the different tissues in their correct position. It also acts as a support to endonasal reepithelisation, which is complete in about 6 weeks. The reliability of free flap fat has been shown experimentally [77] and by different clinical series [36, 108, 109]. Other tissues may act as support for the cranial fossa, such as a pedicled patch of temporal muscle, or microanastomosed free muscular patches (musculus rectus abdominis, musculus latissimus dorsi). Their indications apply to craniofacial removal associated with a large loss of substance of the cranial fossa, overlapping the medial area, to include orbital exenteration, or maxillectomy [49, 111].

## Clinical Applications

Preservation of olfaction in surgery of the anterior cranial fossa may be attempted with every pathology in this area: traumatic, tumoral, vascular or congenital malformation.

### *In Trauma to the Anterior Cranial Fossa*

Post traumatic osteodural leaks of the anterior cranial fossa do not always lead to a complete and everlasting anosmia. The shearing effect on the olfactory fillas by the holes of the cribriform plate is mainly the result of cranial trauma by deceleration. Cranial and craniofacial trauma by direct impact, which cause a fracture of the cranial base with an osteodural leak, may spare olfaction in 54% of the cases in our personal experience, as evaluated immediately after trauma. But œdema of the mucosa of the nasal fossae may be in itself the cause of anosmia, more than a direct lesion of the olfactory structures. On the other hand, it has been shown that the olfactory structures may regenerate. It thus seems risky and unjustified to classify a post traumatic anosmia as permanent after the initial examination only.

All the different patterns of traumatic lesions of the anterior cranial fossa do not cause the same percentage of leaks or a systematic bilateral lesion of the olfactory structures. According to Marchal [73] we may classify the trauma of the anterior cranial fossa into 3 main classes according to the site of impact:

- When the impact is on the nose, there is a driving in of the nose, the frontonasal junction and then the ethmoid. This type of lesion causes leaks in 91% of the cases, it is bilateral through the cribriform plate and the trauma to the olfactory structures is usually of some importance.
- When the impact is initially on the frontal calvaria, the energy thus received causes a main fracture which will spread from the calvaria to the anterior cranial fossa. This streak will go towards the most fragile areas, it goes through one of the cavities of the frontal sinuses, and then on

through the cribriform plate, to end – if it has enough energy – near the ipsi or contralateral optic canal. There are leaks in 89% of the cases, but they are exceptionally bilateral through the cribriform plates, and it is thus logical to propose a technique which will preserve olfaction.

- When the trauma concerns the external orbital process, it may involve the ethmoidal area and the cribriform plate but only unilaterally, with leaks in 63% of the cases.

On the whole, the techniques of preservation of olfaction in repairing the leaks may be used in most of these cases (Fig. 16). Only long term evaluation will allow a precise appreciation of the olfactory function. We won't deal with cases of wounds of the anterior fossa when their origin is due to gunshots.

Surgery through high approaches, whether frontal transsinus or subfrontal, is indicated only when a large repair to the anterior cranial fossa is required and/or when reconstruction of the calvaria must be performed.

The inferior approaches, particularly by endoscopic technique with a partial ethmoidectomy and glueing (most of the time unilateral), are indicated for leaks with a posterior ethmoidal or sphenoidal origin, and are thus entirely appropriate for preserving olfaction.

In case of failure, we never hesitate to combine these approaches. Concerning the superior neurosurgical approaches, out of a series of 30 cases which were admitted to our department with a traumatic osteodural leak proved by a rhinorrhea and/or a pneumatocele, 22 cases have been operated on according to the following criteria: persisting rhinorrhea and/or meningitis.

Among the patients (22 cases), in 8 cases, preservation of olfaction has proved technically impossible because of avulsion of the olfactory lobes by the trauma. In 2 cases, the osteodural leak was frontal, in front of the posterior and vertical wall of the frontal sinus, and it wasn't necessary to perform a dissection of the cranial fossa itself.

But in 12 cases, that is a little more than half the cases, the technique of preservation of olfaction described above has been used, with in 5 cases a bilateral dissection and a bilateral closure of the olfactory structures, in 7 cases, the dissection was unilateral, the other being avulsed by the trauma, but nevertheless the closure was bilateral.

Among these 12 cases, there is no recurrence of the fistula, with a follow up from 4 years to 3 months. Concerning olfactory function in the long term of these 12 cases, it is normal for 5, incomplete for 3 and 4 cases have complete anosmia.

### *In Tumoral Pathology of the Anterior Cranial Fossa*

Preservation of olfaction can be aimed at only for extra-axial lesions and for those which, by their treatment, have spared the cranial fossa and the

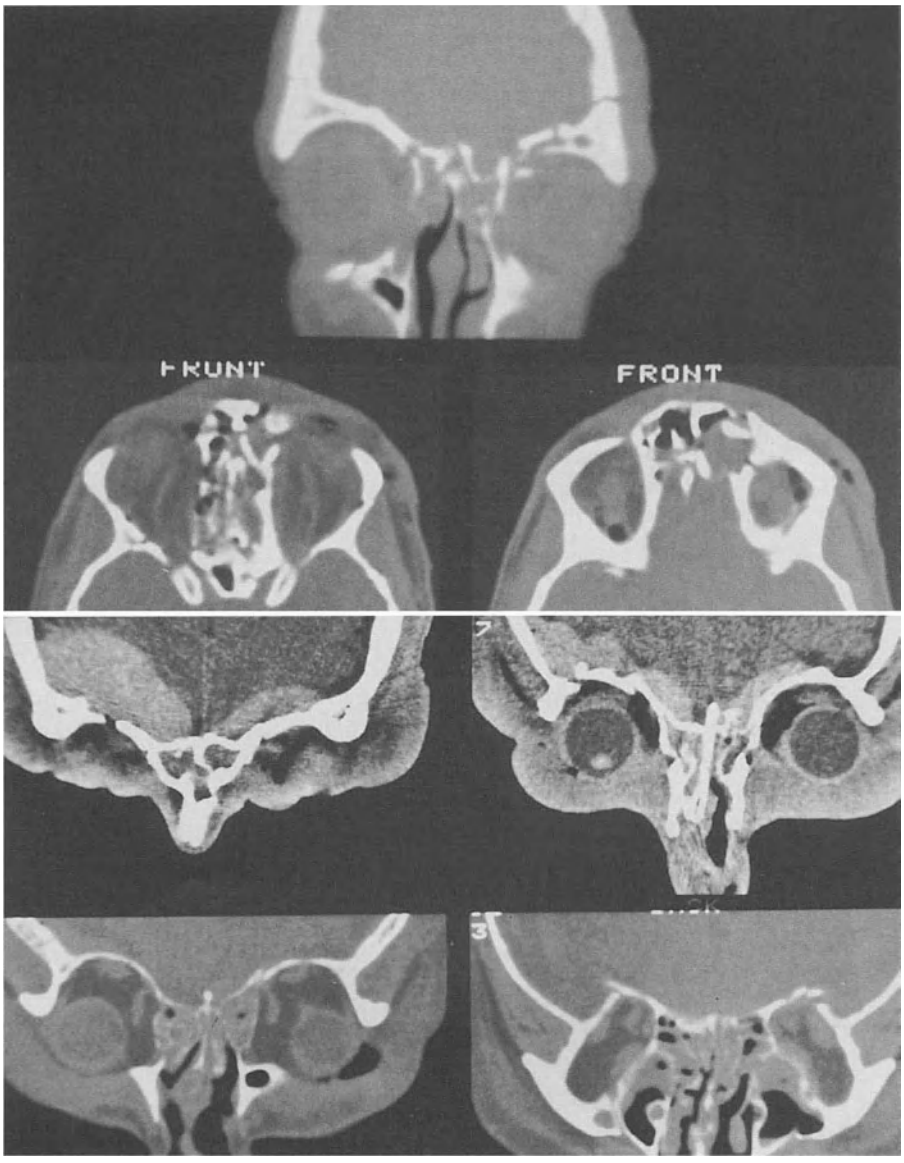


Fig. 16. Head trauma with fractures of the anterior fossa. Examples where the preservation of the olfaction has been applied

olfactory structures. This excludes ethmoidal adenocarcinomas for which the ethmoidectomy represents the basis of treatment, as well as for esthesioneuroblastomas which develop from the olfactory structures themselves.

Thus remain the meningiomas of the anterior cranial fossa and more

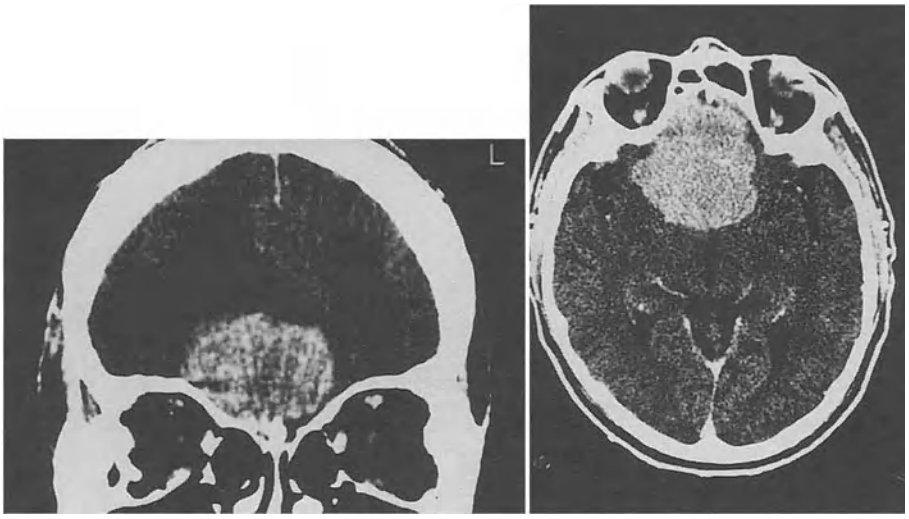


Fig. 17. Meningioma of the anterior cranial fossa. The olfaction has been preserved on the left side

specifically of the olfactory grooves. They are usually quite large. Out of a personal series of 14 cases, the average diameter was 51 mm in all directions; with extremes of 30 to 72 mm in diameter. Their insertion may be asymmetrical between right and left, and their development may respect the arachnoidal plane. Some cases may have spared one olfactory lobe and allow the preservation of olfaction during their removal.

Out of our 14 cases, 1 patient benefited from preservation of the olfaction after removal of a meningioma of 60 mm in diameter (Fig. 17).

As far as meningiomas of the jugum sphenoidale are concerned, we prefer a pterional or frontopterional approach when we want to preserve olfactory function and to have a good control of the pituitary area at the same time.

Lesions with a more central development such as craniopharyngiomas and pituitary macroadenomas with an extension in the 3rd ventricle, may require sometimes an anterior interhemispheric approach. Our experience is limited for these types of lesions with this approach, but the technique of dissection already described may very well be used at least for one olfactory lobe, the second being maybe severed. Figure 18 shows a case of a pituitary macroadenoma operated on with this technique.

### *In Vascular Pathology*

This refers to the treatment of aneurysms of the anterior communicating artery by an anterior subfrontal and interhemispheric approach. Suzuki

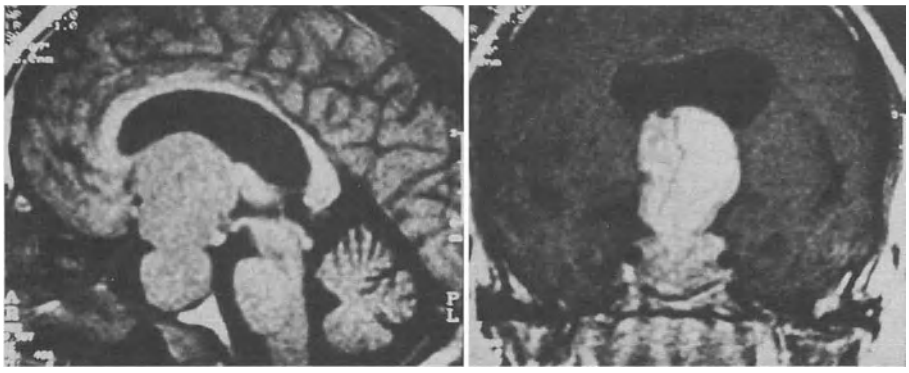

Fig. 18. Macroadenoma of the pituitary gland, removed through a frontal transsinusal and interhemispheric approach

[118] invented this technique of preservation of olfaction in this approach for treatment of these aneurysms. On the technical side, Suzuki proceeds by cutting a bifrontal trans or suprasinus flap and the falx cerebri is cut. He proceeds with alternating retraction of the frontal lobes when dissecting the olfactory cistern. The dissection is said to be easy for the first 2 centimeters behind the olfactory bulb in its cisternal portion; the separation of the tract from the base of the frontal lobe is made with a spatula. The key to success lies in the application of movements and of pressures from above on the olfactory lobe to avoid any distraction. This goes on until the level of the end of the anterior cerebral arteries, the limit of dissection being on average 1.5 cm before the termination of the olfactory tract into three olfactory bands. This procedure does not impair the aneurysmal exposure and dipping which follows. Concerning the results, Suzuki reports 35% of bilateral anatomical preservation, 32% unilateral, and 26% of bilateral lesions. Post operatively, olfaction as evaluated on objective criteria was maintained in 47% of the cases of his series. Castel reports 35% preservation of olfaction out of a series of 15 cases (personal communication).

### *Clinical Applications of Endoscopic Surgery by the Endonasal Approach*

We refer to the experience of the team from the ENT clinic in Grenoble Hospital, our partners for surgery of the cranial fossa. They perform the identification and closure of fistulae by an inferior approach, and use a graft of abdominal fat for obliteration. 19 patients with cerebrospinal rhinorrhea have been treated by this procedure. Among these 19 cases, we acknowlege 6 spontaneous rhinorrheas, 3 meningoceles of the sphenoïd

sinus and one of the nasal roof, 7 cases of post traumatic rinorrhea including 2 cases of recurrence after treatment by a neurosurgical approach for severe cranial trauma with complex fractures of the anterior and middle stage, and 6 cases of post surgical fistulae, 3 after removal of a meningioma of the anterior cranial fossa and 3 after ethmoidectomy performed by a nasal endoscopic approach.

Procedures performed by endoscopy are 7 sphenoidotomies, 2 sphenoidoethmoidectomies and 10 ethmoidectomies. In every case of sphenoidotomy, the removal of the middle nasal concha was necessary to give easier access to the sphenoidal recess. The sphenoidotomy is performed through a purely endonasal approach, its ostium is enlarged and catheterised through the sphenoethmoidal recess. The resection of the anterior wall of the sinus begins on its infero-internal part then on the other edges after the main landmarks of the sphenoid sinus have been checked, i.e. the jugum, the optic nerve and the knee of the internal carotid artery. In other cases, the sphenoid sinus is opened by collapsing the pars ethmoidalis, the wall which separates Onodi's cell from the sphenoid sinus. It is sometimes necessary to add a posterior transethmoidal approach, as the ostium sphenoidale can't be enlarged enough though a simple endonasal approach. The endosphenoidal procedure begins with inspection of all the walls of the sinus with the help of rigid optical instruments, their angle varying from 30 to 70°, leaving the endoscope in a median position so as to avoid any trauma to the optic nerve or the internal carotid artery.

In 6 cases out of 7, the precise origin of the fistula was found and obliterated, in 2 cases at the level of the pituitary fossa, in 2 cases at the level of the jugum sphenoidale, and in 2 cases between the optic nerve and the internal carotid artery. For posterior ethmoidal removal, the fistula was found in the roof of the sinus in 5 cases out of 5, and finally, on the anterior ethmoidal level for 6 cases, the fistula was identified and closed in 5 cases out of 6. In 1 case of a nasal roof meningocele, an anterior ethmoidectomy and middle turbinate removal was performed before removing the meningocele and obliterating the gap.

The fistula has been found 17 times out of 19 during intervention by endonasal endoscopic approach. With an average follow up of the patients of 26 months, 14 cases out of 19 didn't suffer any recurrence of their fistula after the first intervention. Among the 17 patients whose fistula was found and treated, we have 5 recurrences of the rhinorrhea which underwent a second operation by the same technique, that is 5 cases of reintervention out of which only one case was a failure.

Through this approach, olfactory function may be spared: we counted 8 preoperative anosmias out of 19 cases, and 10 post operative normal olfactions out of 19 cases, which means only 1 truly postoperative anosmia due to this technique.

## Discussion

The bulb and the olfactory tract, wrongly called the olfactory nerve, are an extension of the telencephalon. This extension is produced during embryogenesis by the growth of the true olfactory nerves represented by the olfactory fila. The phylogenetic transformations have seen considerable regression of its importance and the development in other proportions of the frontal lobes. The olfactory structures in man are characterized by a small sized bulb and tract. This morphology of the encephalon makes man a microsmatic being. Nevertheless, olfaction is still a very important function for man [38, 124], no longer for the search of food and partner, but for reflexes and behaviour in which it plays a part, as well as emotionally. The loss of olfaction is not as incapacivating a sensory handicap as blindness or total deafness, but still it has repercussions for social life and feeding. A great part of the olfacto-gustative message contained in food is lost with anosmia, which is then reduced to the analysis of the 4 fundamental tastes (sweet, acid, salty, bitter). We must also underline the vital risk form absence of awareness of noxious or dangerous smells (cooking gaz, toxic vapours, fire smoke...). The repercussions of the loss of smell vary, and can induce neurosis in some people, with depression, or a social problem due to the loss of work (cook, perfume maker). Cranial traumas are the most frequent cause of secondary anosmias, as 2 to 8% of the cranial trauma victims present with this handicap [28, 38]. The mechanism can be through direct fracture of the anterior base of the skull, or more often indirect through a shearing effect exerted on the attached olfactory structures of the encephalon or the cribriform plate, causing section of the olfactory fila [124]. Anosmia can be the consequence of surgery which then always has a bad prognosis [41, 75, 126]. Its frequency, estimated at between 10 and 25%, is often underestimated [62, 78, 97]. This operative risk must be taken into account with therapeutic decisions and discussion of the surgical techniques used.

It is important in the surgical treatment of pathologies of the anterior cranial fossa to preserve olfaction wherever it has been spared by the lesion at the skull base (in particular fractures but also in tumoral or vascular pathologies). The olfactory structures constitute a natural obstacle to the exploration of the anterior cranial fossa. We propose exposure most of the time of the anterior fossa in a unilateral way by sub frontal, epidural or combined approach, so as to avoid complete anosmia [10, 23, 71, 123, 127]. The bilateral approach seems more reliable for control of these leaks. Other authors use a paralateronasal and transethmoidal extracranial approach [29, 75, 76]. More recently, the approach has been made by endoscopic endonasal approach through the nostrils, by performing a uni- or bilateral ethmoidectomy followed by closure of the leak. Apart from the case of

exclusive sphenoidal obliteration, these low approach technique cause an alteration of the olfactory membrane in case of bilateral approach and are responsible also for anosmia. Suzuki has shown that preservation of the anatomical integrity of the bulb and olfactory tract during a subfrontal approach comes for their dissection from the inferior face of the frontal lobes [118]. An anatomical study of the arachnoïdal vascularisation and architecture has revealed the constraints and limits of the surgical technique.

The literature is not very precise with respect to the vascularisation and anatomical relationships of the olfactory structures. The arachnoïd architecture of the olfactory region is poorly described and often contradictory in anatomical treatises [65, 84]. The existence of an olfactory cistern was mentioned in anterior anatomical studies (Key and Retzius [53], Lilliquist [70], Richelme [96]), through Yasargil's neurosurgical observations [128] or radiological observations during gaseous or metrisamide encephalographies (Elias [43]). Anyway the relationships of the bulb and olfactory tract to the encephalon and the cranial fossa are worthy of description. We have seen that an embryological explanation for the presence of this arachnoïd cistern can be put forward [46, 85, 101]. The anterior part of the cistern is large, a surgical plane of cleavage can be found through it. This path goes from and is useful dorsal to the bulb and tract as they are attached to the inferior face of the frontal lobe only by the arachnoïd adhesion. Mobilisation of the olfactory structures must be delicate because of the opposition between the light attachment of the bulb to the cribriform plate, and the strong anchorage of the tract to the brain. The choice of a frontal transsinus approach, performed very close to the anterior cranial fossa seems to be the best technique, the easiest and most reliable, when one wants to reduce frontal retraction and obtain a path of dissection really in the cisternal axis.

Spetzler's technique [115] with an epidural mucosa-free dissection, which preserves "en bloc" the olfactory bulbs and the olfactory sensory mucosa, is an interesting alternative, as well as Fujitsu's [32]. This technique has allowed preservation of olfaction in 3 cases out of 4 while exposing and removing sphenoidal tumors (angiofibromas and fibrosarcomas).

## Conclusion

Although often considered as secondary among the sensory functions, olfaction remains for us an important perception in different professional and social situations. It is thus important to preserve it in surgery of the anterior stage wherever possible. Preservation of olfaction can be tried in several different pathologies:

- Traumatic pathologies: in our experience, this technique for preservation of the olfaction doesn't increase the risk of recurrence of fistulae of cerebro-spinal fluid or infection. It can preserve partial or complete olfaction.
- In vascular pathologies, especially for aneurysms of the anterior communicating artery, preservation of olfaction is accomplished in 35 to 45% of the cases.
- This technique is interesting whether by the superior or inferior approach mainly in congental pathologies such as meningoceles, whereas it is only exceptionally of use in tumor pathology.

It is possible to perform because of local anatomical conditions:

- The presence of an olfactory arachnoid cistern giving a plane of dissection.
- And the vascular independence of the bulb and tract.

This type of intervention is feasible as the result of the quality of today's biological glues, and the benefit seems to be long lasting for the patient.

**Acknowledgements**

We wish to thank Pr. J. P. Castel from Bordeaux who kindly allowed us to use his experience in the surgery of aneurysms of the anterior communicating artery through the anterior interhemispheric approach.

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