# Advances in Neurosurgery 14

# Spinal Cord Tumors

# Experimental Neurosurgery

# Neurosurgical Intensive Care

Edited by
H. Wenker M. Klinger M. Brock F. Reuter

With 197 Figures and 65 Tables

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# Proceedings of the 36th Annual Meeting of the Deutsche Gesellschaft für Neurochirurgie Berlin, May 12–15, 1985

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# Preface

This 14th volume of *Advances in Neurosurgery* includes the papers presented at the 36th Annual Meeting of the German Society of Neurosurgery in Berlin, May 12-15, 1985. I would like to take this opportunity to thank the members of the program committee of the Society, Priv.-Doz. Dr. Klinger, Professors Brock, Dietz, Frowein, Lausberg, Wüllenweber, and Dr. Reuter for their assistance in selecting the contributions and in organizing the scientific program.

The first main topic of the meeting was *Spinal Cord Tumors*. Introductory lectures dealing with basic anatomic knowledge, neuropathological aspects, and neurologic problems were followed by reports on examinations using conventional neuroradiology, scintiscanning, computer tomography as well as the most recent method in the diagnosis of spinal tumors, the magnetic resonance tomography. Also presented were the results of a multicentered study on spinal tumors, ascertained in cooperation with 43 German and Austrian neurosurgical clinics. The participants reported in great detail on the statistical data they recorded from 3056 cases and on the scientific findings obtained from this study. The session concluded with lectures on the possibilities for surgical treatment of spinal tumors and on oncologic and radiotherapeutic measures.

*Experimental Neurosurgery* was the second main topic. Leading authorities in the field presented interesting papers on topics such as the therapy of vasculogenetic brain edema, the determination of neurotransmitters in brain tumors, results of cerebral blood flow measurement, and improved operative techniques using laser radiation.

The last day of the meeting was devoted to *Neurosurgical Intensive Care*. Neurosurgeons and anesthetists presented comprehensive papers on measures to protect the brain, which are important in the treatment of severe brain damage. The current state of barbiturate therapy for raised intracranial pressure was discussed in great detail. In addition to the lectures on the therapeutic measures, papers on the diagnosis of brain death and on the ethical and legal problems of intensive care completed the scientific program.

While the 36th Annual Meeting of the German Society of Neurosurgery was being held in Berlin, the Department of Neurosurgery in the Neukölln clinic celebrated its 25th anniversary. We deeply regretted that the founder of the second oldest department of neurosurgery in Berlin, Professor Dr. Helmut Penzholz, who had been invited to give a special lecture on the occasion of this anniversary, had passed away shortly before the meeting. In the presence of his wife, the Congress partici-

pants, and the staff of the Department, we paid tribute to his life and works.

Finally, I would like to express my gratitude to everyone who helped make the 36th Annual Meeting a success and to all of my colleagues for their presentations and their contributions to the discussions. Dr. Margareta Klinger deserves a special word of thanks for her outstanding and untiring efforts in the editing of this volume, and Springer-Verlag for its cooperation and technical assistance.

Berlin Horst Wenker

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# President's Opening Remarks - Reflections on the Bond of Trust Between the Physician and his Patient

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"Reflections on the bond of trust between the physician and his patient" is the subject of this opening address at the 36th Annual Meeting of the German Society for Neurosurgery. In discussing this theme, I would first like to try to define the term "trust" or "confidence". Etymologically, the word "confidence" is related to the Latin term "fides", which means "faith". In the English word "confidence", this faith is emphasized by the suffix "con-". We may therefore state that confidence or trust represents the firm expectation that you can have confidence in somebody, that you can trust somebody. In this sense, trust forms one of the foundations of social relations in many fields of human life, e.g., marriage, family relationships, friendships, but in a special sense also in the relationship between the physician and his patient.

During my 30 years of practice as a physician I have often thought about this bond of trust between the physician and his patient; a period of serious sickness I recently went through intensified these reflections and I would like to present here the results of my considerations.

In the hope of obtaining help a sick human being usually approaches a physician he or she knows, who has helped before or has been recommended by another person. Behind this hope of receiving help, i.e., restoration of health or just an improvement in condition, lies the confidence of the patient in the skills and capability of the physician to diagnose the disorder and to treat it successfully by means of appropriate measures. The sick person accordingly places confidence in the physician to restore him or her to health.

As far as the physician is concerned, he is not only ethically obliged to conduct diagnosis in accordance with the state of the art and to utilize the most promising and latest therapy, he also has to try his best to justify the confidence placed in him in an effort to build a bond of confidence and trust, which is indispensable for both the patient and the physician.

While I was sorting ideas and thoughts for this address I ran across a book *Ärztliches Handeln zwischen Paragraphen und Vertrauen* ("The action of the physician between the letter of the law and the confidence placed in him by the patient"), published in 1984, and found in it a contribution by Johannes GRÜNDEL, Professor of Ethics at the School of Divinity of the University of Munich. The chapter carries the title *Arzt – Patient – Gesellschaft: Perspektiven eines Vertrauensverhältnisses* ("Physician – Patient – Society: Perspectives of a bond of confidence")

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and I would like to quote a few sentences verbatim:

> "Particularly if human health and sickness are regarded as entities, the healing action of the physician is based on the confidence of the patient in the physician. This confidence develops or disappears in conjunction with the ethical standards the medical profession shapes for its actions and makes mandatory for its members. In the ancient world these standards were expressed in the so-called "Hippocratic Oath", which interdicted noxious actions and obliged the physician to direct his efforts toward healing. This code of ethics, which was specific to a particular profession, remained an elitist standard, however, since it was accepted by a defined group of adherents only, not determined by the general social structure of the total society. Today, however, the physician faces the duty of making his help and assistance available not merely to a single group of total mankind, but to any human being, regardless of social status, race, and personality. The 'Hippocratic Oath' therefore no longer suffices."

If, however, the "Hippocratic Oath" is no longer considered sufficient, it is essential for the medical profession – quoting GRÜNDEL again – "...to reflect comprehension of the responsibility involved and not to limit itself to a merely scientific training specific to the selected field." In my own words I would like to try to express these ideas in the following statement: "Being aware of our responsibility to the patient who entrusts him- or herself to us, we not only have to ensure that our skills and knowledge are in line with the latest state of the art and to use the most modern diagnostic and therapeutic procedures available, rather we also have a duty to transmit to the sick person at all times a feeling of security and a conviction that he or she is receiving optimal care, so that the patient will place full confidence in us, even in the event of serious sickness or a life-threatening condition."

Unfortunately within the last few years an increasing erosion of the confidence placed in the physician can be noted in our society, since many different influences are threatening to destroy the bond of confidence between physician and patient. In 1984, Albin ESER, Director of the Max Planck Institute and Professor for Foreign and International Criminal Law in Freiburg, FRG, was justified in pointing out that the current weakening of confidence in the physician is directly based on progressive burdening of the bond between the physician and the patient with legal matters and on excessive requirements concerning the duty to keep the patient completely and comprehensively informed; both these items constitute very fundamental considerations.

This statement from a legal expert appears particularly remarkable to me since it is exclusively the legal profession itself which requires physicians to pass a volume of information to a particular patient that frequently considerably surpasses the scope actually necessary. According to the legal specialists comprehensive disclosure of information to the patient is a condition for self-determination of the patient. If such information is forced onto the patient prior to any diagnostic steps and therapeutic efforts, however, the only purpose of such a practice is the accumulation of precautionary safeguards against possible later lawsuits; it disregards the highly vulnerable and sensitive psychological state of a patient who may be seriously ill. Each physician therefore faces a conflict between the necessity to conduct informative, confidence-building talks with an individual patient in an appropriate form and the requirement to provide complete information in the face of the "whip of the law" (as ESER expressed

it strikingly), information which exceeds reasonable bounds and damages or even destroys the confidence of the patient. Under these circumstances it is not surprising that quite a few physicians, constantly in danger of being sued not for outright malpractice but for providing the patient with incomplete information, retreat towards so-called defensive medicine which does the patient more harm than good.

In addition to this unfortunate penetration of legal matters into the relationship between the physician and his patient, other factors also contribute towards erosion of the confidence of the patient in the capabilities of the physician, e.g., the progressive commercialization of medicine. This problem is described by ESER, as a legal expert, in the following words:

> "While in former times the physician was considered a helper who appeared to be remote from profane financial ambitions, and when, therefore, 'honoring' was regarded in the true sense of the word as the honorable payment of a debt of thanks to the physician, nowadays a formal scale of rates, but even more so (supplementary and superimposed) additional agreements about fees, have forced a contractual element into the relationship between physician and patient, and this relationship therefore hardly differs any more from other commercial contractual relations concerning services rendered. On top of this, such 'functionalization' of the medical services is emphasized by the ever-growing specialization of individual physicians into specific fields of medicine or selected parts of the body. Today the physician is therefore no more the general 'supporter of life' but is frequently considered some kind of 'skilled repairman' for the heart or the kidneys. Anybody paying the 'specialist' a sizeable amount of 'hard cash', however, then expects a corresponding 'service' and a 'refund' or compensation if the medical efforts prove unsuccessful."

Even if ESER were to be correct in some of his statements, he most likely does not identify himself with them and is only attempting to express the opinion of a large segment of "society". As I see it, he does not voice our own concept of our profession.

I was moved, however, to see the physician being referred to as a "repairman" or a "highly skilled specialist". Of course, we are – and in using the word "we" I am particularly addressing the neurosurgeons – no longer the comprehensive helpers in life, but on the other hand nor are we exclusively experts on the brain, the spinal cord, and the nerves. The talks on the third day of this congress, when discussions on problems of neurosurgical intensive care are scheduled, will demonstrate to what extent neurosurgeons are today expected not only to be specialists but also to respond on matters of general medicine and to bear a heavy responsibility in this area.

Following this excursion into the field of legal matters I shall now return to the discussion of more causes of decreased confidence in physicians. I believe that, to a varying degree, the mass media bear significant guilt. Almost every day the boulevard press, and less frequently radio and television, report on the topic of "health". In the course of these messages the "general public" is told in moving words about cases of malpractice – from a pair of scissors being left in the abdominal cavity of a helpless patient following surgery, proceeding all the way to alleged cases of erroneous amputation of a healthy leg instead of the diseased one. Moreover, new and unproven methods of therapy are described in detail and grave warnings are issued about time-honored and scientifically based procedures. Quite naturally, the con-

fidence of a partially informed or a misinformed patient will be shaken if a qualified and scientifically oriented physician starts the correct therapy, which according to the opinion of the patient "medically educated" by unqualified articles in the daily press is not up to the latest standard or is suspected of being dangerous. In this respect some physicians and so-called health practitioners – I will refrain from quoting specific names – are also to be rightly blamed. These people apparently see their goal in life as degrading the well founded knowledge of established medicine and in accumulating sufficient profit from their irresponsible actions to ensure a care-free ripe old age for themselves. Are these persons, rated competent by their own grace, aware of their contribution to the demise of confidence between patient and physician, which can hardly be restored anymore as such publications are eagerly snapped up and disseminated by the media? I seriously doubt it.

The necessary bond of confidence between a patient and his physician is also negatively affected if several different physicians utter divergent opinions on the type of disorder present and the therapeutic steps to be pursued in the presence of or within earshot of the patient. This problem is particularly acute in large clinics and hospitals.

Finally legislature, the labor partners, and hospital administrative offices in the FRG recently made shift duty obligatory and "decreed" new types of allocation of working hours. Physicians are now forced to participate in rigid schedules of on- and off-duty hours which would have been considered strange in former times. As a consequence gaps in the continuity of the flow of information between the physicians concerned with an individual case or between the physicians and the nursing staff will result. At first glance these discontinuities may seem of minor importance, but they appear very important to the patient affected. How, for example, can a physician be informed on each and every detail that has been discussed with patients and their relatives during his 3 days off duty? Such a lapse in the continuity of information will occur particularly in cases where no feedback from colleagues is feasible because they have been forced by the regulations to take compensatory time off after a fixed amount of working hours. This example drastically illustrates the unwise practice – particularly with respect to the bond of confidence between patient and physician – of classifying employed physicians within the same categories as other public servants and of subjecting them to the same standardized administrative regulations, to the disadvantage of the patient.

If, now, the necessity for a bond of confidence between the patient and his physician is postulated, as I have done, and on the other hand an accelerating decrease in the confidence of patients in the medical profession is clearly recognizable, a steady and continuous effort on the part of the physicians to stabilize the bond is most essential. What steps are open to achieve this end? Undoubtedly a whole catalog of reasonable practical measures could be suggested. In my personal opinion, it would be entirely sufficient to demonstrate vividly to "society", i.e., all present and prospective patients, that every physician is always aware of his humanitarian duty without "ifs" and "buts", acts to meet this obligation, always strives to sharpen his knowledge and to improve his skills, and applies his capabilities in diagnostics and therapy without reservation or limitation. I am convinced (of course, the occasional "rotten apple" will always be found) that the overwhelming majority of physicians do not seek any praise for the sacrifices involved in the discharge of their duties, relinquish many facets of daily life, and at the same time practice medicine in such a fashion to leave us amazed at the crisis of confidence that exists between physician and patient.

As the first item I mentioned the humanitarian task of the physician, and I would like to define this term as "humanitas" in the precise sense of the word, i.e., as human behavior characterized by compassion and a readiness to help one's fellow man, not simply as the execution of a type of work specific to a physician. In respect of the activities of a physician I do not interpret this "humanitas" as a sharing of the suffering but as a feeling of responsibility for the patients who place their trust in us, and as a frankness – however qualified and prudently selected – during discussions about the manifesting disorder, diagnostic steps, therapy, and prognosis. Such discussions naturally have to take into account the mentality and the educational level of the patient. Particularly when a disorder is serious and preceding high-risk surgery it seems essential to me to conduct informative discussion with the patient's closest relative as well. Including such a relative in the talks should not be done for forensic reasons, but to support and enhance the mutual bond of confidence between the patient and the physician.

No special comment is necessary concerning the obligation of the physician to keep his medical knowledge up to date. Reading the current literature and participating in meetings and lectures for continued education are indispensable for any physician striving to treat and advise his patients optimally. This 38th Annual Meeting of our Society for Neurosurgery will also provide new insights for the participants and instill them with new knowledge. Continuous improvement of the skill of a physician can be achieved only by steady and diligent practice of the medical profession.

Ladies and Gentlemen, let us hope that such efforts will halt the present decline in the bond of confidence between physician and patient, and achieve its stabilization, which is of such great importance.

# Ernst von Bergmann and the Beginning of Neurosurgery in Berlin

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We are gathered to remember the founding of the Department of Neurosurgery in Berlin-Neukölln 25 years ago today, one of the later roots of neurosurgery and neurosurgical sciences in the old capital of Germany.

Neurology has an extensive tradition in Berlin and was developed long before neurosurgery by scientists such as WESTPHAL and OPPENHEIM. As early as 1910 the annual meeting of the Vereinigung der Deutschen Nervenärzte took place here. The first president of this society, Wilhelm ERB, addressed the assembly with the following words: "Today Berlin already looks back on a glorious and very important past as regards research and teaching in the general field of neurology. Without any hesitation I can here refer to Berlin at this time as being the most important center of Deutsche Nervenpathologie (ERB's term for neurology) in science and teaching". During this period (in 1913) Berlin was also the venue for Fedor KRAUSE's and OPPENHEIM's first famous series of neurosurgical operations, including the first successful extirpation of a quadrigeminal tumor.

Since we are here to consider in particular the history of neurosurgery, we should first go back to the first of the four great pioneers in Germany, Ernst von BERGMANN, the others being Fedor KRAUSE, Otfried FOERSTER, and Wilhelm TÖNNIS. It is remarkable to see, when looking back into history, the importance of the two universities of Würzburg and Berlin at this time. The Würzburg/Berlin axis had already gained significance when the famous surgeon DIEFFENBACH took up the Chair of Surgery in Berlin-Ziegelstraße in the middle of the last century. It was because DIEFFENBACH had been expelled from Würzburg for political reasons that he accepted Berlin. Conversely, VIRCHOW had to leave Berlin in 1849 for political reasons, and he accepted the chair in Würzburg. However, this was for only a short time because the faculty enticed him back as soon as possible. Even the first pioneer of German neurosurgery, Ernst von BERGMANN, who we are commemorating today, had worked in Würzburg before he went to Berlin in 1880, and later, in 1937, TÖNNIS, who was responsible for developing neurosurgery in Germany, came from Würzburg to Berlin.

Curiously enough, up to now the importance of Ernst von BERGMANN for German neurosurgery has been underestimated. Von BERGMANN came from far away; his family had lived for centuries in the Baltic states, more exactly in Livonia, in the north-east of Europe, where his ancestors were well known as Protestant priests. Originally, however, his family had its roots in East Prussia, where one of his ancestors had a small brewery in Pillau. When the family emigrated to the Baltic states in the seventeenth century, it soon entered the academic world


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and the priests of the Bergmann family became widely known. At this time their house, out in the country, even had a workshop where holy books were printed in Latin, Greek, Hebrew, Livonian, and German.

When the well-known Professor of Internal Medicine in Berlin-Charité, Gustav von BERGMANN, visited his ancestors' house in the 20ies he noticed that in the parish there was still no tension between the different nationalities. At that time these little parishes in the Baltic states were still centers of culture and civilization beside the large commercial towns like Riga and Dorpat, so highly developed during the time of the Hansa.

Ernst von BERGMANN studied medicine in Dorpat (now in the Estonian Republic), which at that time was the location for the German-speaking university for the Baltic areas of the Russian Empire. His goal in life was, as he once said, to become a general practitioner with a good income, either in Riga or in Petersburg (Leningrad). However, the rector of the university abruptly put a stop to any such thoughts by stressing that with his intelligence he should become a lecturer at the university; to this end he immediately offered him a lectureship in surgery at the University of Dorpat. Von BERGMANN accepted, even though he was of the opinion that what he had learned at university did not provide an adequate basis for the post, for which reason he requested academic leave. A study tour led him to Breslau, Berlin, and Munich. He returned bursting with ideas and full of new experience and a wealth of knowledge, particularly in the field of pathogenesis and treatment of cranial wounds. Yet this still did not seem to have given him sufficient experience and thus, in the Prussian/Bohemian war of 1866, he worked as a regimental surgeon in the front line of the Prussian army. Also in 1870/71 he seized the opportunity of continuing this work in the German/French expedition, where he turned up not only at garrison hospitals but also at the front line near Paris.

Immediately upon his return to Dorpat in 1871, he was made Professor of Surgery. From then on, he worked continuously, committing to paper the experience and ideas he had gained during the wars. This work on head/brain injuries was published in 1873 and made him famous in the field of war surgery. As a result, when the Russian/Turkish war started, the Czarina at once put him in charge of the whole organization of surgical treatment and for the first time he was able to use a transportable field hospital. However, during this expedition to the Crimea, the Würzburg medical faculty sent him an official order of the Chair of Surgery. This invitation was directed at Dorpat in his absence and was there answered by his wife, who accepted without asking her husband! Upon notification, however, von BERGMANN himself hastily telegraphed to confirm and in 1878 he moved from Dorpat to Würzburg.

This was the time when the successful new method of antisepsis was introduced into the surgery of wounds, though the perpetual contact with carbolic acid was uncomfortable and disagreeable for patients and surgeons alike. Von BERGMANN tried to find other solutions to prevent the infection of wounds.

Moreover, during war surgery he had noticed that the later infection of the wound was usually not due primarily to its introduction into the wound by the bullet, but rather was caused by the surgeon in attempting to remove the bullet from the wound. The logical deduction was to refrain from all major surgery on the battlefield and only to apply a dressing and immobilize the wounded extremity. Much to his surprise and delight, the outcome of this form of treatment was excellent.

But soon his thoughts about improving surgical treatment went further and were stimulated by ideas he had formulated when opening a new hospital in the presence of some of the highest Russian authorities: in an official speech, which then seemed revolutionary, he boldly attacked the architecture and pattern of the present hospitals and added that in his opinion, in breweries the scientific requirements were given as much priority as the outer appearance, whereas surgical wards were not designed with any particular attention to their purpose. The architects of breweries had long been acquainted with the fact that particular fermentation processes required very careful planning of the rooms and special construction of the floors, walls, and ceilings, and that during these fermentation processes they had to be maintained in an extremely clean state. One hardly saw similar attention being given to the construction of the surgical wards. Von BERGMANN believed that all infectious complications, and hospital fever in particular, could only be avoided if the passage of infection from one patient to another was strictly prevented. Such a view had, as a consequence, a new pattern for the wards and led to the introduction of the so-called pavillion system, which had already been very useful in Hamburg at the time of the cholera epidemics. Indeed, Hamburg-Eppendorf was the first such pavillion hospital. Here in Berlin, in the Virchow hospital, the system was later realized in a perfect way.

In summer of 1880 a new professor of surgery for the Ziegelstraße clinic at the University of Berlin had to be appointed and an invitation was sent to von BERGMANN in Würzburg. His arrival at the old clinic was colorfully reported by Carl-Ludwig SCHLEICH in his biography *Besonnte Vergangenheit*. He wrote: "Hardly one stone resisted the energetic grip of the conqueror who had just landed." Furthermore he depicted BERGMANN's personality: "His outer appearance was imposing: He was a tall elegant man, well bearded and with impressive gestures. His speech contained well sounded vowels and he spoke with a slight Livonian accent and a very hard 'rrr'. Particularly impressive was his head, with a high forehead and a well-formed aquiline nose, and sparkling eyes."

The next step in the reorganization of von BERGMANN's clinic was clear after the speech he had previously given in Russia. Logically, he adopted the pavillion system mentioned above, and immediately introduced steam sterilization of instruments and gowns. Next, instead of "antisepsis" with carbolic acid, "asepsis" was developed as the leading and strictly maintained principle for the prevention of infection. One can well understand that in 1890 at the First World Surgical Congress, where 5000 surgeons were assembled from all over the world in the Ziegelstraße hospital, the very clean air was a surprise to all of them. One of the Japanese visitors remarked with surprise: "There is no odor of carbolic acid here." The cool answer of one of the assistants was only: "No Sir, we have not used carbolic acid for the past 8 years in von BERGMANN's clinic."

By the end of the nineteenth century von BERGMANN had made further contributions to neurosurgery by tackling the problem of brain edema and the increase in intracranial pressure. He now also began to treat brain tumors more frequently, though without the degree of success which his compatriot Fedor KRAUSE had achieved in the Augusta-Hospital in Berlin; this was probably due to the lack of such an outstanding neurologist as OPPENHEIM.

Nonetheless, this does not diminish the importance of Ernst von BERGMANN, who contributed much to the technique of neurosurgery, such as the introduction of an electrically driven saw for trepanation of the skull. He also worked on the prevention of brain prolapse and on several other problems in neurosurgery.

In addition von BERGMANN was interested in further education of doctors and he contacted the famous Ministerialdirektor Althoff, suggesting the founding of medical academies alongside the universities, a suggestion which was realized in Cologne, Hamburg, and Düsseldorf around 1902.

Before finishing I should rather like to relate the affair concerning Kaiser Friedrich, the son of Wilhelm I, the Kaiser who founded the German Reich in 1871. Friedrich had developed a problem with his vocal cords and von BERGMANN diagnosed a carcinoma. This was later confirmed by VIRCHOW. Friedrich had already agreed to an operation which would have presumably saved his life even if it meant the loss of his voice. However, his wife, daughter of the Queen, requested a consultation with the British specialist McKENZY, who disagreed with this diagnosis and recommended conservative treatment in a mild climate. The tragic end of this story is well known: Kaiser Friedrich died after reigning for only 99 days. We might ask ourselves what the outcome would have been had the development of the newly united German taken place under the liberal Friedrich instead of Wilhelm II. And we might even further ask what the outcome of subsequent world history would then have been. Incidentally, at that time Ernst von BERGMANN was violently attacked by the camarilla of the court.

Looking back, his life was that of a highly gifted surgeon, an impressive personality, and an energetic man who remained active at the operating table until his death in 1907. His tomb stands in Potsdam near the part of Berlin where he died. As I have already mentioned, his achievements merit that Ernst von BERGMANN be considered as the first of the four pioneers of German neurosurgery.

# Extradural Tumors of the Spine

A. Weidner (Winner of the Travenol-Prize)
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## Introduction

Tumors of the spine can result in either compression of the spinal cord or individual nerve root and/or instability of the spinal column. For either of these reasons, patients are admitted to a neurosurgical or orthopedic hospital.

The majority of tumors involving the spine are metastases, as primary bone tumors prefer the skeletal areas with large growth performances, such as the knee region.

To understand the entire spectrum of spinal tumors, the clinical courses of 320 patients treated at the Department of Neurosurgery of the Medical School of Hannover (head: Prof. Dr.Dr.h.c. H. DIETZ) and at the Orthopedic University Clinic, Münster (head: Prof. Dr. H.H. MATTHIASS) were evaluated.

## Case Breakdown

Of 320 spinal tumors, 148 were metastases, 8 were Hodgkin's disease, and 164 were primarily located in the spine (Tables 1, 2). Only 36 of the 320 tumors were benign. The age at onset of the disease is an important differential diagnostic criterion between benign and malignant tumors. Only 15% of the patients with metastases were younger than 40 years, while over 50% of the patients with benign tumors were under 20 years. Metastasis, therefore, should be suspected when a spinal lesion develops beyond the 4th decade.

Of all tumors, 12% were detected in the cervical spine, 37% in the thoracic spine, and 42% in the lumbar spine. Nine percent of our patients demonstrated involvement of several spinal areas.

## Case History

The length of the history depends on the presence of symptoms or signs necessitating a visit to the doctor. In patients with benign tumors a correct diagnosis is established later than in patients with well known primary malignant disease. Symptoms lasting for over one year without a definitive diagnosis occurred in 25% of all patients with benign tumors, but only in 10% of those with primary malignant spinal tumors. On average benign tumors were diagnosed 15 months after onset of symptoms, whereas in cases of metastasis, treatment was already initiated after an average of 6 months. Particularly osteoid osteomas were over-


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Table 1. Classification of primary spinal tumors and tumor-like lesions

| Histological type | Benign | Cases | Malignant | Cases |
|---|---|---|---|---|
| Osteogenic | Osteoma | 3 | Osteosarcoma | 4 |
| | Osteoid osteoma | 5 | | |
| | Osteoblastoma | 8 | | |
| Chondrogenic | Chondroma | 2 | Chondrosarcoma | 4 |
| | Osteochondroma | 4 | | |
| Giant cell tumor | Giant cell tumor[a] | 5 | | |
| Hematopoetic | | | Ewing sarcoma | 5 |
| | | | Reticulum cell sarcoma | 12 |
| | | | Non-Hodgkin sarcoma | 3 |
| | | | Myeloma | 41 |
| Vascular | Hemangioma | 14 | Hemangio-endothelioma | 1 |
| | | | Angiosarcoma | 1 |
| Fibrogenic | Desmoplastic fibroma[a] | 1 | Fibrosarcoma | 5 |
| | | | Histiocytoma | 2 |
| Notochordal | | | Chordoma | 10 |
| Lipogenic | | | Liposarcoma | 2 |
| Unknown origin | | 3 | | |
| | *Tumor-like lesions:* | | | |
| | Aneurysmal bone cyst | 12 | | |
| | Eosinophilic granuloma | 11 | | |
| | Fibrous dysplasia | 3 | | |

[a]Semimalignant

Table 2. Site of primary malignancy

| Organ | Cases |
|---|---|
| Lung | 35 |
| Breast | 32 |
| Prostate | 11 |
| Kidney/bladder | 9 |
| GI tract | 7 |
| Bone | 7 |
| Uterus | 6 |
| Testis | 6 |
| Skin | 4 |
| Thyroid gland | 3 |
| Unknown | 28 |
| | 148 |

looked for a longer period (up to 3 years), and semimalignant chordomas were finally diagnosed after an average of 20 months (range 1 - 6 years).

In this study diagnosis was established within the first 3 months in 42% of all cervical spine tumors, 52% of thoracic spine tumors, but only 28% of lumbar spine tumors. This is apparently due to the fact that radiological clarification is not immediately considered in general practice in the commonly occurring cases of low back pain.

In 85 of 148 patients with metastases, the primary tumor was well characterized on admission. After the first year of treatment of initial disease, 40% of the patients already showed spinal metastases. Tumors of the breast or uterus and thyroid gland carcinomas metastasized relatively late to the spine (3 - 6 years).

## Findings

Of our patients, 96% complained of spinal pain which increased during the course of the disease, with a very slight reduction in the symptoms after immobilization. Compression of the spinal cord or nerve roots was not detectable in 30%. An incomplete paraplegia syndrome was diagnosed in 25% of the patients at the beginning of therapy, and a complete paraplegia syndrome in 10%. Radicular deficits were seen in 35% of patients.

The neurological deficit symptoms were based upon localization: 39% of the lumbar spine tumors did not demonstrate neurological deficits, while in the cervical and thoracic region only 23% of the neurological findings were normal. Patients with neurological disorders dominated in the neurosurgical case study, therefore showing a selection.

The neurological findings alone did not define the extent of disability: of 142 patients confined to bed, 19 did not have neurological deficits but were exclusively disabled secondary to instability of the spine.

## Therapeutic Results

Catamnestic evaluations were possible in 92% of 320 patients. The tumor was removed surgically in 201 patients (63%), and 88 of this group were additionally stabilized. A complete paraplegic syndrome developed postoperatively in six patients, while four patients died during the first 10 postoperative days.

After surgery, disabilities caused by benign tumors regressed in 74% of cases, while improvement after surgical treatment was also noted in 70% of patients with primary malignant tumors. Only 30% of the patients with primary malignant tumors improved with conservative treatment (radiation, cytostatic drugs).

Due to the short survival expectancy of patients with metastases (see below), evaluation of improvement was restricted to those patients who lived longer than 6 months after the introduction of therapy (81 of 144); thus, for example, only 9 of 35 patients with metastasis from a bronchial carcinoma could be included in this study. With such selection, 44% of the operated patients demonstrated a regression of symptoms, whereas only 27% were improved with conservative treatment.

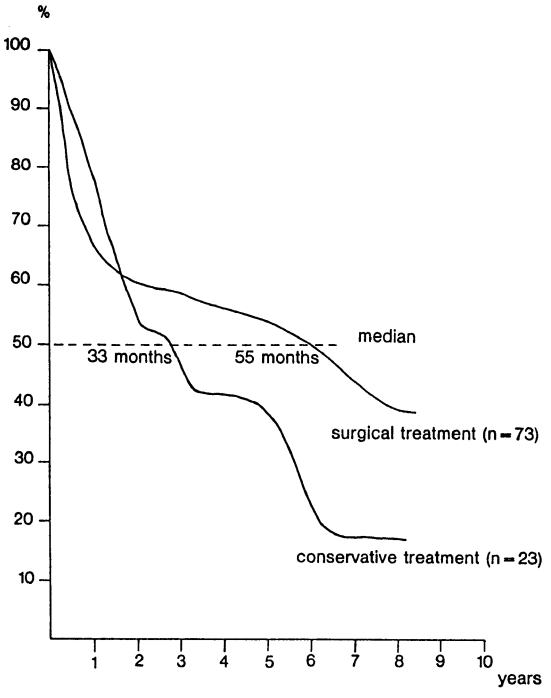


Fig. 1. Survival curves for spinal primary malignant tumors

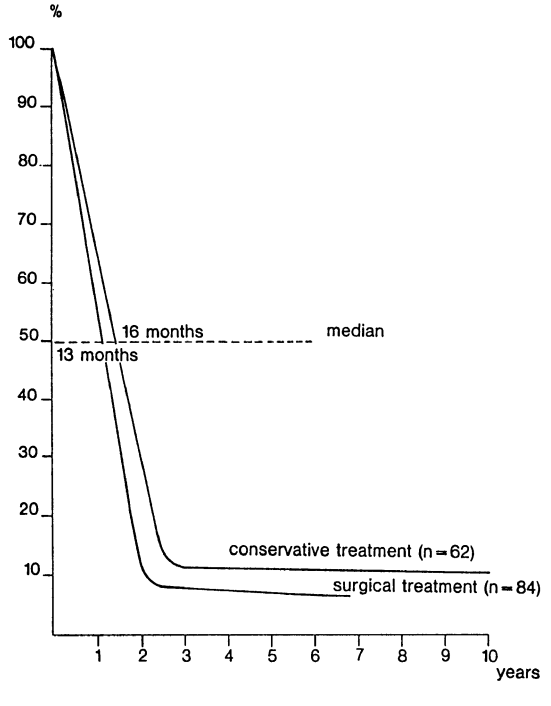


Fig. 2. Survival curves for spinal metastases

## Survival

The survival curves for primary malignant tumors (Fig. 1) and secondary spinal tumors (Fig. 2) demonstrate the different biological reactions of these tumors and also the different influence of surgical measures on the length of survival. Patients with primary malignant tumors lived longer when surgically treated: 55 months vs 36 months. However, in relation to the definitive tumor type, e.g., plasmocytoma, this distinction is not significant.

The median range of the time-span between the onset of symptoms and death in patients with spinal metastases submitted to surgery was 13 months, while patients treated conservatively lived 3 months longer. This difference is not significant, due to the different composition of the two patient groups.

Every report of therapeutic success in spinal metastases should include consideration of the primary tumor, for under similar conditions, the length of survival is essentially determined by the biological pattern and by the adequacy of treatment of the primary tumor. This indicates that treatment of a spinal metastasis can only be performed interdisciplinarily.

Patients with metastasis in other bones, liver, and lung survived, on average, only 4 months after the beginning of therapy and therefore have not been included in the survival curves. Forty-one percent of all the patients with metastases died on the ward.

## Indication for Surgery

In deciding which therapy should be recommended or could be tolerated by the patient, the remaining life expectancy should be taken into consideration. Furthermore, the success of spinal metastasis therapy is undermined if the patient continues to suffer from intractable pain from the primary tumor (e.g., carcinoma of the rectum) or if, shortly after operation, metastases develop in other skeletal areas which make mobilization of the patient impossible.

Indication for surgery is also subject to the tumor localization. For instance, cervical spine metastases can be removed with little stress and do not give rise to essential problems in regard to stabilization.

Benign tumors such as osteomas and hemangiomas have to be excised only when they cause compression of nervous structures. Eosinophilic granulomas in the spine can be treated with radiation therapy.

In plasmocytomas, radiation with accompanying chemotherapy is indicated even when neurological deficits are present, because surgical treatment has not been shown to be superior to conservative treatment. Only if the neurological symptoms deteriorate during oncological therapy are operative decompression and stabilization indicated. There is no alternative to surgery with all other primary malignant tumors.

Exclusive decompression of the spinal cord with laminectomy in extradural tumors increases instability of the spine; thus spinal surgery does not lead to good long-term improvement without knowledge of biomechanics or without experience in handling implantations.

In those forms of metastasis from a primary tumor (e.g., breast, prostate) which have a longer survival time (Table 3), there is a relative indication for surgery when neurological deficits are present. Pallia-

Table 3. Six-month survival rates in patients with spinal metastasis

| | |
|---|---|
| Breast ca. | 72% |
| Prostatic ca. | 71% |
| Uterine ca. | 33% |
| Bronchial ca. | 21% |

tive junction-osteosynthesis is indicated in cases of instability of the spine. In those forms of metastasis (e.g., from bronchial carcinoma) which suggest a life span of 4 - 6 months, or in multiloculuar metastases, surgery should be considered only in exceptional cases (those involving the cervical spine) as oncological therapy has been shown to be superior.

If metastases are suspected, diagnosis must always be secured by a biopsy, so further therapy can be introduced.

## Final Comment

In addition to the question of the choice of the treatment based on our results, I found it was important to consider the view of the patient's relatives: if an operation had been denied, the question of whether "everything possible had been tried" was often encountered. Alternatively, if a patient died shortly after a large operation the necessity of that operation was often questioned. A biopsy establishing the diagnosis gives everyone a realistic impression of the prognosis, thereby avoiding false expectations or new disillusionments. This approach appeared to help both the patient and his relatives psychologically. I find this improvement in the quality of life important although it may not produce a marked neurological or radiological improvement.

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# Intraoperative Spinal Cord Monitoring*

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## Introduction

Despite meticulous microsurgical technique there is a postoperative increase in neurological deficit after spinal cord operations, especially in difficult cases like angiomas or intramedullary tumors (4). Spinal cord monitoring is based on the concept of early intraoperative detection of spinal cord function impairment in order to adapt the surgical technique to minimize possible damage to important structures (1, 2, 3, 7, 13, 15, 17, 18). The personal judgment of the surgeon is supported by the *objective* registration of evoked potentials. In this paper, our method and first results will be presented.

## Methods

A stimulus of 0.1 - 0.3 ms with 10 - 20 mA in peripheral nerves and 2 mA in epidural stimulation is used at a frequency of 5.1 - 5.3 Hz, with 300 - 500 runs on average. Bandwidth is mostly 30 - 3000 Hz. Analysis time varies between 30 and 100 ms. A CA-1000 is used, usually in a four-channel arrangement. Median nerve stimulation is used for cervical tumors, whereas peroneal and cauda equina stimulation is used for lumbar and thoracic tumors. Silver cup electrodes are used on the skin, while silver or platinum ball electrodes are used epidurally and on the medulla. Whenever possible, recordings are simultaneously performed, epidurally rostral from the tumor, at the cervical ($CV_2$+$CV_7$-$F_z$) level, and at the cortical level ($C_z$', $C_3$',$_4$'-$F_z$) (Fig. 1). The continuous intraoperative recording is supplemented by a pre- and postoperative evoked potential examination. First recordings are performed during positioning of the patient, the last one during skin closure.

Three patient groups have been studied: (a) spontaneous fluctuations in nondiseased spinal cord cases, (b) the effects of fentanyl and enflurane, and (c) spinal cord monitoring. The anesthesiology and variability studies will be published in detail elsewhere (12, 17).

Intraoperatively obtained potentials in 20 patients without spinal cord lesions and without spinal cord manipulation (ten with peroneal nerve

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*This paper is not identical to the work submitted for the Travenol prize, as the latter did not lend itself to a shortened version, necessary for this publication. However, this paper does contain a representative part of the work presented for the prize.


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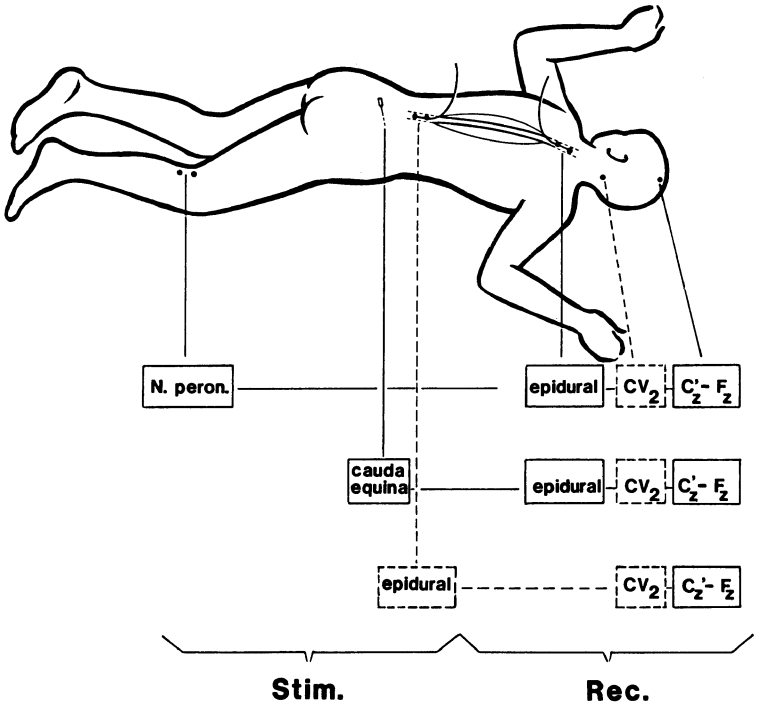


Fig. 1. Schematic presentation of stimulation and recording sites. Less frequently used sites are indicated by broken lines (14)

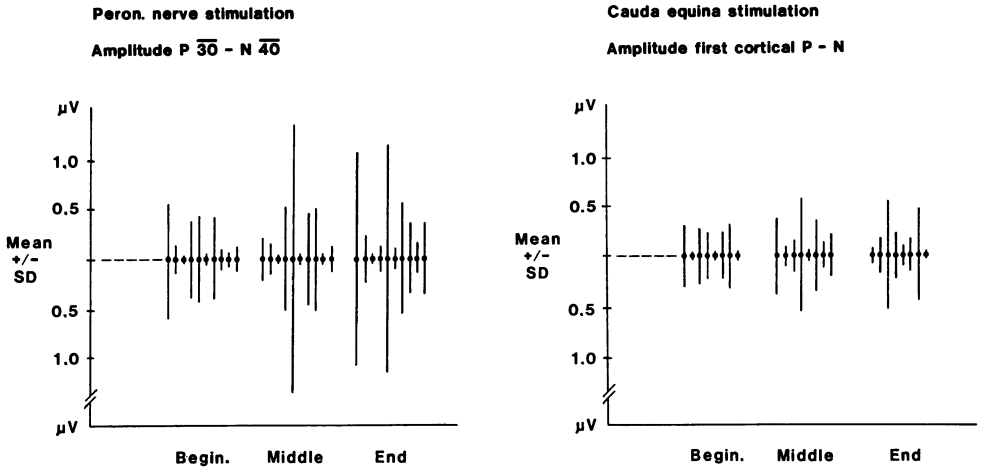


Fig. 2. Comparison of standard deviations of amplitudes of first cortical event after peroneal nerve and cauda equina stimulation in two patient groups with spinal cord pathology and with spinal cord manipulation. There were eight patients in the cauda equina group, ten in the peroneal nerve group. From each patient five recordings taken during the beginning, middle, and end of the operative procedure were used to give the mean value and standard deviation. The variability in the cauda equina group was less marked

stimulation and ten with median nerve stimulation) were evaluated concerning the mean, standard deviation, and coefficient of variability of the amplitude and latency of the first large positive-negative event. Groups of five measurements from the beginning, the middle, and the end of the operative procedure in each patient were compared. A similar procedure was performed in 18 patients with spinal cord lesions (eight with cauda equina stimulation). Thus, it was possible to compare the effects of different stimulation sites and the presence of a spinal cord lesion on the latency and amplitude of intraoperative potentials (Fig. 2).

The influence of fentanyl and enflurane was compared in over 30 patients. Fentanyl and enflurane were used in steps of 1.8 µg/kg, 3.6 µg/kg, and 7.2 µg and 0.5% and 1.0% respectively (17). Flunitrazepam and atropine were used as premedication and 0.2 µg/kg etomidate, 0.01 mg/kg flunitrazepam, 0.1 mg/kg pancuronium, and 66% $N_2O$ were used for induction. Amplitude and latency after median nerve stimulation were evaluated with different levels of the two anesthetic gases but with the same means of induction and premedication.

In 25 cases monitoring was performed: 5 extradural and 5 intramedullary space-occupying lesions, and 15 intradural lesions. The location was thoracic in 16 cases, cervical in 6, and lumbar in 3. Cortical recordings were used in 25 cases, epidural recordings in 18, and cervical skin recordings in 15. The peroneal nerve was stimulated in 23 cases, the median nerve in 19, and the cauda equina in 11. Epimedullary stimulation was used in 3 patients. While in no case were recordings obtainable at all recording sites (e.g., epidural, cervical, cortical), a technical failure rendering any recording impossible occurred in only 1 of 25 cases.

## Results

The spontaneous fluctuation of intraoperatively obtained evoked potentials differed widely depending on the stimulation and recording site and on the presence of a spinal cord lesion.

Cortical potentials after median nerve stimulation were most stable; peroneal nerve evoked potentials showed a high degree of variability. Cauda equina evoked potentials, however, were nearly as stable as median nerve evoked potentials. Amplitudes demonstrated a markedly larger variability than latencies. In patients with spinal cord lesions whose cords were manipulated, there was a marked increase in variability as compared with nonmanipulated nondiseased spinal cords (for details and statistical data see (12)).

The influence of enflurane and fentanyl on the evoked potential was quite different. Subcortical potentials recorded over the cervical spine were less influenced than cortical potentials. The combination of fentanyl and benzodiazepine attenuates cortical potentials in amplitude but hardly affects the latencies of cortical peaks whereas subcortical potentials are unaffected (Fig. 3) (17). With fentanyl-benzodiazepine anesthesia occasionally problems arise in keeping the blood pressure down, but usually these can be managed with low doses of enflurane (0.5%). Factors influencing the intraoperative recording in a negative fashion are numerous: bipolar and monopolar coagulation, 50-Hz noise, irrigation, and use of the ultrasonic aspirator. Very often, however, the reasons for obtaining poor potentials remain unknown. One important reason is that potentials already poor preoperatively were obtained due to the existence of a spinal lesion.

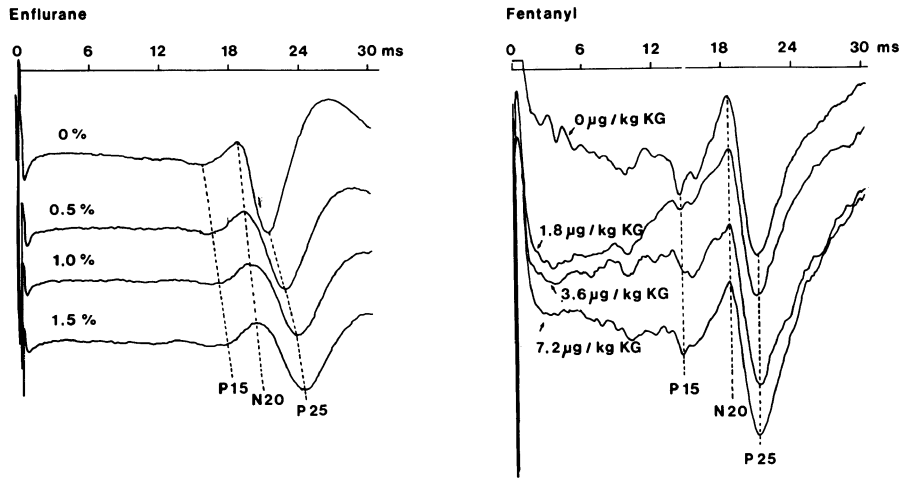


Fig. 3. Effects of enflurane and fentanyl on cortical evoked potentials at varying doses. There is a nearly linear increase in latency with increasing enflurane doses, accompanied by a decrease in amplitude. With fentanyl amplitudes decrease very slightly and latencies remain stable (17)

Short-lasting amplitude and latency changes are common and are not indicative of a significant change unless they remain unchanged for at least 15 min. Longer lasting potential changes were seen in 11 of 25 cases. In eight cases the potential was changed, but it recovered well during the operation in three cases and by the end of operation in five. In one patient with a thoracic disk there was a long-lasting potential loss but it was not possible to discriminate between a technically induced potential loss, as this was only noted during the use of the micro drill. In another case with a longer lasting deterioration in potential there was a postoperative bladder disturbance, without other severe neurological sequelae, which took several months to resolve. No true false-negative monitoring result, however, was noted. (By "false-negative" cases I mean those in which the potentials did not show significant changes but in which there was significant postoperative neurological deterioration.)

## Discussion

Since the concept of spinal cord monitoring was introduced by Croft et al. in 1972, several reports have appeared, mainly from orthopedic series (2, 6, 15, 16). Spinal cord monitoring in neurological series, however, will certainly yield different results, as patients who are neurologically more compromised are usually to be monitored (1, 7, 8, 18). Despite this fairly large number of reports many questions still remain unanswered. Few data, for example, have been published concerning spontaneous potential changes during spinal cord monitoring (5, 18). Very little experience exists with simultaneous recordings from epidural, cervical skin, and scalp leads (Fig. 4). Our technique (Fig. 1) involves as many recording sites as technically possible, and with further experience more details will be obtained concerning the diagnostic yield of various recording sites. Some of our first results (12, 14) demonstrated that cauda equina stimulation is more effective than peroneal nerve stimulation. It has previously been pointed out in an

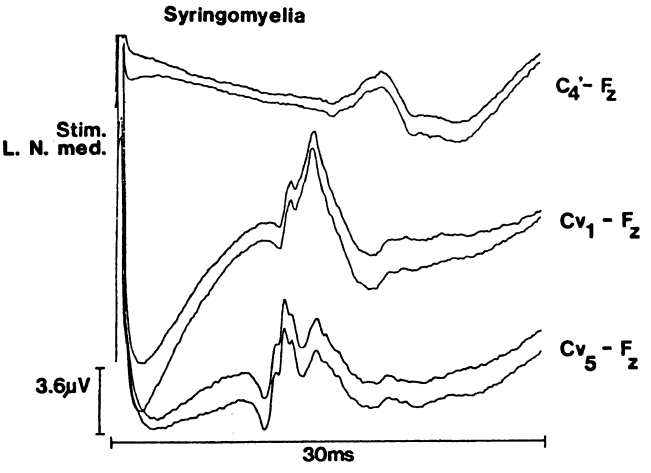


Fig. 4. Intraoperative recordings from the scalp ($C_4$-$F_z$) and the cervical skin ($C_{v1}$-$F_z$, $C_{v5}$-$F_z$) after stimulation of the left median nerve in a case of syringomyelia. Two superimposed recordings demonstrate good reproducibility. These evoked potential tracings show normal features with a cortical negative event around 19 ms and typical triphasic cervical potentials

experimental study in the cat (3, 10) that spinal recordings demonstrate a spinal cord lesion earlier than do cortical recordings. Our limited clinical experience with only 25 cases, in some of which simultaneous spinal and cortical recordings were not possible, does not yet allow a reasonable conclusion concerning this matter. But we have already been able to demonstrate the existence of the evoked spinal cord injury potential (11) in intraoperative spinal cord monitoring in several cases (13). Although the number of cases is too small to allow for a judgment on spinal cord monitoring, we have already been able to demonstrate that spinal cord monitoring in the hostile environment of the operating room is technically feasible and has a low rate of failure. As discussed in more detail elsewhere (17), the anesthetic regime used in our hospital has very little effect on cortical somatosensory potentials and does not affect subcortical SEPs at all. We have therefore been able to establish a technique including anesthesiological methods which allows us to continuously gain more experience with the application of this method in the management of spinal cord pathology. Although there have been no true false-negatives in our series yet, it would be unwise to discount this possibility, which will most likely occur in one of our coming cases as we are dealing with *biological data*. Spinal cord monitoring is a technique in a state of evolution which offers the prospect of enabling the surgeon to adapt his technique on the basis of objective criteria and thus improve the outcome of spinal cord surgery. A definite judgment on its value, however, is not yet possible.

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# Spinal Cord Tumors

# Basic Anatomic Considerations Concerning the Surgical Approaches to the Spinal Column

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The 36th Annual Meeting of the German Society for Neurosurgery discussed surgical approaches to the various parts of the spinal column, the ligaments, and the attachments of the spinal cord and its vasculature. In this paper, data are presented on the approaches to the craniocervical junction in particular, but also to the thoracic and lumbar spinal cord.

## Approaches to the Craniocervical Junction

### *Dorsal Approach*

As a rule, the dorsal approach is made by way of a median incision of the skin between the external occipital protuberance and the spinous processes of the second or third cervical vertebra. The medial sections of the superficial, middle, and deep muscle layers are pushed aside, or if necessary, removed. The m. trapezius begins immediately lateral to the external occipital protuberance at the linea nuchae. Its width is about 28 mm (range 5 - 58 mm) at this point. Below this muscle and between the linea nuchae inferior and the linea nuchae superior on the occiput, is the attachment of the m. semispinalis capitis, which is 62 mm broad on average (50 - 82 mm). The deeper neck muscles include the mm. rectus capitis posterior major et minor, as well as the mm. obliqui capitis inferior et superior. Close to the midline, the m. rectus capitis posterior major runs a course between the usually forked posterior process of the axis and the zone of the transverse section of the linea nuchea inferior and below it. This muscle has a length of about 43 mm (34 - 57 mm) and forms an angle of about 43° (23 - 72°) with the transverse plane. Medial and below this muscle is the m. rectus capitis posterior minor. It originates from the posterior tuberculum of the arcus posterior atlantis, its insertion lying in the median third of the linea nuchae inferior and below it.

In our material the muscle is 27.5 mm long (16 - 36 mm). The obliquus inferior muscle originates from the spinous process of the axis and runs in a diagonal direction laterally and forward to the dorsocaudal surface of the massa lateralis until reaching the root of the posterior arch of the atlas. In our material this muscle is 51 mm long (37 - 66 mm) and forms an angle of about 8° (-8 to +22°) with the transverse plane.

The m. obliquus capitis superior originates from the massa lateralis atlantis and from the lateral end of the posterior arch of the atlas, runs in a dorsal direction and upwards, and ends at the sagittal sections of the linea nuchae inferior. Frequently its fan-shaped insertion extends in a medial direction beyond the transverse section of the in-

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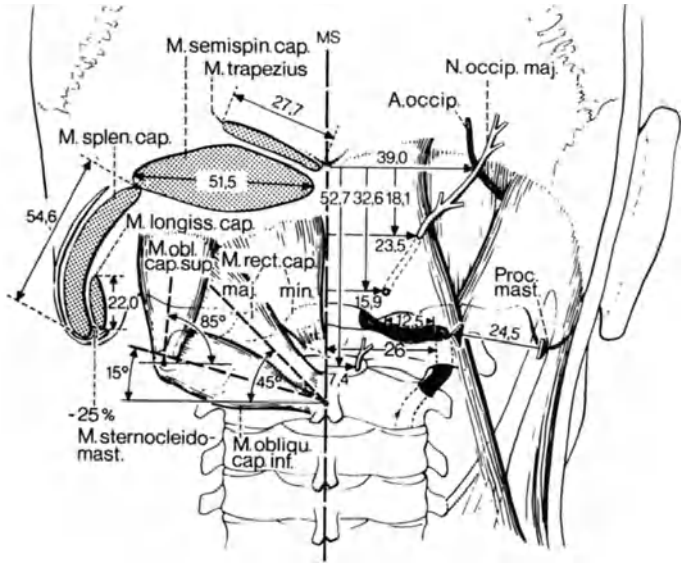


Fig. 1. Measurements of the insertion areas of different muscles on the head *(left side)* and angles of the suboccipital muscles (own material). On the *right side* the area of decussation of the n. occipitalis major on the a. occipitalis is visible (in this area the nerve can be compressed by a fibrous band or a transverse muscle). Also shown are the distance of the entrance and exit zones of the nerve and the trapezius muscle to the protuberantia occipitalis externa and to the sagittal plane. Measurements of the (oblique) distance between the mastoid process and the lateral border of the vertebral artery on the atlas were made by RICKENBACHER (1964)

ferior nuchal line. It has a length of 50 mm (39 - 63 mm) in our autopsy material, and it forms an angle of 38° (22 - 55°) with the Frankfurt horizontal plane (Fig. 1).

The rectus capitis posterior major, obliquus capitis inferior, and obliquus capitis superior muscles form the borders of the so-called trigonum nuchae. In the depth of this triangle, the vertebral artery and its accompanying vein run in the sulcus of the vertebralis artery of the atlas. As a rule the suboccipital nerve leaves the sulcus between the vertebral artery and the accompanying vein, running in a dorsal direction to innervate the so-called short and deep neck muscles rectus captis posterior minor, rectus capitis posterior major, obliquus capitis inferior, and obliquus capitis superior. If a midline approach is chosen (as is the rule), then the so-called septum nuchae, which extends from the external occipital protuberance to the dorsal spinous processes of the cervical vertebrae in the midline, is transected. In our material this septum consists of loose collagenous connective tissue and is frequently traversed by veins. The distance between the skin and the posterior tuberculum of the atlas is about 50 mm in men and 37 mm in women according to our material (Fig. 2). The boundaries are 29 - 70 mm. Again according to our material, the skin over the external occipital protuberance is 7.2 mm thick in males and 6.8 mm thick in females (mean values).

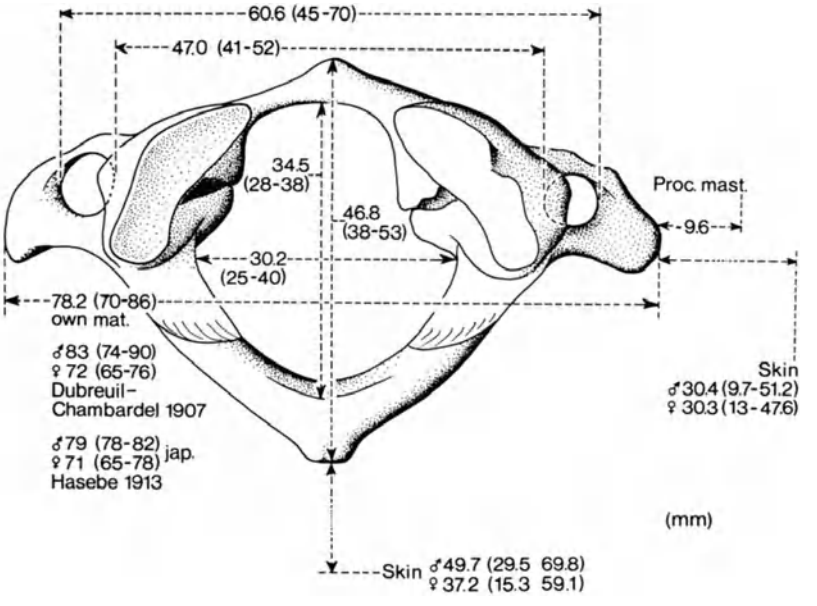


Fig. 2. Upper surface of the atlas, with measurements of its width, the medial lateral borders of the foramen processsus transversi, the width of the vertebral foramen, the length of the vertebral foramen, and the total length. Also shown are our measurements between the massa lateralis and the mastoid process and skin, and between the skin and the tuberculum posterius atlantis

As a rule, the squama occipitalis (lower) and crista occipitalis interna and externa must be removed. When the dorsal lamina of the atlas is removed, care must be taken not to injure the vertebral artery and its accompanying veins. This section of the artery is known as the pars atlantis. It runs from the foramen processus transversi atlantis in a rounded course, first in a dorsal direction, then medially, and then ventrally, or these sections have a more angulated shape. From the pars atlantis of the vertebral artery, muscular branches supply the neck muscles at irregular intervals and form anastomoses with the deep cervical artery, the occipital artery, and others. A further vessel, the ramus meningeus posterior, originates from the pars atlantis of the vertebral artery. This branch serves to supply the dura mater and bone of the occipital squama and anastomoses with other meningeal arteries. A relatively rare occurrence is the exit of the inferior posterior cerebellar artery (PICA) from the pars atlantis of the occipital artery (LANG 1985). If present, the PICA penetrates the dura mater somewhat dorsal to the vertebral artery in these cases and runs dorsal to the ligamentum denticulatum and the accessory nerve. The dura mater is thickened at the posterior edge of the foramen magnum and also into the pericranium. A further thicker zone of dura mater is found in the region of the arcus posterior atlantis, from which the ligaments also run to the spinal dura mater. The spinous process of the axis is usually forked. The multifidus muscles insert from below, as do the semispinalis cervicis and the spinalis cervicis muscles. Occasionally the origin of the multifidus muscle on the arch of the axis is broadened in a lateral direction. If the dorsal arch of the axis is also removed, care must be taken with the course of the second cervical nerve, which exists between the atlas and the axis in a dorsal direction. The nerve

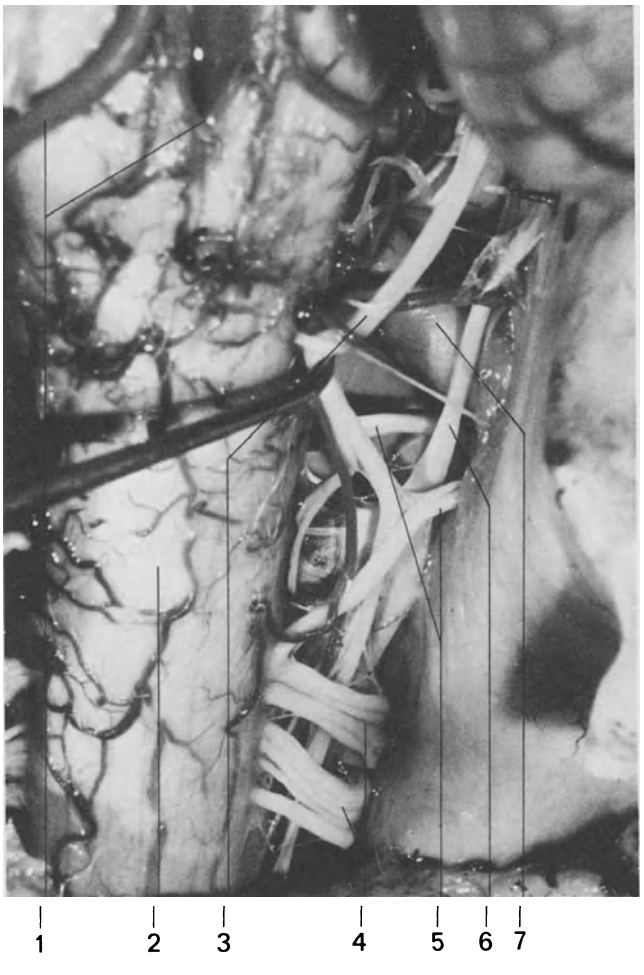


Fig. 3. Exposure of the medulla oblongata and the medulla spinalis and surrounding structures from behind. *1*, PICA and obex; *2*, medulla spinalis; *3*, n. accessorius, displaced to the left; *4*, posterior root fibers $C_2$ (see anastomoses to n. XI and $C_1$); *5*, anterior and posterior root fibers $C_1$; *6*, first serration of the dentate ligament; *7*, vertebral artery

runs dorsal to the lower joint protuberance of the atlas. In the opinion of several authors this nerve may be damaged by rotation of the head. In the axo-atlantal area, the vertebral artery can form convolutions in a dorsal, lateral, or even medial direction. In rare cases this blood vessel does not run through the foramen processus transversus atlantis but medial to it so that it enters the spinal canal after passing through the ligamentum flavum (Fig. 298b in LANZ and WACHSMUTH 1982).

After transecting the dura mater and the arachnoid membrane in the midline, care must be taken not to damage a posterior medullary vein which passes from the medulla oblongata to the sinus occipitalis or to the sinus marginalis of the foramen magnum (Fig. 3). Not infrequently the PICA forms caudal loops extending to the level of the arcus posterior atlantis, and occasionally even lower. In the vicinity of the dura mater, care must be taken to avoid the rami medullares laterales as well as the radicular arteries (see LANG 1983).

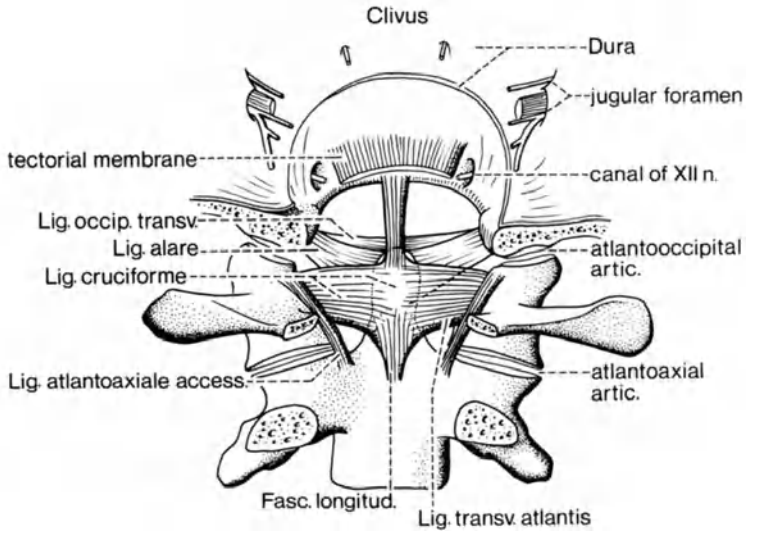


Fig. 4. The most important ligaments of the atlantoaxial joint area

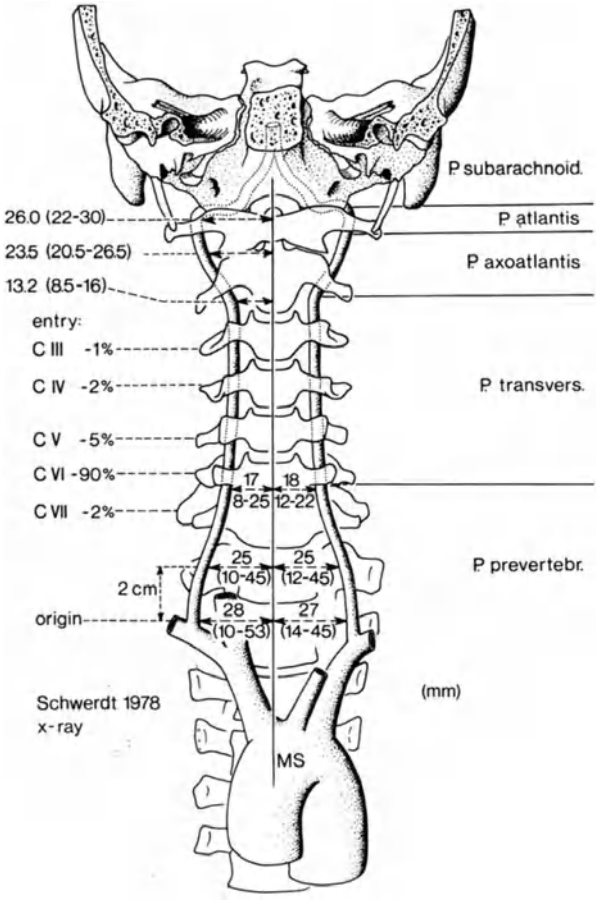


Fig. 5. Paramedian distances of the vertebral arteries and their course in the foramina of the transverse processes [the lower measurements were made from x-rays (SCHWERDT 1978), while the upper and osteological measurements were made in our institute]

*Transoral Approach*

When the transoral approach is used, the mucosa, the pharyngobasal membrane, and the superior pharyngeal constrictor muscle are usually transected in the midline and pushed to the side. At the back of the pharynx parts of the venous pharyngeal plexus are often found. The arterial supply of the upper sections of the pharynx comes chiefly from the ascending pharyngeal artery, which also supplies the prevertebral muscles (together with the vertebral artery) and forms anastomoses with the thyroid arteries. The prevertebral fascia makes it easy to shift the posterior wall of the pharynx in a lateral direction. In front of the spinal column runs the m. longus colli, its pars obliqua superior to the tuberculum anterior atlantis and the longus capitis muscle, diagonally, upward, and medially to the zone lateral to the tuberculum pharyngeum of the clivus. Its uppermost part is imbedded in a thick sheath of connective tissue. In the midline, the anterior atlanto-occipital membrane stretches between the anterior arch of the atlas and the occiput. This consists chiefly of longitudinal fibers. Lateral to it runs the rectus capitis anterior muscle between the lateral laminar section of the anterior arch of the atlas upward and medially to the clivus and dorsally to the insertion zone of the longus capitis muscle. The prevertebral muscles and the anterior atlanto-occipital membrane can be transected and the anterior arch of the atlas removed. From the upper surface of the dens, the alar ligaments run in a lateral and upward direction. The upper surface of the dens is often crossed by the transverse occipital ligament.

The apical ligament of the dens and further small ligaments in the area between the basion and the transversal ligament of the atlas do not have any mechanical importance (Fig. 4). The transverse ligament of the atlas becomes visible after the dens has been removed (see Fig. 358 in LANG 1983). Following the removal of the transverse ligament of the atlas, the longitudinal fascicles of the cruciform ligament, and the tectorial membranes, the dura mater is opened so that the rhomboid ligament and the spinal cord, as well as the vertebral arteries and their branches, are exposed. Figure 5 shows the paramedian distances of the vertebral arteries in the cervical spinal column. It should be emphasized that the transverse section of the vertebral artery occasionally forms loops in a medial direction (particularly $C_3$).

*Retropharyngeal Approach (Fig. 6)*

Following the skin incision at the anterior border of the sternocleidomastoid muscles, this muscle and the greater auricular nerve are displaced in a dorsal direction. The muscles originating from the styloid process and the digastric muscles as well as the styloid process must be transected as a rule, while the mandible and the parotid gland are pushed in an anterior direction. The approach to the craniocervical junction is achieved either by displacing the large vessels forward behind these structures or by displacing the vessels and nerves backward in front of them. A good orientation point is the lateral mass of the atlas, which always extends far laterally and from which a number of muscles insert on coming from a lower direction and proceeding backward and upward. The caudal cranial nerves and the sympathetic trunk now run in the lateral parapharyngeal space. Figure 7 shows the thickness, anastomoses, and ganglia of these nerves.

The lower cervical spine (below $C_3$) and the spinal canal of this section are usually approached from a dorsal as well as from a ventrolateral direction behind the sternocleidomastoid muscle and in front of the large cervical vessels. For further information see Fig. 8.

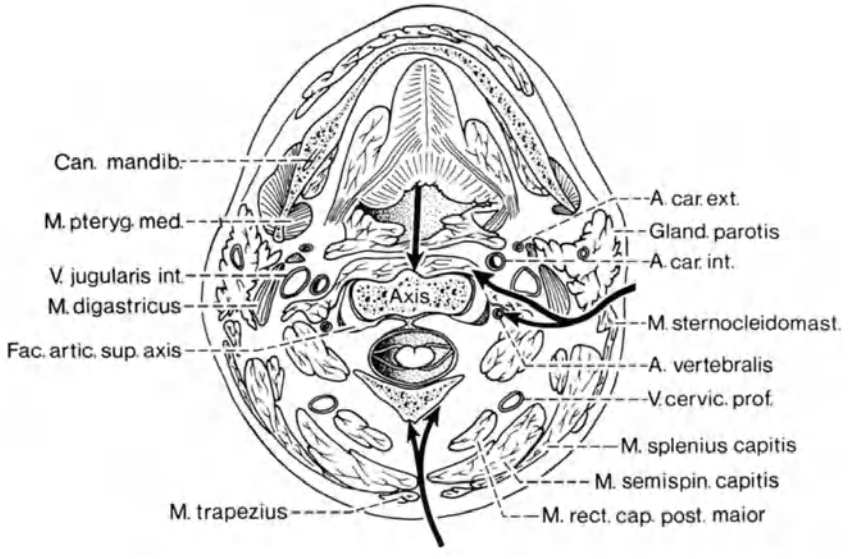


Fig. 6. Transverse section through the level of the facies articularis superior axis, and the most common approaches into this area

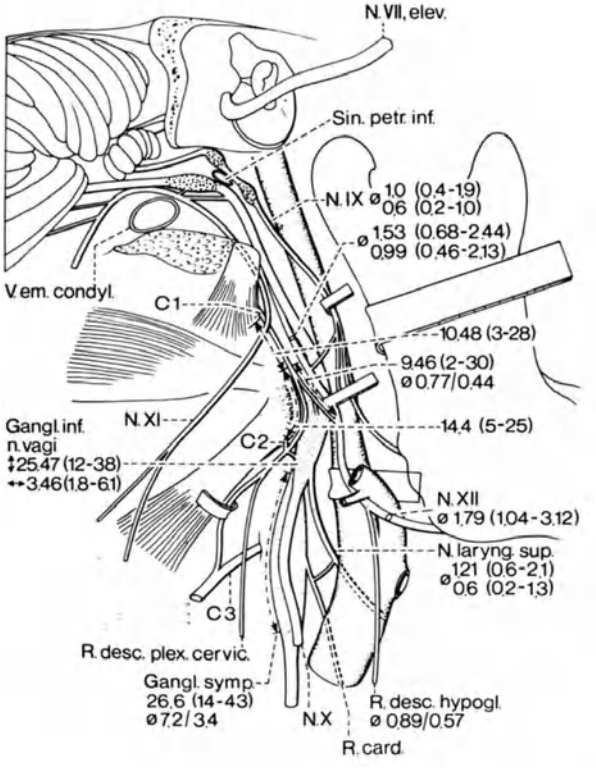


Fig. 7. Course of the lower cranial nerves, diameters of these nerves, and lengths of the ganglia. All measurements are in millimeters. The mandibula and the ninth cranial nerve are displaced anteriorly. The jugular foramen is opened

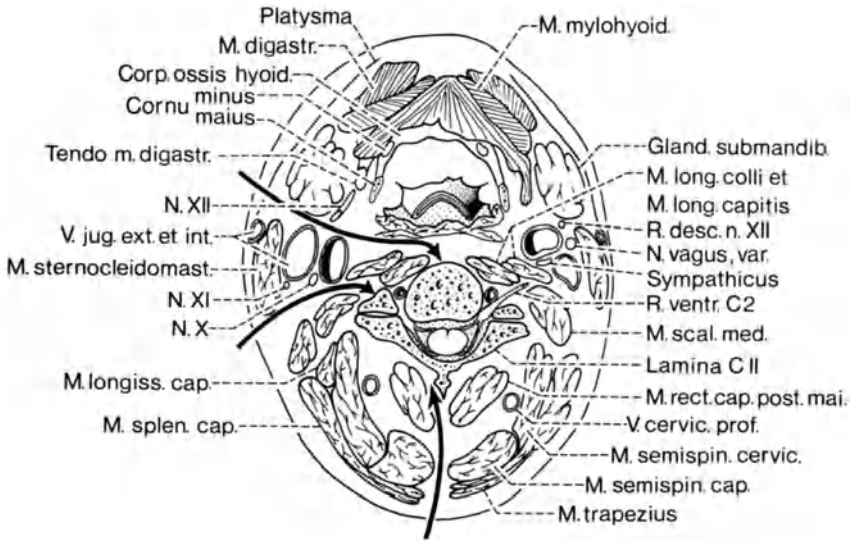


Fig. 8. Transverse section through the body of the third cervical vertebra at the level over high bifurcation (ca. 12%) of the a. carotis communis. *Arrows* indicate the most common approaches in this area

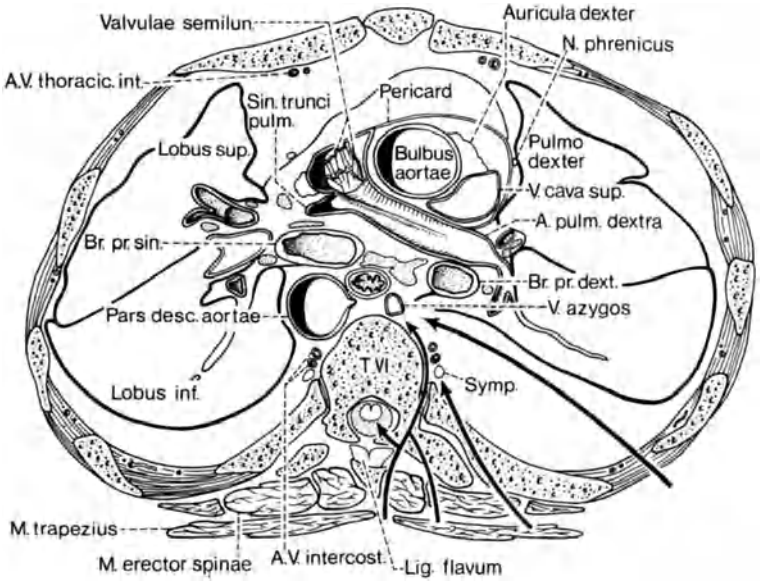


Fig. 9. Transverse section through the sixth thoracic vertebra and the most common approaches to the vertebral column and the spinal cord

In this area, care must be taken to avoid the hypoglossal nerve, the vagus nerve, and the superior laryngeal nerve. The hypoglossal nerve usually enfolds a branch of the occipital artery which reaches the sternocleidomastoid muscle (mastoid branch) and then runs lateral to

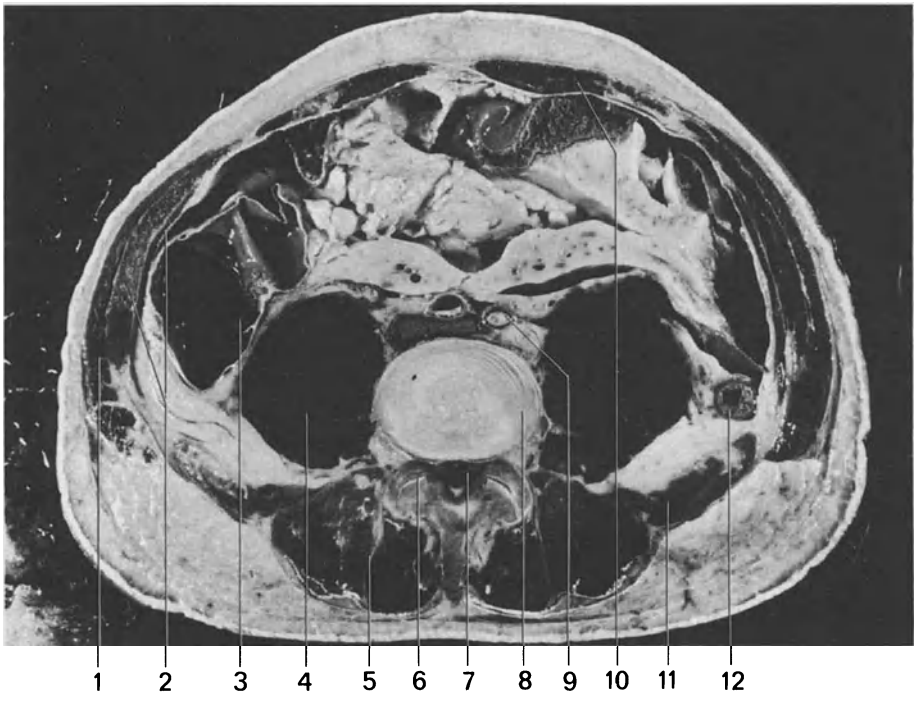


Fig. 10. Transverse section through the intervertebral disc L3/L4 from below). *1*, m. obliquus externus; *2*, m. obliquus internus and m. transversus abdominis; *3*, colon ascendens; *4*, m. psoas; *5*, m. erector spinae; *6*, articulatio zygapophysialis L3/L4; *7*, dura mater and fila radicularia; *8*, symphysis intervertebralis L3/L4; *9*, a. iliaca communis sinistra; *10*, m. quadratus lumborum; *11*, colon descendens; *12*, m. rectus abdominis

the hypoglossus muscle and medial to the mylohyoid muscle to the tongue. The superior laryngeal nerve proceeds from the inferior ganglion of the vagus nerve in 88% of our patient material and after 21 mm divides (3-44 mm) into the internal branch for the mucosa of the upper parts of the larynx and the external branch supplying the inferior constrictor muscle and the cricothyroid muscle. The recurrent laryngeal muscle on the right may originate at the level of the thryoid gland, particularly if the subclavian artery on the right originates at the wrong level, and may, for example, reach the larynx below the cranial loops of the thyroid artery. As a rule, however, the recurrent laryngeal nerve on the right embraces the subclavian artery at its origin from the brachiocephalic trunk and on the left the arterial ligament of Botallo. The nerves then run between the trachea and the esophagus in a cranial direction, supplying these with the tracheal and esophageal branches and innervating all the laryngeal muscles (with the exception of the cricothyroid muscle and the mucosa of the larynx as far as the vocal cords).

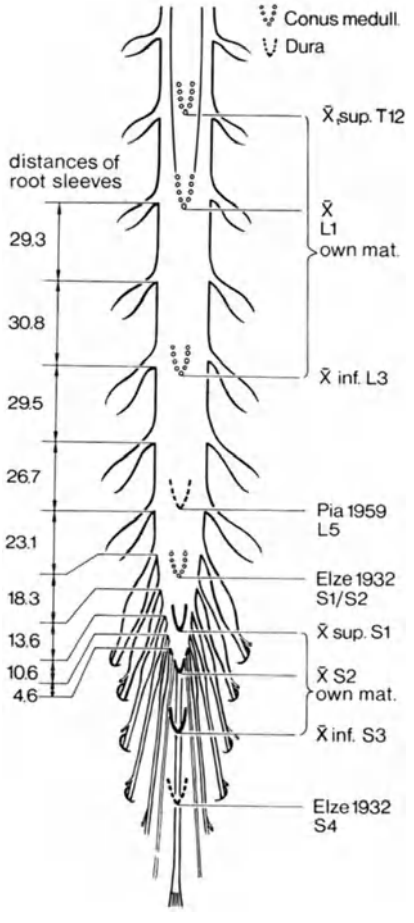


Fig. 11. Distances of the lower borders of the root sleeves in millimeters (mean values) and situation of the conus medullaris and the lower end of the dura sac (Lang and Geisel 1983)

## Approaches to the Thoracic Spinal Cord

Figure 9 shows the approaches to the thoracic spinal cord (cf. KOOS et al. 1985).

## Approaches to the Lumbar Spinal Cord (Fig. 10)

The position of the lower end of the dural sac as well as the spinal cord and its variations is shown in Fig. 11. The vascular supply of the spinal cord (one side) is shown in Fig. 12. For further information see LANG (1983, 1984, 1985).

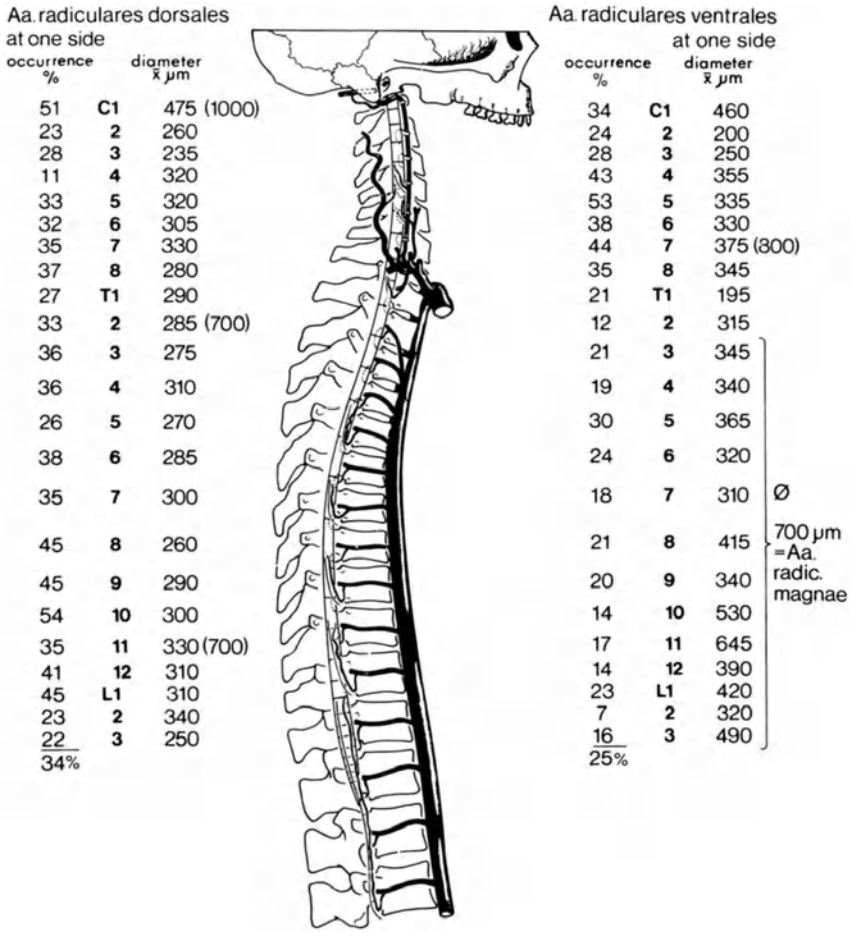


Fig. 12. Aa. radiculares ventrales and dorsales: occurrence and mean diameters of the arteries at different levels (LANG and BALDAUF 1982)

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# Spinal Tumors

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Four hundred and fifty spinal tumors obtained from intraoperative biopsies and postmortems are reviewed. They represent approximately 11% of all tumors of the CNS seen at the Institute of Neuropathology in Berlin between 1969 and 1985. Table 1 shows their distribution according to histological type. Obviously carcinoma metastases constitute the largest group (Table 2). Only seven of these cases, i.e. 6%, have an intramedullary location (Fig. 1); this is, however, a fairly high percentage compared with the data of SCHWECHHEIMER and LEMMINGER (1985), who described four cases of their own and only 77 further patients in the entire literature. This discrepancy may be cleared up by the fact that our intramedullary metastases were exclusively from autopsy material while most of the epidural and many of the intradural-extramedullary metastases were found in biopsy material. Spinal cord infil-

Table 1. Spinal tumors: histological type

| | | |
|---|---|---|
| Carcinoma metastases | 122 | 27.11% |
| Meningiomas | 97 | 21.55% |
| Hematological tumors | 58 | 12.88% |
| Neurinomas, neurofibromas | 50 | 11.11% |
| Gliomas | 47 | 10.44% |
| Mesenchymal tumors | 35 | 7.77% |
| Vascular processes | 25 | 5.55% |
| Others | 16 | 3.55% |
| Total | 450 | |

Table 2. Carcinoma metastases

| | | | % of all tumors |
|---|---|---|---|
| Epidural | 100 | 81.97% | 22.22% |
| Meningeal | 15 | 12.29% | 3.33% |
| Intramedullary | 7 | 5.74% | 1.55% |
| Total | 122 | | 27.11% |

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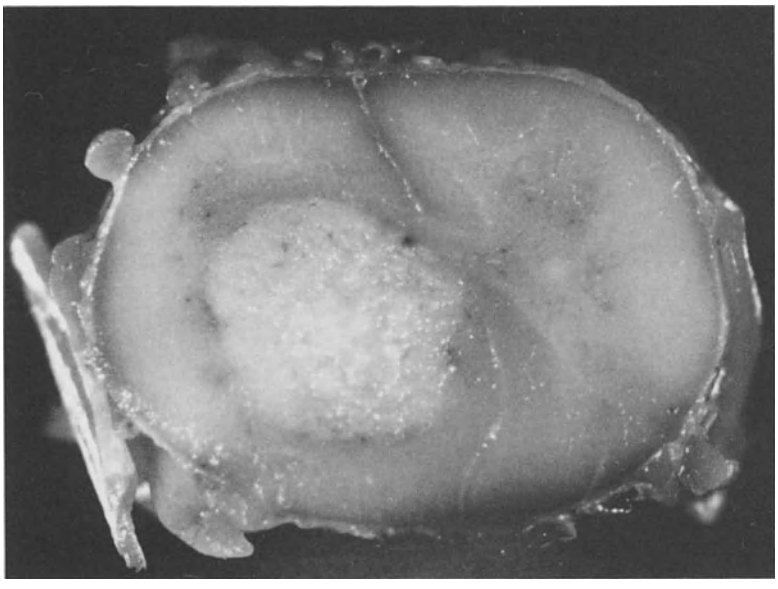


Fig. 1. 68-year-old patient with multiple micro metastases in all major areas of the CNS, but mainly in the gray matter of the cerebral and cerebellar hemispheres as well as in the basal ganglia. Further metastases are present in the subarachnoid space. Bronchial carcinoma was the primary tumor. The figure shows an intramedullary tumor. The distribution of brain metastases follows a vascular pattern, so that hematogenous dissemination is probable. Spinal cord manifestation probably involves the Virchow-Robin spaces as a route for infiltrating tumor cells

tration from an epidural metastasis is fairly infrequent. One reason for this is the barrier function on the dura; above all, however, many of the metastases are operated on before this barrier is penetrated (Fig. 2).

The most common primary tumor was breast carcinoma, followed closely by bronchial carcinoma (Fig. 3) and then by tumors of the kidney, other tumors of the lung, tumors of the gastrointestinal tract, and tumors of the prostate. Meningeal carcinomatosis was often present and the CSF was positive for the tumor cells in all cases in which this investigation was carried out (Fig. 4).

Next to carcinomas, meningiomas represented the second most frequent group of spinal tumors (21%). Most of these cases, 95, were operated on; only two were found at autopsy. Endotheliomatous meningiomas were diagnosed most frequently, although the histological patterns in some cases may allow a diagnosis of psammomatous meningioma. These we found typically in females 60 - 70 years old; that shown in Fig. 5 was taken from a 64-year-old woman. The location of these tumors was the dorsal tracts in 80% of cases. In 5 of the 97 patients a clinical recurrence was observed. In one of these patients von Recklinghausen's neurofibromatosis was diagnosed. Apart from one 47-year-old woman in whom a meningeal sarcoma was diagnosed histologically and who died 9 weeks after surgery, no malignant meningiomas were observed in our series.

Fig. 2. Metastasis from an adenocarcinoma of the lung. Thoracic vertebra 4 and 5. The tumor destroyed the compact bone and infiltrated the epidural space without infiltrating the dura

Hematological tumors constituted the third largest group of our spinal tumors (58 cases). These were diagnosed as plasmocytomas, lymphomas (Fig. 6), or leukemic infiltrates. Leukemic infiltrates are of particular relevance in the assessment of therapy as they may continue to exist in spite of a normal peripheral blood cell count (Fig. 7).

The fourth most frequent group of tumors comprised neurinomas and neurofibromas (50 cases); they represented approximately 11% of all spinal tumors seen. Most of the cases were recognized clinically, and only two were found casually at autopsy. Three of the cases were diagnosed as von Recklinghausen's disease on clinical grounds. The most frequent localization was the thoracic and cervical spinal cord, contrasting with the site of the meningiomas. We would like to emphasize that over 15 years ago we proposed that independent of their structural and ultrastructural patterns, neurinomas can be considered to originate from Schwann cells. They show a tendency to develop comblike folds. This behavior is analogous to that of normal Schwann cells, which involve other structures. In this case the tumoral cells wrap around each other, imitating myelination (Fig. 8).

Only 10% of the spinal tumors were primary tumors of the central nervous system, mostly ependymomas (Table 3). A subependymoma was found once. Clinical recurrence were not infrequent, being found in five

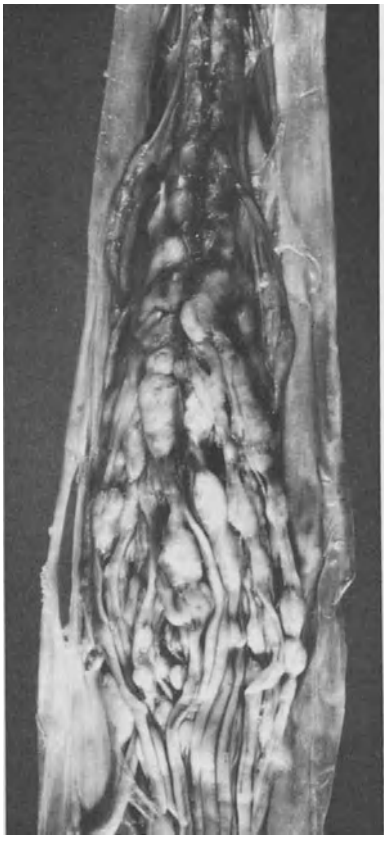
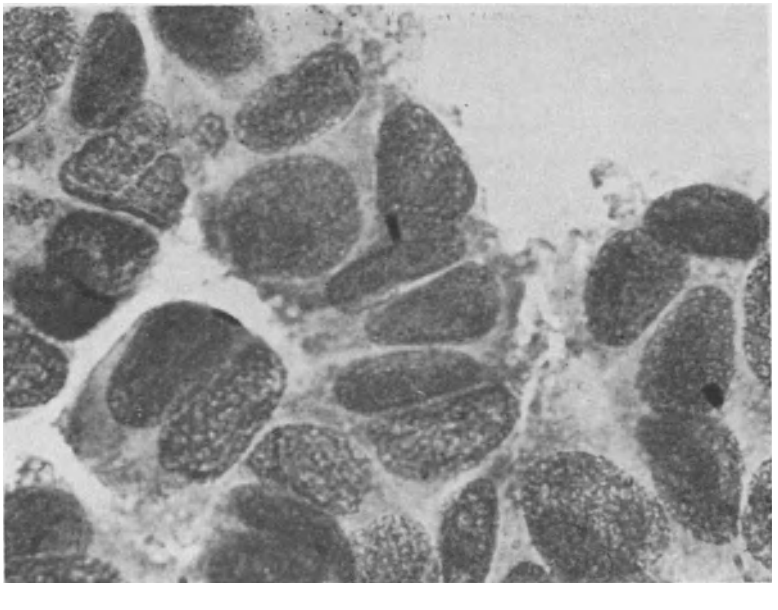


Fig. 3. Multiple micro metastases in the fibers of the cauda equina in bronchial carcinoma

Fig. 4. CSF cytology in meningeal carcinomatosis in a patient with carcinoma of the breast. Polymorphic cell aggregates. Gland-like organization of these aggregates is typical for ductal carcinoma



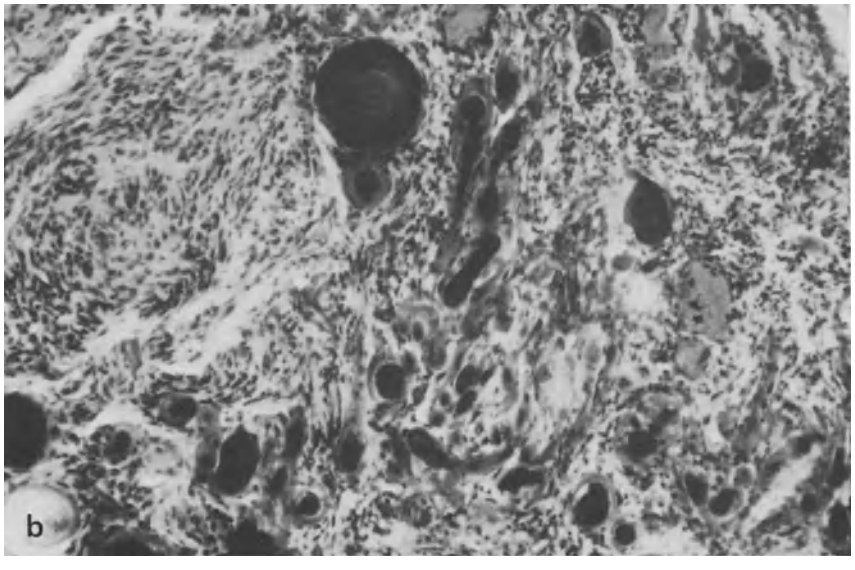




Fig. 5. a Large thoracic meningioma with well demarcated capsule. Slowly growing meningiomas elicit clinical symptoms fairly late and may reach a considerable size. b At the microscopic level the tumor is seen to be an endothelial meningioma with many psammoma bodies

cases. Regional metastases coating the fourth ventricle were found quite infrequently, which contrasts with the findings in the pertinent literature. In a 72-year-old patient meningeal growth of a primarily merely intramedullary ependymoma was observed, as was a tumor of spreading into the medulla in a 27-year-old patient.

Of our 14 astrocytomas of the spinal cord, three must be considered metastases of intracranial tumors (Fig. 9). These metastatic growths were not cystic as a rule. Our cysts occurred in five cases of primary astrocytomas and in the ependymomas. With one exception all gliomas were of low malignancy. One 52-year-old patient developed a glioblas-

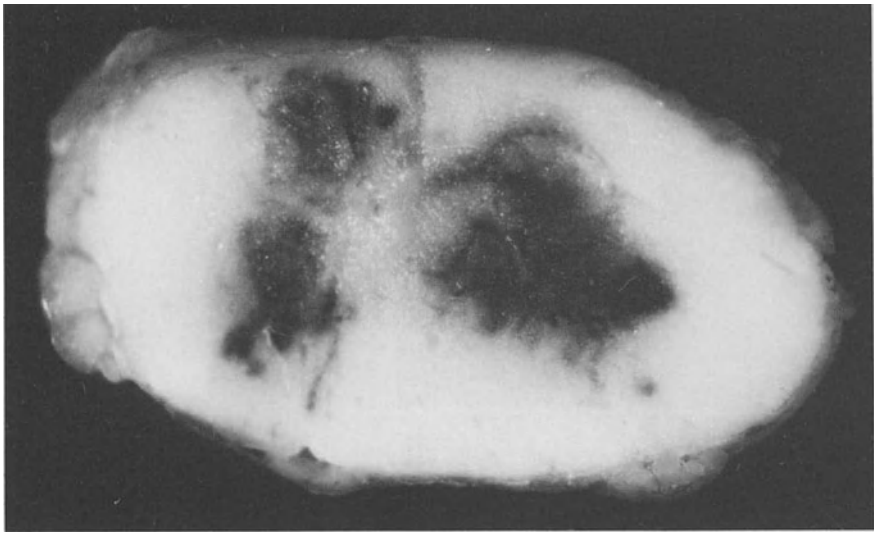


Fig. 6. 30-year-old patient with epidural sarcoma at T3-T7 (reticulum cell sarcoma) postoperatively. Autopsy showed an old hemorrhagic necrosis at T5-T4 with plurisegmental necrotic lesions above and below the area of compression

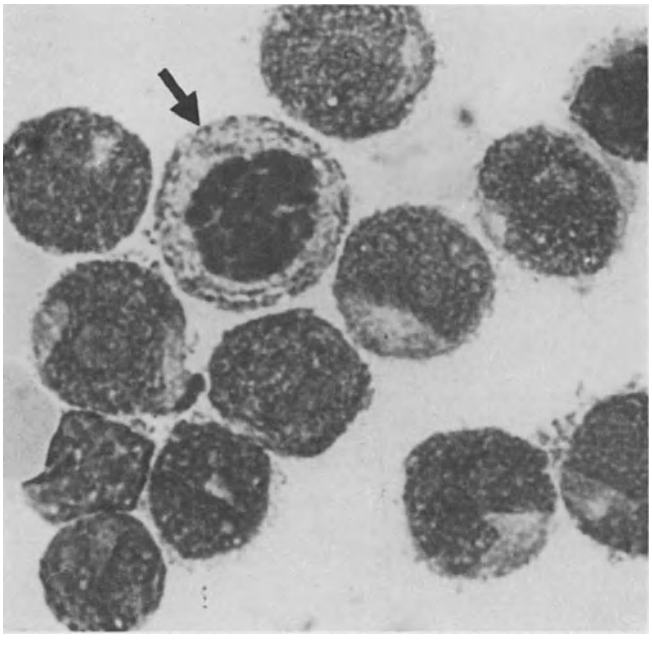


Fig. 7. CSF in lymphosarcoma; 210 cells/$mm^3$; CSF protein 130 mg/100 ml. The tumor cells show prominent nucleoli. The nucleus-cytoplasm ratio is unfavorable. Note mitosis *(arrow)*

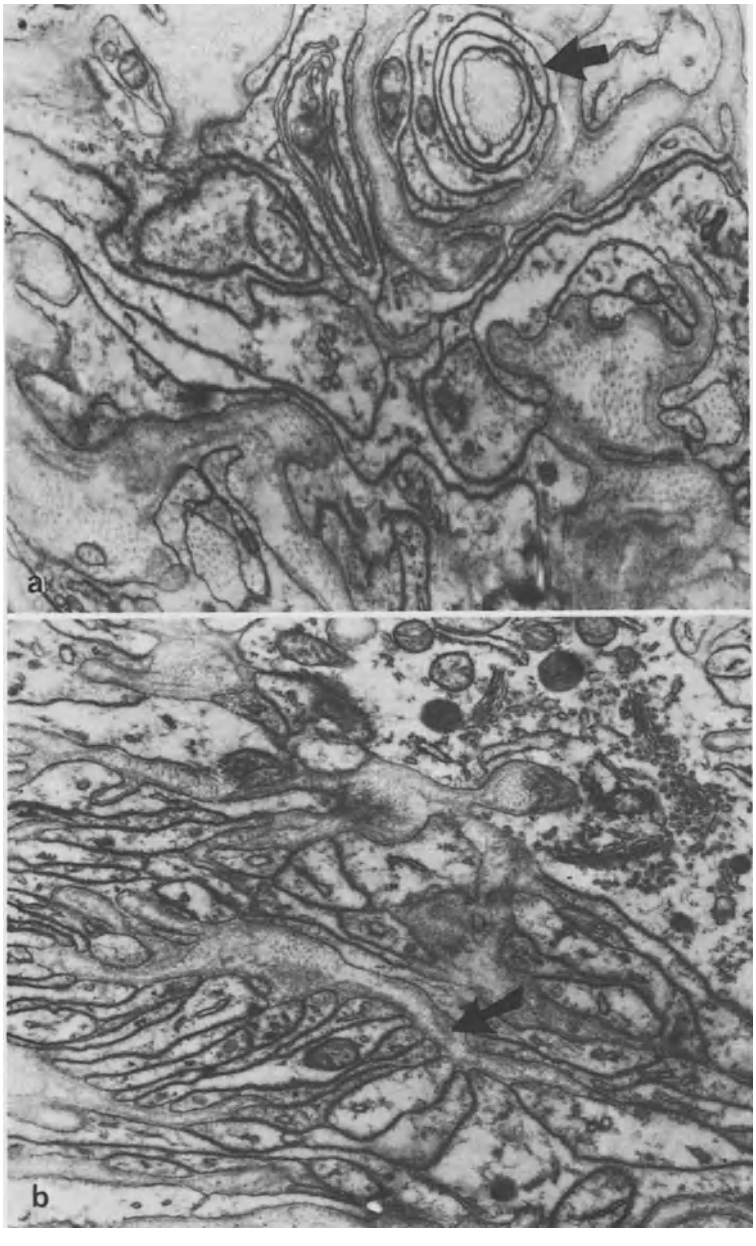



Fig. 8a,b. Multiple circular and enveloping cell processes in neurinoma. Note the folding of cells around bundles of collagen fibers. Original magnification 17000; x 15000

Table 3. Gliomas

| | | % gliomas | % of all tumors |
|---|---|---|---|
| Astrocytomas | 14(3) | 29.79% | 3.11% |
| Ependymomas | 27 | 57.45% | 6.00% |
| Oligodendrogliomas | 2(2) | 4.25% | 0.44% |
| Medulloblastomas | 3(3) | 6.38% | 0.66% |
| Retinoblastoma metastases | 1(1) | 2.13% | 0.22% |
| Total | 47 | | 10.44% |
| Primary | 38 | | |
| Metastases | 9 | | |

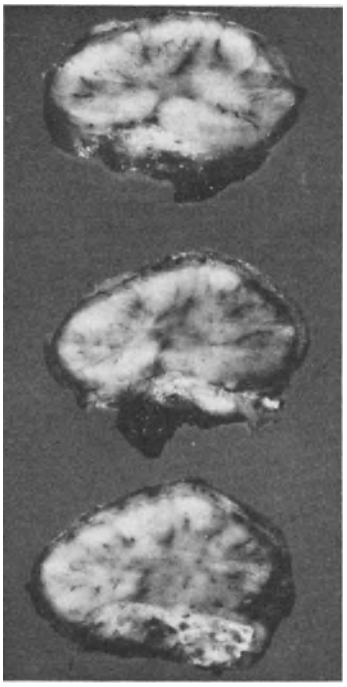


Fig. 9. Astrocytoma as a columnar lesion in the cervical and thoracic cord of a 56-year-old patient. Tumor infiltrated the meninges to the brain stem rostrally and caudally into the lumbar spinal cord

tomatous metastasis 6 years following surgery of a fibrous astrocytoma graded II, with recurrence of this tumor 5 years later, then graded III, and a third recurrence 6 months prior to death.

In contrast to the multicenter study, we do not differentiate astrocytomas and spongioblastomas because of the close relationship between the midline astrocytomas and spongioblastomas: Both tumors contain typical Rosenthal's fiber and are GFAP positive.

One of the most interesting recent findings in spinal tumor is the indication that ependymomas have neurosecretory activity (Fig. 10).

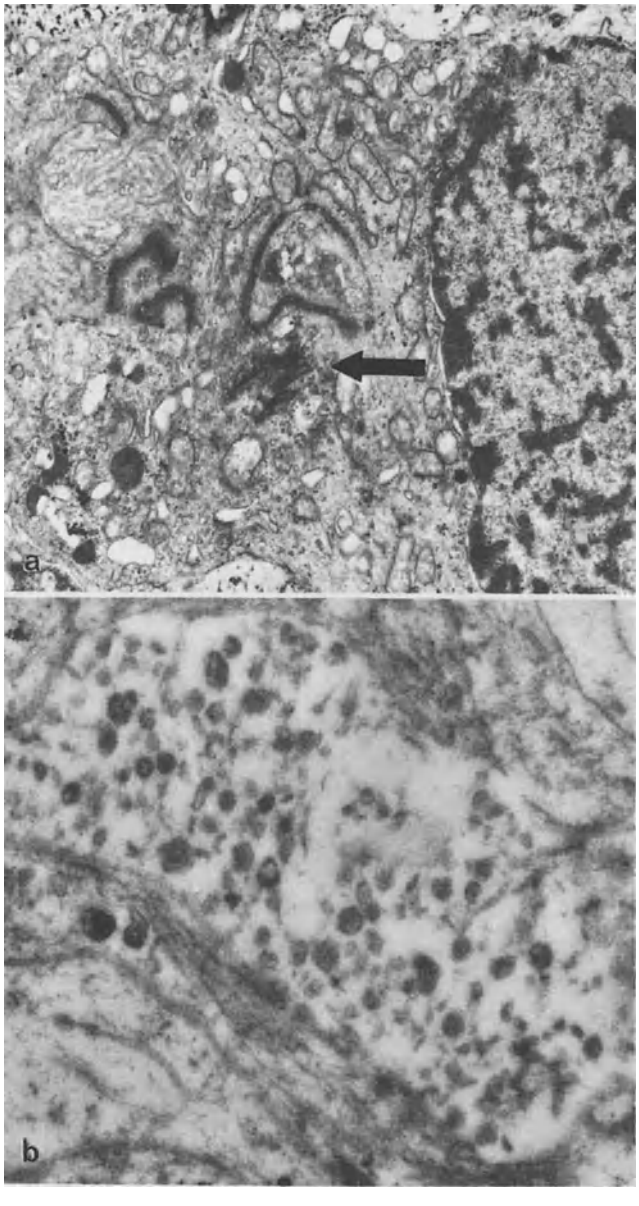



Fig. 10. a Detail of an ependymoma cell; note membrane enveloped tubular structures and tangentially sectioned part of a cilia. Large nucleus with relatively loose chromatin. Magnification approximately x 25000. b Detail of an ependymoma cell; multiple membrane bound vesicular structures indicate secretory activity of the tumor (see text). Magnification approximately x 35000

This is in line with notions on the complexity of ependymal function and local differentiation. Neurosecretory activity of ependymomas is undergoing study in various laboratories. Up to now a secreted substance has not been isolated.

I would like to close with tumors induced experimentally after application of nitrousurea. These are intramedullary gliomas. On a morphological basis they may be classified as "ependymoma like" tumors. They are induced in the cerebrum with a frequency of approximately 1% and

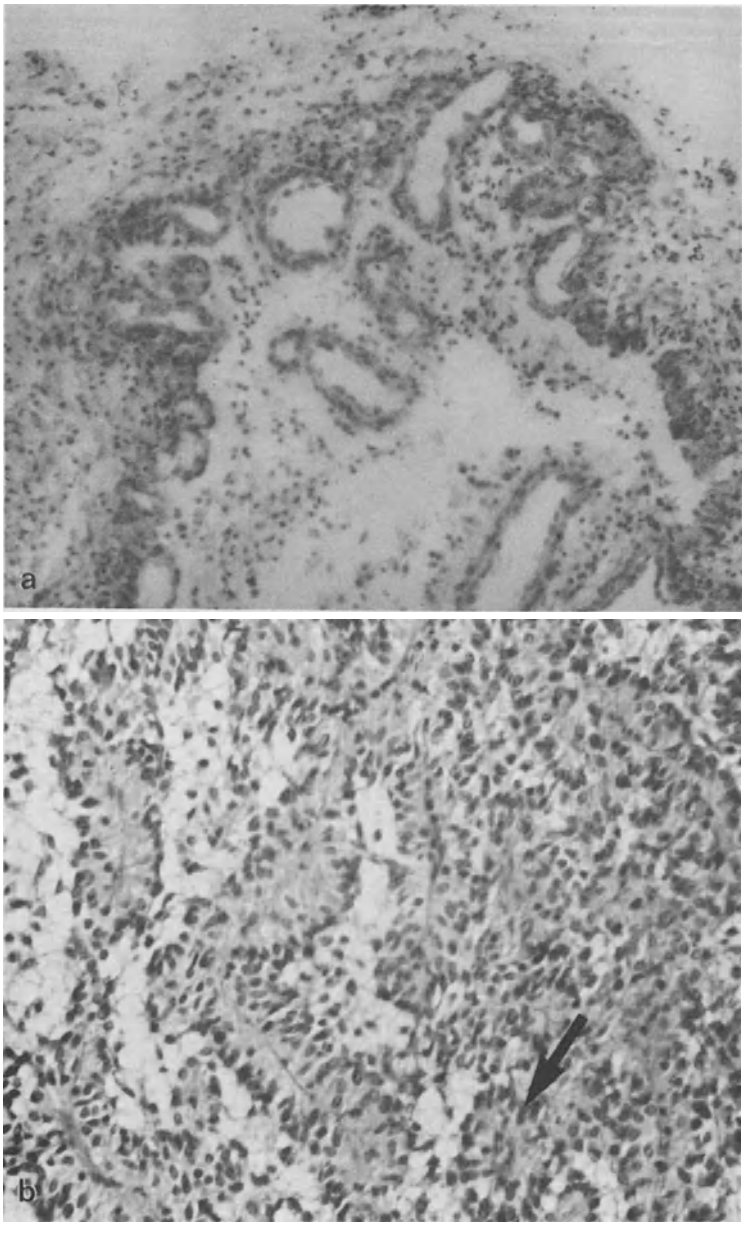



Fig. 11a,b. Experimentally induced "ependymoma-like" tumors of the spinal cord. a Light microscopic appearance; note vascular proliferates delineating the border of the tumor. HE, x 125. b The tumor at its center; note epithelial-like structures made up of cells sometimes showing "rosette-like" formations. Nissl, x 160

are even more frequently produced in the peripheral nerve, while even under optimal conditions less than 1% of the animals develop spinal tumors. A feature of these tumors are vascular proliferations seen at the tumor periphery (Fig. 11). The nature of this still remains somewhat enigmatic as we do not know whether we are dealing with a reactive mesenchymal growth or tumor induction in the vessels themselves.

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# Neurological Problems in Conjunction with Spinal Tumors

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In cases where a broad topic has to be discussed within a comparatively small amount of space, many authors tend to set marks of orientation in the course of their paper by referring to events in medical history. I would also like to follow this pattern, particularly since a summary of the neurology of spinal tumors could only consist of a generalized presentation inappropriate when many readers will be neurosurgeons. I therefore intend to concentrate on a few selected problems, which, while not entirely new, are not solved satisfactorily today in daily practice.

When almost 100 years ago, on 9 June 1887, V. HORSLEY performed the first successful surgical removal of a spinal tumor (at least HORSLEY claims priority for this procedure in a paper published together with GOWERS in 1888), the neurologist GOWERS in London was decisively involved in this therapeutic advance. On the basis of the symptoms GOWERS proved the feasibility of recognizing a spinal tumor and of localizing it. He also motivated and encouraged the surgeon HORSLEY to carry out the necessary surgery.

In his descriptive survey *Jahre der Entwicklung der Neurochirurgie in Deutschland* ("The years of evolution of neurosurgery in Germany"), ably edited by ZÜLCH, TÖNNIS rightly pointed out that the period of time when diagnostics and surgical therapy were united was decisive for the unfolding of neurosurgery into a discipline in its own right.

Within the evolutionary process both the GOWERS-HORSLEY period and the so-called CUSHING-THOMAS period are over and things of the past. One might raise the question of whether in the present phase, which is dominated by aspects of micro-neurosurgery, neurological considerations are still relevant. In the face of modern diagnostics employing advanced technology and sophisticated equipment, the temptation to classify neurological problems, particularly in the field of early diagnosis of spinal tumors, as insignificant may sometimes be close.

I will not here repeat worn slogans of the past, such as "We need more neurology and less contrast medium". We need both of these items, to varying degrees, depending on the specific circumstances.

Every publication about spinal computer tomography or NMR-diagnostics repeats the importance of careful interpretation of the case history and of consideration of the neurological findings to enhance the information obtained by means of the aforementioned procedures. In real life, however, these admonitions are always quickly forgotten or suppressed out of ignorance or for tactical or material reasons. In spite of the enormous diagnostic refinements presently offered, as compared

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with the techniques formerly available, the techniques and instrumentation used in supplementary diagnostics today still have not reached a level that allows reliable identification of a spinal tumor just by using this equipment. Indeed, at least for biological reasons it is questionable whether such perfection will ever be achieved. Special circumstances, e.g., in the atlanto-occipital transition, where the imaging methods frequently leave all other diagnostic means far behind, cannot be generalized. Since the imaging methods are not searching procedures, the case history and the neurological findings are still used for that purpose. Evaluation of these steps no longer rests solely with the neurologist, but forms an integral component of the actions of the neurosurgeon. Preliminary and exploratory diagnostics of spinal tumors should primarily be the duty of the neurologist. However, due to the fascination that modern means of diagnosis has for both patients and physicians, the neurologist is often bypassed. The problems of differential diagnostics definitely demand primary consideration of neurological points of view within progressively structured diagnostics.

Pain frequently constitutes the foremost and the earliest symptom of many spinal tumors. This was the case in the first patient who underwent surgery by HORSLEY 100 years ago, too. The presence, the extent, and the intensity of pain cannot be determined as objectively as disturbances of sensibility, pareses, or disorders of the reflexes, and the problem of "pain as perceived by the patient versus findings as obtained by the physician" has to be resolved. Determination of whether, in the face of an otherwise normal neurological status, "pain" is really based on a pathological cause cannot be the exclusive domain of supplementary diagnostics, with modern techniques, but calls for cooperation with the neurologist. While he cannot be an infallible authority on this type of differential diagnosis, owing to the composition of the groups of patients he continually faces, he has collected more experience on the question of whether the origin of pain is neurogenous or psychogenic.

In many cases the objection that to perform myelography or NMR tomography in cases where no pathological findings can be detected is a hundredfold preferable to failing to detect a spinal tumor at an early stage is certainly not valid in such a one-dimensional form. Because of possible iatrogenic effects our structuring of the diagnostic sequence should avoid any additional tendency for somatization of psychogenic disturbances. Due to the change in the medical scene during recent decades, from a helping function (demand status) toward an offering institution (supply status), the question of a neurogenous or psychogenic origin of symptoms has assumed increasing importance, particularly in the field of pain syndromes. However, simplification of the problem into these two categories may result in many misunderstandings. In this context consideration of disturbances in the general feeling of a patient, which cannot be influenced surgically and the excessive subjective importance of which is not alleviated by the employment of elaborate instrumental diagnostics, may be mentioned.

Improvements in the early diagnosis of spinal tumors in older patients may be difficult to achieve due to the superimposing disorders often present in the 7th and 8th decades of life. While orthopedic causes of pain and difficulties in walking are far more frequent than spinal tumors, neurologists and neurosurgeons in cooperation with orthopedists nevertheless always have to be on the alert for the latter.

Of the three historical areas of medical action – diagnosis, therapy, and prognosis – diagnosis presently occupies the limelight. For the general public, for politicians, and for quite a few physicians, too,

diagnostics are considered the very essence of medical action. However, although determination of the presence and type of disease is obviously essential, an unreflecting diagnostic actionism has proliferated in recent years, contributing to the overrating of diagnostics. As a consequence of this shift in importance, the medical task of prognosis has been neglected. Many neurologically oriented steps of rehabilitation and decisions in social medicine following surgery for spinal tumors demand a prognosis as probable and well founded as possible. The individual prognosis for a patient surgically treated for a spinal tumor – based on general experience, the type of tumor removed, the surgical findings, and the pre- and postoperative status – cannot be formulated competently solely by the physician on duty at a specific ward; rather it requires consultation with the most experienced neurosurgeons of the hospital.

In the descriptive survey mentioned initially, W. TÖNNIS also claimed that the evolution of neurosurgery was retarded by general surgery and even more so by neurology. For reasons of "local patriotism" I would like to enter on record that this statement cannot apply to the time he spent in Berlin. TÖNNIS himself confirmed his good relations with the neurologist P. VOGEL, who placed facilities in the Hansaklinik at his disposal. Moreover, the call by TÖNNIS for the founding meeting of the Deutsche Gesellschaft für Neurochirurgie (German Society for Neurosurgery) to take place in the beginning of October 1939, which failed to materialize due to the outbreak of World War II, announced a lecture by P. VOGEL on "Early symptoms of neoplasms of the spinal cord".

In the course of time the dominating factors in the cooperation between neurologists and neurosurgeons have shifted to some extent. A deceleration or pause in the drive towards even more specialization and more mutual and complementary cooperation between the two disciplines would be highly desirable.

# Differential Diagnosis of Spinal Tumors

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Monolocular syndromes of the spinal cord may have their origin in tumors, but they can also result from many other causes. Under these circumstances the clinical-neurological syndromes may appear quite similar or identical during superficial observation.

In reaching a correct diagnosis, the following are decisive: detailed and intelligent interrogation of the patient concerning the preceding history, careful and methodical neurological and internal examination, selective use and critical interpretation of methods employing pieces of equipment and of laboratory investigations, and the sensible coordination and arrangement of the multitude of individual data into an overall mosaic. In many cases the dynamics of the earlier course of the disorder and the findings obtained during neurological and internal examination and in the laboratory tests are evaluated insufficiently or carelessly, while too much importance is attached to the modern imaging modalities.

Accordingly we have noticed that, to cite but one example, in the presence of subacute or even chronic symptoms involving the spinal cord in the area of the neck, computer tomography and myelography had already been employed without yielding results, although the patient had not been interrogated in enough detail to discover that he had blurred vision in the right eye for 3 weeks 5 years earlier (and had had retrobulbar neuritis of the optic nerve). In another such case insufficient attention had been paid to the words of a patient who in reality was suffering from multiple sclerosis. Other patients may for example show, in addition to a spastic paraparesis of the legs, subtle dissociated nystagmus when looking to the right or slight miosis in the left eye, signs of a multifocal disease of the CNS.

Similar neglect frequently occurs in respect of the CSF findings, particularly if the CSF has been collected during a myelographic procedure. The CSF may, for instance, be contaminated with blood and therefore be discarded, though laboratory analysis would still provide useful information. Another source of neglect is failure to perform some investigations in the laboratory CSF program, such as determination of the protein level or of the IgG quotient, or isofocusing. Accordingly a definite diagnosis between a disturbance in the blood-brain barrier and an inflammatory or immunological CSF syndrome will not be feasible.

Careful recording of the case history, obtained from the patient at rest and including the earlier course of the disorder, meticulous neurological examination, and laboratory reports on the CSF findings will furnish the decisive information for differentiation between a space-occupying unilocular lesion, a non-space-occupying inflammatory lesion,

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a vascular lesion, and other spinal disorders. Subsequently only evoked potentials, electromyography, computer tomography, myelography, angiography, and NMR tomography should be considered, and all should be used *specifically*. The nature and scope of exploratory methods using sophisticated equipment should be determined exclusively by the underlying clinical and neurological findings.

Evaluation of the dynamics of the earlier history of a specific case allows classification of the condition into acute, subacute, chronic, and intermittent forms. In the case of an *acute* onset, epidural and intraspinal *bleeding*, e.g., resulting from an angioma or from marcumar therapy, can be suspected. Severe meningeal, pseudomeningitic, and/or radicular pain indicating the location of the lesion lends credibility to such a diagnosis, and it can be confirmed by the presence of blood in the CSF fluid and by the CT findings. Spinal *ischemia* or *infarction* also starts acutely, but as a rule they are not associated with pain. In most cases these manifestations are identified by the generally precisely circumscribed, typical neurological symptoms (such as an arteria spinalis anterior syndrome with paraplegia) while the functions of the posterior cord are still intact, and possibly via a spinal angiogram. In most cases normal findings are obtained during examination of the CSF. If an inflammatory CSF syndrome is discovered by the laboratory investigations, the presence of *vasculitis*, e.g., immunovasculitis, panarteriitis nodosa, or Heubner's arteriitis associated with lues, should be considered.

All *inflammatory* disorders of the spinal cord will develop rather *subacutely*. In this context *multiple sclerosis* should be mentioned as the form of myelitis seen most frequently. The characteristic features of this disease can be summarized as multiple small foci and progression of the disorder at intervals, i.e., features which can ascertained from the case history and the neurological findings. Where doubts exist, detection of an immunological CSF syndrome, such as slight lymphocytic/monocytic pleocytosis, or a normal or insignificantly elevated level of the total protein together with an elevated IgG fraction will confirm the diagnosis. Autochthonous IgG production in the CSF can be recognized by the higher IgG ratio between the CSF and the serum (even if the CSF should be contaminated with blood), or by the appearance of $\gamma$-globulins in the CSF which cannot be demonstrated in the serum. Modern isofocusing, a procedure we have been using for approximately a year now, allows easily identification of such globulins.

In the less frequent cases of *primary chronic* spinal multiple sclerosis, differential diagnosis from a spinal tumor may be difficult. An elevated IgG in the CSF, as just described, or additional disturbed visually evoked potentials (even if no visual problems are mentioned in the history) are almost always also present, however. In dubious cases myelography will be necessary. Worsening of the condition as a result of this exploratory procedure is highly unlikely and can be neglected considering the importance of elimination of ambiguities from the diagnosis. Computer tomography will be helpful only if the source of the trouble can be localized with precision clinically. NMR tomography may certainly be advantageous in such a case.

*Zoster myelitis* also has a subacute course. This disease is quite frequent and is not always associated with radicularly marked eruptions of shingles or even defined small blisters on the skin. The disorder may produce a classical Brown-Séquard syndrome resembling the effects of a spinal tumor. In such cases in addition to the clinical analysis, laboratory examination of the CSF is again essential, since the CSF will show a mild lymphocytic-meningitic syndrome typical of zoster myelitis.

Tuberculous meningomyelitis, possibly associated with monoclonar spinal symptoms, is certainly seen less frequently. The course of this disorder ranges from subacute to chronic. The clinical signs of meningitis are absent in most cases or are unremarkable. Radicular symptoms of irritation may be present and should be noticed. Additionally a search should be conducted for other manifestations of tuberculosis, e.g., at the nerves of the brain. The history is frequently uneventful or does not produce any useful hints. Again, in such cases the CSF is usually altered in a characteristic fashion, showing moderate lymphocytic pleocytosis together with a high level of total protein, an elevated level of IgG, and a low level of sugar. Additionally, the other indicators of tuberculosis are seen in the laboratory investigations, on X-rays, and in other diagnostic procedures.

The same clinical and neurological symptoms and a similar CSF syndrome are occasionally caused by *lues cerebrospinalis*.

We have recently seen cerebral and spinal tuberculous and syphilitic manifestations more frequently again. These diseases, which formerly had been widespread, should accordingly even today not be disregarded and neglected. Sarcoidosis may likewise produce the symptoms described.

The discovery in 1982 through 1984 by BURGDORFER that *meningoradiculitis* associated with erythema migrans, as transmitted by ticks (Banwarth's polyradiculitis), is caused by a borrelia, i.e., a *spirochete*, can almost be rated sensational. In the meantime severe subacute to chronic cases of myelitis with paraplegia caused by this germ have also been described. We ourselves have treated a young man with chronically progressive paraplegic symptoms at the level 5 - 6. The results of the laboratory tests corresponded to the findings in cases of syphilitic meningitis, the other important disease caused by spirochetes. The discovery of *Borrelia burgdorferi* finally allowed a specific form of therapy, unfortunately at a time when a substantial spinal defect syndrome had already developed. At least, however, treatment with penicillin resulted in immediate and complete restoration of the CSF and in clarification and termination of the adverse disease process. If therapy is started early enough, the disease is therefore distinctly curable.

Due to shortage of space I must refrain here from discussing the multitude of other inflammatory diseases which might cause or simulate monolocular syndromes of the spinal cord, but which occur only infrequently.

The spinal disorders of the meninges caused by *cancer* or various types of *lymphoma* most certainly have to be mentioned, however. In addition to local symptoms in the spinal cord they frequently cause radicular pain and parestheses or defects, particularly if they form epidural encircling sleeves. They may result in syndromes in the CSF as well if they infiltrate the subarachnoid space. Such infiltration is characterized by a high level of total protein and the presence of tumor cells.

Predominantly *chronic* or *chronically intermittent* syndromes of the spinal cord, which may simulate a spinal tumor, occur in cases of *myelopathies resulting from radiation damage*. While the current literature contains many articles warning of this kind of damage, such cases are still seen. This type of damage hardly ever responds to therapeutic efforts.

The problems of *cervical myelopathy* and other disease processes associated with a narrow spinal canal shall be mentioned only in passing.

Systemic disorders deserve some attention also. *Funicular myelosis* in cases of vitamin $B_{12}$ deficiency, capable of giving the impression of

a poorly defined paraplegic syndrome, may serve as an example. Spastic paraparesis, a positive Babinski reflex, posterior cord symptoms, absence of Achilles tendon reflex, and uncomfortable parestheses represent a typical combination of indicators for such a deficiency. A *spastic spinal paralysis* very seldom occurs and should be diagnosed only when a hereditary influence can be proven. Even *aresorptive hydrocephalus* might induce somebody with limited experience to start spinal diagnostics in cases where there is difficulty in walking together with a bilaterally positive Babinski reflex and prominent difficulties in urinating while the organic psychosyndrome is hardly noticeable or has not been explored sufficiently.

In concluding, *psychogenic syndromes* should also be mentioned. To an inexperienced investigator they might look like a monolocular syndrome of the spinal cord and trigger extensive diagnostic procedures.

## Summary

I would like to emphasize again that careful recording of the history, taking the dynamics of the course of the disorder into account, detailed clinical and neurological examination, and differentiated evaluation and interpretation of the CSF findings should be the decisive directional factors in the process of differential diagnostics. Sophisticated equipment and computers are really efficient diagnostically, tolerable for the patient, and economically justifiable only if preceding diagnostic efforts without equipment have been carried out with skill and the results evaluated exhaustively.

I know very well that in the face of crowded surgical schedules and the multitude of other specialized duties neurosurgeons frequently cannot afford to spend the time to comply with my demands. If a neurosurgeon is in doubt as to the differential diagnosis of a spinal tumor, he should not hesitate to seek the assistance of an experienced neurologist. We as neurologists are always ready to utilize the advice of neurosurgeons without any scruples if we need it. Perhaps both fields could intensify their cooperation in the future. I think, for example, that a neurological consultant could furnish valuable assistance in the neurosurgical department of a hospital.

# Diagnosis by Examination of Cerebrospinal Fluid in Spinal Tumor Cases

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In 1891, H. QUINKE wrote a report in the *Berliner Klinische Wochenschrift* on "Lumbar Puncture of the Hydrocephalus". Less widely known is the fact that, during his time in Berlin in 1872, he was able to establish the "existence of a connection between the subarachnoid spaces of the brain". He also noticed that "dye particles" – for QUINKE vermillion, for us isotopes or contrast media – "move from the medulla to the brain as well as from the brain to the spinal cord". Thus he determined that "flow takes place in the subarachnoid fluid from back to front as well as in the opposite direction".

Today, in the age of nuclear spin and computer tomography, it is easy to forget that cerebrospinal fluid can assist in the detection of CNS diseases in ways that are not possible with X-ray technologies. Not infrequently, a moderate to strong disturbance in the blood-cerebrospinal barrier can tentatively point to a tumor in the same localized hypodensity which might lack significant mass on a CAT scan. Equally often the detection of an independent immune reaction in cerebrospinal fluid will produce evidence for the presence of the spinal form of multiple sclerosis, although myelography has been negative. However, even when myelography yields results, the cerebrospinal fluid should be subjected to simple and conclusive laboratory analysis.

In clinical practice only cerebrospinal diagnostics which combines minimal effort with a high degree of diagnostic conclusiveness should be pursued. The minimum requirement in this case would be determination of the cell count, cell type, total serum protein, and protein picture in the form of electrophoresis of cerebrospinal fluid or determination of individual protein contents.

## Evidence of Protein in Cerebrospinal Fluid

In 1910, NONNE and FROIN indicated for the first time that certain characteristic changes take place in the cerebrospinal fluid beneath a spinal interruption – a finding which has long since been known as the Nonne-Froin syndrome. Here normal or only slightly higher cell counts appear alongside xanthochromia and a massive increase in protein. The passage of cerebrospinal fluid is obstructed in the so-called Queckenstedt experiment. Above the mass, in a suboccipital position, normal cerebrospinal fluid appears. If we carry these findings over to present conceptions of cerebrospinal fluid, we will see the increased total serum protein amount as evidence of a disturbance of varying degree of the blood-cerebrospinal barrier. In such a case the electrophoresis of the cerebrospinal fluid contains the picture of the serum electrophoresis. That is, the picture of the cerebrospinal elec-


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trophoresis, which was originally typical, begins to resemble the serum electrophoresis. While the percentage values of the cerebrospinal electrophoresis show only small changes, the absolute values provide much earlier evidence for a disturbance of the blood-cerebrospinal barrier (summarizing report: GLASNER 1980).

In a case such as this, the cerebrospinal fluid IgG will, during determination of original contents, amount to 10% or less of the total serum protein value over an area of 0 - 100 mg/dl of total protein. With protein values higher than 100 mg/dl it is more correct to give this percentage of the cerebrospinal IgG as 15% or less of the total protein, in order still to be able to recognize the increase in cerebrospinal IgG as a disturbance of the blood-cerebrospinal barrier. The Nonne-Froin syndrome or the disturbance of the blood-cerebrospinal barrier is the most frequent (but also the least tumor-specific) evidence among massed spinal lesions with short-term symptoms.

## Cerebrospinal Findings

Corresponding to the Nonne-Froin syndrome in the area of the protein diagnosis of cerebrospinal fluid, a number of tumors produce a non-tumor specific inflammatory pleocytosis, which is characterized by normal or slightly higher cell counts. Most importantly, the cell picture will contain monocytic-phagocytic cell elements. It is essential to note that cell changes in cerebrospinal fluid depend on the type, the localization, and the size of the tumor. Simultaneously we cannot neglect the fact that a wide range of cell pictures originate during initial changes in the tumor cells in cerebrospinal fluid, and that these pictures also depend to a large degree on the means of the fluid's technical display. Slowly growing benign tumors, e.g., signal meningiomas, at first display normal cell findings in cerebrospinal fluid. Only much later can an unspecific inflammatory pleocytosis be detected due to increasing pressure on the nervous system.

Only a few tumors are accessible to a cytological diagnosis of cerebrospinal fluid. Generally, quickly growing tumors with a tendency to metastasize are more accessible to such a diagnosis. First among these is medulloblastoma, which is detectable through the presence of typical medulloblastomal cells in the cerebrospinal fluid. Carcinomatous cells with a large range are also frequently detectable in the fluid, as long as there is corresponding infestation of the CNS. The percentage of 15% has been given in respect of the specific tumor cell yield in the case of brain tumors; in the case of CNS metastases this target number is around 30% (KÖLMEL 1978).

## Other Cerebrospinal Findings

Although it has received little attention in recent years, the detection of circulating specific antibodies against tumor cells is an area of great importance in tumor diagnostics. Intrathecal antigens, that is, tumor-associated antigens which are detectable in cerebrospinal fluid, have until now only been identified in the form of the carcinoembryonic antigen (CEA) in cases of carcinomatosis, breast ca, bronchial ca, vascular ca, and malignant melanoma. The identification of such titer in the cerebrospinal fluid correlates with the treatment situation of metastases in the CNS. CEA has until now not been identifiable in cases of primary CNS tumors. The $\alpha$-fetoprotein has only been found in increased quantities in the cerebrospinal fluid in cases of CNS metastasis, as signaled by the presence of testicular carcinomas.

Certain brain tumors can also lead to raised α-fetoprotein levels. The degree to which connected systematic studies will yield additional cerebrospinal parameters in cases of tumor attacks on the CNS remains to be seen.

Cerebrospinal fluid has today, some 100 years after the beginning of clinical diagnosis of cerebrospinal fluid marked by the first lumbar puncture, found its place among other diagnostic procedures. Along with pictorial diagnosis, it can also produce additional clues in the narrow diagnostic area of spinal tumor cases; it is, to a much greater degree, in the position to indicate phlogistic and chronically phlogistic processes in cases where pictorial processes may tend to be negative. In any case, it is certain that cerebrospinal fluid, continuously involved in the exchange of material with the CNS and its alterations, will retain its key function in diagnostics of the future.

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# Conventional Radiologic Diagnosis of Spinal Tumors

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Every responsible diagnostician selects that examination strategy which provides maximal diagnostic information with minimal risk to the patient. Additional radiologic techniques are justified only when they are needed to answer questions of differential diagnosis or therapy.

The examination sequence for intraspinal tumors has been changed by modern noninvasive imaging techniques. While noninvasive techniques have led to a marked reduction of the use of conventional radiologic techniques (i.e., plain films, myelography, spinal angiography), our experience indicates that they by no means replace conventional methods. The information provided by conventional techniques is still necessary.

This is particularly true of simple plain films. As the first diagnostic step, they continue to form the basis of any specific techniques required to obtain additional information. In many cases, radiologically demonstrable changes in skeleton and extravertebral soft tissue not only show the level of localization, but also can indicate the nature of the underlying process.

The example of a patient with cauda equina syndrome is presented in Fig. 1a. The conventional sacral tomogram shows high-grade fusiform widening of the upper sacral canal extending to S2 with lateral displacement of the thinned bounding walls. Since all contours are preserved, the extent of the lesion can be clearly identified in both the craniocaudal and the transverse plane. According to these criteria, the lesion is an expansively growing benign mass, in this case a large neurofibroma.

Due to the pressure type of erosion, slowly growing lesions arising from within the vertebral canal itself can widen the spinal canal. According to the literature, erosion is detectable in more than 40% of all juxtamedullary tumors and even in 10% of slowly growing intramedullary lesions.

This widening of the canal, therefore, can be visualized in the sagittal and/or the frontal plane. Excavations at the posterior surface of the vertebral body are characteristic for canal enlargement in the sagittal plane. When these pouches are multisegmental, the underlying process is a tumor with a strong tendency to longitudinal growth, one characteristic of gliomatous lesions, e.g., ependymomas of the filum terminale that fill the entire lumbar canal. When these excavations are monosegmental or bisegmental, the process is probably not a gliomatous process.

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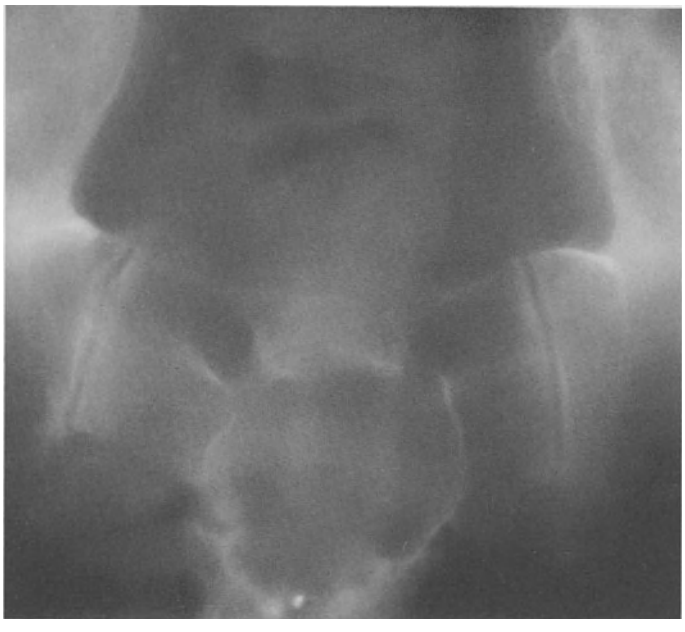


Fig. 1

Figure 2a shows a prominent pouch protruding deep into vertebral bodies L3 and L4. The mass is a glomus tumor, a very rare intraspinal tumor. The radiograph in Fig. 2b was made 4 years earlier, immediately after surgery; at this time, the areas of pressure erosion were far less pronounced. The follow-up film clearly documents a recurrence.

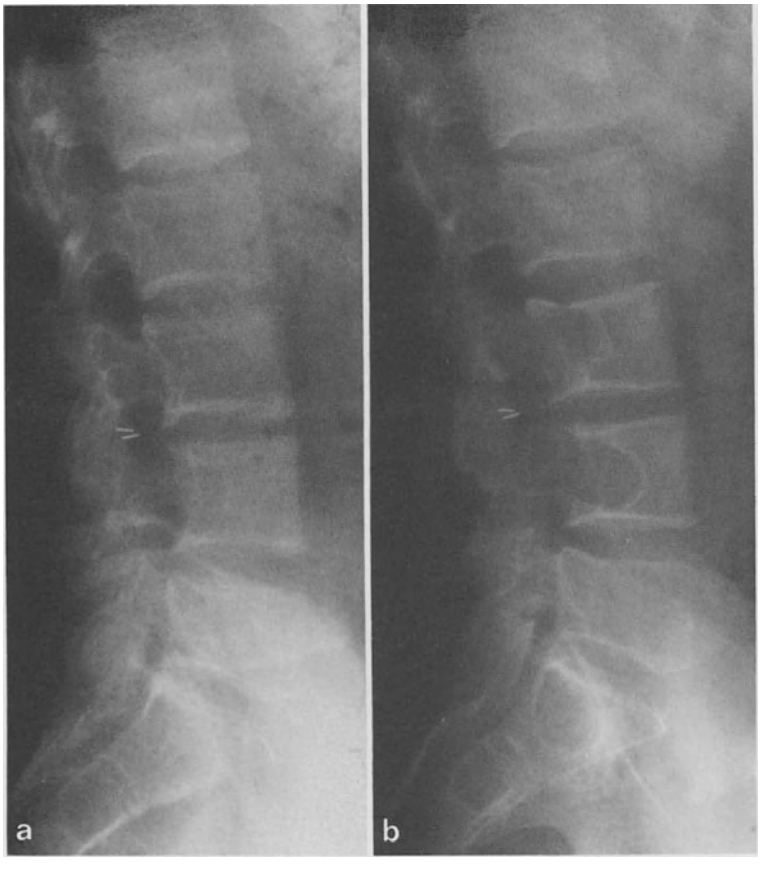
Characteristic signs of canal enlargement in the frontal plane are changes on the medial surface of the pedicle junction and subsequent widening of the interpedicular distance.

Figure 3a shows the normal pedicle as a vertical ovoid shadow with convex delineation of the lateral and medial junctions. Thinning and concave deformation of the medial pedicular junctions is visible at the body of the twelfth thoracic vertebra; the changes are more pronounced on the right side. The severe lateral displacement of these junctions leads to pathologic widening of the interpedicular distance. Here as well, monosegmental or oligosegmental localization of the changes with unilateral accentuation tends to indicate a nongliomatous rather than a gliomatous tumor.

In our opinion, the described widening of the canal is typical, almost pathognomic, for slowly growing intraspinal tumors. The signs of syringomyelia-induced canal enlargement are different (Fig. 3b).

The lateral view of the cervical spine shows the high profile of all vertebral bodies. This deformation is the result of the inhibition of vertebral growth in the sagittal plane due to increased intraspinal pressure before skeletal maturation. The distance between the posterior surfaces of all cervical vertebral bodies and the laminar line is also widened. The contour of the posterior surface of the vertebral bodies is smooth; no posterior pouches are evident. The widening of the intraspinal spaces over a long segment of spine together with the atypical vertebral body profile is characteristic of hydromyelia.

Fig. 2




The enlargement of the intervertebral foramina occurring with dumb-bell tumors, is one of the typical erosive changes associated with benign lesions. Figure 4a shows a typical example of enlargement of intervertebral foramen C5-C6 due to a dumb-bell schwannoma. Figure 4b shows extension of a dumb-bell schwannoma into the thorax. The paraspinal portion of a thoracic dumb-bell schwannoma, which is particularly well demonstrated on this chest film, is situated extrapleurally in the sixth intercostal space.

In contrast to intramedullary and juxtamedullary tumors of the spine, osteoclastic and osteoplastic destruction is evident with primary and secondary tumors of the bone. The most frequent form is metastases from malignant tumors, which, because of their rapidly infiltrating growth, quickly invade the epidural space. The radiologic signs of tumor infiltration in the vertebra itself are well known, i.e., changes in the shape of the involved vertebral body and reduction of the vertebral axis due to spontaneous fractures; they are presented here only for the sake of completeness. Figure 5a shows an osteolytic metastasis in the body of the fifth lumbar vertebra with obliteration of the right lamina and the pedicle. Figure 5b shows an osteoplastic metastasis; the thickening, particularly at the right half of the fused body of the seventh thoracic vertebra, is not to be overlooked.

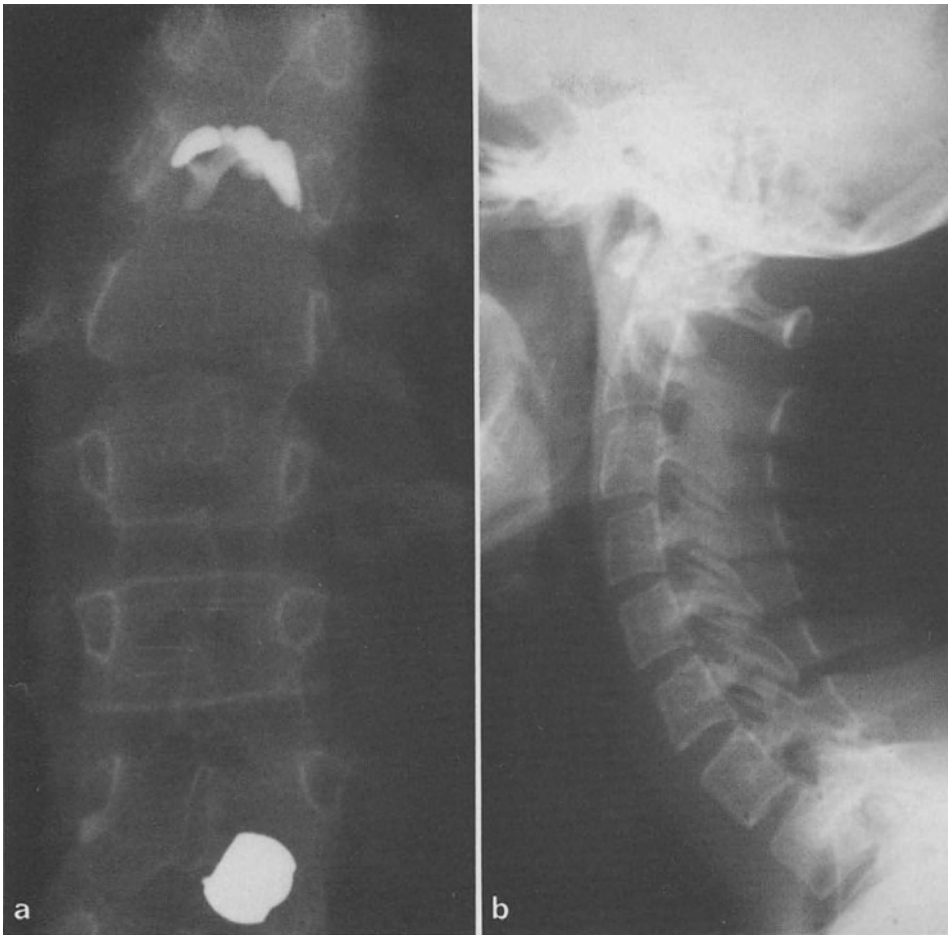



Fig. 3

Primarily benign tumors, such as an aneurysmal bone cyst, rarely produce sensory impairment. These bone cysts are characterized by multilocular cystic cavities bounded by intensified longitudinal cancellous lamellae.

The cauda equina syndrome present in such cases is produced by the narrowing of the canal and the intervertebral foramen induced by tumefaction of the vertebral body and extension of the process into the pedicle.

Myelography is the most reliable conventional radiologic method for detecting a tumor, determining its exact localization, and assessing its extension. The myelographic signs of the tumor depend primarily on its position in relation to the dura mater and/or the cord: The intramedullary tumor expands the cord, narrowing the subarachnoid space internally on all sides. Depending on the position of the juxtamedullary tumor, the cord is displaced posteriorly, laterally, or anteriorly. The subarachnoid space is widened on the tumor side and narrowed on the

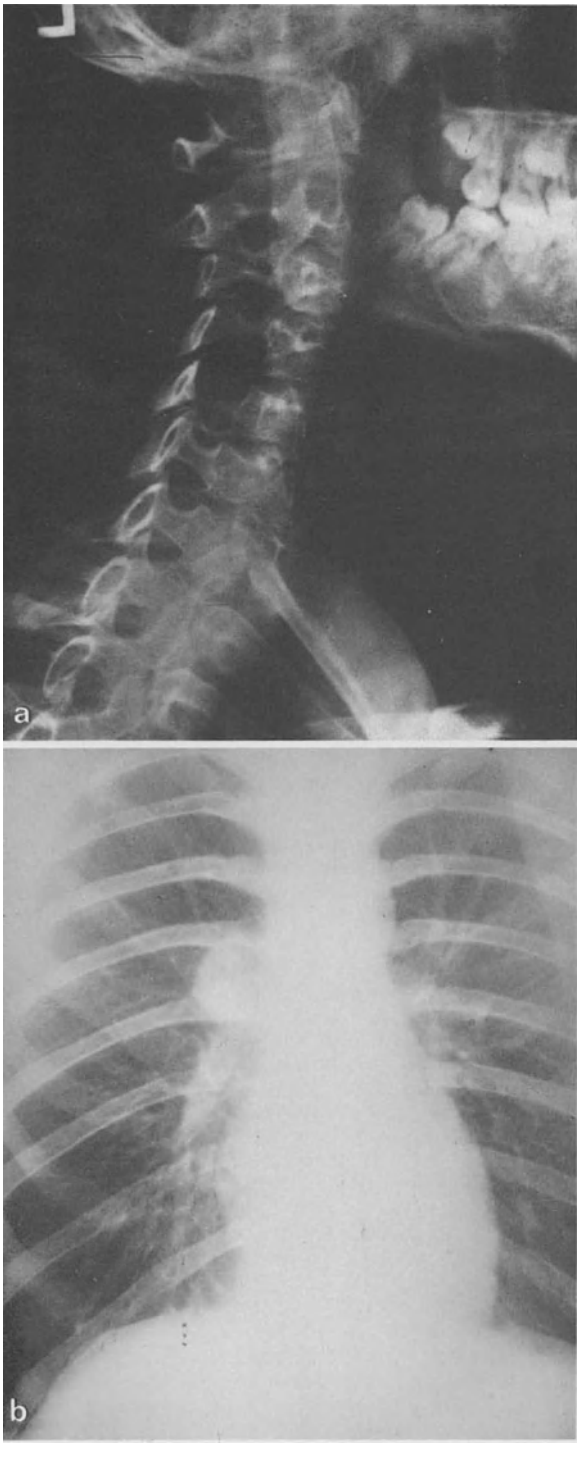



Fig. 4

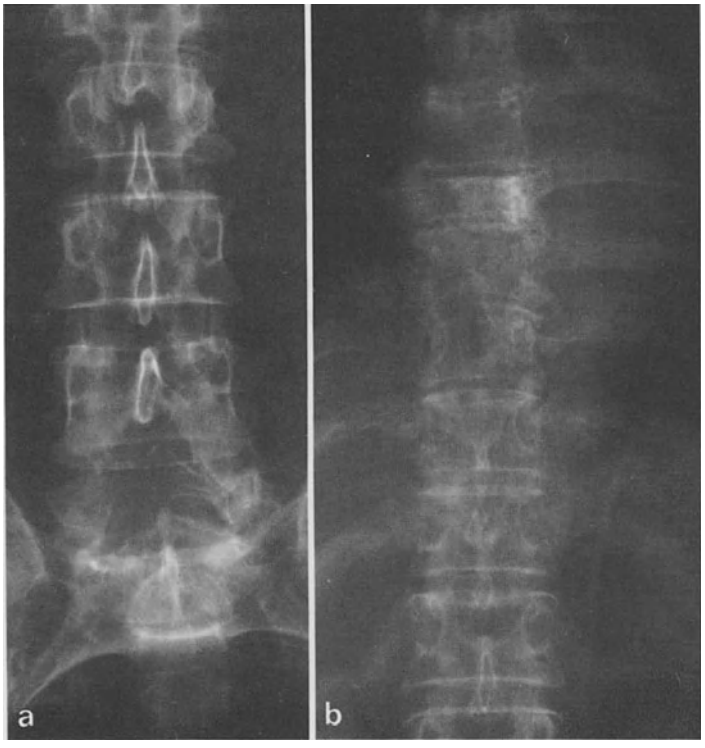



Fig. 5

opposite side. The tumor itself, or parts of it, is accurately imaged, since it is in direct contact with the contrast medium. An epidural process enlarges the epidural space and compresses the dural sac externally.

Figure 6a shows an intramedullary process in the cervical part of the medulla with considerably expanded cord shadow and filiform thinning of the soft tissue-free subarachnoid space, which is compressed against the pedicles. This lesion is an ependymoma. The characteristic appearance of a juxtamedullary tumor is shown in Fig. 6b. The cord shadow is displaced to the right; the subarachnoid space is widened on the left side of the tumor; and the top of the contrast medium column has a sharp concave margin. On the lateral view, the cord shadow is displaced posteriorly, and the posterior segment of the subarachnoid space is widened. This lesion is a posteriorly situated meningioma.

The epidural process is ultimately identified by enlargement of the epidural space. Depending on the localization, the column is more or less abruptly displaced away from the bony wall of the canal and toward the opposite side.

In Fig. 7a, the process lies to the right and laterally; the contrast medium-filled dural sac is displaced medially, away from the right pedicle. The column narrows at the point where the mass compresses the dura. This defect is a neuroblastoma that protrudes through the intervertebral foramen and into the epidural space.

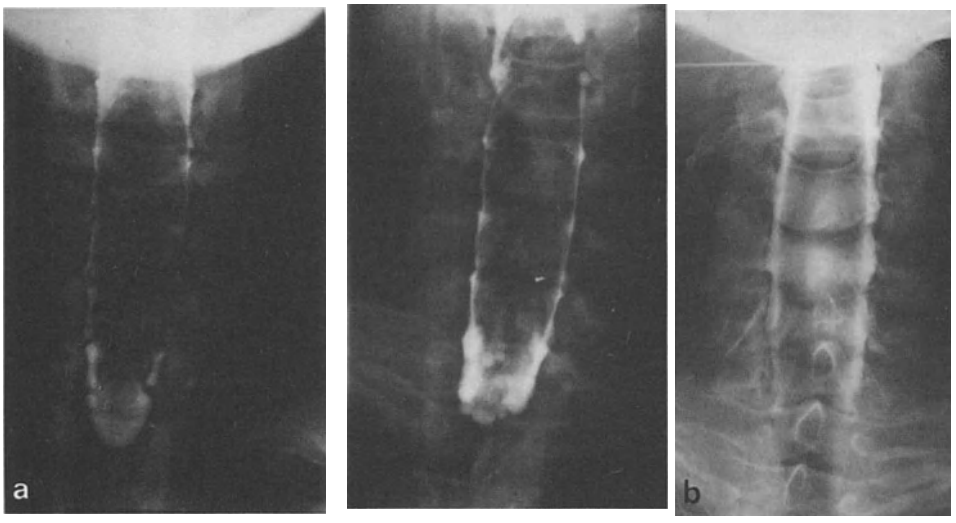


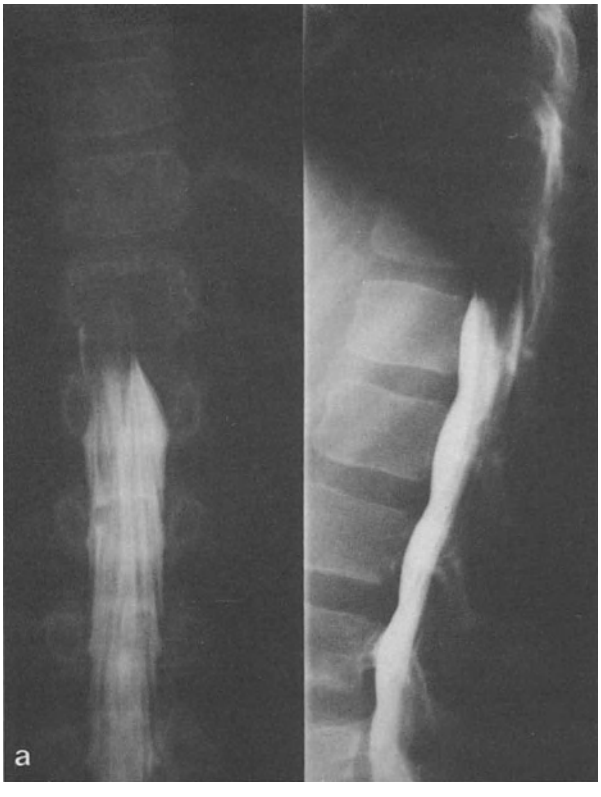

Fig. 6

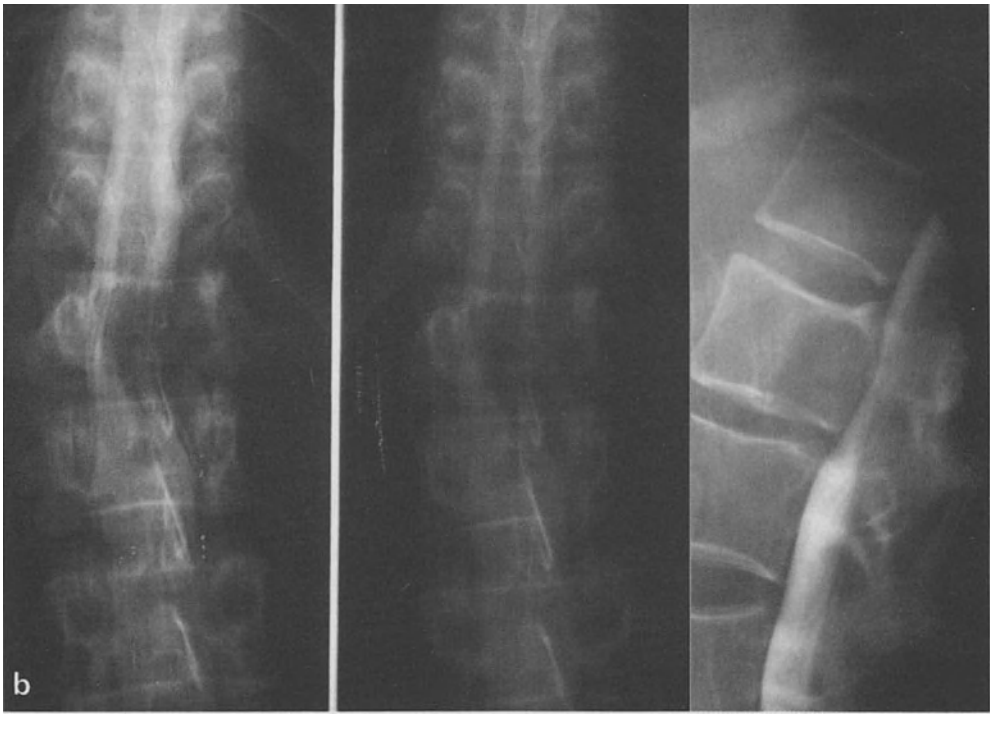
Most extradural processes are malignant. A benign tumor, a schwannoma arising from the extradural segment of the nerve root, however, is presented in Fig. 7b; this schwannoma has a paravertebral portion, but no intradural extension. The lateral view shows a posterior pouch extending deep into the cancellous bone of the body of the first lumbar vertebra. The column is displaced and arched posteriorly, but is narrowed more from the right and laterally. Both the size and the position of the tumor within the spinal canal, therefore, are easily identifiable on the myelogram, and, in this particular case, are even better visualized than on the CT scan, which, however, does provide more optimal delineation of the extravertebral portion.

An extradural process can even be differentiated from an intradural process in the cauda equina region, where the column is homogeneously radiopaque due to the absence of the cord shadow. Consequently, the example of an intradural tumor, such as an epidermoid, shows a clear filling defect in the center; the rest of the column is regularly displaced laterally and arched. The bisegmental pressure type of erosion at the pedicles serves as a valuable aid in establishing the radiologic diagnosis. This type of erosion does not occur with extradural tumors. Extradural malignant processes, particularly those with cuff-like growth around the dural sac, however, concentrically compress the column immediately above the block of contrast medium flow. The more or less extensive destruction at the vertebral column is characteristic of a malignant process.

The two concluding examples demonstrate the broad spectrum of information provided by angiography of the spine. The main indication for spinal angiography, of course, is spinal subarachnoid hemorrhage, which is generally caused by an arteriovenous racemose aneurysm. Figure 8a shows such an aneurysm on a supraselective arteriogram of the left intercostal artery IX. Adamkiewicz's artery branching off it is the major feeder vessel to the severely dilated anterior spinal artery which supplies the aneurysm in the cauda equina. The differentiation of certain tumors, e.g., hemangioblastoma, is only possible on the arteriogram.

Fig. 7



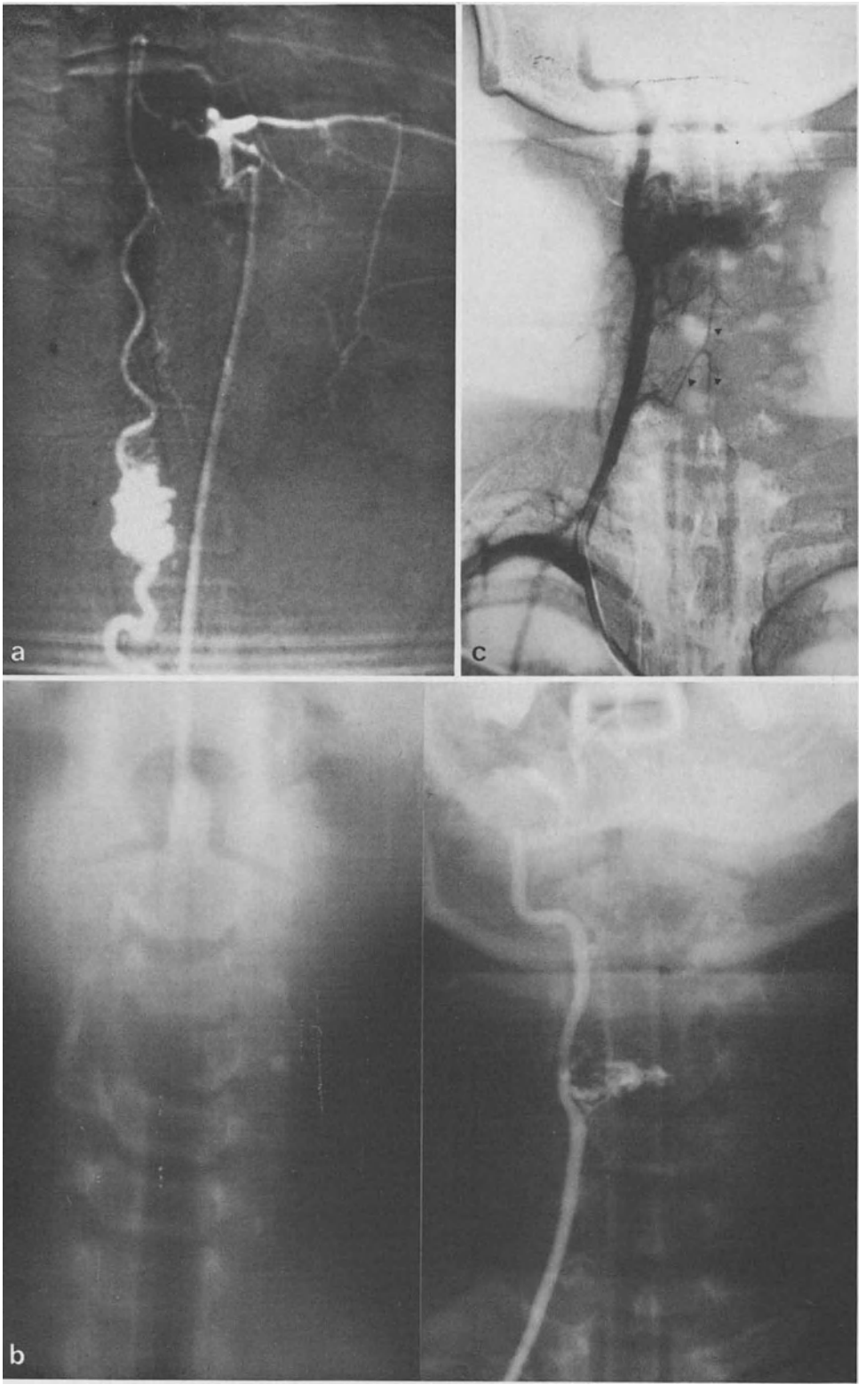



Fig. 8

Figure 8b shows an osteoblastoma in the body of the fourth cervical vertebra. The surgeon requested the film prior to resection of the tumorous vertebra to determine the vascular supply of the tumor. The extensive osteolysis of the right half of the vertebral body is shown on the left. Selective angiography of the vertebral artery demonstrates marked deviation of the course, vascular constriction at the level of the tumor, and pathologic vessels.

Figure 8c shows that the contrast medium pools during the course of the series until the entire tumor is filled. The anterior spinal artery, which is now visualized, is not involved in the vascular supply of the tumor.

I leave it to the reader to assess the importance of these findings.

# Nuclear Medicine in the Diagnosis of Spinal Tumors

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There is hardly any other area of diagnostics using nuclear medicine which has undergone such enormous changes as organ-related scintigraphy of the central nervous system. At the time when scintigraphy of the brain was used, deduction of the presence of a brain tumor was possible (if at all) only by evaluation of the extent and the dynamics of a disturbance in the blood-brain barrier. As soon as cranial transmission computerized tomography started its triumphal entry into neuroradiological diagnostics, brain scintigraphy instantly became obsolete.

With respect to space-occupying spinal processes, again indirect methods are the only means at the disposal of the physician employing nuclear techniques. Among such procedures scintigraphic demonstration of the subarachnoid space following lumbar injection of radioactively labeled albumin derived from human serum, so-called myeloscintigraphy, may be mentioned just for the record, as a historical reminiscence. What is left now? Not a great deal, but what is left is important.

First I would like to make a basic statement: In respect of spinal tumors, scintigraphic methods for spatial localization are hardly acceptable anymore where high resolution of closely spaced different morphological structures is required. The strong points of nuclear medicine can be found in an entirely different area and this shall be explained by means of a simple and instructive example: Cranial transmission computer tomography (TCT) is incapable of determining the sections of the brain activated during analytical listening to the Goldberg variations by J.S. Bach. This can be accomplished, however, via positron emission computer tomography (PET) if glucose labeled with a substance radiating positrons and with a very short half-life is injected into the bloodstream.

Most readers are probably familiar with the very interesting transverse tomograms obtained by American teams in Los Angeles and Boston.

Scintigrams are always prints of the function or sequential images of a defined functional subunit. Deductions regarding morphological changes are always feasible and diagnostically productive in an indirect manner, via the functional subunit shown in images only.

In most cases an organic carrier substance is used for a particular isotope. The more that is known about such a carrier with respect to the physiology of the metabolism, the pharmacokinetics, or the immunological situation (keyword: monoclonal antibodies), the better one can evaluate and interpret the images obtained via scintigraphy.

Computer tomography and methods using nuclear magnetic resonance (NMR) at present dominate the field of imaging. This situation will most

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likely form a challenge for experimental nuclear medicine to expand and improve functional imaging by way of new procedures, such as positron emission computer tomography, which is, however, demanding in every respect.

These introductory remarks have been rather extensive, but I think they are necessary. I shall now proceed to the question of what diagnostic methods are presently offered by specialists in nuclear medicine in respect of space-occupying spinal lesions. Looking at data collected at the Klinikum Neukölln, this question can be easily answered. Out of 3055 spinal tumors 1314 or 43% were metastases; 139 or 4.5% were plasmacytomas.

Bone scintigraphy was performed in 741 of the 3055 cases, corresponding to approximately 24%. Positive pathological findings were seen in 68% of the scintigrams. Approximately half of these findings referred to single locations, the other half to multilocular foci. Considering these figures, it is evident that bone scintigraphy is distinguished by a high diagnostic discriminating rate, although, and this has to be added immediately, the specificity of the method is rather low.

Explanation of the data regarding the individual underlying diseases within the body of cases mentioned above would require considerably more space than is available. I therefore instead suggest the following approach to meet the special requirements of presurgical diagnostics in cases of space-occupying spinal lesions from the point of view of nuclear medicine: On all occasions when conventional radiology, myelography, computer tomography (including computer-assisted myelography), and even procedures using NMR (if available) have left some doubt about the nature of the tumor concerned, e.g., whether an autochthonous tumor is really present or not, one or, even better, two whole body investigations should be carried out with methods of nuclear medicine, i.e., bone scintigraphy and bone marrow scintigraphy. The former explores the osseous sector and the latter the bone marrow. One might call this arrangement "dual scintigraphy" within the framework of screening and staging. A few words on the details of this method: While the use of a phosphonate complex labeled with Tc-99m identifies osseous restructuring processes, a defined microcolloid derived from human serum albumin and likewise labeled with Tc-99m permits imaging of the reticuloendothelial system.

Both procedures are relatively inexpensive, simple, and available at any time and without any risk for the patient. If skilfully coordinated they can be conducted almost simultaneously with all radiological methods (including computer tomography). Including the necessary waiting periods, which can be utilized for other diagnostic purposes, bone scintigraphy requires approximately 3 h to perform, and bone marrow scintigraphy only approximately 1 h.

What are the reasons for employing two procedures instead of just one? Evaluation of the aforementioned data reveals that if one classifies the spinal metastases according to the underlying primary tumor, bronchial carcinoma is most frequent, followed by carcinoma of the breast, prostatic carcinoma, hypernephroma, and non-Hodgkin's lymphoma. Manifestations of Hodgkin's disease occur with nearly the same frequency as metastases of follicular carcinoma of the thyroid gland. From our experience in working with oncological patients we know that bone metastases from bronchial carcinoma, hypernephroma, and breast carcinoma are often silent on bone scintigraphy. They are too small to be resolved as "cold lesions" (i.e., osteolytic lesions without reactions) by the gamma-camera or have not yet resulted in secondary complications affecting the bone structure (pathological fractures, etc.). Foci of plasma-

cytoma are almost always silent on bone scintigraphy, and to a certain extent this is true for non-Hodgkin's lymphoma and Hodgkin's disease also. In such cases bone marrow scintigraphy may provide clues via proof of malignant infiltration of the bone marrow (demonstrated as "cold lesions"), swelling of the bone marrow, or (in cases of Hodgkin's disease) bone marrow activation.

Since the parameters of nuclear medicine are not very specific for the individual case, in my opinion all findings obtained by means of the procedures described should be discussed across various disciplines with experts in nuclear medicine, radiologists, neurologists, oncologists, and, of course, neurosurgeons.

I can imagine that in the future continued compilation of statistics on spinal tumors and closer analysis of the effectiveness and appropriate sequence of the diagnostic procedures employed will yield an improved diagnostic rate. Such improvement may reduce the frequency of unpleasant surprises for the surgeon during surgery and possibly help to avoid some surgical interventions by indicating radiation therapy and chemotherapy to be appropriate.

# Spinal Tumors: Magnetic Resonance Imaging

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As a noninvasive method of investigation, i.e., without intrathecal enhancement, computed tomography (CT) has proved disappointing in spinal tumors. Exceptions are advanced extradural malignancies and calcified, lipomatous or unusually vascular intradural masses (SARTOR 1980). Magnetic resonance imaging (MRI), on the other hand, despite its only recent addition to the radiologic armamentarium, has already demonstrated great diagnostic potential in such lesions (MODIC et al. 1983; MODIC et al. 1984; NORMAN et al. 1984; SARTOR et al. 1985). The following report is an account of our own experience with this new method at the Mallinckrodt Institute of Radiology.

## Subjects and Methods

Between August 1983 and March 1985 slightly more than 1400 subjects had neuroradiologic MRI studies. Of these a total of 260 were examined in the spinal region, and 28 were eventually shown to have a tumor. The breakdown of these tumors by histology is given in Table 1.

Table 1. Breakdown of spinal tumors ($n = 28$; WHO classification) studied with MRI

| | | | |
|---|---|---|---|
| Astrocytomas | 1 | Neurinomas/neurofibromas | 3 |
| Ependymomas | 4 | Hemangioblastomas | 3 |
| Neuroblastomas | 2 | Lipomas | 2 |
| Ganglioneuromas | 1 | Vasc. malformations | 2 |
| Pres. neuroep. tumor | 5 | Local ext. from reg. tumor | 1 |
| | | Metastases | 4 |

Almost always a superconducting 0.5-T imager operated at 0.35 T (Magnetom M, Siemens) was used. Less than 20 subjects were examined with a 2.0-T machine operated at 1.5 T (Magnetom H, Siemens). Essentially, the headcoil was selected for the investigation of the cervical spine, while the body coil became necessary in studies below this region. Occasionally, a prototype surface coil was employed to evaluate a specific area in more detail, most often in the thoracolumbar segment. Except for a few cases the slice thickness was 10 mm. Sectioning in sagittal planes was preferred, but frequently axial slices were obtained as well. Coronal imaging was rarely found rewarding due to the


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physiologic bends of the spine. The imaging technique was exclusively spin echo (SE), with T1-weighted (TR 300 ms/TE 30 ms), "balanced" (1500/30), and T2-weighted (1500/120) sequences performed in nearly all cases.

## Results

Examples of the *normal spinal anatomy* on MRI are shown in Fig. 1. T1-weighted images were found to be best for evaluating the gross morphology of the cord, while T2-weighted images allowed superior assessment of the thecal sac. "Balanced" or T1/T2-mixed images were optimal as far as the spinal column was concerned.

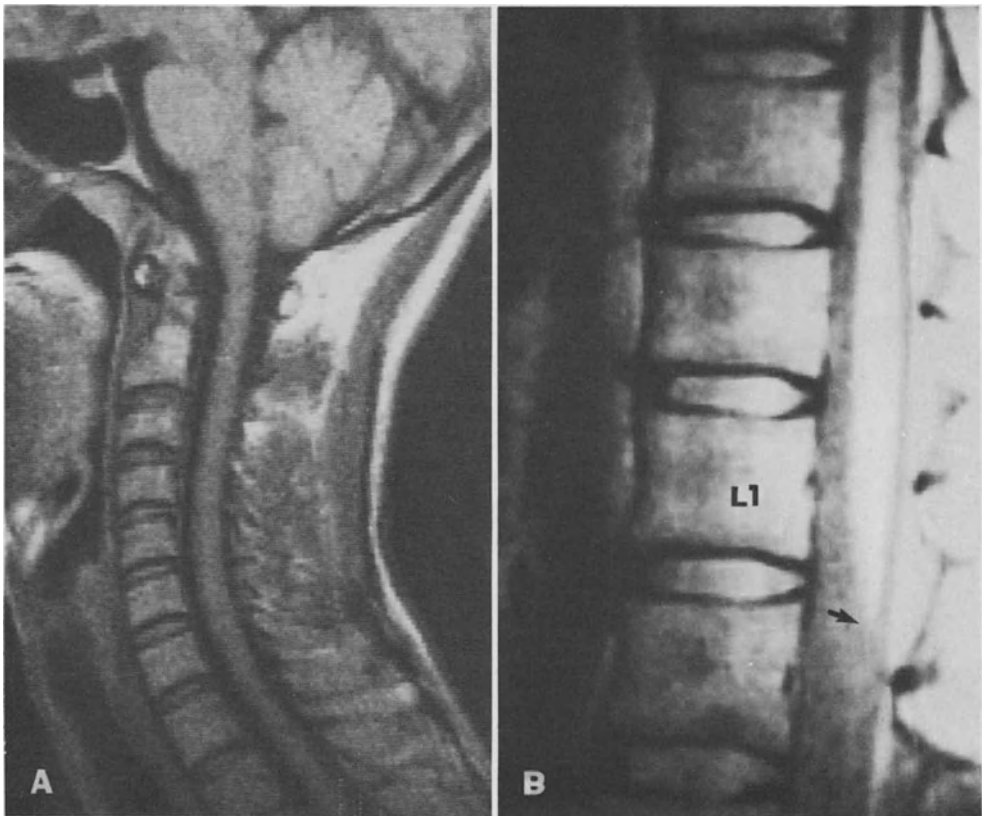



Fig. 1 A,B. Normal MR anatomy of spine. A T1-weighted image of midsagittal section of cervical region. Fat or fatty tissue appears bright, while ligaments and bone as well as CSF- and air-filled spaces are dark; cord has intermediate signal intensity. The size of the subarachnoid space may be overestimated because it has a similar shade of gray to adjacent vertebral structures. B T1/T2-mixed surface coil image (courtesy of Dr. Heller, Munich) of midsagittal section of the thoracolumbar region, including the conus medullaris *(arrow)*. An increase in the signal intensity of CSF relative to vertebral column allows better appreciation of the size of the thecal sac. Also note the improvement of spatial resolution

Focal widening of the cord secondary to *intramedullary tumors* was, therefore, easily recognizable on T1-weighted images. However, the neoplastic tissue did not necessarily exhibit abnormal signal intensity, unless there was a cystic or a very vascular component. In such an event, observed in an ependymoma and a hemangioblastoma (Fig. 2), the lesion appeared inhomogeneous. Differentiation of tumor-associated cavities from true syringohydromyelia was possible by means of "balanced" and T2-weighted images: With increased T2-weighting the signal of solid tumor components rose considerably, but the signal of normal neural substance next to a non-neoplastic syrinx remained fairly low. In addition, patients with syringohydromyelia frequently had a Chiari I malformation, an abnormality readily recognized on sagittal sections of the cervical cord. Hypertrophied feeding and draining vessels of hemangiomas appeared as serpentine bands of low signal intensity. As regards the determination of the overall length of intrinsic cord tumors, MRI was felt to be more reliable than all other radiodiagnostic modalities. Of particular help were "balanced" and T2-weighted images which showed the lesions to have a significantly higher signal intensity than the adjacent normal segments of the cord (Figs. 3, 4). The patient's history and clinical findings always had to be taken into consideration, though, since in a number of cases non-neoplastic conditions were very similar in appearance to intramedullary tumors (Fig. 5). MRI proved quite helpful in follow-up, although tumor recurrence was difficult to distinguish from gliosis (Fig. 6).

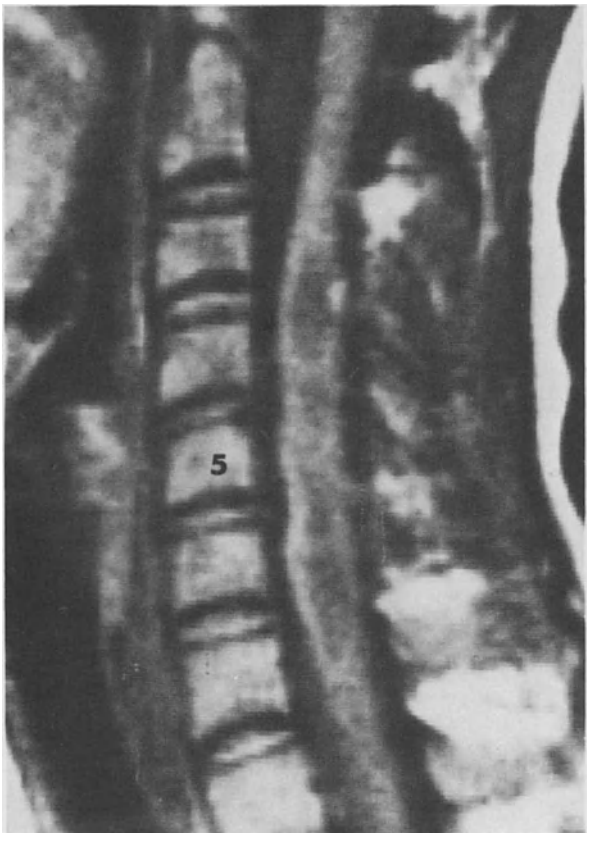
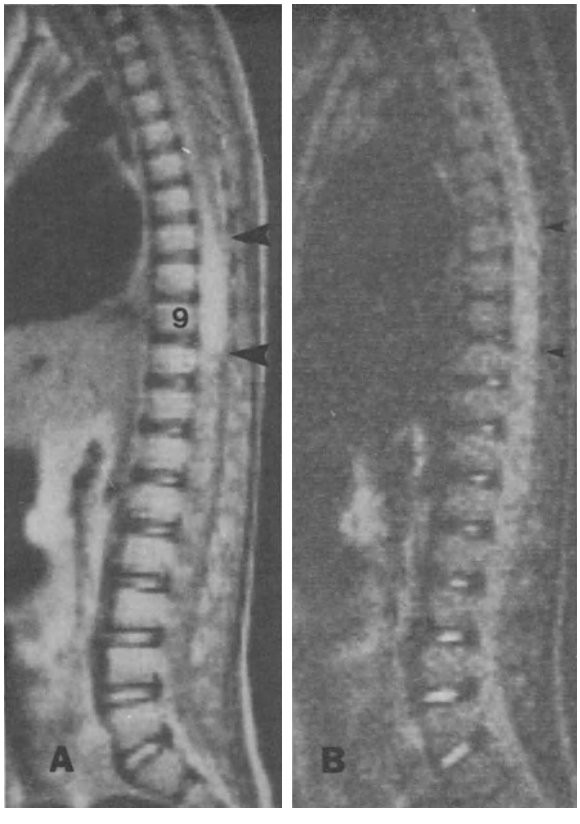



Fig. 2. Hemangioblastoma of cervical cord in a patient with von Hippel-Lindau disease. T1/T2-mixed image of midsagittal section revealing inhomogeneous appearance of cord with signal characteristics suggestive of a centrally located cyst. Note the wavy anterior contour of the cord. Widening of the cord extends from the level of C2/3 to the level of the lower endplate of C7. Multiple cerebellar lesions; clinically neurologic deterioration with tetraparesis



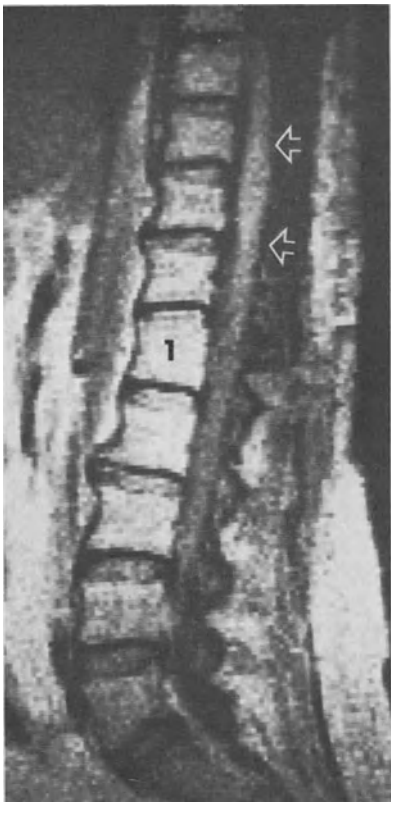




Fig. 3

Fig. 4

Fig. 3 A,B. Astrocytoma of thoracic cord in a child. A T1/T2-mixed image of midsagittal section. B T2-weighted image of same slice. High signal intensity permits determination of superior and inferior borders of lesions *(arrows)*. Widening of the cord extends from T7 to T9/10

Fig. 4. Recurrent ependymoma of lower thoracic cord. T1/T2-mixed image of midsagittal section demonstrating focal widening of the cord (between *arrows*) as well as a slightly increased signal

*Extramedullary-intradural tumors* were generally less well detectable than intrinsic cord masses, except when consisting of lipomatous tissue (Fig. 7). There was no meningioma in this group. However, judging from our experience in intracranial meningiomas, this type of lesion may be a challenge for MRI. A plaque-like neurinoma at the level of C2 was thought to represent a cord tumor, though in retrospect the appearance of the (widened) subarachnoid space above and below the mass could have led to the diagnosis. This lesion was correctly localized by CT-myelography. A comparatively large dumb-bell neurinoma, on the other hand, was easily appreciated on T1-weighted images, including its foraminal and extraforaminal components (Fig. 8).

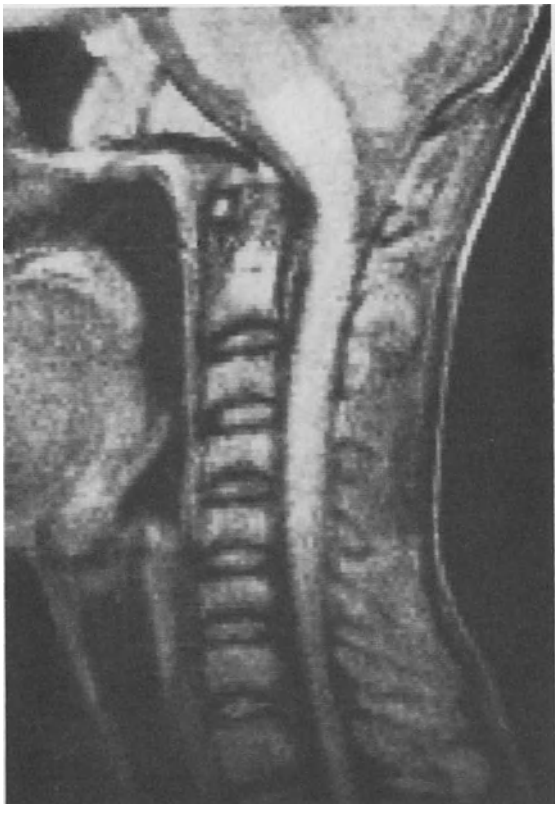
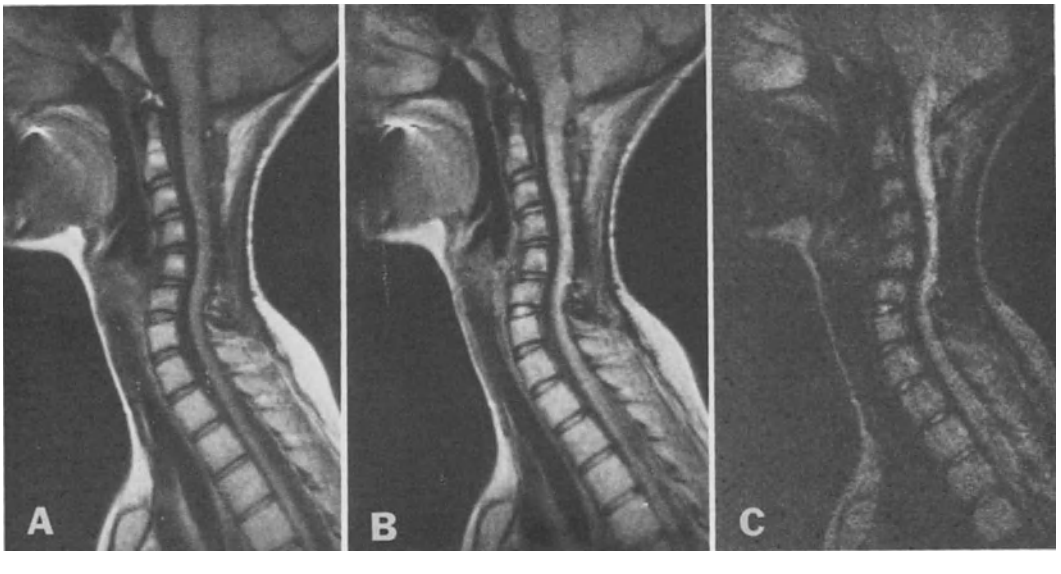


Fig. 5. Radiation myelitis of cervical cord mimicking intramedullary tumor. T1/T2-mixed image of midsagittal section showing fusiform widening of the upper and middle third of the cervical cord with increased signal intensitiy of neural substance. 15-year-old male previously treated with radiation and chemotherapy for rhabdomyosarcoma of nasal cavity



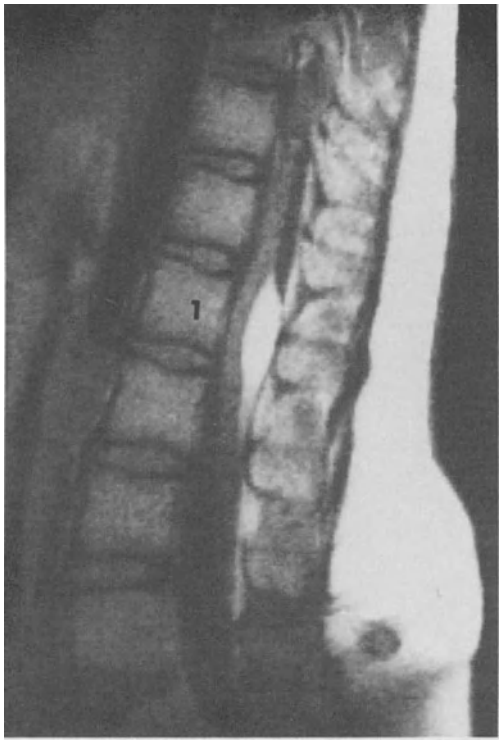


Fig. 7. Extramedullary-intradural lipoma involving conus/epiconus region. T1-weighted image of midsagittal section showing anterior displacement of cord by the mass. The high signal intensity of the lesion is characteristic for fat; compare with subcutaneous fat of the back. The patient had urinary difficulties and radicular symptoms. There was no associated abnormality of bony structures

In *extradural tumors* including metastases and malignant infiltration from lymphomas and leukemias, MRI reliably showed encroachment upon the dural sac (Fig. 9) as well as involvement of the spinal column. The latter manifested itself in a decrease of the normally high signal intensity of the vertebral bodies. Multiplicity was easily recognizable. In one lymphoma case with rapid development of paraparesis the extent of the intraspinal mass was so well shown that a myelogram was felt unnecessary. The patient underwent emergency radiation treatment on the basis of the MRI findings alone, with the T1-weighted images being of greatest importance in this situation.

Fig. 6 A-C. Presumed recurrent ependymoma of cervical cord. A T1-weighted image of midsagittal section; B corresponding T1/T2-mixed image; C corresponding T2-weighted image. Slight enlargement of cord, especially at craniospinal junction. The low signal intensity at the level of C3 on the T1-weighted image suggests a cystic cavity. High signal areas on "mixed" and T2-weighted images are partially due to gliosis rather than tumor alone

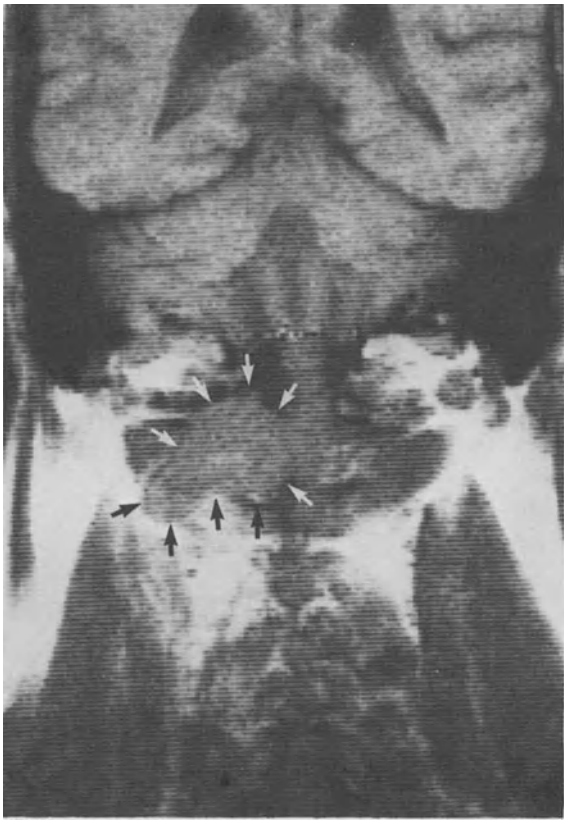


Fig. 8. Dumb-bell neurinoma at level of C1/2. T1-weighted coronal image revealing entire extent of lesion, including foraminal and extraspinal components *(arrows)*. Note widening of subarachnoid space above and below the intradural portion of the mass; cord pushed over to opposite side

## Discussion

In the evaluation of spinal tumors, MRI appears to be a step forward, particularly with respect to intramedullary and extradural masses. Compared with myelography and CT-myelography, the new imaging modality has the advantage of showing the cord in a direct rather than indirect fashion (NORMAN et al. 1984). Therefore, intramedullary lesions (including non-neoplastic ones) without significant change in gross morphology, though inaccessible to conventional radiographic methods, may be revealed by MRI. In addition, MRI may provide information about the internal composition of lesions presenting as unspecific masses on myelography, thus aiding in differential diagnosis (SARTOR et al. 1985). The fact that MRI is superior regarding determination of the longitudinal extent of intramedullary tumors will certainly influence patient management in the years to come. Its excellent demonstration of extradural mass lesions also makes MRI an attractive alternative to myelography (and possibly the method of choice in the not-so-distant future) for emergency evaluation of patients with acute onset of paraparesis. Over time, the number of myelographies requested to rule out or rule in intramedullary and extradural tumors, respectively, is therefore likely to decrease.

So far, MRI has been only moderately successful in intradural-extramedullary tumors. The relatively small size of many such lesions is probably part of the problem (SARTOR et al. 1985). However, with thin-

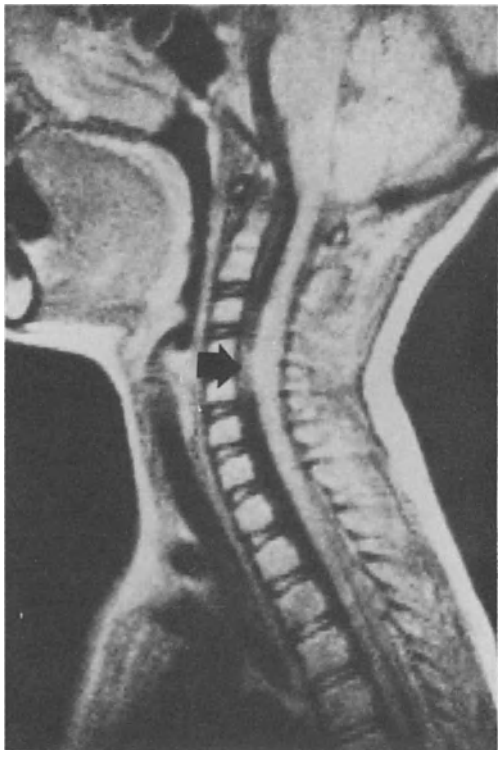


Fig. 9. Extradural metastatic fibrosarcoma of midcervical region in a child. T1/T2-mixed image of the midsagittal section demonstrates focal obliteration of the anterior subarachnoid space *(arrow)* without evidence of cord compression

ner slices (5 mm and below), imaging in at least two planes, and increased use of (improved) surface coils, most diagnostic difficulties should be overcome. Theoretically, because of its multiplanar capabilities, MRI should be more informative than CT-myelography with respect to exact topographic localization of extramedullary-intradural tumors. Twice already, we have been able, in the cervical region, to show a "tumor" to represent, in reality, a large disc herniation (SARTOR et al. 1985). These lesions were well visualized as anteromedullary masses on midsagittal images; the cord appeared flattened and displaced posteriorly. Both patients had been diagnosed elsewhere on clinical and myelographic grounds as having an intramedullary tumor. In one case an operation had been performed, but the cord biopsy yielded only "unspecific neural tissue".

Among the weaknesses of MRI compared with conventional radiologic studies are: (1) inferior visualization of bony structures, (2) lack of detecting subtle calcifications (which may assist in differential diagnosis), (3) similar signal characteristics of CSF and certain soft tissue lesions, and (4) a number of artifacts, of which many will be removed with further progress in technology. Among the strengths of MRI are: (1) direct rather than indirect visualization of the spinal cord, (2) superior soft tissue discrimination, (3) lack of bone-induced artifacts, (4) imaging in multiple planes without the need to move the patient or accept inferior spatial resolution, and (5) absence of radiation hazards and morbidity, provided certain patients are excluded from the examination.

*In conclusion*, MRI is a very promising tool of investigation in suspected spinal tumors. It appears to have the capability of replacing myelography in many diagnostic situations. Similarly, except in the evaluation of bony structures, CT will probably further lose importance.

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# Spinal Tumors: A Multi-Center Study of the Deutsche Gesellschaft für Neurochirurgie

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According to the literature, spinal tumors were successfully removed surgically for the first time approximately 100 years ago by W. MACEMEN (1883) and V. HORSLEY (1887). Since that time surgery has been performed on thousands of spinal tumors all over the world, though spinal tumors constitute only 2% of all tumors.

In 1972 NITTNER commendably reported, in a substantial contribution to a manual, on 4885 cases of spinal tumors. Very few statistical investigations in the literature are based on comparable large numbers of cases. In his postdoctoral thesis required for qualification as university lecturer, WEIDNER reported in 1981 on 310 cases of extradural tumors of the spinal column and in 1982 MAN-KAI CHENG reported on 1693 patients who had been treated for spinal tumors in various hospitals of the People's Republic of China in the years 1950 through 1975.

Improved diagnostic possibilities and progress in the treatment of spinal tumors led to the preparation of a collective set of statistics, with 43 German and Austrian hospitals for neurosurgery participating. A list of the contributing hospitals and physicians is enclosed as an appendix to this chapter.

In the 43 hospitals mentioned, between 1 January 1979 and 31 December 1983, i.e. a 5-year period, surgery was performed on a total of 3056 patients with spinal tumors. The statistics include all tumors resulting in damage to the spinal cord, the cauda equina, the lamina of the spinal cord, and the spinal nerve roots. Histological investigation was performed on 3048 tumors; the histological diagnoses are listed in Fig. 1.

The very low number of gliomas, constituting only 2.4% of all spinal tumors, is remarkable. The percentage of the intramedullary tumors grouped together as gliomas is significantly lower than 10, even when adding the ependymomas, which are quoted as an individual group and occur with a frequency of 5.5% of the total cases.

In comparison with the percentages quoted above, NITTNER classified 13.2% and CHENG 10% of all spinal tumors as gliomas. This remarkable discrepancy can be explained by the significant increase in cases of surgery on metastases. A total of 43.1% of all tumors covered by this joint German-Austrian study were metastases. By contrast, in the statistics of NITTNER metastases represented 6% and in those of CHENG only 5.5% of cases. Of the spinal tumors in the study, 19% were meningiomas and only 12% neurinomas. However, in the literature a ratio of 1:1 between meningiomas and neurinomas is quoted.

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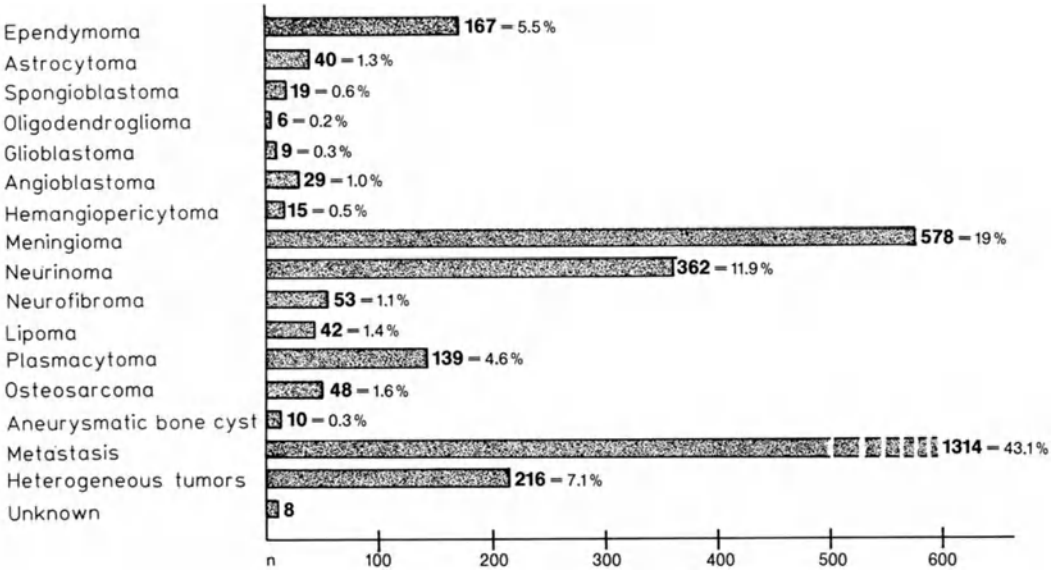



Fig. 1. Histology of 3048 of the 3056 spinal tumors

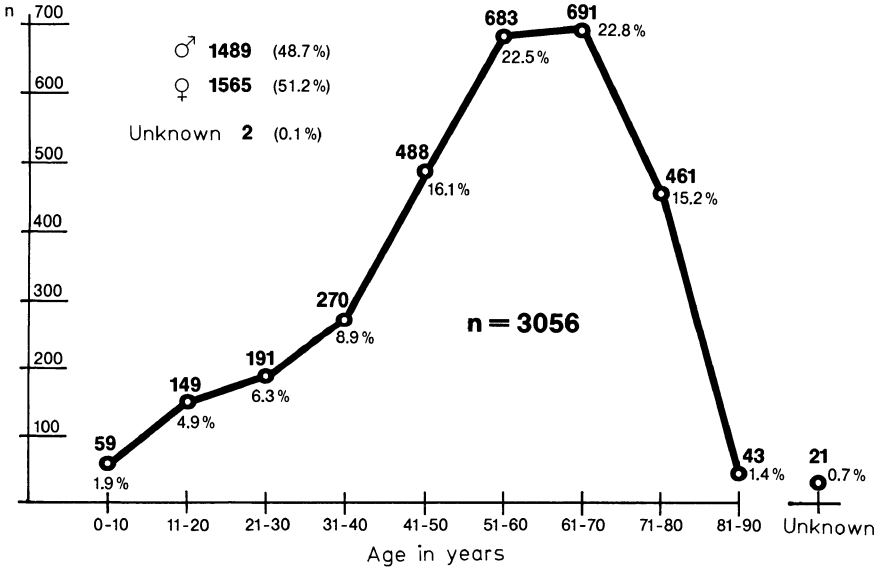



Fig. 2. Age and sex distribution of the 3056 patients

The age and sex distribution for the 3056 patients with spinal tumors is shown in Fig. 2. The peak age of occurrence for such tumors are the sixth and seventh decades of life. In comparison with the results of the earlier investigations by NITTNER, an upward shift in the peak age of occurrence can be recognized.

In total a ratio of 1:1 was observed for men and women with spinal tumors. However, meningiomas were found much more frequently in women

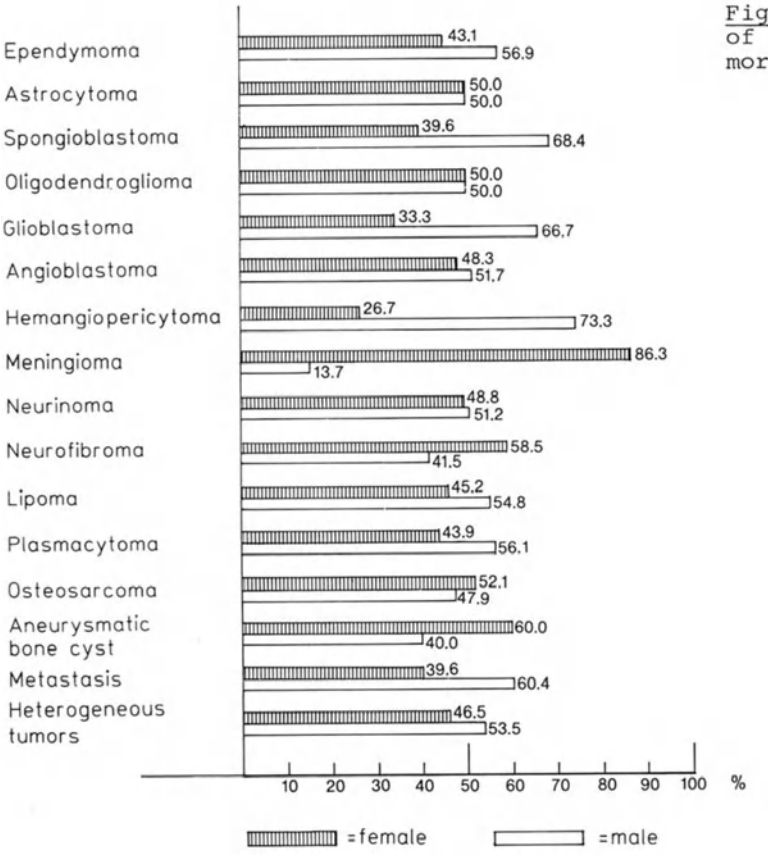



Fig. 3. Sex incidence of various spinal tumors in 3047 patients

than men (86.3% vs 13.7%; see also Fig. 3). In 1301 patients with spinal metastases, the primary tumors were, in decreasing order of frequency, bronchial carcinomas (15.4%), tumors of the breast (12.3%), tumors of the prostate (9.1%), and hypernephromas (8.5%) (see Fig. 4). An almost uniform distribution of the spinal tumors across all areas of the spinal column was observed; the tenth thoracic segment was affected most frequently (in 185 cases or 6.1%; Fig. 5).

As regards their localization, the tumors were classified into intramedullary, intradural-extramedullary, intra- and extradural, extradural, and intra- and extraspinal tumors (Fig. 6). Among the intramedullary tumors, ependymomas were most frequently found (62.6% of cases). In addition, 10.4% were metastases; this result cannot be explained at first glance and merits further investigation. The second and third groups were mainly composed of meningiomas (47.8%) and neurinomas (23.8%), while in the fourth and fifth groups metastases (71.1%) were mainly noted. Primary tumors of the vertebrae were demonstrated in only 11.7% of all cases.

Pain was the principal initial symptom of spinal tumors. Independent of the location or type of tumor, pain was described to be local or radicular. In decreasing frequency, paresis of individual muscles and sensation disorders (Fig. 7) constituted other primary symptoms. The

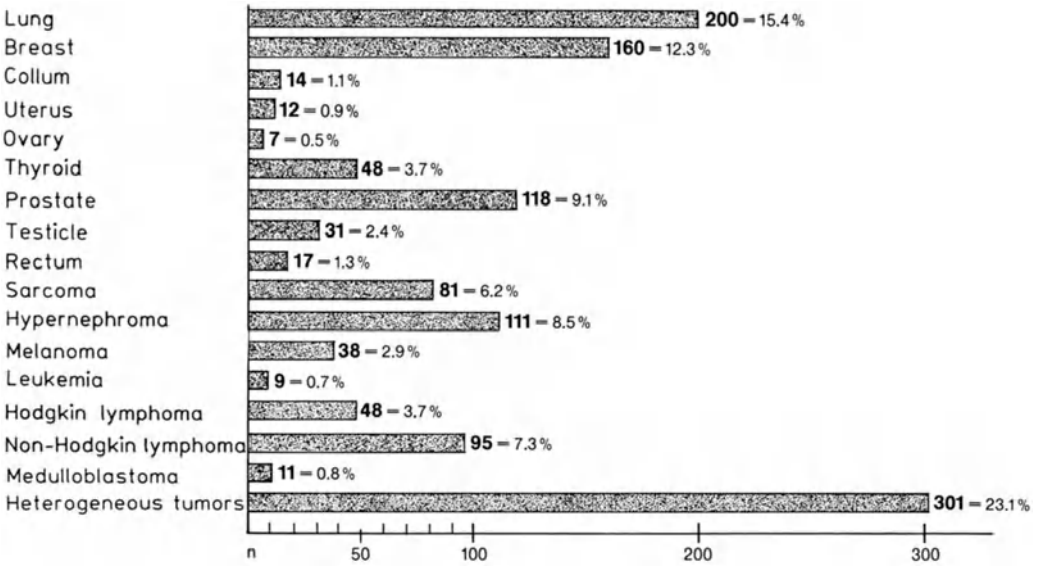
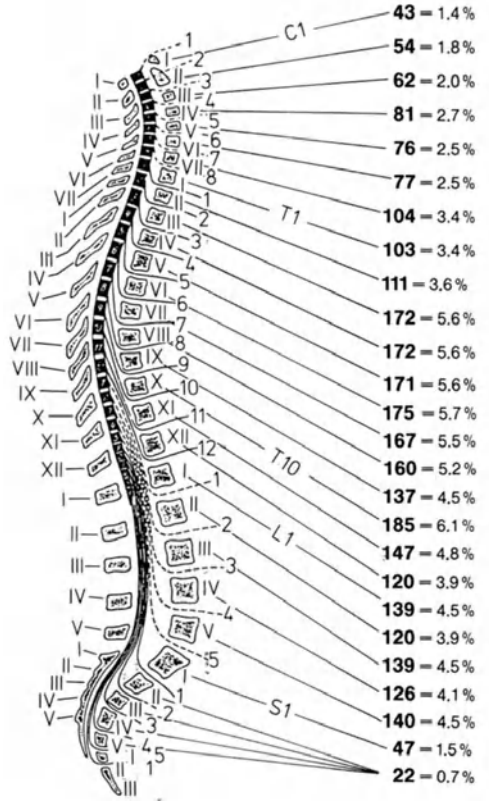



Fig. 4. Primary tumors in 1301 patients with spinal metastases




43 = 1.4%
54 = 1.8%
62 = 2.0%
81 = 2.7%
76 = 2.5%
77 = 2.5%
104 = 3.4%
103 = 3.4%
111 = 3.6%
172 = 5.6%
172 = 5.6%
171 = 5.6%
175 = 5.7%
167 = 5.5%
160 = 5.2%
137 = 4.5%
185 = 6.1%
147 = 4.8%
120 = 3.9%
139 = 4.5%
120 = 3.9%
139 = 4.5%
126 = 4.1%
140 = 4.5%
47 = 1.5%
22 = 0.7%

Fig. 5. Segmental localization of 3056 spinal tumors (diagram from Hansen, K. and Schliack, H., Thieme, 1962)

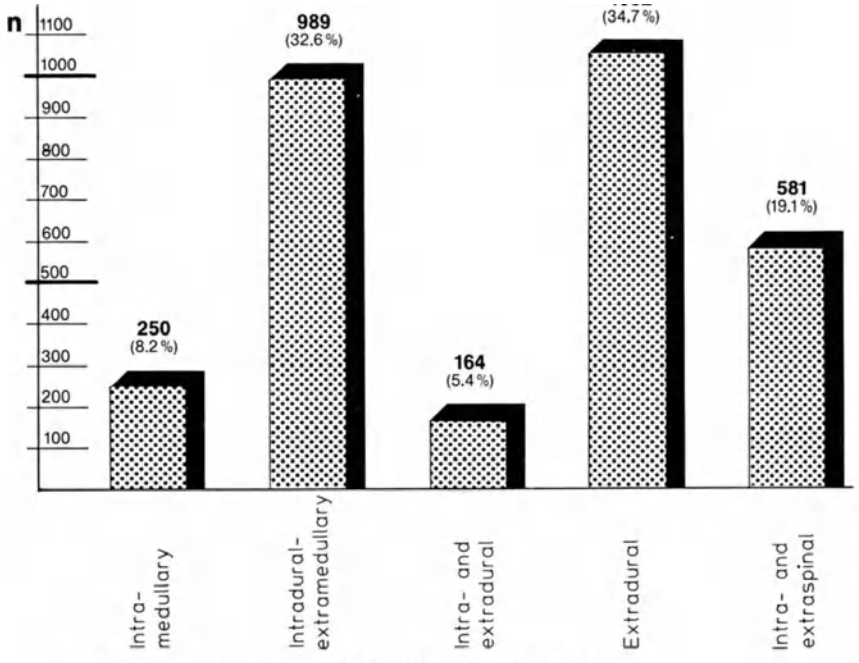



Fig. 6. Localization of 3035 spinal tumors

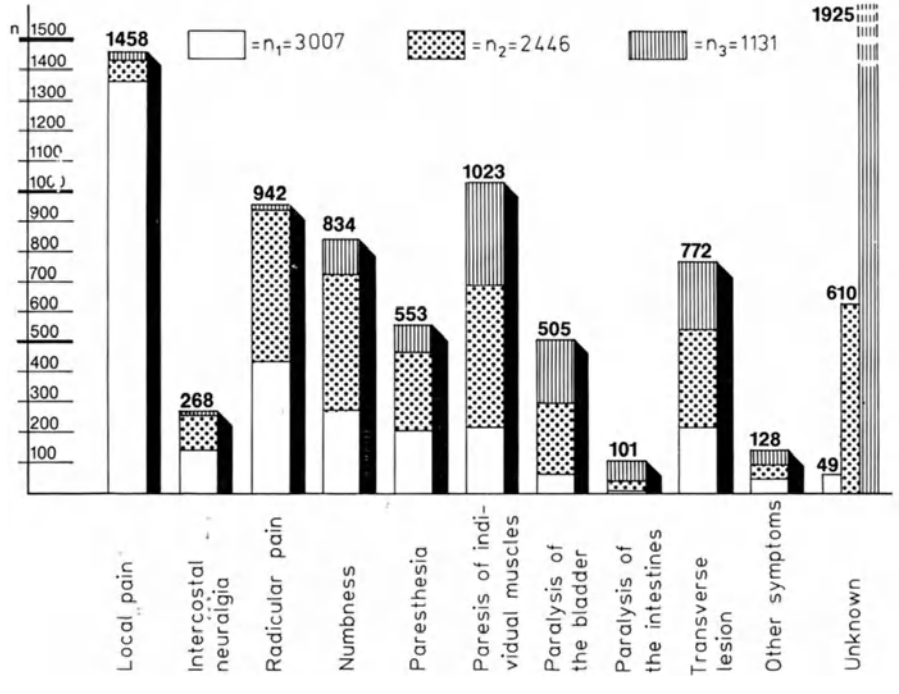



Fig. 7. Initial symptoms of spinal tumors in 3056 patients (three of the initial symptoms could be noted)

frequency of hemi- and quadriplegia as the initial symptom was unusually high, however. In 26.5% of 2991 patients incomplete quadriplegia represented the primary neurological finding. Additionally in 257 patients, corresponding to 4.5% of all cases, total quadriplegia was noted as the first neurological indication of a spinal tumor. The frequency of other unusual neurological findings, such as paralysis of the bladder, pareses of reference muscles, impaired reflexes, and spastic phenomena associated with disturbances of sensation, is shown in Fig. 8.

Examination of the CSF was performed in 1768 out of 3056 patients. Elevated levels of protein or of both protein and the number of cells were noted in 61.2% of the cases. In 20.5% of the samples CSF findings were normal (Fig. 9). Examination of the CSF for tumor cells was carried out in isolated cases only; consequently no statistical analysis could be made.

In 2413 patients roentgenology was performed. In accordance with the large number of spinal metastases present, destruction of the vertebral arches, of the stems of the vertebral arches, and of the vertebral bodies formed the pathological changes seen most frequently. In 37% of the patients X-rays of the spinal column showed no pathological changes in spite of the tumors present (Fig. 10).

Myelography was performed in 2807 patients in whom the presence of a spinal tumor was suspected. Bowl-shaped obstructions of the contrast medium were found in 1061 cases, corresponding to a frequency of 36.2%. This number of obstructions correlated approximately with the frequency of meningiomas and neurinomas demonstrated. Myelographic findings which were without unusual features were seen in an insignificantly low percentage of cases only (Fig. 11).

Responses to the question about the type of surgical procedure used showed the following percentages: In 89.8% of all patients treated surgically laminectomy was performed, and in 7.6% hemilaminectomy. In only isolated cases was so-called extended fenestration carried out.

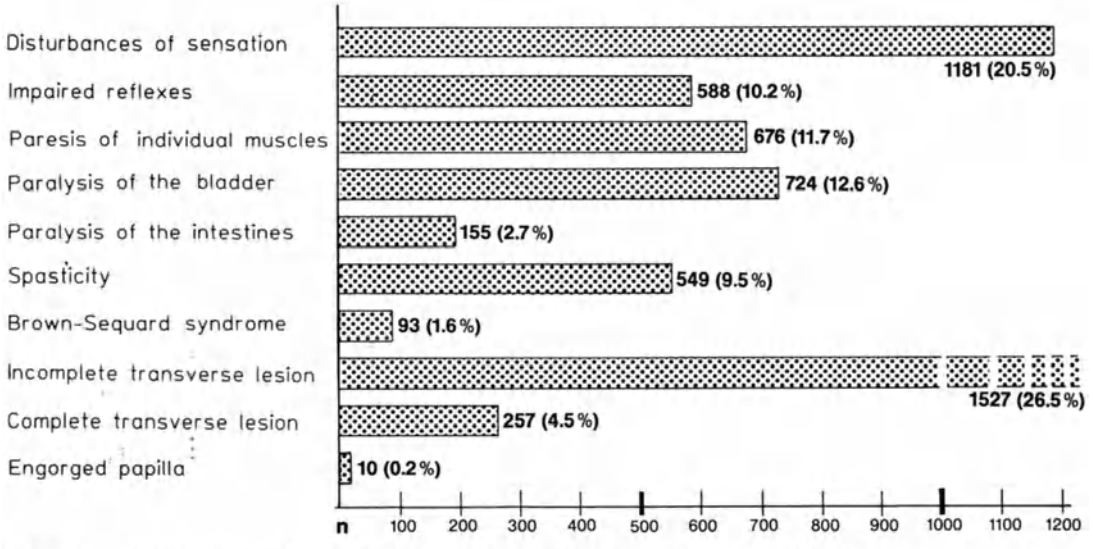



Fig. 8. 5760 initial neurological findings in 2921 patients

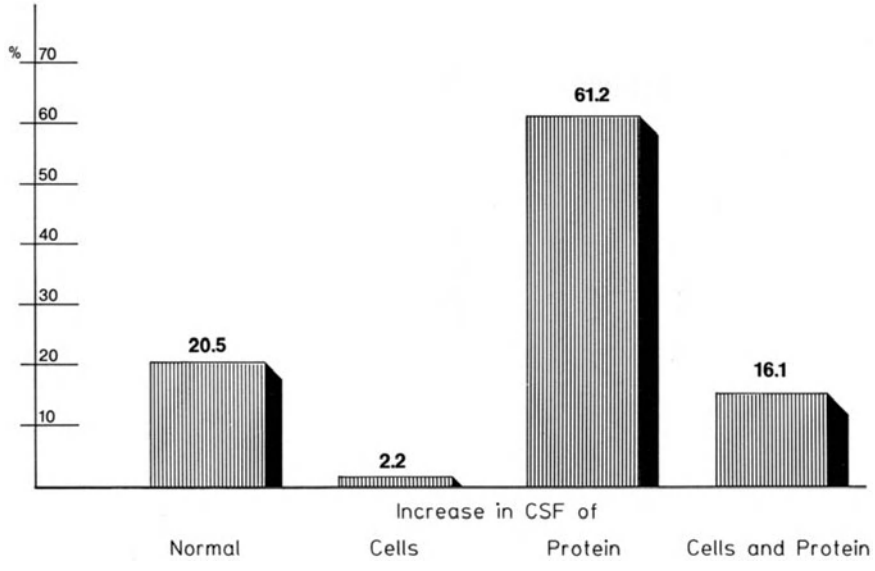



Fig. 9. Results of CSF analysis in 1768 patients

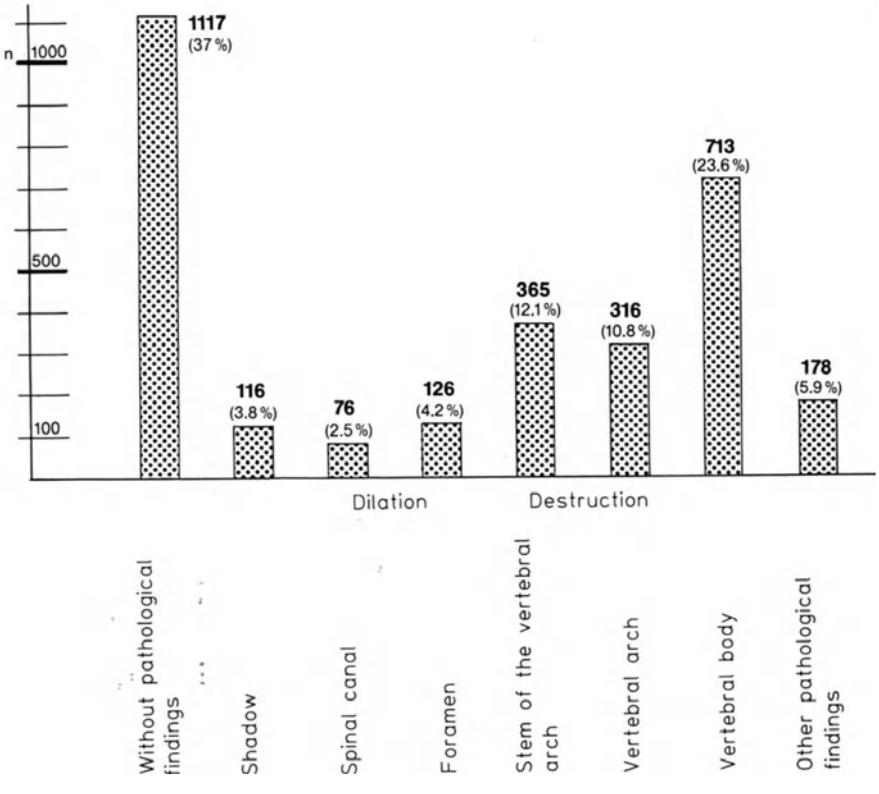



Fig. 10. 3017 X-ray findings in 2413 patients

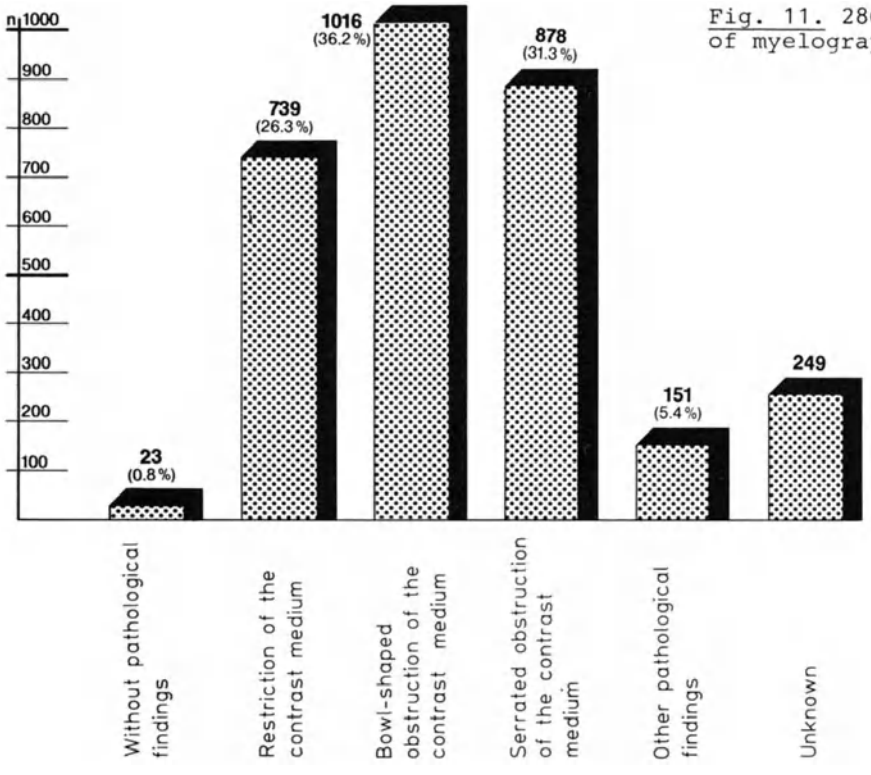



Fig. 11. 2807 findings of myelography

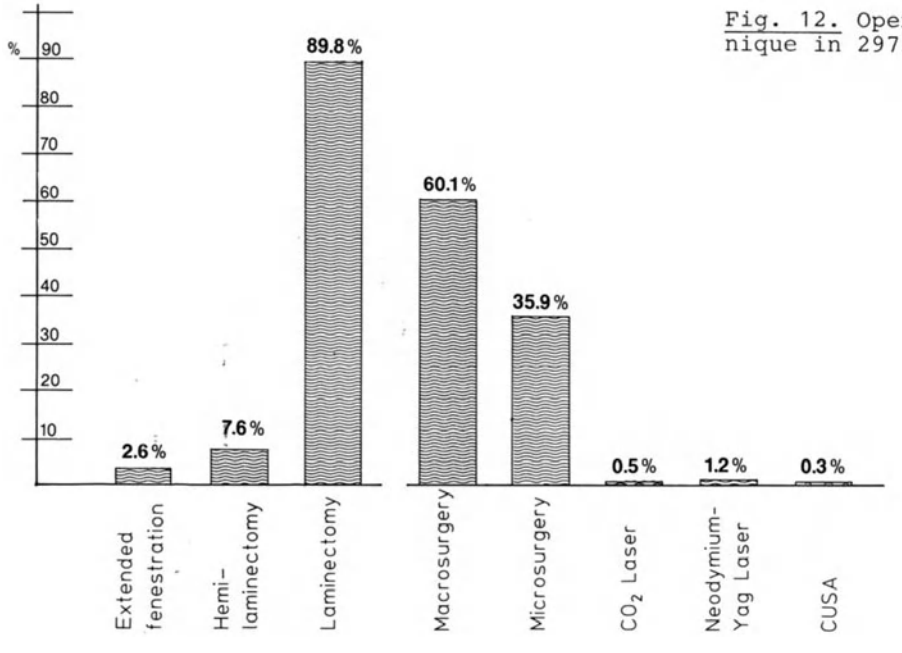



Fig. 12. Operative technique in 2975 patients

Approximately two-thirds of the patients underwent macrosurgery, while one-third were treated via microsurgery. The dominance of macrosurgery was most likely due to the high incidence of metastases (Fig. 12).

Total extirpation of a tumor, the most hoped for aim of surgical intervention, was achieved in 1373 patients (45.8% of all cases). In another group of 1302 patients (43.4%) a partial resection of the spinal tumor was performed. In 6% of cases decompression only was provided, and in 4.7% merely a biopsy was performed (Fig. 13).

Injury of nerve roots (1333 cases) and of caudal fibers (23 cases) was mentioned as the most frequent intrasurgical complication. These large numbers can only be explained by the fact that the occurrence of intentional and necessary cutting of nerve roots in cases of spinal neurinomas and meningiomas was included in the numbers quoted. Intraoperative hemorrhages, which could not be stopped or were managed with considerable difficulty, occurred in 186 patients and might have had its origin in the large number of metastases treated surgically.

In spite of all the troubles arising during surgery, such as injury to nerve roots, gross hemorrhage, etc., postoperative subjective and objective improvement and relief were noted in most patients (Fig. 14). Of a total of almost 3000 patients in whom surgery was carried out, 68.2% reported an improvement in their condition even at an early stage, i.e., while still hospitalized. Corresponding to these subjective statements, the neurological findings showed a postoperative improvement in 59.7% of patients. However, in 10% of patients treated surgically, a worsening of condition was noted postoperatively.

The early results following surgery are clearly related to the radicalness of the surgical intervention. Following total extirpation of a spinal tumor, improvement was obtained in most of the cases. Partial resection resulted in an improvement in more than 50% of patients. Simple decompression, however, also provided relief and reduction of discomfort in many cases (Fig. 15).

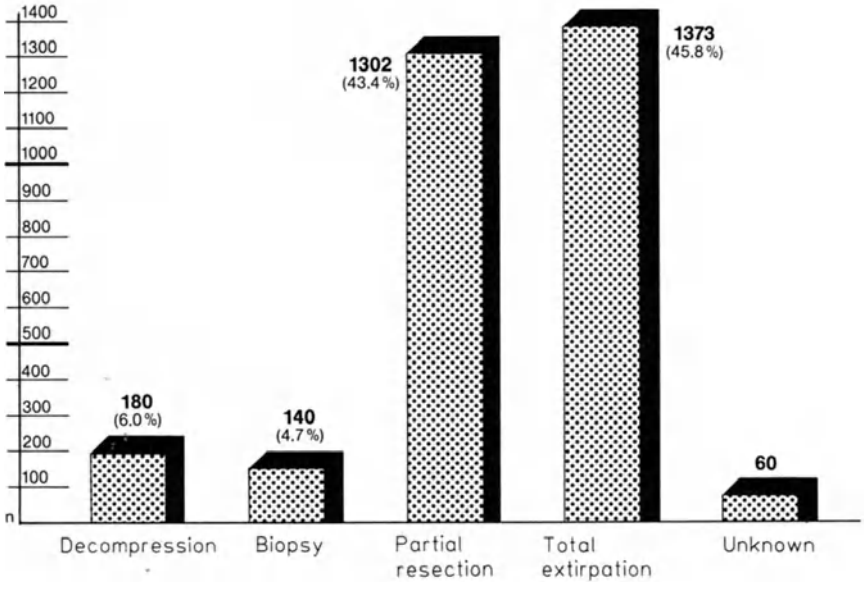



Fig. 13. Methods of operation in 2996 patients

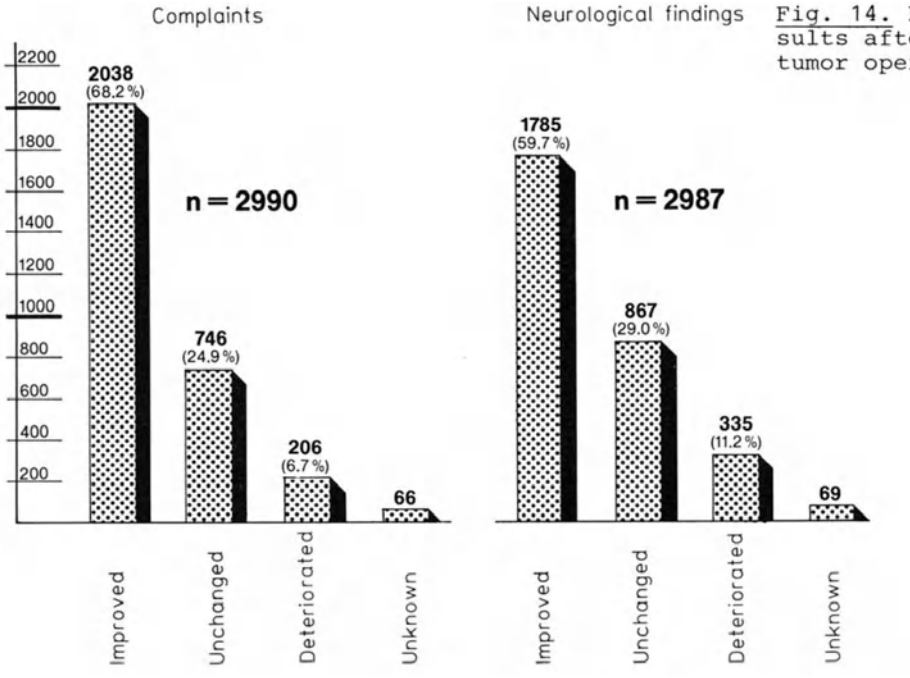



Fig. 14. Early results after spinal tumor operations

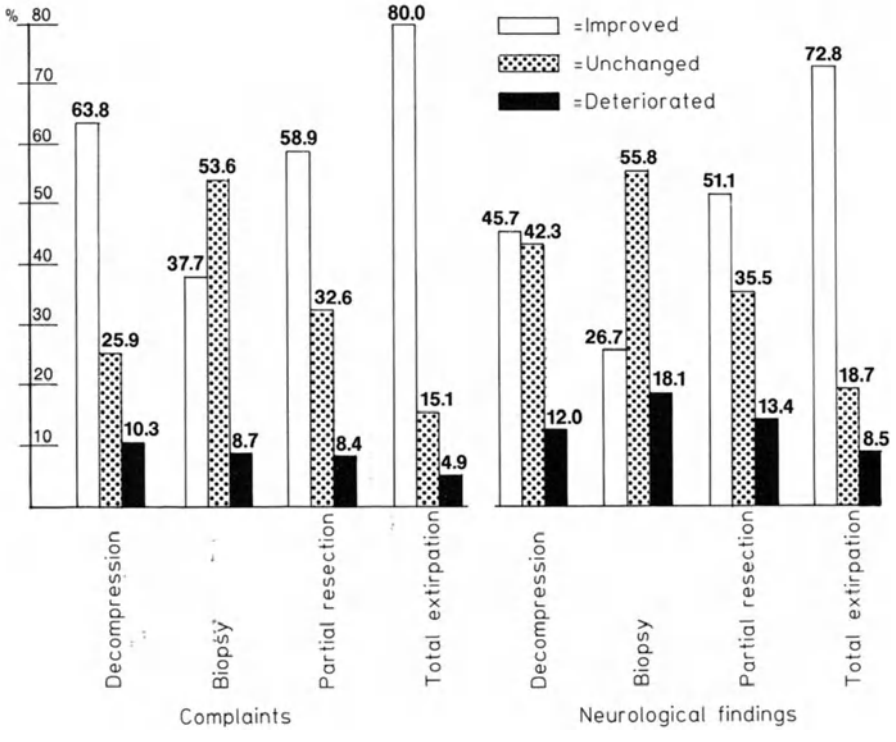



Fig. 15. Early results in 2950 operated patients with spinal tumors, according to form of treatment

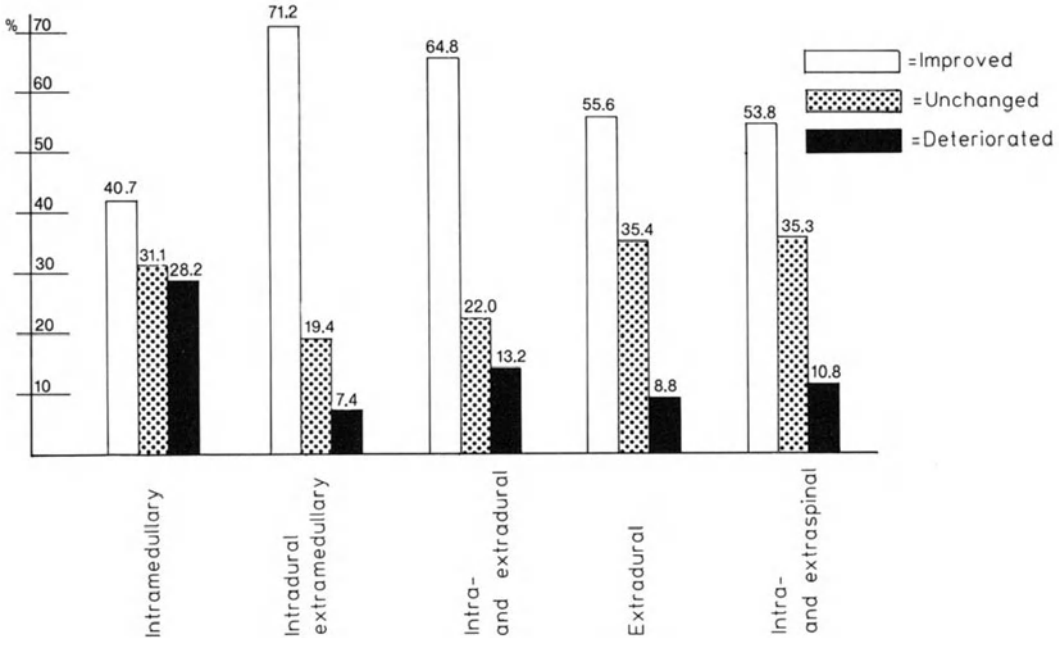



Fig. 16. Relationship between localization of spinal tumors and postoperative neurological findings in 2970 patients

Figure 16 illustrates the relationship between tumor location in the spinal cavity and the early postoperative results. The optimal early results seen in groups 2 and 3, with an improvement in more than two-thirds of cases, are most likely related to the large numbers of meningiomas and neurinomas in these groups.

Information on the late results following surgery was furnished for 1624 patients, corresponding to only 50% of all patients covered by the study. Moreover in 20.1% of the patients on whom information was made available, very interesting questions concerning the ability to return to work or a bedridden condition were not answered. Almost one-third of the patients in whom the later history was taken were able to work again in their earlier occupation or in another profession. The chance of a successful return to work depends, of course, to a large extent on the type of tumor diagnosed and on the possibility of its surgical removal. To quote actual percentages, more than 70% of the patients with spinal neurinomas, more than 50% with meningiomas, more than 30% with spinal ependymomas, but only slightly more than 10% with metastases were able to work again. As indicated above, generally speaking almost two-thirds of the patients for whom late results were available were unable to work postoperatively, bedridden, or were dependent on a wheelchair for mobility (Figs. 17, 18). A close correlation exists between the radicalness of surgical intervention and the late results of that surgery. Only total extirpation of spinal tumors resulted in a large percentage of patients experiencing long-term improvement and being able to return to work (Fig. 19).

Following surgery for spinal tumors, postoperative treatment consisted in most cases in nonspecific therapy involving physical procedures and the administration of medication. In less than 10% of the total cases was this therapy conducted in a rehabilitation center. Irradiation with X-rays was performed postoperatively in approximately 18% of patients, while cytostatic drugs were used in approximately 6% and a combination

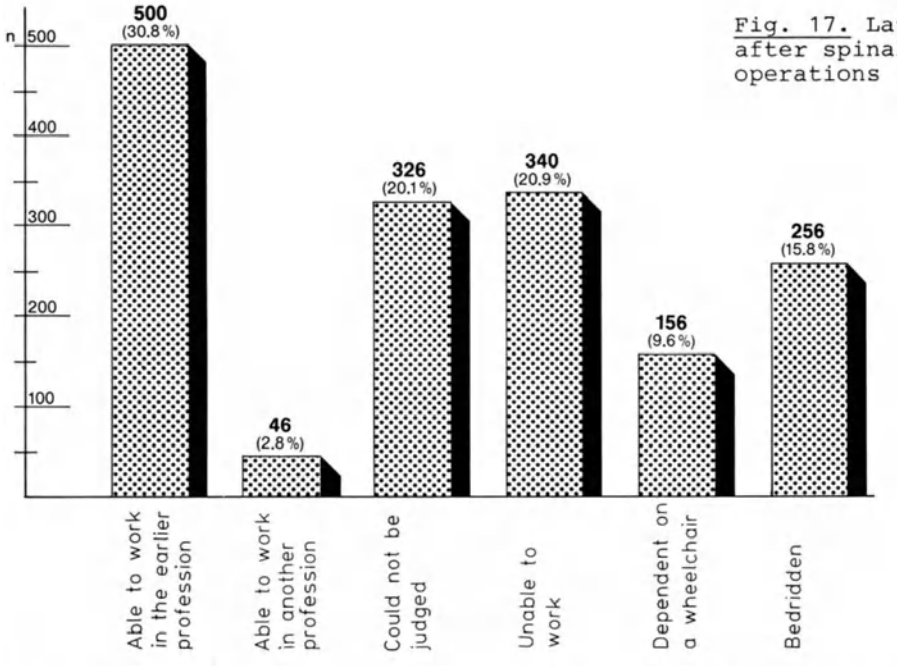



Fig. 17. Late results after spinal tumor operations (n = 1624)

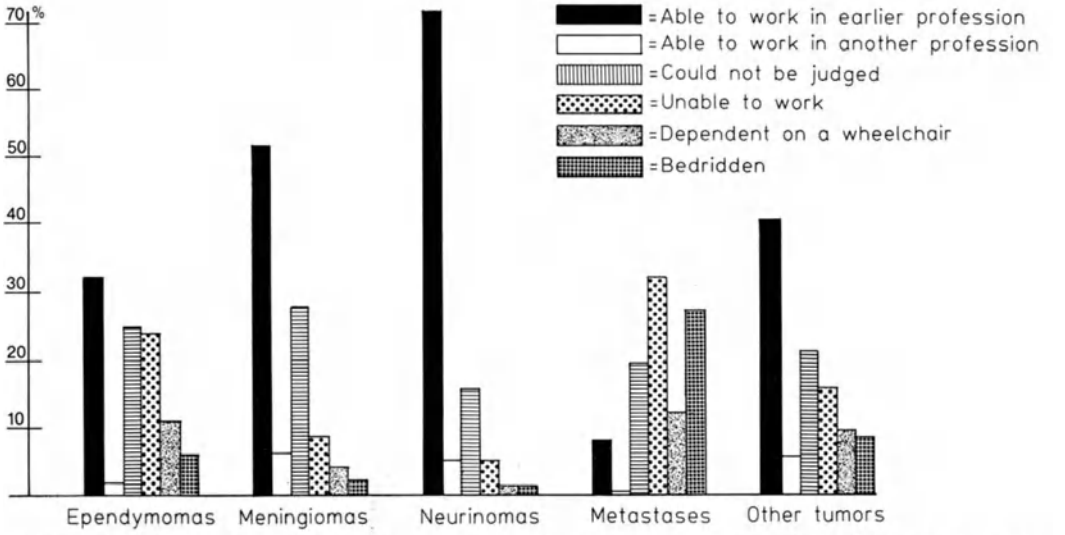



Fig. 18. Late results after spinal tumor operations in 1208 patients, according to type of tumor

of irradiation and cytostatic drugs in 8% of patients for whom information was furnished (Fig. 20).

When the data on surgical treatment of relapses were evaluated, it was found that in the case of earlier metastases relapses can be expected within a comparatively short time. Surgery as a consequence of relapse following surgery for spinal metastases was performed in 36 patients within the first 3 months after the initial surgery, in 28 patients within the first 6 months, and in a further 29 within the first year.

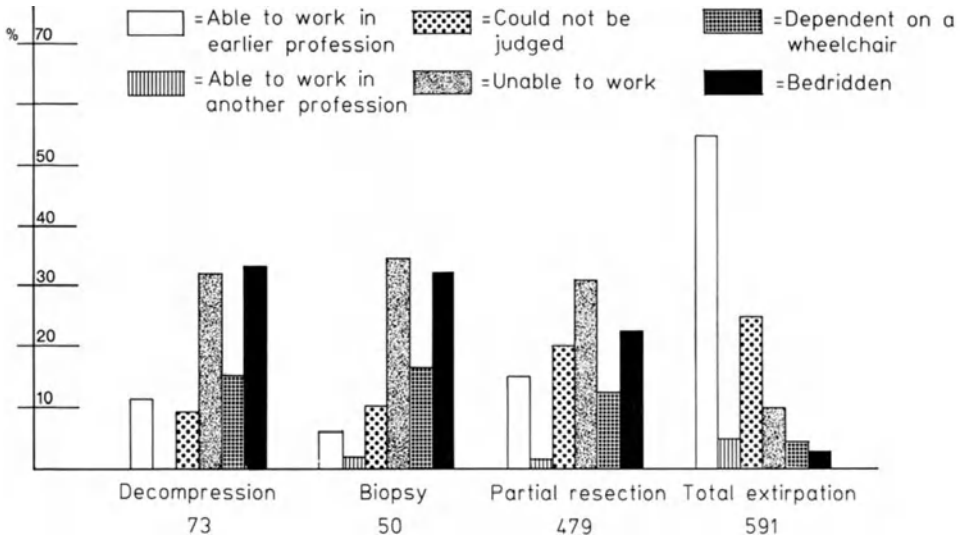



Fig. 19. Relationship between the operative method and late results in 1193 patients

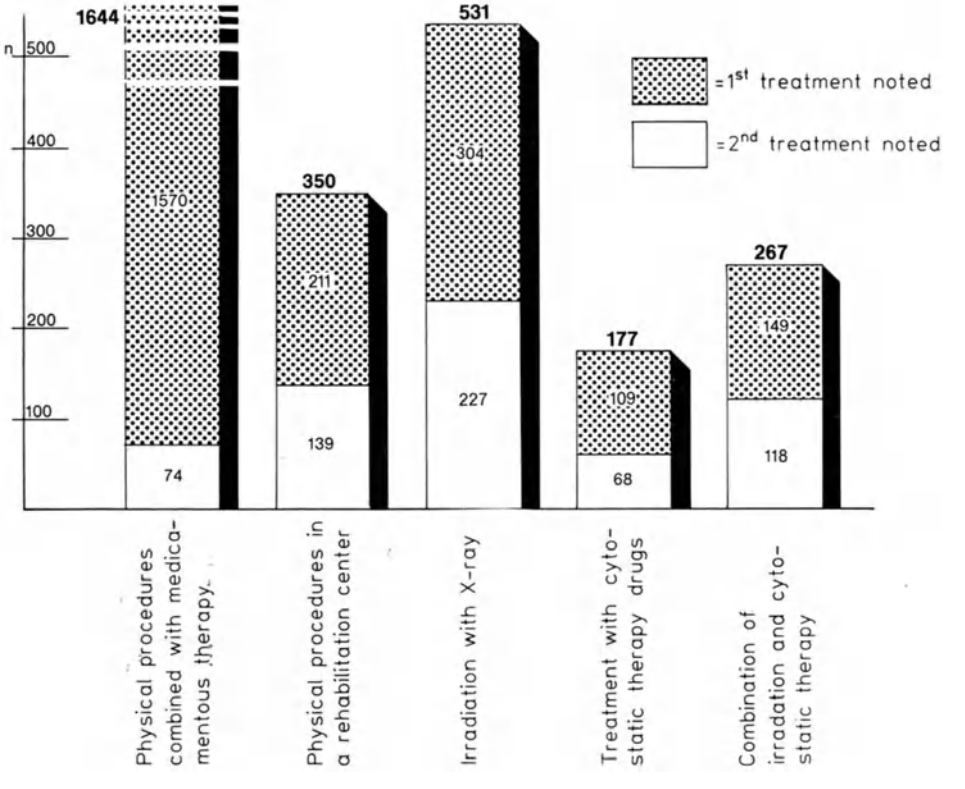



Fig. 20. Postoperative treatment of patients (two different forms of treatment could be noted)

In this context, however, the question of whether the new tumors are true relapses or just remnants of earlier tumors which continued to grow remains open. Surgical procedures intended to stabilize the spinal column were designated as secondary, subsequent surgery. Such procedures were performed in 97 patients and involved surgery to substitute vertebra, to insert wedges or plates, to attempt stabilization by means of wire or Harrington rods, etc. Since their number was comparatively low, classification of these secondary surgical steps was omitted.


## Summary

In 43 hospitals for neurosurgery in the Federal Republic of Germany and Austria a total of 3056 patients afflicted with spinal tumors were treated surgically between 1 January 1979 and 31 December 1983. Of all tumors, 43.1% were metastases. The number of gliomas was significantly below 10%.

In comparison with earlier statistical investigations the peak age of incidence of spinal tumors has risen.

Meningiomas were found in women in 86.3% of cases, a significantly higher frequency than in men, while for all other spinal tumors the sex ratio was approximately 1:1.

The initial symptom most frequently noticed was local or radicular pain, followed by pareses and impairment of sensation. In 30% of patients incomplete or total quadriplegia was the initial symptom, an unexpectedly high rate.

Elevated levels of protein and elevated numbers of cells in the CSF, changes in the spinal column documented roentgenologically, and pathological myelographic findings were found in the majority of patients.

In almost 90% of all patients treated surgically laminectomies were performed. Macrosurgical procedures were dominant. Total extirpation of spinal tumors proved feasible in 1373 patients, corresponding to 45.8% of cases.

The early and late results of surgery were clearly related to the radicalness of the surgery and to the biological behavior of the tumor.

Postoperative therapy with cytostatics or X-rays was carried out only to a limited extent. Similarly, postoperative surgery aiming at stabilization of the spinal column was performed in only a small number of patients.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## Appendix: List of the Contributing Departments and Physicians

| | |
|---|---|
| Aachen | J. Bröcheler, W. Krenkel |
| Berlin-Charlottenburg | R. Baerwald, E. Kazner |
| Berlin-Neukölln | W. Cramer, Ch. Härdel, N. Kirchhoff, P. Lust, M. Meltzer, F. Reuter, H. Wenker, S. Zarm |
| Berlin-Steglitz | M. Brock, B. Heppner |
| Berlin-Wilmersdorf | B. Bingas, M. Fichtl, F. Golestan |
| Bielefeld | M. Conzen, H. Sollmann |
| Bonn | D. Moskopp, R. Wüllenweber |
| Damp | H.D. Kunft |
| Dortmund | T. Paavola, H. Palleske |
| Düsseldorf (Univ.) | U. Dietrich, U. Hülsbrink-Deußen, W.-J. Bock |
| Duisburg<br>Städt. Kliniken | W. Bettag, K. Boudemagh, H. Wandt |
| Duisburg<br>Ev. Krankenanstalten | P. Böhm, G. Kremer |
| Erlangen | R. Fahlbusch, M. Morgenstern, M. Klinger |
| Essen (Univ.) | W. Grote, C. Roosen |
| Frankfurt (Univ.)<br>Allg. Neurochirurgie | R. Lorenz, M. Rittierodt, W.-J. Steudel |
| Frankfurt (BG) | B. Hübner, K. Leyendecker |
| Freiburg (Univ.)<br>Allg. Neurochirurgie | H.R. Eggert, A. Laborde, W. Seeger |
| Graz | L.M. Auer, G. Vlaries, F. Heppner, G. Papaeftlymiou |
| Hamburg-Altona | H. Finkemeyer, J. Krüger, M. Weißflog |
| Hamburg-Heidberg | G. Schadunt, G. Simon, S. Ziegler |
| Hannover (MHH) | D. Dietz, H.G. Höllerhage, M. Lorenz, V. Seifert, D. Stolke |
| Heidelberg | G. Schackert, St. Kunze |
| Herdecke | W. Ischebeck, M. Schierenberg |
| Homburg/Saar | B. Barbier, F. Loew |
| Karlsruhe | B. Böhm, J. Liesegang |
| Kiel | H.-P. Jensen, F. Koschorek |
| Koblenz<br>Ev. Stift | H. Altenburg, H.-G. Böcher-Schwarz, P. Schönhofer |
| Köln (Univ.) | R. Firsching, R.A. Frowein |
| Mainz | W.E. Haeberle, K. Schürmann, Th. Wallenfang |
| Meppen | G. Sandvoß |
| München (Univ.) | W.R. Lansksch, F. Marguth, J. Obermüller |
| Münster (Univ.) | M. Brandt, T. Gruia, W. Walter |
| Offenbach | H. Fromm, Ch. Lenz |
| Oldenburg | P. Blankenberg, K. Napitupulu, U. Sander |

| | |
|---|---|
| Regensburg | P. Gruß, H. Tannenbaum |
| Salzburg | H.E. Diemath, H. Kollmann |
| Seesen | E.R. Schäfer |
| Siegen | U. Hase, P.-L. Richter, M. Sabbag, H. Ütkü |
| Stuttgart | K.H. Holbach, D. Orio-Glaunec |
| Trier | K. Faulhauer |
| Ulm | F.O. Miltner, P. Oldenkott, Ch. Schmidt |
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*D. Augustin, G. Fuchs, W. Hopfenmüller*

# The Use of Transthoracic and Ventro-lateral Access in the Surgical Treatment of Extradural Spinal Tumors in the Thoracic and Lumbar Areas

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## Introduction

Surgical treatment of ventral extradural space-occupying lesions of the spine is commonly performed by means of decompressive laminectomy. While relief of the spinal cord or the cauda equina usually results in temporary reduction of pain and of neurological disturbances, the long-term results of such therapy are unsatisfactory. Thus in the current literature on surgery almost all authors uniformly report very poor results (e.g., 1, 7, 8). In 1965 BRICE and McKISSOCK (1) traced the later condition of 145 patients who had initially suffered from ventral thoracic space-occupying lesions, including thoracic herniation of intervertebral disks, which had been treated by means of laminectomy. In merely 30% of the cases was the result termed satisfactory. No patient with an exclusively ventral lesion showed an improvement. The poor results of decompressive laminectomy on the one hand and the good results that have been obtained by means of an anterolateral transthoracic approach to the thoracic spinal column on the other (2, 3, 6, 7) make it attractive also to remove ventral thoracic and lumbar spinal lesions ventrally, as has long been the practice in the cervical area. The steps to achieve ventral access to the thoracic and lumbar sections of the spinal column have been sufficiently standardized in the course of recent years (4, 9). In cooperation with traumatologists and surgeons specializing in surgery of the thorax and the abdomen, this surgical route should therefore be selected for surgical interventions. Describing three selected cases, this paper is intended to present the indications for the procedures suggested, the surgical details, the results obtained, and the possible complications to be considered during (Fig. 1):

1. Ventrolateral extraperitoneal access to the lumbar part of the spinal column (L3)
2. Thoraco-phrenico-lumbar access to the thoraco-lumbar transition (T12)
3. Transthoracic access to the thoracic part of the spinal column (T4).

## Case Reports

### *Case 1: M.M., Female, 66 Years Old*

The patient was first hospitalized in December 1980 for severe pain in the back and a developing cauda equinus syndrome. Roentgenographic investigation revealed a tumor of the third lumbar vertebra with myelographically demonstrable ventral compression of the cauda equina. Decompressive laminectomy was performed and the diagnosis of chordoma verified.



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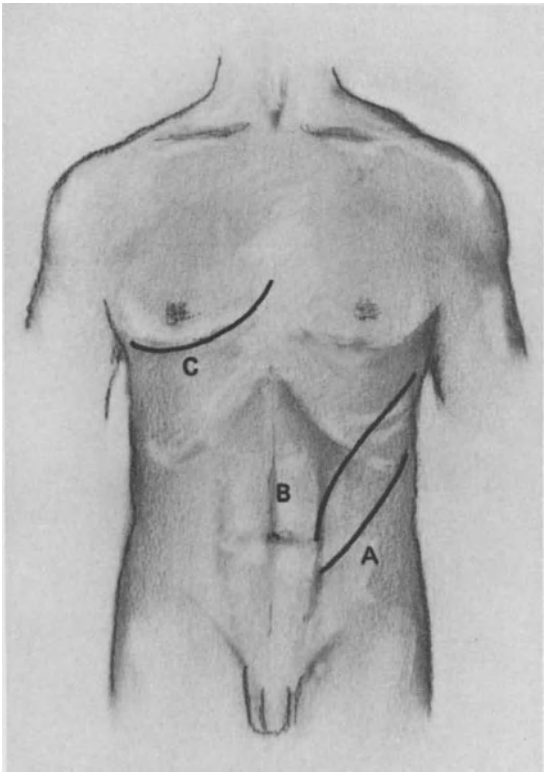


Fig. 1. *A*, ventrolateral extraperitoneal access; *B*, thoraco-phrenico-lumbar access; *C*, transthoracic access

Following good clinical improvement, toward the end of 1981 problems again developed. Radiotherapy with a dose of 40 Gy was carried out. The condition of the patient improved at first, but then the spinal segment treated by surgery and radiotherapy proved unstable. Accordingly dorsal stabilization by means of insertion of a laminated endoprosthesis (5) became necessary in July 1982. Due to recurrence of the tumor and progressive paralysis of the legs, the tumor was extirpated for the first time during October 1983, from the left side via a ventrolateral approach. The defect was refilled with spongiosa obtained from the pelvis and the endoprosthesis inserted earlier was removed. Since instability developed again later, dorsal stabilization, this time employing Harrington rods, was again performed in April 1984. Surgery in October 1983 and in April 1984 took place in a clinic specializing in orthopedics, not in our hospital. Owing to unbearable pain and rapidly progressing paraparesis of the legs the patient was again admitted to our hospital in October 1984. Given the symptoms present and the confirmation of recurrence of chordoma (Fig. 2), extirpation of the tumor and replacement of that part of the vertebra removed with a block of homologous spongiosa, combined with ventral reinforcement of the affected area by means of an attached metal plate, were indicated to achieve maximum removal of the tumor. Due to the condition of the patient, surgery had to be performed acutely; ventrolateral extraperitoneal access from the left-hand side was again selected.

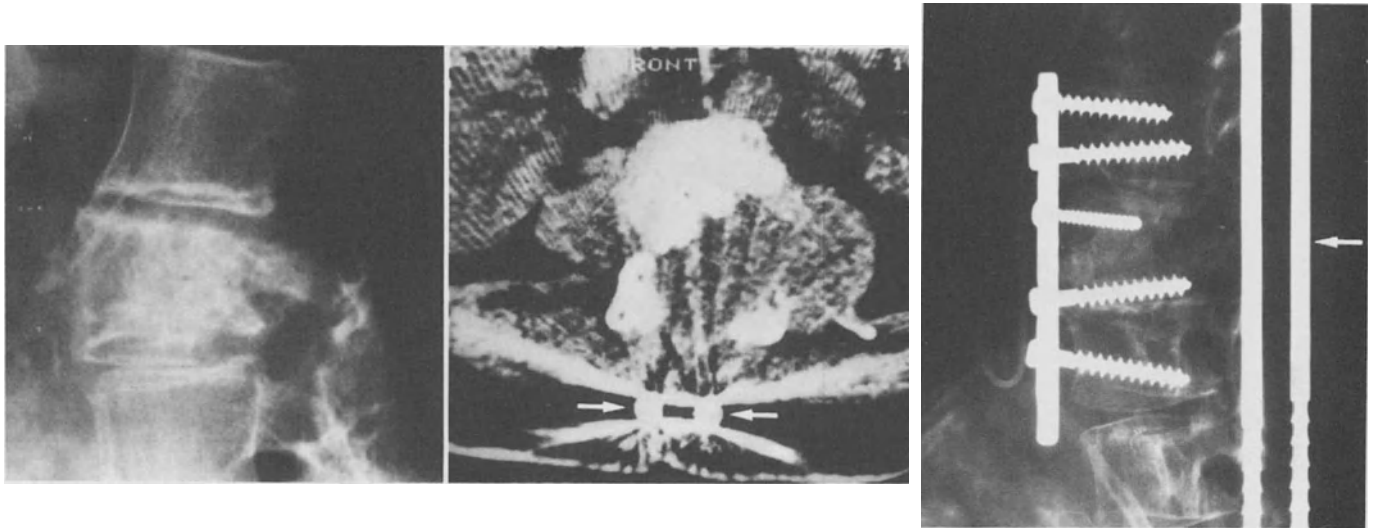


Fig. 2. *Left:* Recurrent chordoma of L3. *Center:* Computer tomogram of L3. The tumor has already destroyed the vertebral body extensively and extends toward the left into soft tissues. The *arrows* indicate dorsal Harrington rods inserted during earlier surgery. *Right:* Postoperative X-ray of the site after removal of the tumor and the destroyed part of the vertebra, showing replacement of the affected vertebral body by a homologous block of spongiosa as well as the ventral stabilization of the area by means of a reinforcing plate. The screw in the center is used for fixation of the implant. The *arrow* indicates the Harrington rods left in place

*Case 2: K.G., Male, 52 Years Old*

The patient showed considerable sintering shrinkage of the 12th thoracic vertebra (Fig. 3) and clinically severe pain in the back. Sensory disturbances were present at the level of T12. A ventral spinal space-occupying lesion was demonstrated by means of myelography and computer tomography (CT). In July 1984 decompressive laminectomy was performed and the area of the spine affected stabilized by means of insertion of a laminated endoprosthesis. Histologically the presence of a chordoma was suggested, later to be corrected to suspected metastasis. Upon discharge from the hospital the patient was without pain or neurological disturbances. To correct loosening of the endoprosthesis and to relieve recurring pain the site of the initial surgery had to be revised and the endoprosthesis replaced by a substitute in October 1984. While the patient subsequently was at first without pain, difficulties in the healing of the surgical wound developed. Shortly thereafter pain returned and dysesthesias were manifested in the legs. CT confirmed the presence of a tumor recurrence. Under these circumstances ventral surgical intervention via a thoraco-phrenico-lumbar approach, in spite of an existing dorsal surgical wound, seemed indicated. In addition to extirpation of the tumor, replacement of the removed vertebral material with autologous spongiosa obtained from the pelvis and reinforcement of the spinal section by means of a ventrally attached metal plate (Fig. 3) were performed. Histologically, the tumor was finally diagnosed as a metastasis of an adenocarcinoma. Repetition of a search for the primary tumor, which had already been conducted in July 1984, proved fruitless.

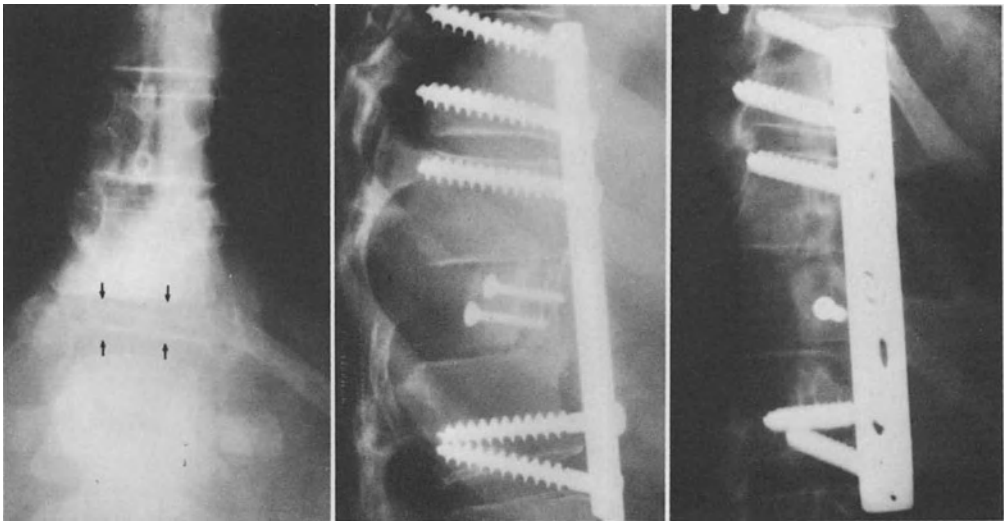

Fig. 3. *Left:* Compression of T12 (indicated by *arrows*) in a case of destruction of the vertebra by a metastasis. *Center and left:* Postoperative X-rays of the site following removal of the tumor and of the destroyed vertebral body. Autologous spongiosa has been used for replacement of the missing vertebral body. The small screws are used for joining of the assembly of spongiosa parts. A reinforcing plate is attached for stabilization

*Case 3: L.M., Female, 64 Years Old*

The patient exhibited a progressive paraplegic syndrome starting at T4, which was incomplete with respect to motoricity and sensation. Decompressive laminectomy in the area of T4-T6 was therefore performed in September 1984. Myelography showed a space-occupying lesion located ventrally; involvement of a vertebra was not confirmed. Samples of epidural tissue obtained during surgery were not histologically verified as cancerous. However, after an initial significant reduction of the symptoms of neurological disorder, just 1 month later the condition of the patient again worsened progressively. X-rays and CT this time confirmed the presence of a destructive tumor of T4 (Fig. 4). Since high fever persisted, exclusion of a parallel inflammatory process was not possible. The history of the patient revealed carcinoma of the uterus, however, and the tumor could therefore be primarily classified as a metastasis. For the surgery necessary, ventral intervention via a transthoracic approach (Fig. 1) was strongly indicated. The tumor was extirpated and the defect compensated with "Palacos" material. For stabilization of the area affected, a reinforcing plate was attached ventrally (Fig. 4).

## Description of the Surgical Procedures Employed

*Ventrolateral Extraperitoneal Access*

This type of access can be used for the lumbar vertebrae 2-5. Intervention from the left-hand side is preferable, since the aorta can be much more easily mobilized than the vena cava inferior. The patient is positioned on his back, with the upper part of the body in an angled position. The skin incision is shown in Fig. 1 *A*. After cutting of the abdominal wall (mm. obliquus externus and internus, m. transversus), the peritoneum is medially displaced from the m. quadratus and the

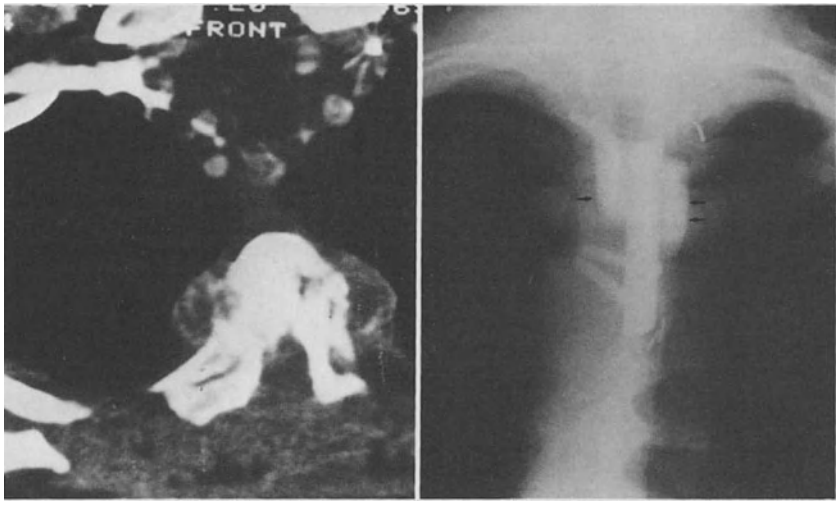


Fig. 4. *Left:* CT of a destructive metastasis in T4. *Right:* Following extirpation of the tumor, the defect was replaced by a block of 'Palacos' material (indicated by *arrows*). The site of surgery was additionally stabilized by means of attachment of a reinforcing plate

m. psoas and held back by means of hooks. Damage to the n. genitofemoralis and the n. cutaneus femoris lateralis as well as to the ureter has to be carefully avoided. The procedure described allows good demonstration of the lumbar vertebral bodies 2-5. Depending on the extent of the intervention required, several aa. and vv. lumbales may have to be tied and cut. The aorta can be carefully displaced toward the right. The tumor and the vertebral bodies affected are then removed. The truncus sympathicus has to be carefully watched for during this procedure. After removal of the adjacent intervertebral disks the substitute material to replace the defects is inserted between the slightly spread vertebral bodies and held in place by a ventrally installed plate (Fig. 2).

*Thoraco-phrenico-lumbar Access*

While the patient is situated in the same position as described for ventrolateral extraperitoneal access, and entry is from the left-hand side for the reasons described, this type of access permits one to reach the thoracolumbar transition of the spinal column. The incision into the skin is made at the cranial edge of the 9th rib from the axillar line via the arch of the ribs toward the umbilicus (Fig. 1 *B*). After cutting of the muscles of the abdominal wall and demonstration of the peritoneum, the rib arch is cut between the 8th and the 9th rib. Following splitting of the intercostal muscles a rib retractor can be inserted. The peritoneum can now be detached from the abdominal wall and the diaphragm, and, following detachment from the diaphragm, laterally dislodged medially for approximately 1 to 2 cm from the place of attachment to the diaphragm. The lung has to be held back cranially by means of a long hook. The diaphragm can then be cut step by step up to the hiatus aorticus as well as the crus sinistrum. After luxation of the diaphragm the aorta can be demonstrated and the access to the thoracolumbar transition is open.

*Transthoracic Access*

With the patient resting on his back, the upper and central parts of the thoracic section of the spinal column can be reached via a submamillary cut (Fig. 1 *C*). Surgery has to proceed from the right-hand side due to the location of the heart. Following lifting of the m. pectoralis major and of the m. serratus anterior as well as of the intercostal muscles, two or three ribs are severed in the area of the cartilaginous transition and a rib retractor inserted. One or several intercostal arteries have now to be demonstrated, tied, and cut. Subsequently the mediastinal pleura is split and access to the vertebral bodies is open.

## Results of Surgery and Complications

In all three patients freedom from pain and complete reversal of the previous neurological disturbances was achieved. Thanks to the attachment of reinforcing plates ventrally and the already existing dorsal stabilization in cases 1 and 2, mobilization of the patients was feasible rapidly postoperatively. Healing of the wounds posed no problems. Within the follow-up period of 6 months no loosening or dislocations of the stabilization devices was observed. Complications traceable to surgery were seen only in case 1. This case involved repeat surgery due to a recurring tumor, rendering the surgical procedure more difficult. Consequently in the course of surgery injury to the ureter oc-

curred; this was repaired immediately by splicing and suture, healing subsequently without problems. Postoperatively an ileus developed, which responded to conservative therapy.

## Discussion

The cases presented in this paper demonstrate the insufficiency of decompressive laminectomy for ventral lesions of the spinal column, while the various types of ventral access, which superficially might appear complicated, are well tolerated. During laminectomy the tumor cannot be removed and frequently only small quantities of sample tissue can be obtained, resulting in uncertainties in the histological evaluation of the specimen. In comparison with these circumstances, ventral intervention permits extensive or complete removal of the tumor.

Stability of the spinal column of the patients is a second, very important point to be considered. In the course of laminectomy frequently the very last intact facet of articulation maintaining stability is removed and laborious measures for stabilization, harboring specific complications, become necessary. By contrast, if intervention is performed ventrally, the stability of the spinal column is generally restored. Where stability appears to be marginal following replacement of vertebral bodies, means of stabilization such as reinforcing plates or Steinmann nails can be utilized without problems. The materials used to substitute for the vertebral bodies removed have to be selected according to the prognosis for the specific patient. While in patients suffering from metastases simple plastic parts are sufficient, autologous or homologous parts of bone should be considered for patients with a longer life expectancy.

In agreement with other authors (1-3), our experiences with ventral access to the thoracic and lumbar sections of the spinal column showed the procedure, based on the work of LOUIS (4) and WATKINS (9), to be safe and effective. The histories of the patients presented in this paper certainly permit the conclusion to be drawn that, in the treatment of ventral extradural tumors, ventral access should be primarily selected. Given the favorably low rate of complications to be expected (3), these considerations also apply to malignant lesions. The AO plates and the screws we used (see Figs. 2-4) have a limited field of use and probably are not optimal. Evaluation of the experiences to date shows that in some cases the use of reinforcing plates may not be necessary, or that the employment of Steinmann pins may be indicated, particularly if the most recent spreading techniques are used and ventral access is selected.

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# Unilateral Approaches to Spinal Tumors

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Bilateral laminectomy is usually recommended for the removal of extramedullary and extradural spinal tumors (5, 8, 10, 11). However, clinical (2-4, 9) and experimental (7, 12, 13) investigations have found that dorsal ligaments and intervertebral articulations are of functional significance. Extensive removal of these structures may result in vertebral instability. Only seldom have more limited approaches with preservation of these structures been tried (2, 6, 14-17). In the following, unilateral approaches to spinal tumors in comparison with conventional laminectomies are described and discussed.

## Patients

From 1979 to 1983, 166 patients were operated on for extradural and extramedullary tumors. There were 105 patients (35 female, 70 male) with extradural tumors and 61 (41 female, 20 male) with intradural extramedullary tumors, mostly meningiomas and neurinomas (Table 1). Mean age in the extradural group was 52±20 years (4–79 years), in the extramedullary group 49±20 years (3–80 years). Most of the tumors were located within the thoracic spine (Table 2).

## Surgical Technique

The patients with cervical and thoracic tumors down to D3 were operated on in a sitting position. Operations at lower levels were done in a prone position. In 56 patients with extradural lesions and 19 patients with extramedullary tumors, a conventional laminectomy was performed. In 91 patients a unilateral approach was chosen (Table 2). After a midline incision was made, the vertebral arches on the tumor side were exposed and, depending on the size of the tumor, a hemilaminectomy or partial hemilaminectomy was performed with a high-speed drill. This approach can, if necessary, be extended laterally by partial removal of the medial parts of the articular facets and the pedicle of the vertebra. A medial widening of the approach is possible by bevelling the base of the spinous process.

By this technique, the dorsal, homolateral, and ventral aspects of the dura become visible, provided the epidural space is not occupied by a tumor. During removal of extradural tumors, the contralateral aspect of the dura and the contralateral roots also come into sight. In these cases, only the contralateral ventral aspect of the epidural space cannot be controlled. If necessary, this unilateral approach can be extended over several levels. In extramedullary lesions, the dura is opened only over the tumor. The normal spinal cord should become visible at the earliest after the tumor is removed. Thus touching the


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Table 1. Histology of spinal tumors operated on between 1979 and 1983

| | Extradural tumors | | Extramedullary tumors | | Overall total |
|---|---|---|---|---|---|
| | Laminectomy | Unilateral | Laminectomy | Unilateral | |
| Ependymoma | - | - | 1 | - | 1 |
| Angioblastoma | - | - | - | 1 | 1 |
| Hemangiopericytoma | - | - | 1 | 1 | 2 |
| Meningioma | - | - | 5 | 16 | 21 |
| Neurinoma | - | 2 | 8 | 22 | 32 |
| Lipoma | - | - | 2 | 1 | 3 |
| Plasmocytoma | 2 | 3 | - | - | 5 |
| Osteosarcoma | 1 | 1 | - | - | 2 |
| Osteoclastoma | - | 1 | - | - | 1 |
| Metastatic tumors | 48 | 32 | - | 1 | 81 |
| Others | 5 | 10 | 2 | - | 17 |
| | 56 | 49 | 19 | 42 | 166 |

Table 2. Location of tumors and operative approach

| | Extradural tumors | | | Extramedullary tumors | | | Overall total |
|---|---|---|---|---|---|---|---|
| | Laminectomy | Unilateral | | Laminectomy | Unilateral | | |
| Cervical | 11 | 7 | 18 | 4 | 13 | 17 | 35 |
| Thoracic | 36 | 20 | 56 | 5 | 20 | 25 | 81 |
| Lumbar | 9 | 22 | 31 | 10 | 9 | 19 | 50 |
| | 56 | 49 | 105 | 19 | 42 | 61 | 166 |

spinal cord can usually be avoided. Displacement or retraction of the spinal cord was not necessary in any patient with an extramedullary tumor.

## Results

Intraoperative complications occurred with the same frequency in both laminectomy and unilateral approach groups (Table 3). Major bleeding was observed in extradural tumor cases in both groups. However, bleeding did not influence the postoperative result. In one case in the unilateral group, the spinal cord was damaged by undue traction at the tumor and its surface became slightly soft. But no additional postoperative deficit could be observed. In one case in each group one spinal nerve root was transected in order to remove ventrally situated tumors.

Classification of postoperative results (Table 4) was based on the neurological deficits upon release from hospital in comparison with neurological deficits before operation. The patient's condition was consid-

Table 3. Frequency of intraoperative complications in laminectomies and unilateral approaches

| | Extradural tumors | | Extramedullary tumors | |
|---|---|---|---|---|
| | Laminectomy | Unilateral | Laminectomy | Unilateral |
| None | 50 (89%) | 45 (92%) | 19 | 39 (94%) |
| Spinal cord injury | - | - | - | 1 (2%) |
| Root injury | 1 (2%) | - | - | 1 (2%) |
| Bleeding | 5 (9%) | 3 (6%) | - | - |
| Others | - | 1 (2%) | - | 1 (2%) |
| | 56 | 49 | 19 | 42 |

Table 4. Results regarding motor deficits following laminectomy and unilateral approaches

| | Extradural tumors | | Extramedullary tumors | | Overall total |
|---|---|---|---|---|---|
| | Laminectomy | Unilateral | Laminectomy | Unilateral | |
| Improved | 29 (52%) | 24 (50%) | 9 (47%) | 27 (64%) | 89 (54%) |
| Unchanged | 20 (35%) | 23 (47%) | 6 (32%) | 12 (29%) | 61 (37%) |
| Worsened | 7 (13%) | 2 (4%) | 4 (21%) | 3 (7%) | 16 (9%) |
| | 56 | 49 | 19 | 42 | 166 |

ered improved when postoperatively the muscular strength of the legs was raised by one grade on a scale of six grades at least (0 = no innervation, 5 = normal strength). The condition was considered worse when the strength of the legs dropped at least one grade. The patients were released from the neurosurgical clinic an average of 8 days after the operation. Due to the very different nature of the tumors, later results were not considered relevant for the assessment of the advantages and disadvantages of the two approaches.

In the group of extramedullary tumors, better results were obtained with a unilateral approach (Table 4). Postoperative deterioration following unilateral surgery was less frequent than after laminectomy. In the group of extradural tumors, there was no major difference between the two approaches in terms of the frequency of immediate postoperative improvement. Neurological deficits nevertheless appeared more often following laminectomy. Therefore, with respect to the immediate postoperative results, it may be concluded that the unilateral approach for removal of extradural and extramedullary tumors is at least not disadvantageous.

In four extradural tumors and one extramedullary tumor, the intended hemilaminectomy had to be enlarged into a complete laminectomy. In one meningioma of the thoracic vertebral column, the site of the tumor was expected to be on the other side as a result of an insufficient preoperative myelography. After additional resection of the opposite half of the arch the tumor could be removed without difficulties. In four extradural metastatic tumors, the spinous processes and the opposite

half of the arches had to be removed, since they were widely infiltrated by the tumor, which was not seen on preoperative X-rays.

## Discussion

From experimental investigations (7, 13) it may be deduced that preservation of dorsal ligaments and intervertebral articulations of one side during removal of extradural and extramedullary spinal tumors will reduce postoperative vertebral instability. However, this can be proved only after a rather long period of observation, which is impossible in predominantly malignant extradural tumors. Thus the issue of laminectomy or a unilateral approach to extradural tumors could be regarded as insignificant. On the other hand, even in extradural tumors, postoperative deterioration occurs more seldom after surgery using a unilateral approach. This is obviously due to the fact that ventrally situated lesions are removed more easily by the unilateral approach, which allows manipulation in front of the spinal cord without displacing it. Moreover, additional trauma to the spinal cord pressed in a dorsal direction by a ventrally situated tumor, which may occur at the sharply cut upper and lower edges of a laminectomy, can be avoided by a unilateral approach. These factors probably account for the better results of unilateral approaches in patients with extramedullary tumors.

In conclusion, apart from the better preservation of the stability of the vertebral column, unilateral approaches to extradural and extramedullary spinal tumors produce better functional postoperative results. Only in a few exceptional cases will a primary bilateral laminectomy be necessary. The basic prerequisite for choosing a unilateral approach is knowing on which side the tumor is located.


## Summary

The results of laminectomy and of unilateral approaches performed on 166 patients with extradural and extramedullary tumors are compared. The immediate postoperative results among extramedullary tumors as well as extradural tumors were definitely better following unilateral approaches. It is concluded that apart from a few exceptional cases, unilateral approaches to these lesions are preferable.


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# The Transsacral, Transcoccygeal Approach to Prevertebral Spinal Tumors

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Rare retroperitoneal tumors of the sacrococcygeal region present special therapeutic problems (2-4). Their narrow topographic relationship to the plexus lumbosacralis, the presacral blood vessels, and the intestines explains the necessity for an exact preoperative diagnosis (Table 1). This decides whether an anterior transabdominal, a lateral retroperitoneal, or a posterior transsacral approach should be chosen or whether a two-sided, combined anteroposterior approach will be effective.

In the past 2 years we have used the posterior approach in eight patients with tumors in the sacrococcygeal region (Table 2). The operations were always performed in cooperation with the surgical department of traumatology. Six of the eight patients had been operated on up to seven times before.

Table 1. Techniques used in preoperative diagnostics

| Standard techniques | Additional techniques |
|---|---|
| X-ray (plain radiography, multidirectional tomograms | Rectoscopy |
| CT, MRI | Contrast enema |
| Myelography | Intravenous urogram |
| | Cystometry |

Table 2. Type of tumor in eight patients with tumors in the sacrococcygeal region, in whom the posterior approach was used

| | |
|---|---|
| Chordoma | 3 (3) |
| Metastasis | 2 (1) |
| Chondrosarcoma | 1 (1) |
| Neurinoma | 1 (1) |
| Meningocele | 1 |

( ) = Patients with previous operations

A lumbosacral medial incision is performed both on the cranial and the caudal side over the gluteal region, dependent on the extent of the tumor. At the upper tumor pole, the cauda equina sac and/or nerve roots are revealed. Because of the functioning of the sphincter it is important to reveal the nerve roots at S2 and S3 completely. With unilateral section the likelihood of urinary bladder function and large intestine function being maintained is 50% (1, 2). A subjective dysfunction should be taken into consideration as a result of a two-sided loss of sensibility in the S4 dermatome.

In between the nerve roots the anterior wall of the sacrum is resected. The extent of tumor removal depends on the growth characteristics of the tumor. In one case only an extended biopsy of a highly vascularized hypernephroma metastasis was performed.

Only once was the total resection of a presacral, space-occupying lesion successful. After multiplanar CT of the presacral space a large meningocele had been assumed. The preoperative myelogram demonstrated no connection with the subarachnoid space. At diagnostic transsigmoidal needle biopsy, cerebrospinal fluid flowed away. Postpuncture bacterial meningitis occurred. CT control (Fig. 1) revealed inflammatory wall thickening of the meningocele. As soon as this complication was cured, the benign tumor was totally extirpated without opening the specimen. Figure 2 demonstrates the functionally insignificant bony defect.

In all the other cases only a subtotal tumor resection was successful, e.g., a chordoma operated on seven times previously (Fig. 3) or an extended neurinoma surgically treated twice.

The tumorous or therapeutic damage to the iliosacral joints makes iliolumbo-sacral osteosynthesis necessary to maintain the ability to walk, as in the case of a young man with an extended chondrosarcoma. Figure 4 demonstrates the osteosynthesis: cement filling of the tumor cavity was employed, and for fixation special pelvic plates were used.

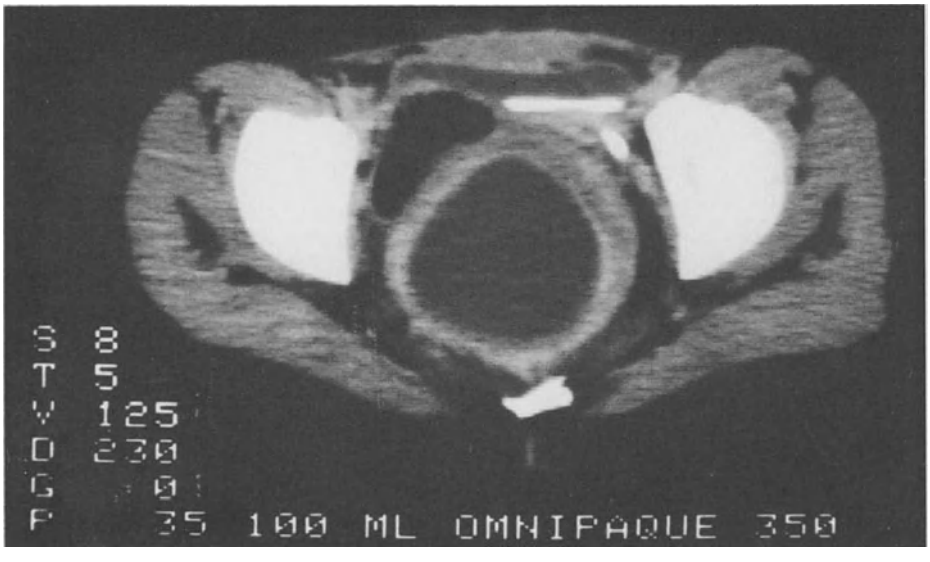


Fig. 1. Presacral meningocele. Inflammatory wall thickening after meningitis, induced by a diagnostic, transsigmoidal puncture of the mass. Myelographically there was no visible communication to the CSF system

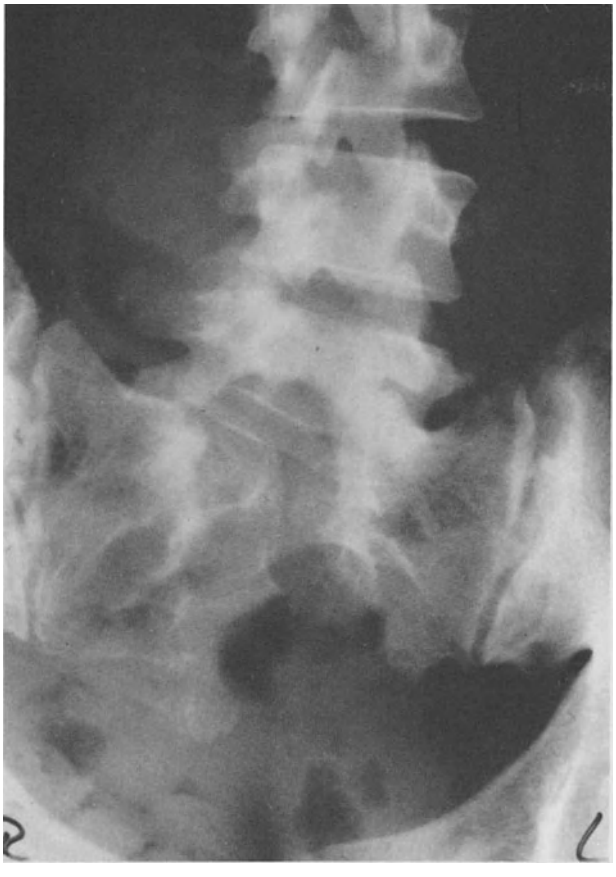

Fig. 2. Bony defect in the sacrum after posterior resection of the meningocele

The risk of the operation increases with the number of previous operations; thus all the complications (Table 3) were found in two previously operated patients. The malfunction in the healing process led to osteomyelitis and subsequent removal of the AO plates.

In the interest of quality of life and life expectancy, these tumors should be treated in an interdisciplinary manner. The aim is to achieve the most radical initial removal of the tumors possible, dependent on their histology, even if combined operations are necessary.

Table 3. Complications

| | |
|---|---|
| Meningitis | 2 |
| Sphincter dysfunction | 1 |
| Wound infection | 1 |

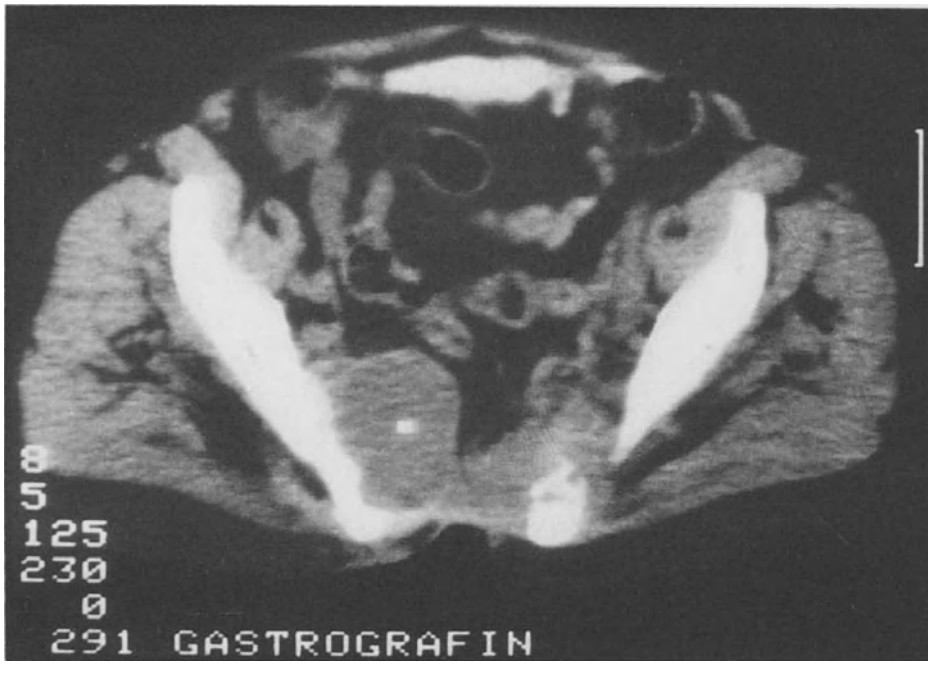


Fig. 3. Extensive chordoma

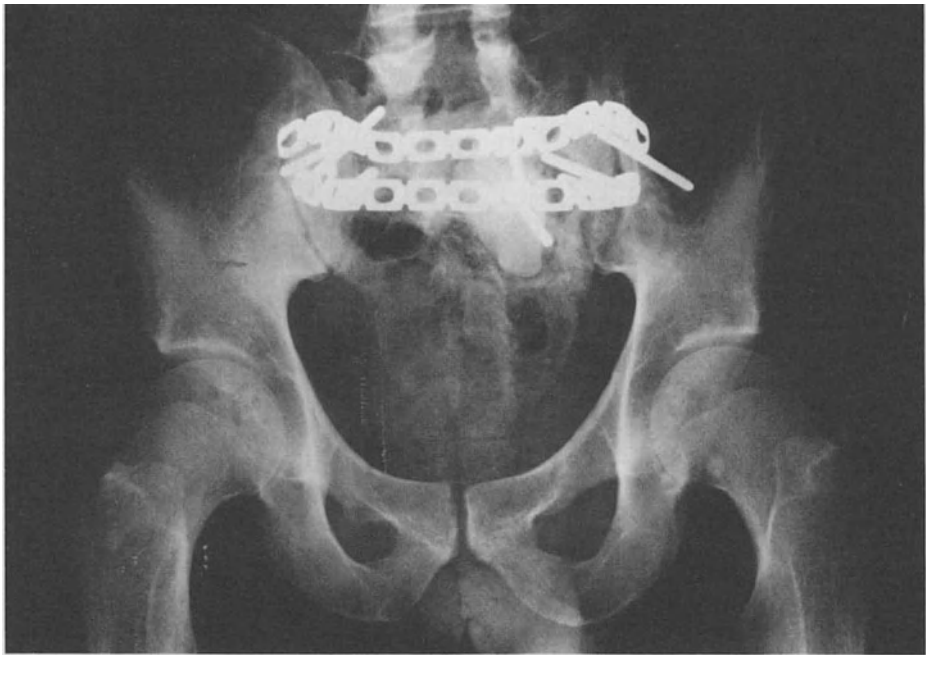

Fig. 4. Partial resection of a chondrosarcoma. Combined ilio-lumbo-sacral osteosynthesis with bone cement and metal plates

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# Operative Treatment of Aneurysmal Bone Cysts of the Spine - Radical Excision and Spinal Stabilization

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About 20% of all aneurysmal bone cysts (ABCs) are reported to appear along the spinal column, with a predilection for the lumbar spine (2-4, 13, 18). The term ABC was coined in 1942 by JAFFE and LICHTENSTEIN (5, 6) following detailed description of two cases and is now generally accepted. ABCs of the spine show a marked predominance in the second decade of life but can occur at any age; in addition there is a slight preponderance of female patients (3, 4, 16, 18). The tumor growth can extend into every part of the affected vertebra, involving the posterior elements in ca. 60% and the vertebral body in ca. 40% (4). Not seldom, more than one vertebra is involved or the tumor may spread into the adjacent soft tissue (4).

The extension of the tumor determines the clinical picture. Usually there is localized or radicular pain along the spinal axis and the dermatomes, in combination with localized tenderness. When the tumoral spread has involved the vertebral canal, the typical signs of spinal cord compression which depend on the level of the tumor will occur.

The micromorphological features are summarized in Table 1. The light microscopic appearance consists of various sized blood-filled cysts and sinuses that are separated by septa of fibrous tissue which occasionally contain giant cells and premature bony substance. The electron microscopic picture shows that the walls of the sinuses are lined with endothelial cells showing small gaps through which the erythrocytes can come into contact with the interstitium (14) (Table 1).

Table 1. Micromorphology of aneurysmal bone cysts

| |
|---|
| *Light microscopic appearance* |
| - Cavernous blood-filled system of dilated sinuses and cysts |
| - Septa of fibrous tissue containing giant cells and premature bone substance |
| - Sinuses lined by endothelial cell layer |
| *Electron microscopic appearance* |
| - Fenestrations in the endothelial cell lining of the sinus wall |
| - Contact of blood cells with interstitium |

Differential diagnosis of ABCs consists of giant cell tumors, osteosarcomas, osteoblastomas, cavernous hemangiomas, and secondary malignant bone tumors (3, 13, 18), but today the alternatives can usually be excluded because of sophisticated radiological methods. In the plain radiological picture or tomogram the classical sign of an ABC is an extending or ballooning osteolytic cavity that in most cases has already led to destruction of the affected part of the vertebra (1, 4, 15). Usually myelographic examination is only able to show unspecific displacement or incomplete or complete block of the contrast media column. During spinal angiography there may sometimes be a diffuse inhomogeneous stain of the tumor with prolonged venous outflow, but usually only discreet displacement of the spinal vessels can be seen (7, 20). Nevertheless, preoperative spinal angiography is still necessary to demonstrate the vascular supply of the spinal cord in order to avoid important vessels during the operative approach (2, 3, 10, 11, 16).

Today computerized tomography of the spine is the most eminent diagnostic tool because it shows the direct pathological and anatomical picture of the bone cyst and the consequent destruction of the adjacent vertebral components, and provides important information for the planning of the tumor excision.

Scintigraphic examinations may still be used in order to detect multiple lesions and for postoperative follow-up (1, 15) (Table 2).

Table 2. Staging of aneurysmal bone cysts of the spine

| Stage | Morphology | Radiology | Clinical picture |
|---|---|---|---|
| 1 (initial stage) | Small osteolytic lesion in vertebral body lamina, and/or pedicle | Osteolytic cavity | Symptomless |
| 2 (destructive stage) | Progressive destructive tumoral growth, expansion and ballooning of vertebral body, lamina, and/or pedicle | Osteolytic cavity surrounded by eggshell of "blown-out" cortex | Pain, tenderness, neurological symptoms |
| 3 (stabilizing stage) | Progressive formation of premature bone substance | New bone formation with thickened bony mass | Symptoms of spinal cord compression |

Below we report on six cases of ABC which have been operated on in our department between 1979 and 1985.

## Case Reports

### *Case 1*

Five months prior to admission to our department this 12-year-old girl complained of progressive pain and restricted movement of the neck. Conservative treatment did not show satisfactory results. On admission neurological examination revealed no abnormalities except for local tenderness at the C4/C5 level and restricted painful movements of the

cervical area. Plain X-rays showed destruction of the spinous process and lamina of C5. A cervical CT scan additionally demonstrated ballooning of both pedicles of C5 and tumor extension laterally into the soft tissue of the dorsal neck musculature.

On 12 April 1979 laminectomy and pediculotomy of C5 were performed, including total extirpation of the tumor. A wire cerclage from C4 to C6 was used for posterior stabilization.

The postoperative course was uneventful. Control X-rays one year after the operation showed that the wire cerclage had broken, with anterior dislocation and impression of C5 and development of kyphosis. The neurological status remained normal. On 25 March 1982 anterior stabilization was performed with an autologous bone graft and fixation with an osteosynthetic plate at the C5/C6 level. Three years later the patient is symptom-free, neurologically normal, and working full time.

*Case 2*

This 19-year-old girl had a 3-month history of radicular cervical pain radiating into the right arm at the C7/8 dermatomes. Plain X-rays, tomographic, and scintigraphic examinations and selective angiography of the supra-aortic branches in another clinic revealed a cystic bone tumor of C7 with ballooning of the right transverse process.

On admission the patient complained of persistent cervical and arm pain but the neurological examination was normal. On 11 March 1980, using a ventrolateral approach, the cystic lesion within the vertebral bone of C7 and the right transverse process was excised. The postoperative course of the patient was uneventful.

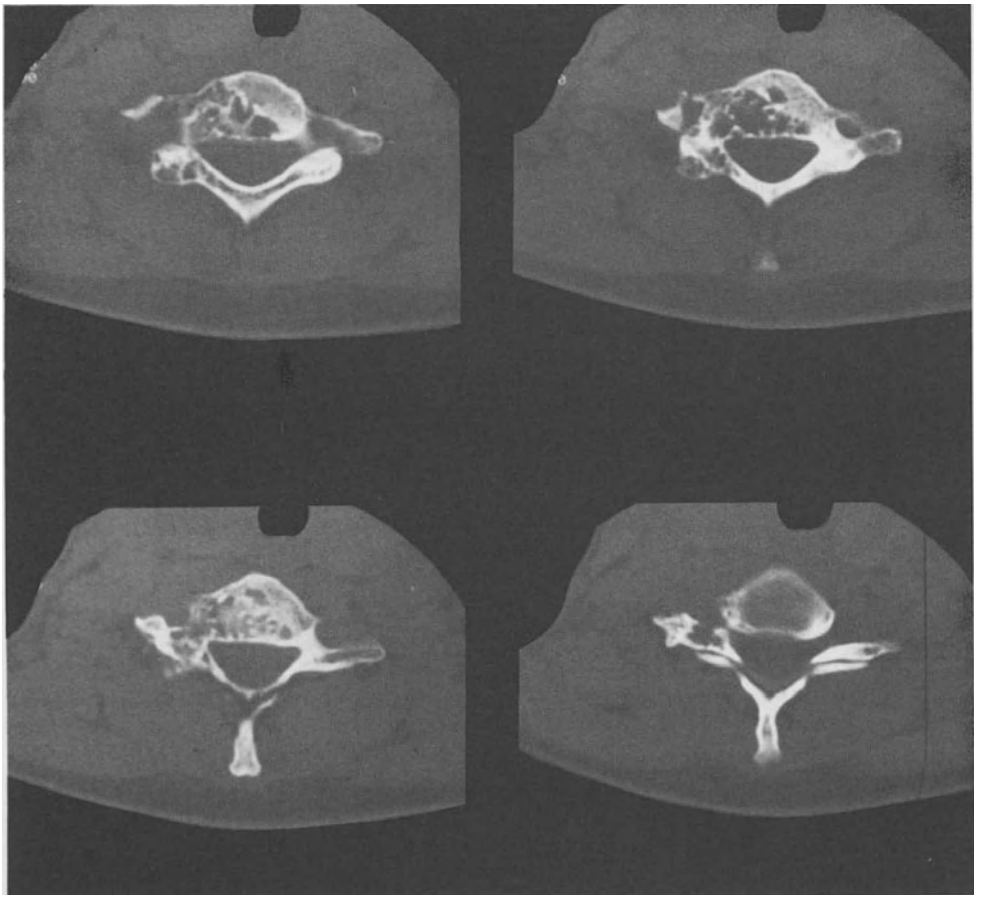
From January 1984 on the patient developed progressive restriction of neck movement and radicular pain and paresthesia radiating from the right cervical area into the right arm. A cervical CT scan revealed recurrence of the ABC with extension into the right lamina and pedicle of C6 and T1. Operation was performed on 3 October 1984. In cooperation with the thoracic surgeons the thyrocervical trunk, which took part in the vascular supply of the tumor at the level of C7, was ligated. Using an anterior approach the vertebral body of C7 was excised and autologous bone graft stabilization and fixation with an osteosynthetic plate performed.

On 13 December 1984, following laminectomy of C7, excision of both laminae and vertebral facets was performed. Additional dorsal fixation with an autologous bone graft and osteosynthetic plates was carried out. After the operation the patient was secured for 3 months in a three-point orthopedic fixation device. On follow-up examination 4 months postoperatively she was pain-free and neurologically normal (Fig. 1).

*Case 3*

This 40-year-old patient had had a history of right-sided cervical and brachial pain for several years. Because of progressive pain and weakness of the right arm the patient was examined in another hospital. Plain X-rays revealed destruction of the dorsal part of the first rib on the right side with extension into the transverse process of T1.

On 29 April 1983 partial excision of the tumor was performed. Control CT scans 6 months later showed progressive tumoral growth with nearly



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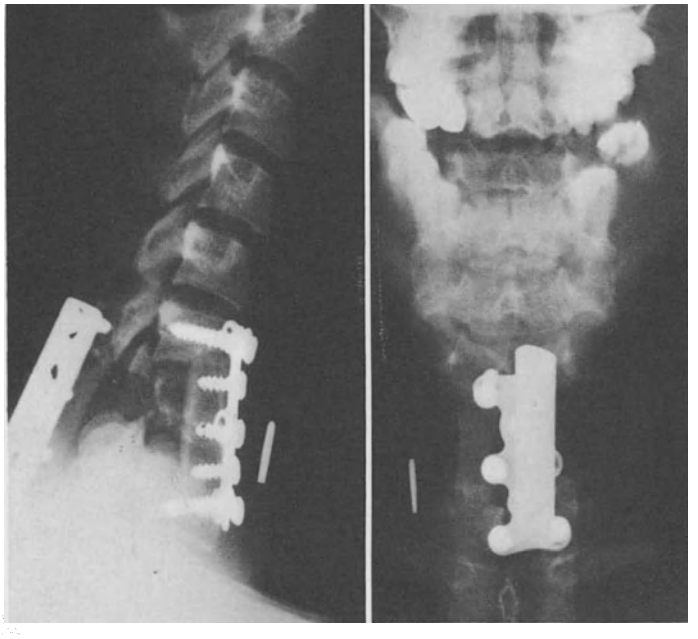

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Fig. 1. Case 2.a Preoperative computer tomography with ABC of C7. b Postoperative X-ray

complete destruction of the right half of the vertebral bodies of C7 and T1 and lysis of the pedicles.

A neurological examination on admission showed severe weakness of the right arm with hyperreflexia, hypoesthesia, and hypalgesia. On 14 December 1983, following costotransversectomy and laminectomy, the tumor was totally excised. Bone graft fixation of the removed bodies of C7 and T1 and fixation with two osteosynthetic plates was performed (Fig. 2).

Directly postoperatively the weakness of the right arm was increased. On follow-up examination 2 1/2 years later the patient was symptom-free and the paresis of the right arm had disappeared. Except for light hypoesthesia and hypalgesia of the right arm the patient was neurologically normal.

*Case 4*

This 16-year-old patient had a 1-year history of progressive pain in the upper cervical-thoracic area with restricted movement of the neck. Three weeks prior to admission the patient developed progressive numbness and weakness of both feet with severe gait disturbance.

Neurological examination on admission revealed spastic paraparesis with a sensory level at T4. There was severe local tenderness of the cervical-thoracic area, and hyperreflexia of the lower extremities with a positive Babinski's sign. A spinal CT scan showed a tumoral process with ballooning and lysis of the spinous process and both laminae of T1, and two small osteolytic areas in the lateral part of the vertebral body of T1.

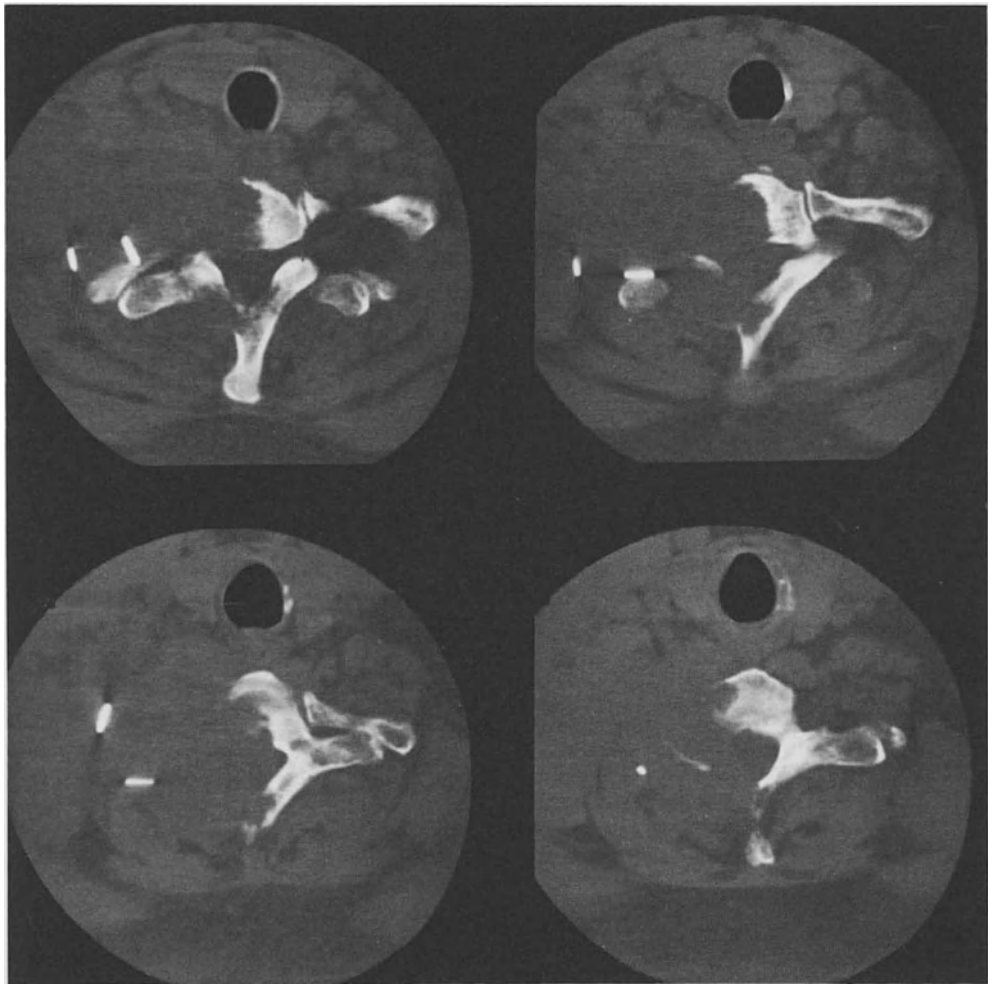
On operation on 29 August 1984, following laminectomy of T1, the tumorous areas were totally excised. Dorsal fixation with two osteosynthetic plates was performed. Postoperatively there was progressive improvement of the neurological status, especially of the spastic gait disturbances. On 2 October 1984, after the diagnosis of an ABC had been established histologically, a second operation was performed with dorsal interposition of autologous bone graft. On follow-up examination 6 months postoperatively, the patient was symptom-free, without any gait disturbances, and neurologically normal.

*Case 5*

This 13-year-old girl had a riding accident on 7 August 1984 during which she fell from a horse. Routinely performed X-rays of the thoracic spine revealed an osteolytic process within the vertebral body of T12. On admission to our clinic the neurological examination was totally normal. A CT scan of the thoracic spine showed osteolysis and ballooning of T12 and both pedicles. There was a partially bony impression of the spinal cavity and dura.

On 17 September 1984 the operation was performed in cooperation with the orthopedic surgeons. Using an anterior approach through the abdomen the vertebral body of T12 was removed, anterior stabilization was carried out with a homologous bone graft, and fixation was achieved with two osteosynthetic plates. Thereafter the patient was put into the prone position, laminectomy and total extirpation of the tumorous parts in the pedicles were performed, followed by dorsal stabilization with autologous bone graft and fixation with a Knodt retractor (Fig. 3).

a



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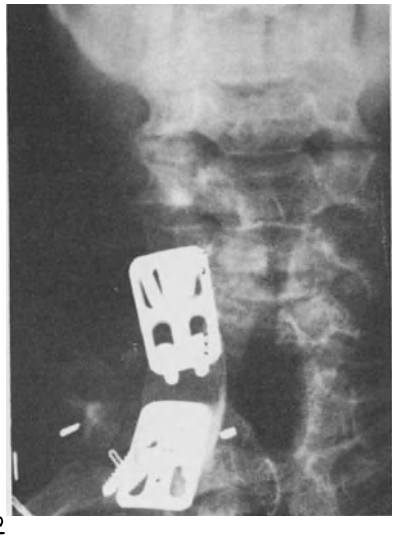


Fig. 2. Case 3. a Preoperative computer tomography with ABC of C7 and T1. b Post-operative X-ray

On follow-up examination the patient was still supplied with a three-point orthopedic fixation device but could move freely and was symptom- and pain-free. Neurological examination remained normal.

*Case 6*

Two years prior to admission this 13-year-old boy developed progressive pain in the upper lumbosacral area which radiated into both legs. X-rays of the lumbar spine showed ballooning and partial destruction of the left pedicle and transverse process of L1.

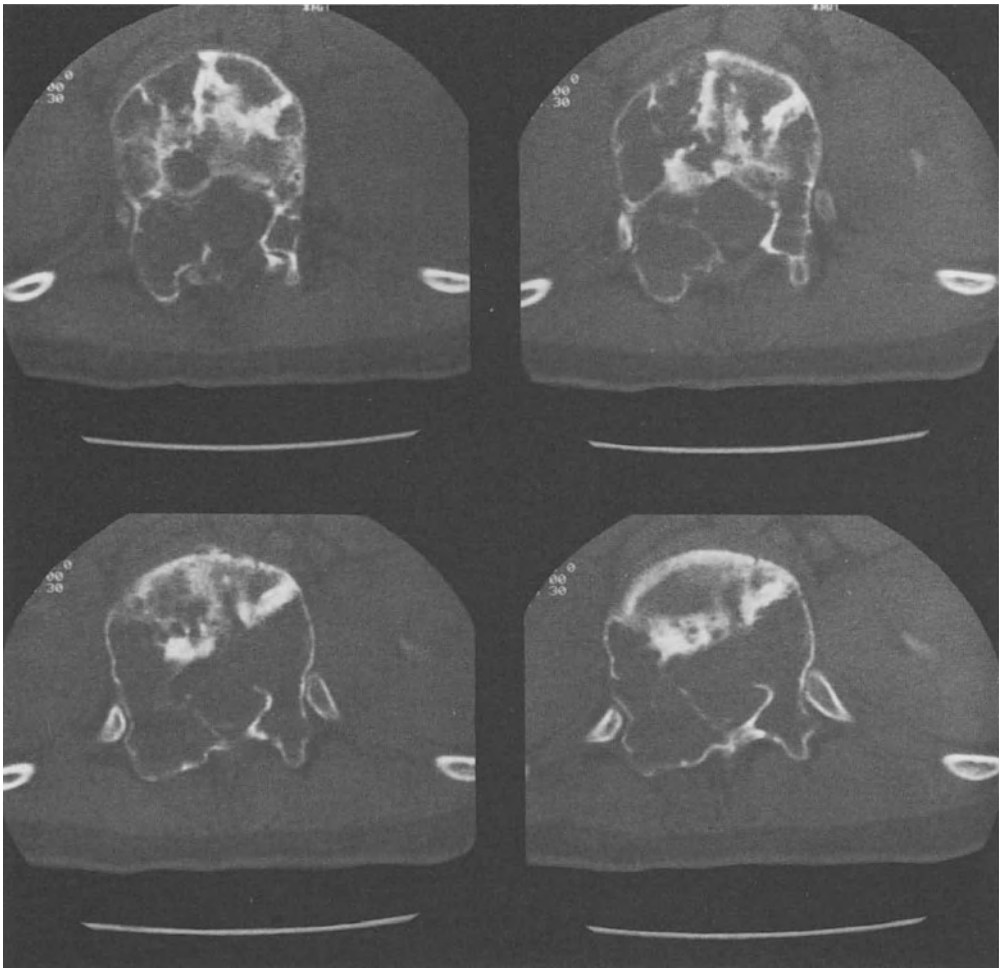
Neurological examination on admission revealed marked tenderness at the L1/2 level. A lumbar myelographic examination demonstrated a small impression of the contrast media at the L1 level. On 6 August 1979 a left L1 hemilaminectomy was performed. The tumorous areas as described above were excised. The postoperative course was uneventful.

On follow-up examination 6 years later the patient was symptom-free and neurologically normal, but control X-ray scans of the lumbar spine showed a tumor recurrence with destruction of the body of L1. During the second operation using an anterior transabdominal approach the vertebral body of L1 was removed, followed by homologous bone graft replacement and fixation with osteosynthetic plates. Thereafter dorsal fixation was performed from T12 to L1 with a Knodt retractor and interposition of autologous bone.

## Discussion

In all of our patients radical tumor excision was possible. In two patients only did the laminae including the vertebral joints have to be removed. In the other four patients, because of progressive tumoral growth involving the vertebral body, pedicles, and /or laminae a partial (one patient) or complete (three patients) resection of the vertebral body and the adjacent part of the rib and laminae was necessary. The resulting defect was filled with autologous or homologous bone graft and spinal fusion was performed using osteosynthetic plates in order to gain immediate stability and to avoid kyphotic scoliosis. The anterior and dorsal surgical approaches to the spine have been described in detail elsewhere (8, 9, 17, 19).

In summary: The primary goal of operative treatment of ABCs has to be radical excision followed by spinal fixation. This is even more necessary because of the usually tender age of the patients and the 30%-50% probability of recurrent growth following only partial tumor removal, and additionally radiotherapy after incomplete excision of bone cysts may lead to sarcomatous change (12, 18).



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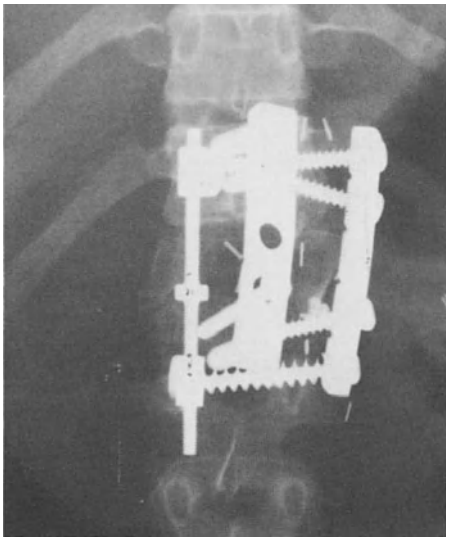

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Fig. 3. Case 5. a Preoperative computer tomography with ABC of T12. b Postoperative X-ray

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# Osteosynthesis in Patients with Malignant Tumors of the Cervical Vertebral Column: Indications, Technique, and Results

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## Introduction

Of the 379 spinal tumors operated on in our clinic, 210 have been extradural. Of these, 15 were situated in the cervical vertebral column, and 14 out of the 15 patients needed stabilizing measures after operative decompression. Here we were able to make use of our experience with 140 osteosynthetic procedures on diseases of the vertebral column (2, 3).

## Indications

The indications for operation were tumoral instability with threatening medullary and radicular compression as well as pathological compression fractures and luxations with increasing neurological deficits. When other metastases were present we considered it to be a contraindication to operation when we could not expect mobilization of the patient after the operation or when a far advanced, final stage of the disease was present.

## Technique

The choice of approach was made on the basis of preoperative investigations, such as X-ray, CAT scan, myelography, myelo-CAT scan, and scintigraphy.

If the tumor was situated within the vertebra, we used the ventral approach. The tumor-invaded vertebra was, together with the adjacent nucleus pulposi, removed micro- and macroscopically by subtotal spondylectomy. In 11 cases we removed the ligamentum longitudinale posterius as well, as it was infiltrated with tumor or an epidural tumor pannus was present. The stabilization was effected by a bone cement prosthesis, which was interlocked with the adjacent vertebrae by way of cut-out grooves. The medulla was protected from the polymerization heat by a piece of Marbagelan placed on the dura. The low-viscosity cement (Refobacin-palacos-E-flow) was preferred for the fixation of the vertebra as it can easily be applied with a syringe and penetrates into the grooves more readily than high-viscosity cement. In this way we achieved a better fixation. During the polymerization phase we put in a preformed vertebral plate which was fixed with screws to the cement while it was hardening. After the hardening of the cement the platelet was fixed to the adjacent vertebrae with two screws on each side. The predrilling, thread cutting, and fixation of the screws was done under image intensification. This procedure was made significantly

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easier by using X-ray negative retractors (1). For optimal fixation into the anterior and posterior vertebral cortex as well as the spongiosa, corticalis screws with spongeose thread were used; in this procedure one should ensure that the dorsal vertebral cortex is reached by 1-1.5 threads of the screw (Fig. 1).

If the small vertebral joints and arches are involved or a dorsal tumor pannus is present, then a combined dorsoventral approach is used. Following the ventral procedure in the supine position, the dorsal approach is accomplished in a sitting position with a sharp fixture. After decompression (laminectomy, hemilaminectomy, foraminotomy) an osteosynthetic connection is performed with Kirschner wire, wiring, a hooked plate, and high-viscosity cement (Refobacin-palacos) (Figs. 2, 3).

This combined procedure was necessary in two cases, while 11 could be sufficiently treated with a ventral operation only. With one osteolytic lesion of the right massa lateralis of C1 the stabilization was effected after subtotal removal of the tumor from dorsal by occipitocervical fusion with an "occipital plate" after Wolter and corticospongial chippings (Fig. 4).

All patients were mobilized from the first postoperative day onwards, with a supportive collar to be used for 4-6 weeks. Eleven patients were treated with radiotherapy after the wound had healed, and one patient with cytostatic drugs only. Three patients with plasmocytomas were also treated by cytostatic means following the radiotherapy.

## Results

The results are shown in Table 1. Infections or neurological deterioration did not occur in any of the cases. In two patients the screws loosened, and once a correction was found necessary; in the second case further surgery was not required, as no trouble was present after more than 1 year of check up. In one patient there was local bleeding, causing asphyxia and requiring operative revision.

## Discussion and Conclusion

Our aim in the treatment of malignant tumors of the cervical vertebral column is to improve neurological deficits, to cure them, or to prevent them by means of a prophylactic operation. By curing the pains and keeping arms and legs mobile, and by ensuring independence from external help, the quality of life shortened by the underlying disease should be improved.

Our results illustrate that this aim is quite realizable to a high degree, given suitable indications and operative techniques. The complication rate is minimal and the indication for operation is therefore to be regarded liberally. Interdisciplinary cooperation with the radiotherapy and oncological departments contributes to improvement of the results.

Table 1. Results of compound osteosynthesis in 14 patients with tumors of the cervical vertebral column

| No. | Age | Sex | Level | Tumor | Operation ventral/dorsal | | X-ray treatment cytostatic therapy | | Stable column arms, legs > usable | Death |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 57 | ♂ | C4 | Broncho-genic ca. | 7.9.78 | v | Ø | | Until death | 14.9.78 |
| 2 | 64 | ♀ | C4+C5 | Plasma-cytoma | 12.5.82 | v | R44 Gy | C | + | |
| 3 | 51 | ♂ | C5+C6 | Hyperne-phroma | 8.6.83 | v/d | R39 Gy | | Stable, but local tumor recurrence with paraparesis 3,84 | |
| 4 | 32 | ♂ | C1 | Carcinoma, origin unkn. | 23.11.83 | d | R36 Gy | | + | |
| 5 | 44 | ♀ | C6 | Breast ca. | 27.1.84 | | R40 Gy | | + | |
| 6 | 62 | ♂ | C5 | Plasmacytoma | 14.5.84 | v | R20 Gy | C | + | |
| 7 | 50 | ♀ | C5 | Ovarian ca. | 28.5.84 | v | R20 Gy | C | Until death | 19.11.84 |
| 8 | 60 | ♀ | C5+C6 | Carcinoma, origin unkn. | 3.7.84 | v | Ø | | + | |
| 9 | 54 | ♂ | C5+C6 | Broncho-genic ca. | 9.8.84 | v | R43 Gy | | + | |
| 10 | 58 | ♂ | C4 | Plasmacytoma | 14.9.84 | v | R35.7 Gy | C | + | |
| 11 | 57 | ♀ | C7+T1 | Breast ca. | 27.9.84 | v/d | R41 Gy | | + | |
| 12 | 62 | ♀ | C6(C5+C7) | Breast ca. | 28.11.84 | v | R42 Gy | | + | |
| 13 | 75 | ♂ | C5+C6+C7 | Non-Hodgkin lymphoma | 29.11.84 | v | | C | Until death | 16.3.85 |
| 14 | 59 | ♂ | C7 | Gastric ca. | 20.3.85 | v | R41 Gy | | + | |

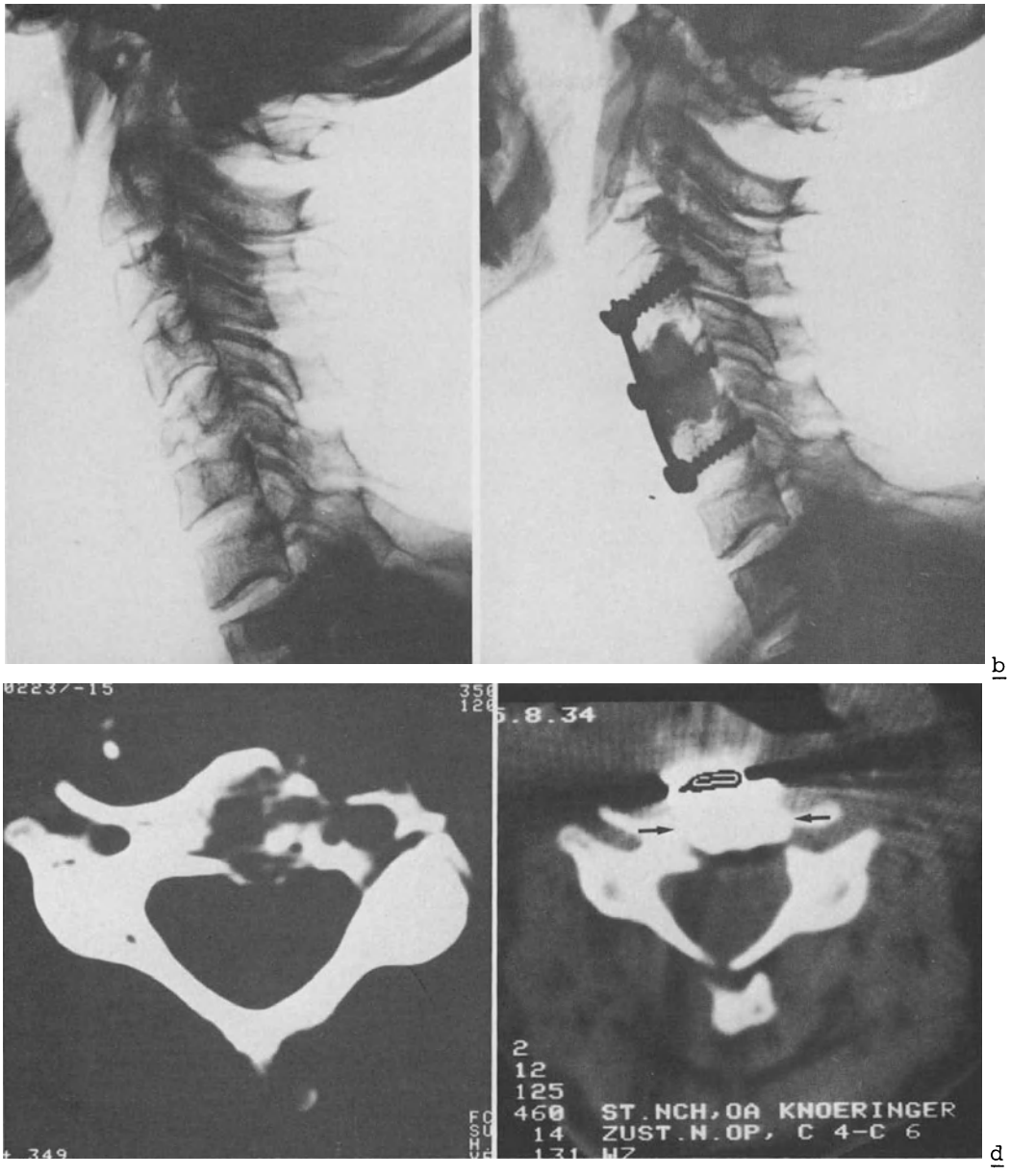



Fig. 1a-d. Case 7. Roentgenograms and CAT scans of a C5 metastasis from an ovarian carcinoma pre- and postoperatively. b Compound osteosynthesis was performed with low-viscosity cement, platelet, and screws. The screws penetrate the dorsal vertebral cortex with 1.5 threads. The bone cement is interlocked with the adjacent vertebrae, filling the prepared grooves. d shows a CAT scan of the bone cement prosthesis at C5 (between the *arrows*)

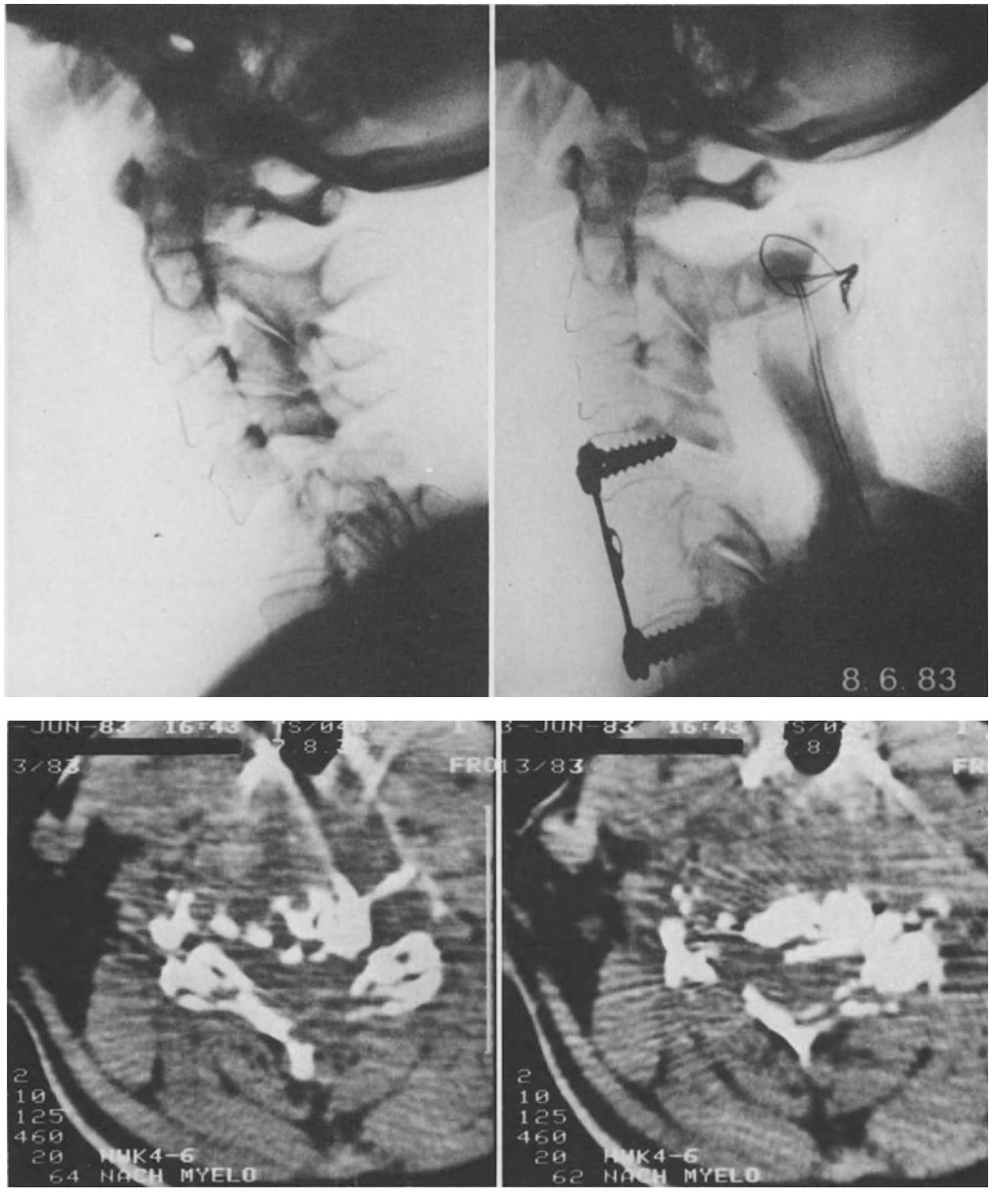
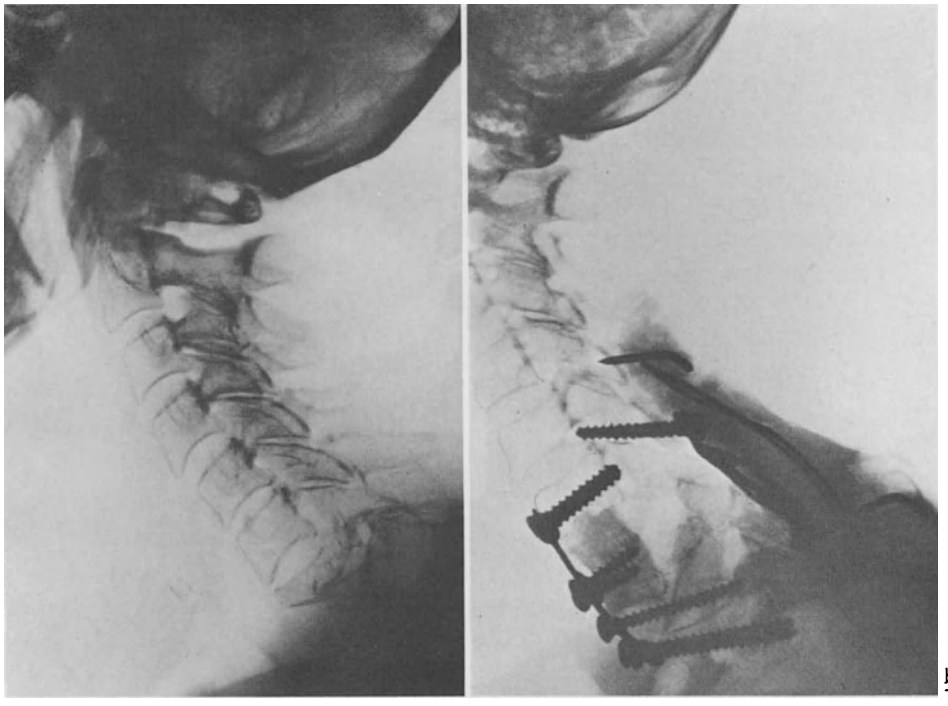



Fig. 2a-d. Case 3. Roentgenograms and CAT scans of a C5 and C6 metastasis from a hypernephroma. There is osteolysis of the vertebral bodies, joints, and arches, and kyphosis of the vertebral cervical column. b Roentgenogram after ventrodorsal decompression and stabilization. Preoperative CAT scans are shown of C5 (c) and C6 (d)



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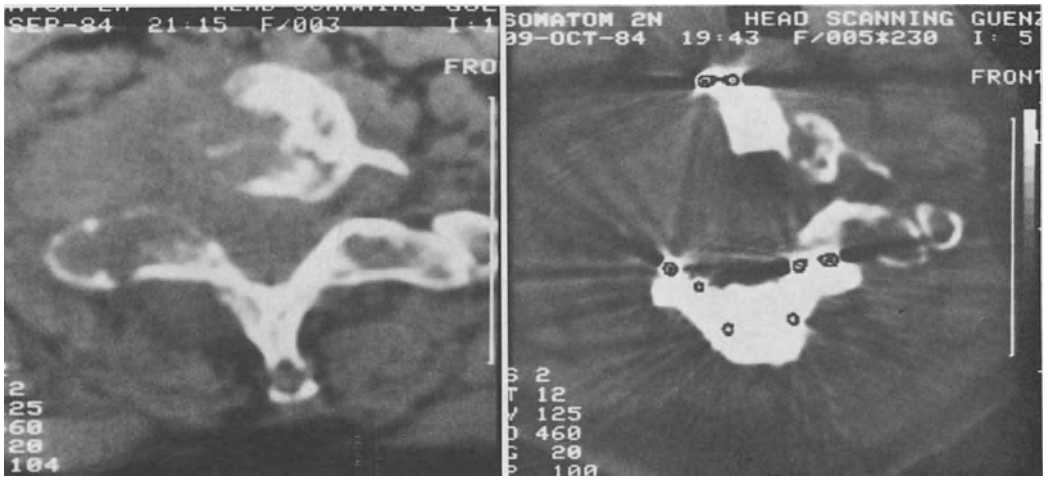
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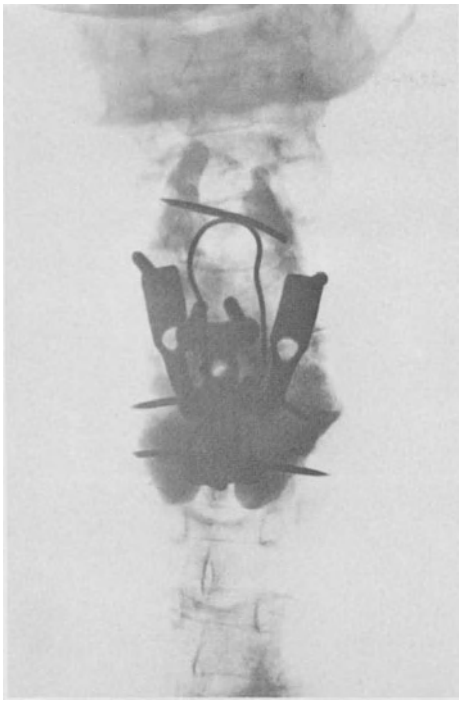
Fig. 3



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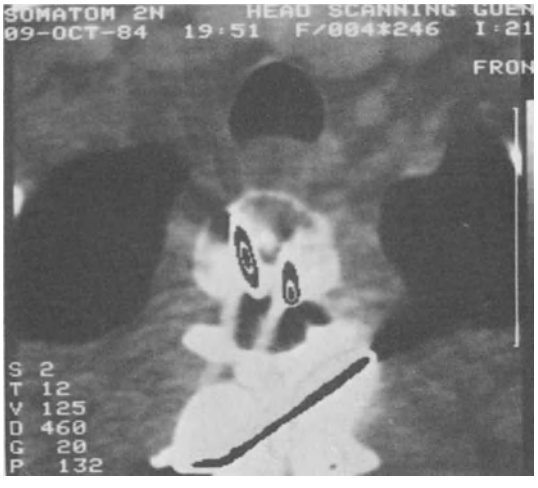


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Fig. 3a-f. Case 11. Roentgenograms of a C7/T1 metastasis from a breast carcinoma; a preoperative appearance with pathological compression fracture and luxation; b postoperative appearance after ventrodorsal repositioning, decompression, and stabilization. Compound osteosynthesis ventrally: low-viscosity cement, platelet, and screw fixation at C6, T1, and T2. Compound osteosynthesis dorsally: high-viscosity cement, Magerl hook platelet, Kirschner wire, and interspinosal wiring. CAT scans of C7 at identical levels; d preoperative, e postoperative; f CAT scan at T2 for demonstration of the ventral and dorsal fixation

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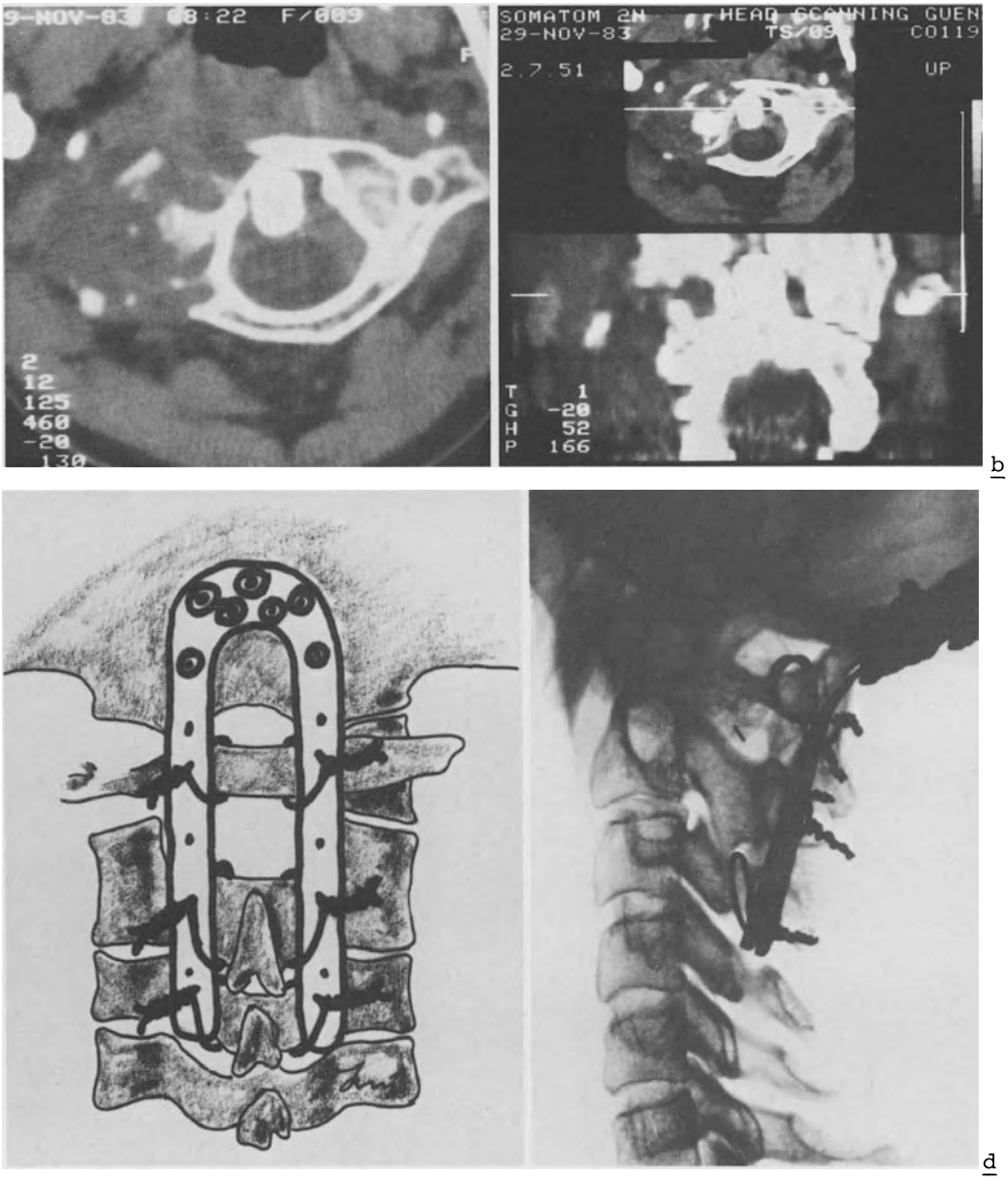


Fig. 4a-d. Case 4. CAT scan and coronal reconstruction of C1 showing an osteolytic process of the right massa lateralis (metastasis – origin unknown). c and d demonstrate the dorsal stabilization by a Wolter occiput plate screwed on the occiput and wired with the arches C1, 2, and 3. The roentgenogram shows a solid bony fusion from the occiput to C3

# Osteosynthesis with AO Plates in the Cervical and Lumbar Regions of the Vertebral Column in Cases of Spinal Metastases

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Owing to regular control examinations in cancer patients, more and more asymptomatic cases of spinal metastasis are being observed. In these patients radiation is still the first treatment to be employed. However, in patients with impending or progressive myelopathy – with or without previous radiation – surgical treatment is indicated (1, 5). There are nevertheless special problems in cases of tumorous infiltration of the lower cervical and lumbar spine (Fig. 1).

During the last 2 years 112 patients have been operated on for spinal metastases in our clinic. In only 14 patients (12%) was simultaneous osteosynthesis with AO plates thought to be indicated (3, 6, 7) (Fig. 2). These 14 patients were aged from 37 to 80 years, and there were ten women and four men. In five cases the anterior operative approach to the spine was chosen, while in nine the approach was posterior; seven times the approach was to the cervical region and seven times to the lumbar region.

Ventral stabilization was performed after spondylectomy and placement of a bone graft by H- and Wolter osteosynthetic plates (2) (Figs. 3, 4). Dorsal stabilization was performed after laminectomy using AO plates, according to the technique of ROY-CAMILLE (4, 8, 9). All the patients could be mobilized immediately after the operation without additional external fixation. Eleven patients were able to walk without help until their death. The survival time varied between 1 and 26 months, averaging about 6 months.

Rebleeding and disturbance of wound healing were never seen. X-ray showed loosening of a screw in one patient, though without clinical symptoms or instability of the ventral fusion (4). In three patients neurological symptoms grew worse postoperatively, in two cases owing to progressive radicular paresis.

## Discussion

Despite the more aggressive nature of the surgical treatment described – decompression and simultaneous stabilization – the average survival time is not prolonged in comparison with other treatments. However, the ability to walk until death and the reduction of radicular pain give patients a certain independence and represent an amelioration of the quality of life (this was the opinion of seven of twelve patients).

The anterior or posterior approach is used in accordance with the localization and extension of the tumorous infiltration of the vertebral body.

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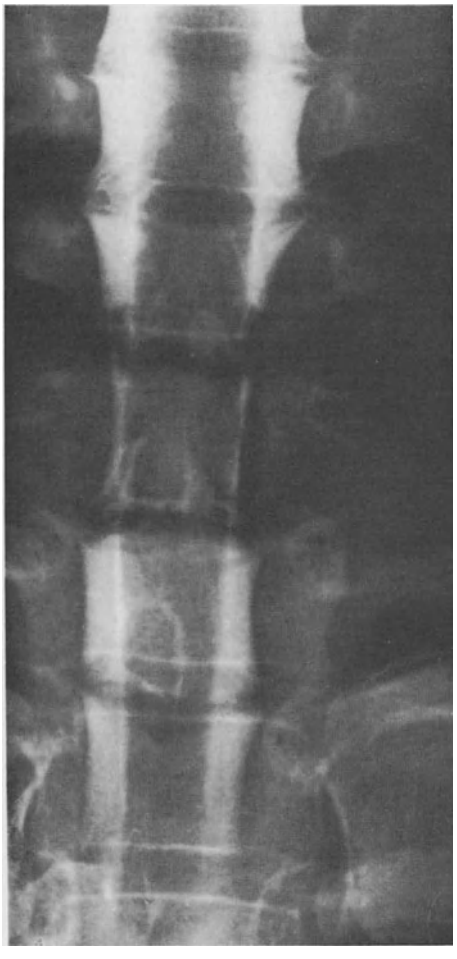

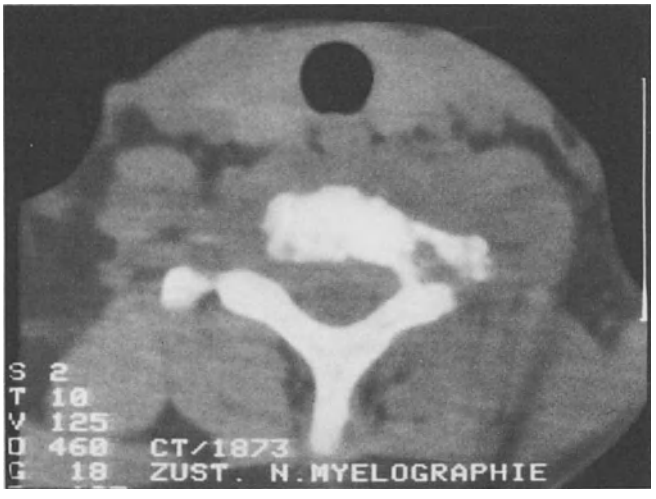


Fig. 1. *Left:* cervical myelopathy, a.p. view; space-occupying lesion about C7 (Hodgkin's lymphoma). *Right:* corresponding CT scan

Fig. 2. Lateral X-ray. *Left:* osteolysis ► with compression of T1 (breast cancer). *Right:* postoperative appearance showing bone graft and ventral osteosynthetic Wolter plate

Summary

In 14 of 112 patients with spinal metastases in the cervical or lumbar spine we performed either ventral or dorsal spondylodesis depending on the localization and extension of the osseous destruction. This method did not affect the survival time but did improve the quality of life.

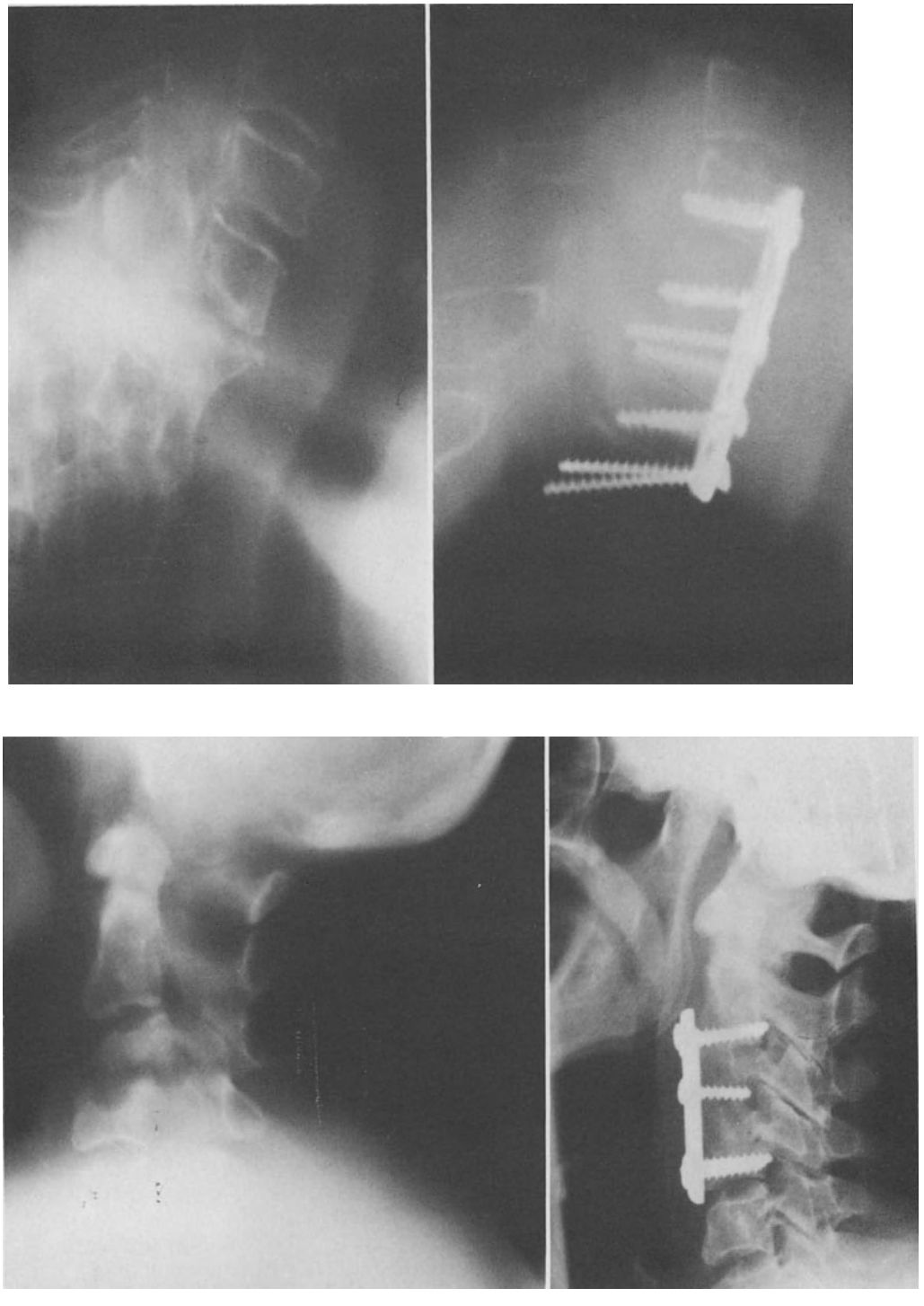

Fig. 3. *Left:* X-ray showing osteolysis of C3-4. *Right:* postoperative appearance: ventral spondylodesis

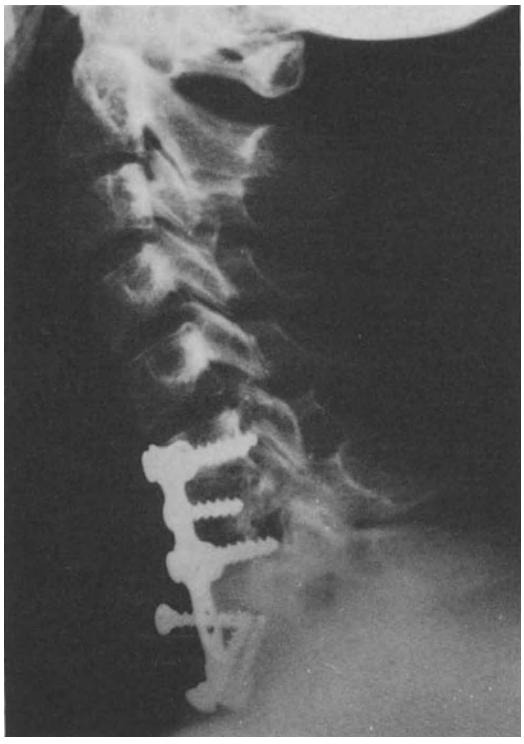

Fig. 4. X-ray 1 year after osteosynthesis with H-plate (Hodgkin's lymphoma at C7); one screw is seen to be loose

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# Differential Diagnosis and Operative Treatment of Rare Intraforaminal Space-Occupying Lesions

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The typical sciatic syndrome or unilateral radicular deficits are most often caused by disc herniation, but they may also be caused by an intraforaminal tumor. Depending on the lateral position of these tumors their most common apparent symptoms may be pain, loss of sensation, or weakness in the extremities. Therefore the differential diagnosis may prove very difficult. In most of our cases the anamnesis and certain clinical findings as well as additional neurological criteria caused us to suspect that the neurological deficits could be caused by tumor-like tissue. Thus we were able to modify our surgical indication and operative procedure in advance.

## Material and Approach

In the last 10 years 6641 patients were operated on for disc herniation in our clinic. These herniations were localized mostly in the lower lumbar and lower cervical region. During the same period 409 patients were operated on for spinal tumors or other space-occupying lesions in that region. We statistically analyzed the clinical data of these patients in a retrospective study to obtain more information on intraforaminal tumors, which may simulate degenerative diseases of the spinal cord.

## Results

Spinal cord tumors are still relatively rare entities. We had 260 patients with benign tumors; the other third of the patients had malignant tumors. Approximately 50% of the tumors studied were located in the thoracic region. Bladder and bowel symptoms appear quite late, as they are caused by cervical cord tumors. However, one of the early symptoms may be progressive constipation and, eventually, difficulty with urination. The cervical spine is less often involved than the thoracic spine; the lumbar spine is rarely involved, and the sacral spine almost never. On the other hand, in the lumbar and cervical regions one encounters other extrinsic lesions, such as protruded discs, much more commonly than in the thoracic area. The incidence of symptomatic lumbar disc herniation significantly exceeds that in the cervical spine, and greatly surpasses that in the thoracic spine.

Table 1 provides details on the tumors we found. The high incidence of meningiomas is obvious. They were mostly localized intradurally and in the thoracic region, rarely in the cervical region (ratio 5:1). Because of the relatively slow growth of benign tumors of the spinal cord, years may go by before long tract signs make their appearance. Extra-

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Table 1. Pathologic cell type of spinal cord tumors ($n = 409$)

| Tumor | No. | (%) |
|---|---|---|
| Meningioma | 83 | (20.3) |
| Metastatic or primary extension of extradural malignancy | | |
| Carcinoma and malignant melanoma | 78 | (19.1) |
| Lymphoma | 47 | (11.5) |
| Hodgkin's | 3 | |
| Sarcoma | 31 | |
| Myeloma | 13 | |
| Schwannoma | 63 | (15.4) |
| Gliomas | 56 | (13.7) |
| Astrocytoma | 6 | |
| Glioblastoma | 5 | |
| Ependymoma | 39 | |
| Miscellaneous | 6 | |
| Blood vessel tumors and anomalies | 15 | (3.7) |
| Primary bone tumors | 13 | (3.2) |
| Osteoblastoma | 6 | |
| Osteoclastoma | 1 | |
| Osteoid osteoma | 3 | |
| Osteochondroma | 2 | |
| Aneurysmal bone cyst | 1 | |
| Granuloma | 12 | (3.0) |
| Eosinophilic granuloma | 3 | |
| Nonspecific | 9 | |
| Lipoma | 9 | (2.2) |
| Neurofibromatosis | 7 | (1.7) |
| Neuroblastoma | 4 | (1.0) |
| Epidural abscess | 4 | (1.0) |
| Ganglioneuroma | 3 | (0.7) |
| Dermoid | 3 | (0.7) |
| Chordoma | 2 | (0.5) |
| Neurofibroma (malignant) | 1 | (0.2) |
| Pheochromocytoma | 1 | (0.2) |
| Teratoma | 1 | (0.2) |
| Miscellaneous undiagnosed | 7 | (1.7) |
| Tumor cysts | 4 | |
| Other | 3 | |

dural tumors in the thoracic region are almost always metastatic in nature. They may be localized in the lumbar and cervical region, too (ratio 6:2:1). With the onset of typical symptoms of pain, associated with numbness and weakness, one must always consider the possibility of a metastatic tumor. Neoplasms metastatic to the spinal cord did not stem from one predominant primary tumor. We found metastases with their origin in cells of the breast, kidney, lung, prostate, and thyroid in similar proportions. Meningiomas and metastatic neoplasms are by far the most favorable groups of tumors. Sarcomas were only localized in the thoracic region. In this group are included osteosarcoma, Ewing's sarcoma, and lymphosarcoma. Multiple myeloma (plasmocytoma) is localized primarily in the thoracic region, like the blood vessel tumors. Myeloma of the spine is most often solitary and only rarely multiple. The Schwann cell neoplasms of the nerve root were localized equally frequently in the thoracic and lumbar regions, and less often in the cervical region (ratio 3:3:2). In the total group of gliomas which were localized in the thoracic and cervical regions, we found no oligodendroglioma. It was less common for intramedullary tumors to cause pain as an early symptom. An additional 10.0% of the tumors were of the rarer benign types, including lipomas, dermoids, blood vessel tumors, and primary bone tumors. As in any large group of tumors which are pathologically analyzed, a certain number cannot be definitely classified. We have shown this under the heading of "miscellaneous undiagnosed" in Table 1.

*Examples*

Below are some examples of very rare intraforaminal findings:

In a 47-year-old male with a right-sided radicular L4 and L5 syndrome we found a hyperdense intraforaminal structure on the CT scan (Fig. 1). It looked like part of a herniated disc but had produced an osteolytic lesion in the vertebral body next to it. Upon operation we found sequestrated disc material; the osteolytic reaction was only a local response to the impressed disc material.

Especially a radicular syndrome of the thoracic region could be caused by intercostal neuralgia, pain following herpes zoster, tumor pain, or a disc herniation which is usually presented in the lower thoracic segments. Sometimes the protruded intervertebral disc is calcified. In the example shown in Fig. 2 the lateral part of a calcified disc in the upper lumbar region is extruded intraforaminally.

In nine patients with thoracic lesions we found nonspecific inflammatory but granulomatous tissue in the intraforaminal space. We supposed that it was partly composed of altered disc material which could cause a nonspecific inflammatory response in its region. In Fig. 3 hypertrophic bone and a hyperdense process are visible intraforaminally. The histological examination gave us no indication of a tumor or a herniated disc.

We found ganglioneuromas in three cases. This is a benign tumor usually without symptoms. The body scan of one 18-year-old man showed a partly calcified tumor as big as a coconut in the paravertebral intra-abdominal region (Fig. 4). A part of this tumor bulged into the intraforaminal space of the thoracolumbar region. One should bear in mind the frequency of spinal cord tumors in the thoracic region as a source of abdominal and visceral pain.

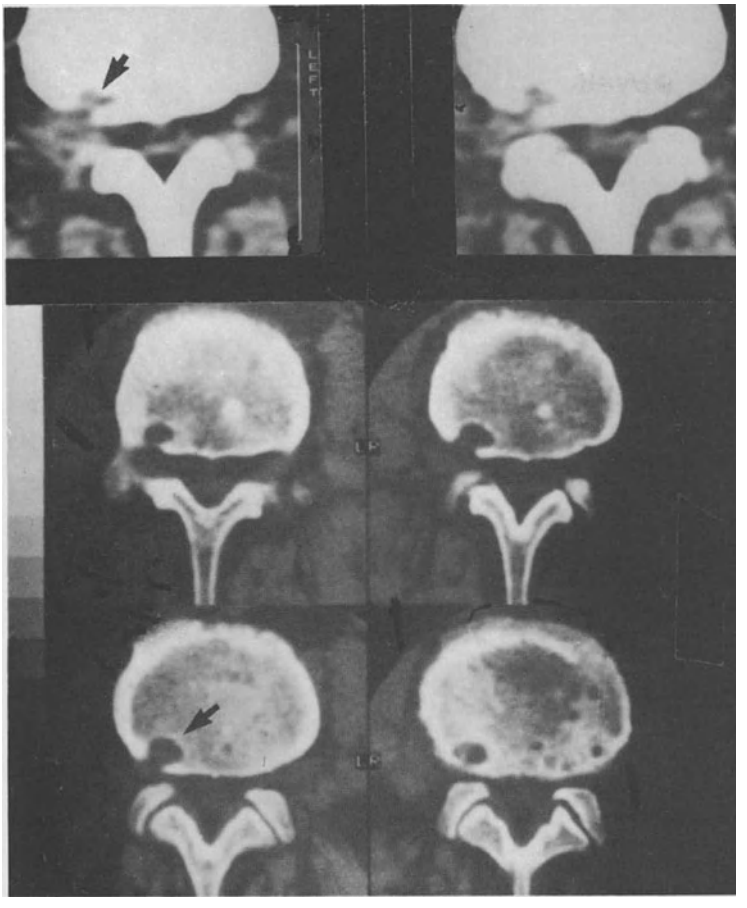

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Fig. 1. K.W. ♂ 47 years. Intraforaminal sequestrated disc material with osteolytic lesion in the vertebral body next to it

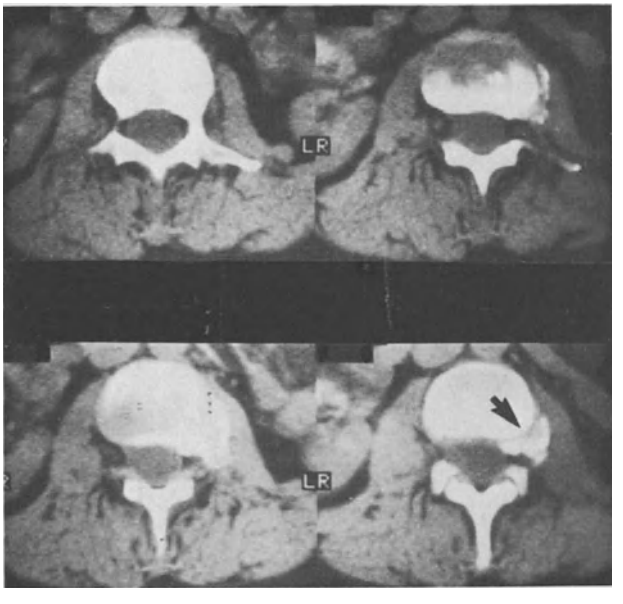


Fig. 2. A.O. ♀ 53 years. Calcified lateral disc herniation, L2/3, left

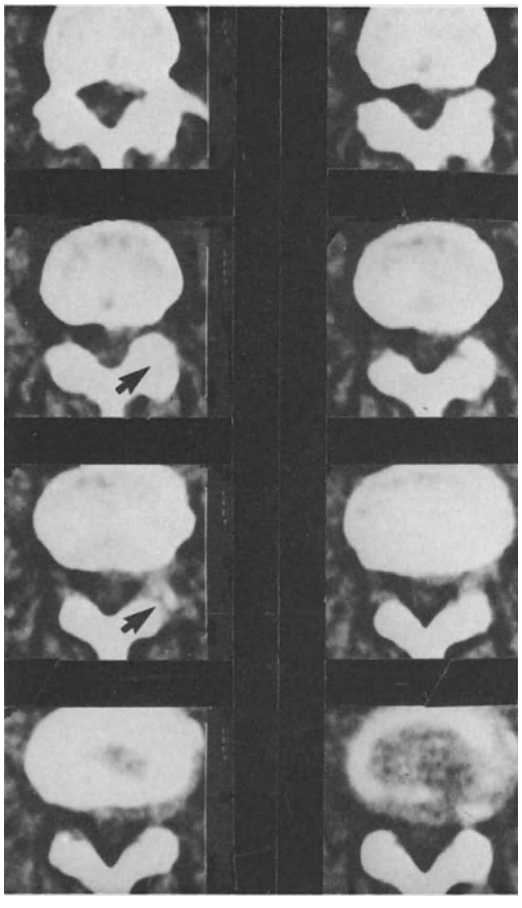

Fig. 3. K.S. ♂ 49 years. Non-specific granulomatous and partly calcified tissue, L3/4, left

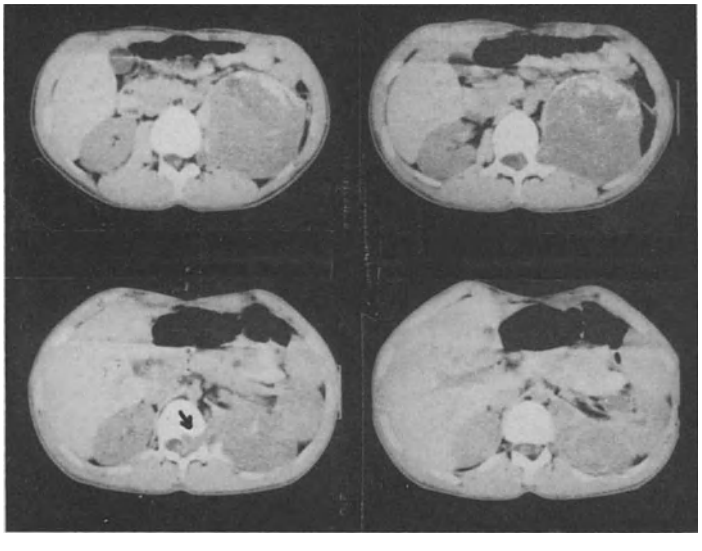

Fig. 4. Y.C. ♀ 18 years. Ganglioneuroma, T12/L1, left

## Operative Proceedings

We prefer the CUSA system (*c*avitron *u*ltrasonic *s*urgical *a*spirator) in soft and solid tumors with less blood vessels, for example in plasmocytomas. With this system, paratumorous neural structures could be preserved and differentiated in an excellent manner. The Neodymium-YAG laser system was used in sarcomas which had infiltrated into the muscle and bone from their primary point of origin. These do have a propensity for excessive bleeding, which can be stopped with the laser light. Thus we use the laser in tumors with constantly active bleeding, hard, tough, and partly calcified tissue.

## Conclusion

Although spinal cord tumors are relatively rare entities, the persistence, severity, and progression of a radicular syndrome should arouse the suspicion of the examining physician to the point of performing definitive studies. This emphasizes the necessity for a meticulous and chronologically accurate history from the patient to determine whether or not one is dealing with a progressive lesion. The latter, of course, does not prove the presence of a spinal cord tumor, but it may tend to favor this diagnosis. A correct diagnosis may often be extremely difficult. Pain was one of the most common local symptoms, and was frequently the initial manifestation.

Surgery should not be postponed even in the more malignant tumors, in which a surprisingly good, although temporary, result is often obtained after surgical decompression. An attempt should be made to remove as much tumor as possible if it is malignant.

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# Acute Leriche Syndrome in the Differential Diagnosis of Acute Paraplegia

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## Introduction

Acute embolic occlusion at the bifurcation of the aorta is known as the acute Leriche syndrome. This syndrome is always a dramatic occurrence, although variations in the clinical symptomatology make errors in diagnosis possible.

## Patient Material

In a retrospective study, the medical records of 41 patients with Leriche syndrome were studied. All patients were admitted to the Chirurgische Universitätsklinik Erlangen between 1968 and 1982. Sixteen were women and 25 men. Their ages ranged from 27 to 85 years, the average being 66.5 years.

The chief symptom of the syndrome is a sudden, whip-like pain in the lower extremities. This pain spreads in a cranial direction, extending to the segment affected by the lesion. The lower extremities are cool, the skin is pale, and the pulse in the femoral, popliteal and foot arteries is impalpable.

Eight patients had a history of cardiac infarction. In 14 cases there were cardiac arrhythmias, especially absolute arrhythmia in cases of atrial fibrillation.

Incomplete or complete paraplegia was observed in 18 of the 41 patients. The neurological signs ranged from slight disturbances in sensation in the lower extremities to complete paralysis of the legs with anesthesia and analgesia, loss of reflexes, and loss of stool and bladder control (Table 1).

Table 1. Symptoms of acute Leriche syndrome in the 41 patients treated at the Chirurgische Universitätsklinik Erlangen between 1968 and 1982

| | |
|---|---|
| Sudden occurrence of intense pain in the lower extremities | 41 |
| Lower extremities cold, pale, and cyanotic | 41 |
| Femoral, popliteal and foot pulses absent | 41 |
| Complete or imcomplete paraplegia | 18 |

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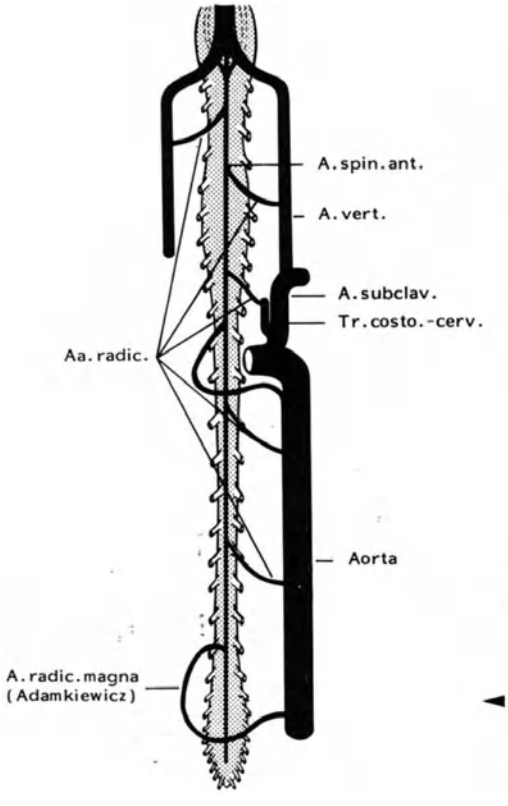
In two cases myelography was performed without revealing any abnormality. Thrombectomy was performed with a Fogarty catheter in 31 cases. Two patients received an Y prosthesis; in two cases transaortal embolectomy was performed and in two other patients thromboendarterectomy was carried out. At the time of admission, four patients were in a moribund state, so that an operative procedure was no longer possible. The interval between the sudden onset of pain and the time of surgery ranged from 1 h to 2 days.

Of the 37 patients who underwent surgery, 14 died, as did the four patients who were in an inoperable state. The causes of death were tourniquet shock and heart failure.

## Discussion

The arterial supply of the thoracolumbar spinal cord is chiefly by way of the arteria radicularis magna, which enters the spinal cord between D6 and L5 (Fig. 1). This artery usually originates from the lowest intercostal arteries and only rarely from the two upper lumbar arteries (5, 6).

JELLINGER (6) describes three levels of involvement. About 12% of cases occur at the highest localization, affecting the middle thoracic third; 62% occur at the middle localization, affecting the lower thoracic spinal cord; and 26% occur at the lowest localization, affecting the spinal cord from the level of the first lumbar vertebra in a distal



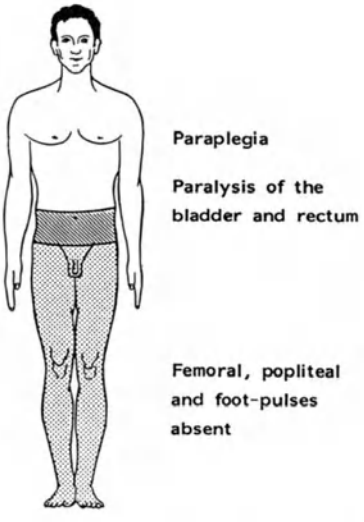




Fig. 2. Acute Leriche syndrome. Diagrammatic representation of the symptomatology from D10 downward in a 47-year-old male patient

◄ Fig. 1. Acute Leriche syndrome. Aortography reveals an acute occlusion in the abdominal aorta (infrarenal)

direction. The bifurcation of the aorta lies at the level of the fourth lumbar vertebra. When there is a low localization of the arteria radicularis magna and an aortic embolus which extends far upward, complete paraplegia may occur (1-4, 7, 11) (see Fig. 2). The cause of this symptomatology is ischemia of the caudal spinal cord, finally leading to myelomalacia. When there is infrarenal occlusion of the aorta (Fig. 3), the ischemic damage to the lumbosacral plexus will lead only to partial neurological deficits in the lower extremities.

The combination of sudden, whip-like pain with paraplegia and neurological deficits of the lower extremities may be mistaken for a medial lumbar disc. However, the diagnosis of acute Leriche syndrome may be confirmed by the other signs of acute vascular occlusion, such as the cool and pale skin of the lower extremities, the loss of pulsation in the femoral, popliteal, and foot arteries, and a feeling of coldness in the lower extremities (2, 3, 8-10). Performing a myelogram does not provide any additional information.

The mortality in our patients was over 40%. The prognosis depends on the interval between the onset of acute ischemia and surgical removal of the embolus (Fig. 4). Removal of the embolus is performed with a Fogarty catheter by way of an arteriotomy in the groin. It is necessary to admit the patient to a department of vascular surgery immediately following pain relief and heparinization. Admission of such a patient to a neurosurgical or neurological department causes unnecessary loss of time.

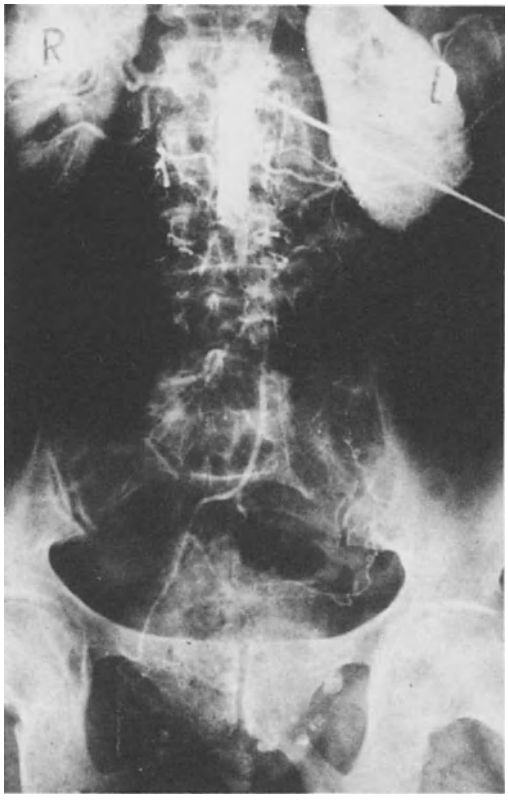



Fig. 3. Aortography shows the infrarenal occlusion of the aorta in a case of acute Leriche syndrome

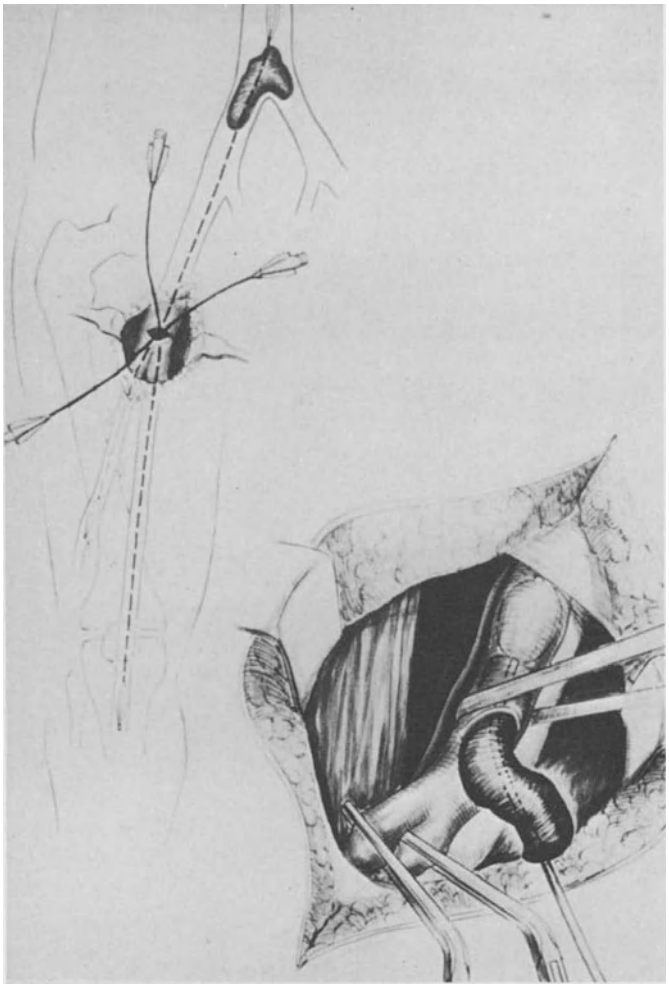


Fig. 4. Diagrammatic representation of the surgical removal of an embolus using the Fogarty catheter


## Summary

A total of 41 patients aged 27-85 years were admitted to the Chirurgische Universitätsklinik between 1968 and 1982 with the diagnosis of acute Leriche syndrome. In all cases there were symptoms of acute ischemia of the lower extremities. Eighteen patients had incomplete or complete paraplegia with loss of bladder control, so that the possibility of a medial lumbar disc had to be included in the differential diagnosis. The mortality of over 40% can be lowered only by referring these patients to a department of vascular surgery immediately.

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# Misdiagnoses in Spinal Tumors

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A rare disease with a widespread symptomatology is always liable to lead to incorrect diagnosis, and spinal tumors both are seldom and show manifold symptoms.

Between 1970 and 1983, 358 patients were operated on for spinal tumors in the Neurosurgical Department of Düsseldorf University; in the same period about 2000 patients were operated on for intracranial tumors. The overall estimated incidence of intracranial tumors is 1 per 5000 inhabitants per year; thus the incidence of operable spinal tumors may be assumed to be 1 per 30 000 at the most, including metastases.

When recording the data of our 358 patients, misdiagnoses made prior to admission were registered. The data were evaluated by electronic data processing.

The most frequent tumors were metastases of carcinomas (24.6%), followed by spinal meningiomas (17.3%) and gliomas, including ependymomas (13.1%); 11.7% of the patients had neurinomas, 8.7% metastases of sarcomas, and 6.4% plasmacytomas.

Among the symptoms local and radiating pain was very common: back pain occurred in 39.9%, lumbago in 22.3%, and neck pain in 11.5%. Three-quarters of the patients complained of radicular pains. Disturbances of micturition were present in 48.3%. Insecurity in walking was experienced by 59.5%, while 33.2% were unable to walk. Rare symptoms were scoliosis (5%), loss of weight (3.6%), Bernard-Horner syndrome (1.4%), and respiratory insufficiency (0.8%).

In 24.3% of cases, information regarding former misdiagnoses could be found in the patients' records. This is the same quantity as found by KUHLENDAHL and ISCHEBECK (1975) in their survey on multiple sclerosis and other misdiagnoses in spinal processes; they wrote: "There is no doubt, however, that, in fact, the percentage of wrong diagnoses, also among these 2637 cases, has been far larger, but the available sources and medical records could provide no proof of this. It is a common experience that early diagnosis of a space-occupying spinal process is rare. In this sphere we have to take into account a fairly wide and 'grey' diagnostic margin. Thus the statistical data given here cannot be completely flawless. They must, at least, represent the lowest limit of reality".

In our series the misdiagnoses were subdivided into nine groups: (I) disc diseases (24.6% of the misdiagnoses), (II) spondylosis (16.1%), (III) multiple sclerosis (6.9%), (IV) other neurological diseases (20.7%), (V) circulatory disturbances (10.3%), (VI) herpes zoster


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(1.1%), (VII) myelopathy (2.3%), (VIII) cardiac disorders (2.3%), and others (13.8%). Table 1 shows the different misdiagnoses attached with these groups.

Among the different tumors misdiagnoses were most frequent in angiomas (47.1%), neurinomas (33.3%), meningiomas (29.0%), and gliomas (27.7%). In 19.3% of the metastases of carcinomas and in 22.6% of the metastases of sarcomas a wrong diagnosis was made. There is a widespread distribution of the particular misdiagnoses in relation to the different tumors (Table 2). Disc diseases were diagnosed in 17.6% of the angiomas and

Table 1. Groups of misdiagnoses

| | |
|---|---|
| Disc disease: | Lumbago |
| | Sciatica |
| | Disc hernia |
| | Disc prolapse |
| | Root compression syndrome |
| Spondylosis: | Cervical syndrome |
| | Thoracic syndrome |
| | Myogelosis |
| | Signs of wear |
| | Rheumatism |
| | Scheuermann's disease |
| Multiple sclerosis | |
| Other neurological diseases: | Polyneuropathy |
| | Neuropathy |
| | Intercostal neuralgia |
| | Deficiency of cyanocobalamin |
| | Virus encephalomyelitis |
| | Arachnitis |
| Circulatory disturbances | |
| Herpes zoster | |
| Myelopathy | |
| Cardiac disorders | |
| Others: | Tuberculosis |
| | Pneumonia |
| | Biliary system disease |
| | Spine fracture |
| | Hypernephroma |
| | Arthrosis |
| | Skeletal disorders |

Table 2. Tumor types and misdiagnoses

| | Gliomas, includ. ependymomas | Neurinomas | Meningiomas | Angiomas | Metastases of carcinomas | Metastases of sarcomas | Total |
|---|---|---|---|---|---|---|---|
| Total no. of cases | 47 | 42 | 62 | 17 | 88 | 31 | 358 |
| Disc disease | 10.6% | 9.5% | 4.8% | 17.6% | 4.5% | - | 6.4% |
| Spondylosis | - | 7.1% | 4.8% | - | 3.4% | 6.5% | 3.9% |
| Multiple sclerosis | - | 2.4% | 3.2% | - | - | - | 1.7% |
| Other neurological diseases | 4.2% | 9.5% | 6.5% | - | 5.7% | - | 5.0% |
| Circulatory disturbances | 4.2% | 4.8% | 3.2% | 11.8% | - | - | 2.5% |
| Herpes zoster | - | - | - | - | 1.1% | - | 0.3% |
| Myelopathy | - | - | - | - | - | - | 0.6% |
| Cardiac disorders | - | - | - | - | - | - | 0.6% |
| Others | 8.5% | - | 6.5% | 17.6% | 4.5% | 16.1% | 3.4% |

in 10.6% of the gliomas. Disc disease and spondylosis were the misdiagnoses in 16.1% of the neurinomas and 9.6% of the meningiomas. In meningiomas and neurinomas, both slowly growing tumors, other neurological diseases and multiple sclerosis were often misdiagnosed, whereas circulatory disturbances were diagnosed in 11.8% of the angiomas; thus a quarter of all misdiagnosed circulatory disturbances belonged to spinal angiomas.

Corresponding to the distribution of disc diseases, these were misdiagnosed in 10.6% of the tumors localized in the cervical spine and in 10.4% of the tumors of the lumbar spine; in 6.3% of the latter spondylosis was diagnosed, too. In only 5.5% of the tumors of the thoracic spine was a misdiagnosis of disc disease made, and in 4.4% a misdiagnosis of spondylosis. The incidence of misdiagnosed multiple sclerosis was 6.4% and that of other neurological diseases 12.8% in tumors of the cervical spine. In the thoracic spine tumors a diagnosis of multiple sclerosis was made in 1.1%, of other neurological diseases in 6.1%, and of circulatory disturbances in 3.9%. Herpes zoster (0.6%, one case) and cardiac disorders (1.1%, two cases) were misdiagnosed only in tumors of the thoracic spine – herpes zoster in a case of metastasizing carcinoma, cardiac disorders in two elderly patients complaining of sensibility loss in the T5 dermatome.

Disc disease and spondylosis were misdiagnosed in 15.5% of the intradural extramedullary tumors but in only 7.6% of the extradural and 12.5% of the intramedullary tumors. The ratio of wrongly diagnosed other neurological diseases was nearly the same in all three groups, but circulatory disturbances were assumed in 7.7% of the intramedullary tumors and in only 1.2% of the extradural and 2.8% of the intradural extramedullary tumors.

Our study also shows a typical preponderance of misdiagnoses relating to the age of the patients. Multiple sclerosis was misdiagnosed only in patients in the 3rd and 4th decades of life. Circulatory disturbances were the wrong diagnosis in nine patients over 40 years of life. Of the 18 patients in whom other neurological diseases were supposed, 14 were between 41 and 70 years of age. Disc diseases showed no typical peak, but spondylosis occurred predominantly in patients over 40 years old.

Our study of misdiagnoses in spinal tumors must not be misinterpreted as a tribunal of diagnostic insufficiency, but it does illustrate how difficult the right diagnosis of a rare disease may be.

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# Tumors of the Craniocervical Region: Difficulties in Diagnosis; Microsurgery and Laser Surgery

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The first systematic report of tumors in the craniocervical region was given by ELSBERG in 1925 and by ELSBERG and STRAUSS in 1929. In 185 tumors of the spinal cord, they found six (3.2%) extramedullary tumors situated in the craniocervical region. In 1954 DODGE and LOVE reported on intra- and extramedullary tumors in the foramen magnum region: only 40% of the extramedullary tumors were estimated surgically treatable.

Undoubtedly, the situation has changed greatly during the last two decades due to refined diagnostic and surgical tools. At present, all extramedullary and most of the intramedullary tumors of the craniocervical region can be treated by surgery.

Even though the diagnostic facilities (CI scan, metrizamide myelography, NMR) are considerably improved, the time lapse between onset of the first symptoms of foramen magnum and upper cervical cord tumors and surgery has continued to range from 6 to 96 months with an average of 37.3 months (HIRANO, 1983).

## Material

In the Neurosurgical Department of the University Hospital of Hamburg-Eppendorf, ten tumors of the craniocervical junction were operated on between 1982 and 1985 (Table 1). Seven of them were situated extramedullarly and three intramedullarly. Histological examination of the extramedullary tumors revealed six meningiomas and one neurinoma. The three intramedullary tumors consisted of one ependymoma, one astrocytoma, and one melanoma. The average interval between the onset of symptoms and surgery was 17 months (from 6 to 37 months). The most frequent initial symptoms were uncharacteristic pain in the neck and the occipital skin, sometimes combined with a dysesthesia in this region. All patients suffered from weakness of their extremities at the time of diagnosis.

In two cases the neurological examination before surgery yielded a nearly complete tetraparesis. Cranial nerve involvement (Table 2) included palsy of the 11th nerve (twice), deficits of the nerves 9-12 (twice), and a unilateral disturbance of the 5th nerve (once).

In eight of ten cases, metrizamide myelography, sometimes performed in combination with CT scanning, led to the diagnosis. Skull and cervical spine X-ray, angiography, and enhanced CT scans delivered additional information. Four patients underwent NMR examination, and in two cases the final diagnosis was only obtained by this examination.


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Table 1. Tumors of the craniocervical region, 1982-1985 ($n = 10$)

| | Age/sex | Initial symptom | Anamnesis (months) | Diagnosis |
|---|---|---|---|---|
| 1 | 47/female | Stiffness of the neck | 13 | Meningioma |
| 2 | 2/female | Pain in the neck | 6 | Ependymoma (intramedullary) |
| 3 | 58/male | Dysesthesia | 11 | Neurinoma |
| 4 | 28/female | Dysesthesia in the right shoulder | 6 | Meningioma |
| 5 | 17/male | Pain in the neck | 12 | Meningioma |
| 6 | 63/male | Weakness in the left hand | 31 | Meningioma |
| 7 | 39/female | Pain in the left shoulder | 25 | Meningioma |
| 8 | 71/female | Weakness in the right leg | 36 | Meningioma |
| 9 | 50/female | Pain in the neck, left-sided hemi-dysesthesia | 12 | Melanoma (intramedullary) |
| 10 | 47/male | Nausea | 17 | Astrocytoma (intramedullary) |

Table 2. Tumors of the craniocervical region, 1982-1985 ($n = 10$): cranial nerve involvement ($n = 5$)

| | Cranial nerve palsy | Other neurological findings | Diagnosis |
|---|---|---|---|
| 1 | 9th - 12th | Tetraparesis | Ependymoma (intramedullary) |
| 2 | 11th | Tetraplegia | Meningioma |
| 3 | 11th | Hemiplegia (right) Hemiparesis (left) | Meningioma |
| 4 | 5th | Tetraparesis Hemidysesthesia (left) | Melanoma (intramedullary) |
| 5 | 9th - 11th | Astereognosis, right hand Ataxia, right leg | Astrocytoma (intramedullary) |

## Operation

All tumors were removed under microscopic view through a posterior approach including cervical laminectomy (C1-C3) and scanty suboccipital craniotomy in prone position. In three patients the removal of the tumor was achieved with the aid of the $CO_2$ Varipuls laser (Table 3). Laser surgery was applied in two intramedullary tumors and in a meningioma situated ventrally to the cord and growing around the vertebral arteries and along the upper cervical roots into the intervertebral

Table 3. Tumors of the craniocervical region, 1982-1985 ($n = 10$): results

| | Histological diagnosis | Removal | Laser | Clinical result | Complication | Death |
|---|---|---|---|---|---|---|
| 1 | Meningioma I-II | Total | - | Improved | - | - |
| 2 | Intramedullary ependymoma II | Subtotal (irradiation) | Yes | Unchanged | Aseptic meningitis | - |
| 3 | Neurinoma | Total | - | No complaints | - | - |
| 4 | Meningioma III | Total | Yes | Improved | - | - |
| 5 | Meningioma II-III | Total | - | Improved | Aseptic meningitis | - |
| 6 | Meningioma II-III | Total | - | No complaints | - | - |
| 7 | Meningioma I | Total | - | Improved | Aseptic meningitis | - |
| 8 | Meningioma | Total | - | Improved | - | - |
| 9 | Intramedullary melanoma | Total | Yes | Improved | - | - |
| 10 | Intramedullary astrocytoma | Subtotal | - | Improved | Gastric bleeding | - |

foramina. The $CO_2$ Varipuls laser was applied in pulse mode only, guided by a micromanipulator at the operation microscope. Total tumor removal was feasible in all patients with extramedullary tumors and in one patient with an intramedullary melanoma. In the two patients with intramedullary astrocytoma and ependymoma, the mass of the tumor was removed, but the extirpation was incomplete. No operative death occurred.

Postoperative neurological examination showed improvement in all but one patient. In this patient, suffering from an intramedullary ependymoma, the neurological state after operation was unchanged. Postoperative radiotherapy was performed, without any effect on the neurological state. In one patient the postoperative course was complicated by severe gastric hemorrhage that required gastroscopic intervention.

The history of two of the three patients who were operated on with the aid of $CO_2$ Varipuls laser is briefly presented below:

Six months before the diagnosis was established, a 28-year-old woman noticed sensory disturbances in her right shoulder and arm. A short time later, weakness of her right arm and leg appeared. Metrizamide myelography demonstrated a ventral and right lateral tumor mass extending from the C1/2 level down to C4. Intraoperatively the mass was identified as a meningioma growing extradurally, tightly adherent to the cervical roots (including C4) and to the vertebral artery. Having removed the bulk of the tumor, the $CO_2$ laser was used to detach the tumor from the cervical roots and the vertebral artery and to achieve hemostasis in the osseous part of the tumor bed. Two weeks after operation the patient left the hospital with continuous improvement of the paresis of her arm.

A 50-year-old woman suffered from nuchal pain for 12 months. A left-sided hemidysesthesia including the patient's face developed. Cervical spine and skull X-ray, metrizamide myelography, and enhanced CT scan failed to demonstrate the tumor. NMR investigation detected the suspected tumor in the medulla oblongata. The patient was operated on. After dorsal midline incision of the spinal cord by $CO_2$ laser, a small tumor sample was taken by microforceps for histological examination. It was diagnosed as melanoma. The tumor was then evaporated by laser. Two and a half weeks after operation the patient could be discharged home. Except for slight dystaxia of the left leg, the neurological signs disappeared. Since detailed examination did not reveal any other melanomatous lesion, the tumor must be considered a primary intramedullary melanoma.

## Discussion

The diagnostic problems with craniocervical space-occupying lesions are known from many reports. They most frequently are misdiagnosed as multiple sclerosis. The reason for the high frequency of delayed and false diagnoses seems to be the uncharacteristic primary symptoms and the local anatomic situation. Due to the wideness of the upper cervical spinal canal and cisterna magna, extramedullary tumors, which are mostly situated ventrally to the cord (LEVY et al. 1982), produce vascular and local compression of the upper cord rather than occlusion of the spinal canal. Thus, the symptoms may vary in a wide range depending on location and extension of focal compression of the upper spinal cord or inferior brainstem.

CT scan evaluation of the foramen magnum region is more difficult than in higher or lower levels. Especially in this region CT can be mis-

leading due to artifacts. This region is also difficult to visualize by metrizamide myelography. Thus, NMR is now the most reliable diagnostic tool.

During the period reported, all craniocervical tumors were operated on. They were all approached via a dorsal midline incision. Microscopically total tumor removal of all extramedullary tumors was achieved, even if the larger part of the tumor was attached to the clival dura. The tumor extension itself and a slight asymmetry of tumor growth proved to be sufficient to render a unilateral dorsolateral approach to the tumor possible. The transoral transclival approach appeared to be dispensable.

The use of $CO_2$ laser equipment represents a valuable improvement, especially in the surgery of intramedullary tumors, since it allows tumor removal with minimal mechanical irritation of the cordal tissue surrounding the tumor. The $CO_2$ Varipuls laser enables the surgeon to evaporate even the thinnest tumor layers without damaging the vicinity; also, delicate brainstem and cranial nerve structures can be preserved even if rigid tumors are tightly attached to them or surround them.


## Summary

The authors reported on ten tumors of the craniocervical junction, seven extra- and three intramedullary, operated on between 1982 and 1985. They were all approached by the dorsal route, even if they were situated ventrally to the cord. All patients survived. They all improved except one. NMR turned out to be the diagnostic method most reliable in this region. The value of pulsed $CO_2$ laser surgery for the treatment of craniospinal tumors is emphasized.


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# Diagnosis and Treatment of Space-Occupying Lesions at the Craniocervical Junction

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## Introduction

Until recently the detection and correct interpretation of space-occupying lesions at the craniocervical junction constituted one of the most demanding problems of neurology and neurosurgery. Quite frequently a correct diagnosis was reached only when almost complete tetraplegia had already developed. Time and again these difficulties have been mentioned in the literature concerning tumors in the area of the foramen magnum (1-10). The availability of the latest imaging procedures, such as computer tomography (CT) with high resolution and nuclear magnetic resonance (NMR) imaging, has since greatly facilitated the diagnosis of space-occupying lesions at the craniocervical junction.

The clinical symptoms of such lesions can show great variety. Pain in the neck or in the back of the head, indications of elevated intracranial pressure, impaired sensation in the dermatomes C1 and C2, and medullary symptoms of varying severity, where pareses might develop and be combined with atrophy in the muscles of the arms, are of great importance diagnostically. An intermittent course of the disorder with manifestations of pareses spaced at intervals is also sometimes observed.

Accordingly discrimination between these lesions and cases of encephalomyelitis disseminata or chronic degenerative spinal diseases might be difficult. Consideration of the possibility of the presence of such tumors by the physician treating the patient and consequent initiation of determined radiological exploration are decisive for the timely detection of tumors in this area. In addition to meningiomas at the foramen magnum, particularly ependymomas, hemangioblastomas, chordomas, tumors involving malformations (epidermoid and dermoid cysts), giant aneurysms of the vertebral artery, various kinds of cyst, and the Arnold-Chiari syndrome are seen. Skillful combination of CT, NMR, and conventional radiological procedures often allows correct classification of the disorder prior to surgery.

## Patient Material and the Results of Surgery

During the period 1979 through 1985 a total of 13 patients with tumors or other space-occupying lesions at the craniocervical junction were observed (see also Table 1). In all cases dorsal access was selected during surgery. Using techniques of microsurgery, the tumors were removed and the malformations of the vessels in this area eliminated, while the nerves of the brain and the medullary functions were largely preserved. In one case only, involving a clivus chordoma, did removal

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Table 1. Tumors and other space-occupying lesions at the craniocervical junction (reported from the Department of Neurosurgery, Klinikum Charlottenburg, and the Rudolf-Virchow-Krankenhaus, West Berlin, and covering the years 1979 - 1985)

| Kind of lesion diagnosed | No. of patients |
|---|---|
| Meningioma | 6 |
| Ependymoma | 1 |
| Hemangioblastoma | 1 |
| Dermoid cyst, epidermoid cyst | 3 |
| Chordoma of the clivus | 1 |
| Giant aneurysm of the vertebral artery | 1 |
| | 13 |

of a substantial remant of a tumor have to be performed via a transoral approach. According to our experience, careful management also permits complete removal of meningiomas located directly in front of the medulla at the anterior edge of the foramen magnum without resulting in major neural damage. In the series of cases described, no death occurred during surgery; morbidity amounted to 31% of the cases.

A few short remarks may be made regarding the meningiomas found. In four of our six cases of this disorder, due to the considerable diagnostic problems present in all these patients, almost complete tetraplegia existed preceding surgery. In the case of the last patient (female) of this group, the enormous potential and benefit of NMR was strikingly demonstrated. NMR imaging clearly showed the extension of the tumor from the lower edge of the clivus up to the C1/C2 level (see Fig. 1). Following removal of the tumor situated in front of the medulla via microsurgery, the patient, who had been tetraplegic and in need of artificial respiration preceding surgery, was able to walk again without assistance a few weeks later.

## Case Reports

The following reports are intended to describe four patients with uncommon lesions at the craniocervical junction, some of which posed considerably more difficult surgical problems than the meningiomas found in this region.

### *Case 1: Chordoma of the Clivus*

The patient Hikmet M. (male) was 31 years old. In February 1985 a mucus-forming tumor in the nasopharynx associated with bone destruction was removed. The subsequent course of the disorder was initially uneventful. Starting in the middle of March, headaches and shortly thereafter tickling paresthesia in the hands and feet and an increasingly worn-out feeling were noted. At the end of March the patient had to be hospitalized in a neurological clinic. During his time at the hospital the condition of the patient acutely worsened. He developed a tetraparesis and beginning paralysis of the caudal nerves of the brain. Examination by means of CT revealed a destructive tumor at the lower

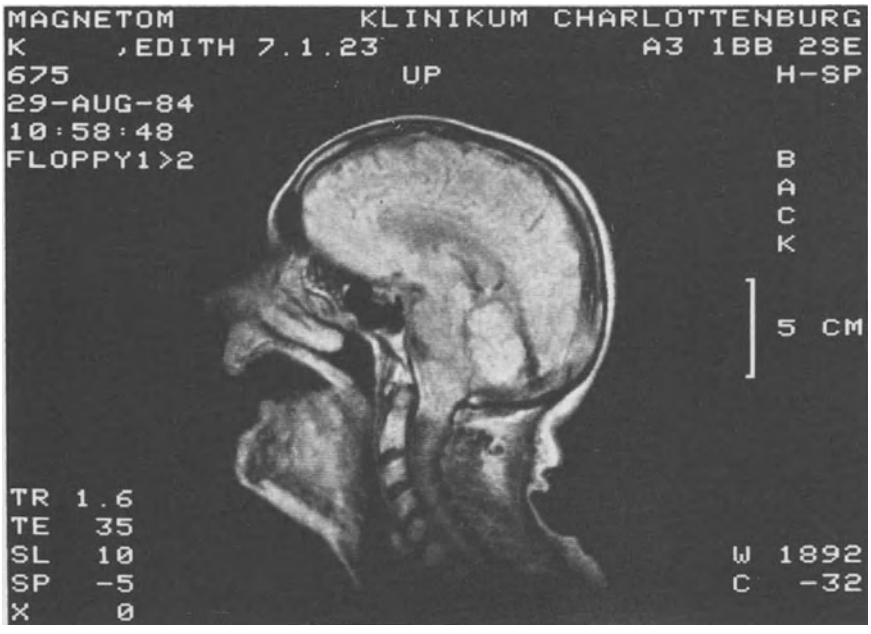



Fig. 1. Tomogram of a 61-year-old female patient (mediosagittal section, emphasizing T2) with tetraplegia due to surgically verified meningioma of the foramen magnum, obtained using NMR. The tumor slighly exceeds the pons and the medulla in signal intensity. The tumor begins in a wide configuration reaching from the lower part of the clivus up to the center of the dens epistropheus

edge of the clivus with invasion into the spinal canal. Investigation using NMR showed a tumor measuring 5.0 × 4.0 × 3.5 cm extending from the dorsal wall all the way into the posterior cranial pit and the spinal canal. Recent bleeding into the tumor was suspected. The medulla was dorsally translocated by 1.5 cm (see Fig. 2a-c).

Surgery was performed on 16 April 1985, involving extirpation of an extended, bumpy tumor with gross hemorrhage via dorsal access. The growth reached from the junction of the vertebral arteries down to C1/C2 and had partially spread extradurally. Parts of the tumor in the direction of the clivus had to be left in place. Following slow postoperative recovery with renewed ability to walk, the remnants of the tumor in the area of the clivus were completely removed transorally in cooperation with an otolaryngologist, using the CUSA device and employing microsurgical techniques. Subsequent recovery of the patient was uneventful. The neurological defects subsided again except for a somewhat broad gait.

*Case 2: Dermoid Cyst*

The patient Helga G. was 44 years old. Since August 1981 the patient had complained of frequent headaches flashing in the direction of the vertex, which could be provoked by movements of the head, e.g., during yoga exercises. While all neurological findings were normal the patient

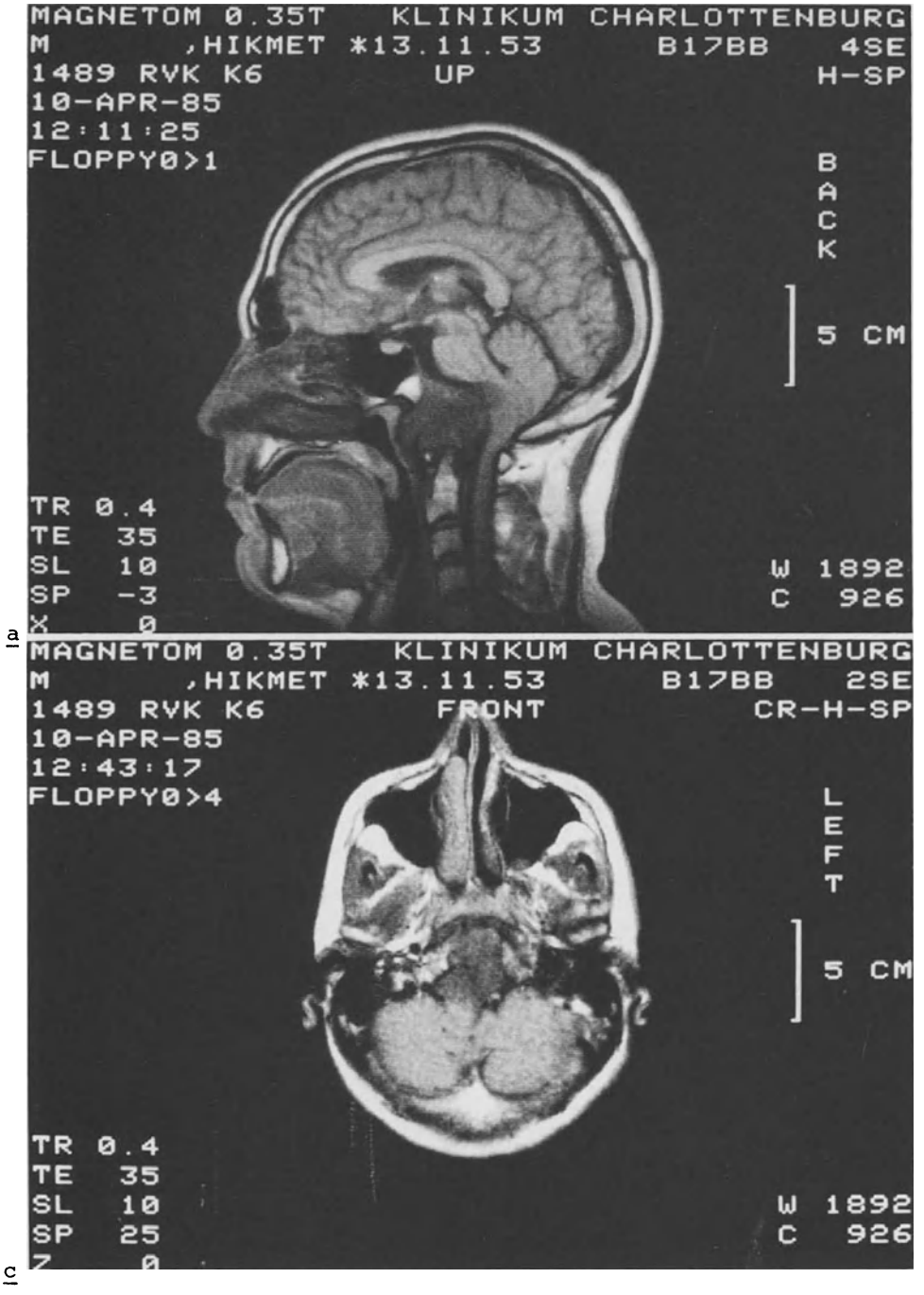
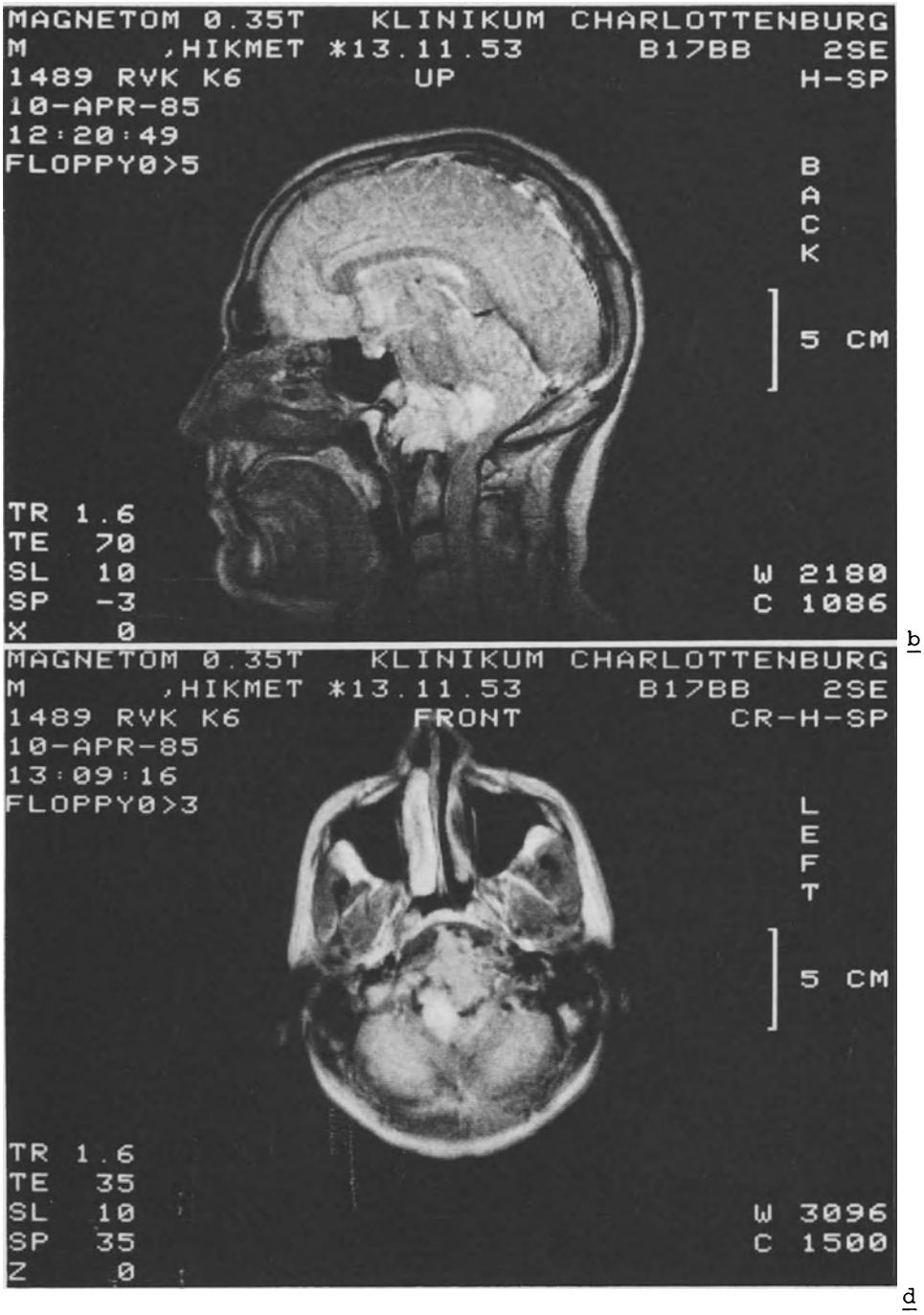



Fig. 2a-d. Tomograms obtained via NMR (tomograms a and c emphasizing T1, tomograms b and d emphasizing T2, mediosagittal and axial sections) of a 31-year-old male with a chordoma of the clivus. In the pictures emphasizing T2 a hemorrhage into the tumor shows particularly strong signal intensity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1489 RVK K6 UP H-SP
10-APR-85
12:20:49
FLOPPY0>5
B
A
C
K
5 CM
TR 1.6
TE 70
SL 10
SP -3
X 0
W 2180
C 1086

b


MAGNETOM 0.35T KLINIKUM CHARLOTTENBURG
M ,HIKMET *13.11.53 B17BB 2SE
1489 RVK K6 FRONT CR-H-SP
10-APR-85
13:09:16
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E
F
T
5 CM
TR 1.6
TE 35
SL 10
SP 35
Z 0
W 3096
C 1500

d

was afraid that a tumor might be present. Consequently CT was performed. Without the use of a contrast medium a highly hyperdense tumor was detected at the craniocervical junction (dorsally) extending until C1/C2.

Surgery was performed on 10 June 1982 and comprised total extirpation of a dermoid cyst measuring 4 × 4 × 6 cm, filled with a dark brown, highly viscous fluid. A suboccipital dermal sinus, connected with the cyst through the occipital bone, was discovered as the point of origin, hardly noticeably superficially. Following the uneventful surgical intervention, provocation of headaches was no longer feasible.

*Case 3: Multiple Hemangioblastomas*

The patient Peter M. was 20 years old. He was hospitalized for severe pain in the neck and the back of the head, left dysmetria, left hypoesthesia from C2 to T3, increasing paraparesis, and crises of excessive brain pressure. Utilizing CT, NMR, and subtraction angiography (involving the right cerebellar hemisphere, the medulla oblongata at the level of the foramen magnum, and the central cervical cord), the presence of multiple hemangioblastomas was demonstrated. Assuming inoperability of the tumors, a valve to relieve high pressure was implanted on 8 September 1984. At the express request of the patient direct surgery was performed on 11 September 1984. A cherry-red nodular tumor in the wall of a cyst with a volume of 30 $cm^2$ in the right cerebellar hemisphere was extirpated, together with a solid nodular tumor the size of an olive from the medulla at the craniocervical junction. Histological examination of the two tumors proved them to be hemangioblastomas. Following surgery transitory weakness of the left m. deltoideus and m. biceps was noted, together with severe impairment of the locating sense in the left arm, inability to stand and to walk, and flash-like dystonic hyperkineses in the left arm. The patient was discharged from the hospital 2 months later with a remaining impairment of the detailed motorics of the left hand, improvement in the locating sense in the left arm, and an insecure gait when walking in the fashion of a tightrope walker, which was even more pronounced with closed eyes. The neurological disturbances subsided gradually subsequently.

*Case 4: Giant Aneurysm of the Vertebral Artery*

The patient Martin Sch. was 55 years old. In November 1983 the patient noted a reduction in the ability to sense temperatures in the right half of his body; later he developed paresthesia in the same area, including the right half of his face. In December 1983 the patient showed hemilateral weakness on the left-hand side which was particularly pronounced in the arm. He was hospitalized with the diagnosis "infarction of the brain stem". CT performed on 9 January 1984 showed an extensive hyperdense focus in the area of the foramen magnum in a projection onto the medulla. Angiography of the vertebral artery yielded no additional clues. NMR performed on 2 February 1984 demonstrated in a mediosagittal section an oval lesion measuring 2.0 × 3.5 cm, exhibiting varying signal intensity in the area of the craniocervical junction ventrally to the extremely compressed medulla oblongata, which was grossly translocated backward, and in the area of the spinal cord in the neck (see Fig. 3). No definite diagnostic hints on the disorder were obtained, but a thrombosed aneurysm was suspected.

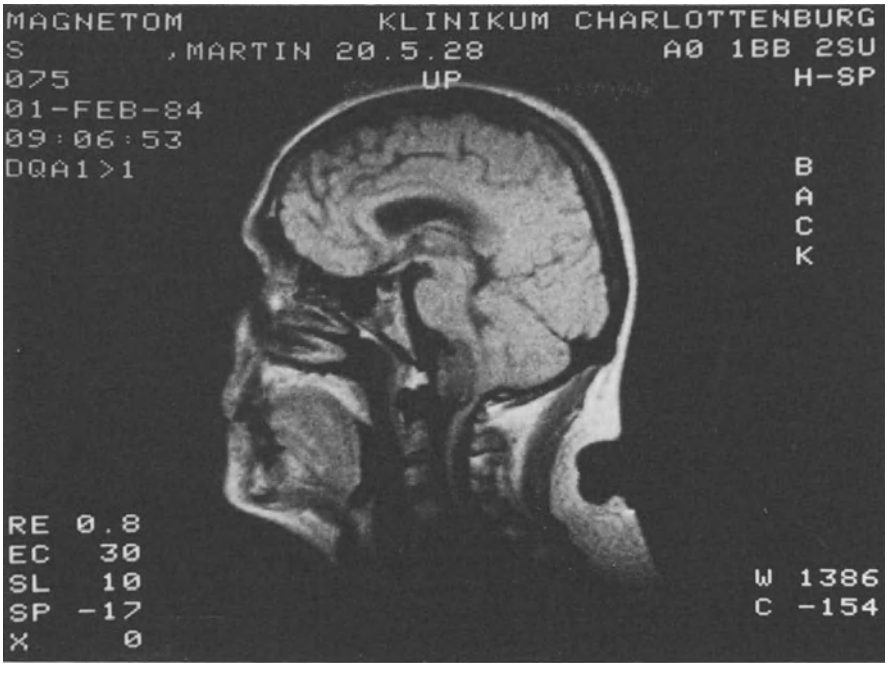


Fig. 3. Tomogram obtained via NMR (T1 emphasized) of a 55-year-old man with giant aneurysm in the area of the foramen magnum (oval area showing low signal intensity). Gross dorsal displacement and compression of the spinal cord in the area of the neck. The entrance and the exit of the blood vessel can be recognized as ribbons not furnishing a signal (black ribbons)

Since the neurological disturbances intensified rapidly and an impairment of the function of the bladder developed, surgical intervention was decided upon (2 February 1984). A thrombosed giant aneurysm of the right vertebral artery located in front of the medulla was removed via microsurgery. The initial artery was closed with clips above and below the malformation of the vessel, since a sufficient collateral supply of blood via the left vertebral artery was available.

Following surgery, a medium degree hemiparesis on the right-hand side persisted, swallowing was impaired, and dysarthria was present. The neurological disturbances manifest before surgery then subsided. Tracheotomy was performed followed by 3 months of intensive therapy. When the patient was finally discharged from the hospital he was able to walk, although a slight hemiparesis persisted on the right-hand side. A slight dysarthria was still noticeable in his speech. Swallowing was not impaired and showed no disturbances.

## Conclusions

Recently developed new imaging procedures such as CT with high resolution and particularly procedures utilizing NMR nowadays permit reliable diagnosis of lesions at the craniocervical junction, which earlier had proved very hard to localize and identify. An indication for such in-

vestigations can be derived from the clinical picture, which, however, is rarely characteristic and unequivocal. Encephalitis disseminata represents the most important disorder to be considered in differential diagnostics. Using a dorsal access, most tumors at the craniocervical junction can be removed without major risks and with preservation of the vital functions of the brain stem, if microsurgery is applied skillfully and if modern supplementary equipment, such as the CUSA device, is available. Some processes, such as a chordoma of the clivus, require combined, bilateral transoral and dorsal intervention.

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# Inclination of the Odontoid Process in Children and Adults - an Anatomical and Functional Investigation

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## Introduction

The odontoid process of the axis is the most peculiar structure of the upper cervical spine. It is the center of the median atlantoaxial joint, which functions as a pivot articulation. The annular articulation, formed by the anterior arch and the transverse ligament of the atlas, is apposed to the anterior and posterior surfaces of the odontoid. The axis of the odontoid process does not generally coincide with that of the body of the second cervical vertebra in adults. Depending on the very individual curve of the cervical column, the odontoid might be straight or inclined dorsally or ventrally (5, 6). The purpose of this paper is to analyze the nature of distortion in the odontoid. This includes measurement and comparison of its degree of inclination both in young children and in adults. X-rays of median-sagittal sections of the odontoid which were made for the study of trabecular structure in adults were functionally interpreted on the basis of density distribution and architecture with respect to the degree of odontoid angulation.

## Material and Method

A simple method was elaborated and adapted to lateral roentgenograms of the second cervical vertebra of young children and adults (Fig. 1), for the purpose of measuring odontoid angulation. The axes of 55 children (age: 0 - 37 months) and 178 adults (age: 36 - 87 years) were isolated. After removal of soft tissues lateral roentgenograms were made. A median-sagittal section (thickness 2 mm) of the vertebral body and the odontoid of the adults was made with a bandsaw. Roentgenograms of these sections were analyzed in detail.

## Results

In babies up to 2 months old, the odontoid process was inclined dorsally (lordotic dens) in all but one case, in which it had a ventral inclination (kyphotic dens). The angle of inclination in the former cases ranged from 4° to 15° (Fig. 2). From 2 to 16 months of age, the degree of dorsal inclination increased steadily. In one case, this dorsal tilt had reached an angle of 28°. At the age of 17 - 37 months the mean value of dorsal inclination was 21.6°.

The adult odontoid process was, with the exception of four cases, inclined dorsally. The angles measured ranged from -3 to 31°, the mean value being 12° (Fig. 3).

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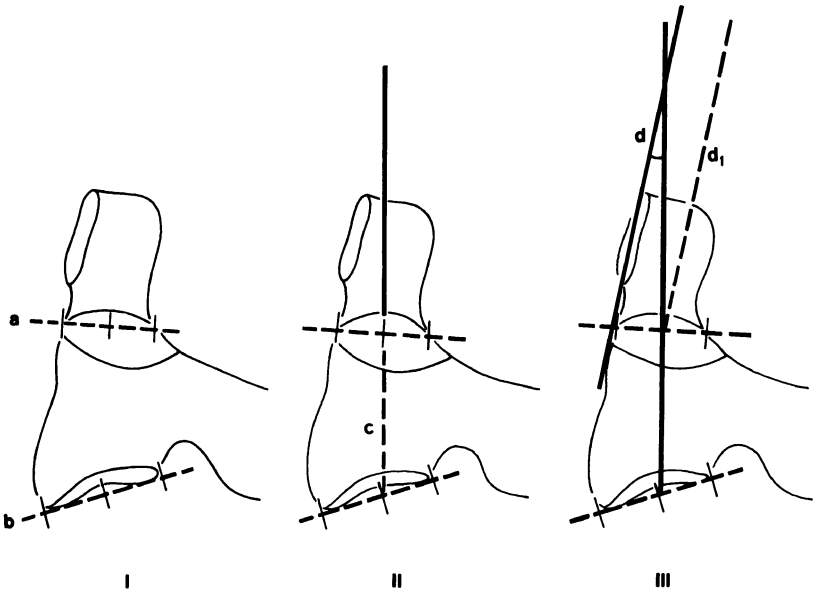


Fig. 1. Schematic illustration of how the inclination of the odontoid process was measured. a, The distance between the anterior and posterior projections of the lateral facet onto the base of the odontoid is halved. b, Division of the distance between the anterior and posterior edge of the base of $C_2$ into two equal distances. c, A straight line $c$ is drawn through the midpoints of $a$ and $b$. d, The tangent to the anterior facet of the odontoid crosses the line $c$, forming the angle of inclination. The axis $d_1$ of the odontoid is parallel to this tangent

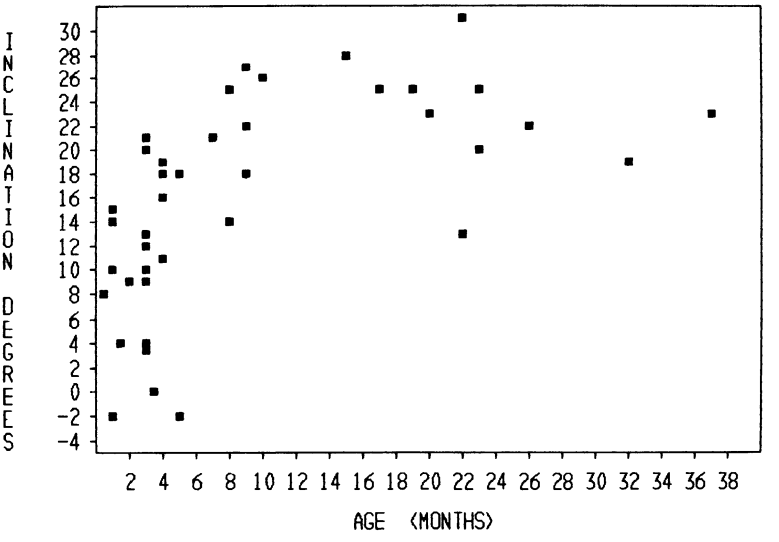


Fig. 2. Inclination of the odontoid process in children at the age of 0-37 months

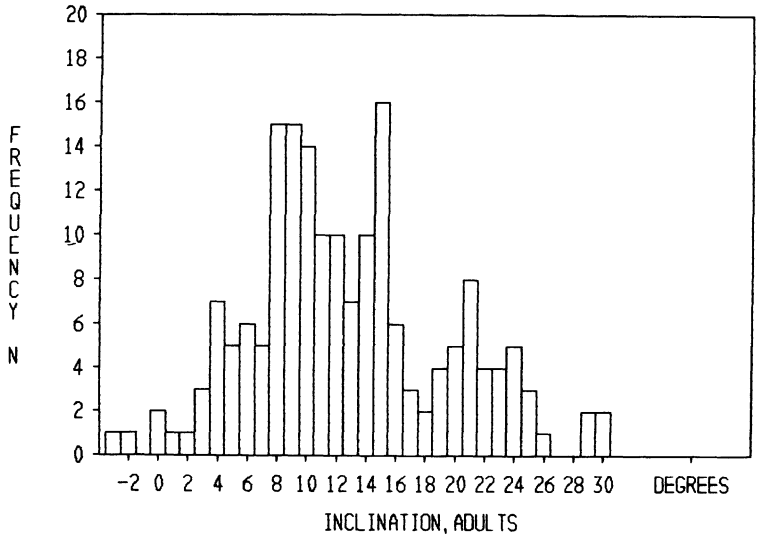


Fig. 3. Inclination of the odontoid process in adults

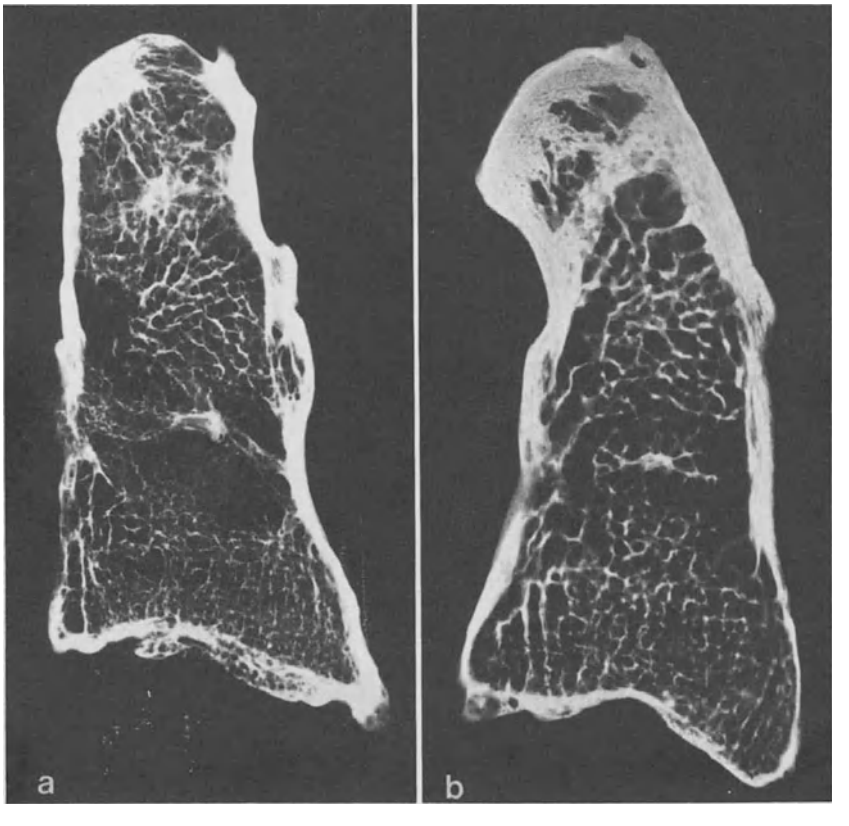


Fig. 4a,b. Roentgenograms of midsagittal sections of a nearly straight (a, dorsal inclination 7°, 75 ♀) and a lordotic (b, inclination 25°, 73 ♀) odontoid

## Discussion

The adult spine has characteristic curves in the sagittal plane. The thoracic and pelvic curves are termed primary curves because they are present during fetal development. The cervical and lumbar curves are compensatory or secondary, and are developed postnatally (3). The varying sagittal position of the odontoid process in young children of the age group studied seems to be closely correlated with the development of the cervical lordotic curve. The odontoid starts to incline dorsally, from its original nearly vertical position, as soon as the child is able to hold its head up (between the ages of 2 and 4 months), and to sit upright (at about 9 months). When the child begins to walk (at 12 - 18 months), the lordotic inclination of the odontoid is accentuated, as is the cervical curvature. Up to the age of 37 months, a consolidation of the lordotic inclination can be registered with a reduced mean value of 21.6°. The most significant finding in adults is that there is a mean angulation of only 12°. This may indicate a decreasing cervical lordosis with age, an observation which was mentioned by FICK (2) and DREXLER (1).

The odontoid process' posterior angulation is of special functional interest in flexion and extension of the upper cervical points. LEWIT and KRAUSOVA (7) have demonstrated the anteroposterior tilting of the atlas during flexion and extension. Inclination of the odontoid will aid and supplement this tilting movement; this is because the anterior arch of the atlas is able to slide more extensively on the ventral facet of a dorsally angulated odontoid. If, however, the odontoid has an excessive dorsal inclination, it may reduce the anteroposterior diameter of the spinal canal when the head is extended under compression (8). The distribution of bone tissue and the internal architecture of the odontoid process are well adapted to specific mechanical stress (4), e.g., the trabeculae of the nearly straight odontoid (Fig. 4a) run horizontally, uniting the two articular facets, which are situated nearly at the same height. In the center of the odontoid there is a dense bony core. The trabecula in the lordotic odontoid (Fig. 4b) form a bundle which arises from the ventral articular facet. This bundle curves downward and crosses over to the opposite side. A second, less distinct bundle intersects the first at a right angle. In the lordotic odontoid the groove-like posterior articular facet is generally located posterocaudally to the anterior articular facet.

These results lead to the conclusion that the nearly straight odontoid process is subjected to axial compression stresses, which are transmitted by the two articular facets located at the same height. The dorsally inclined odontoid, however, shows a trabecular pattern which is characteristic where bending stress is found.

## Conclusion

The odontoid process of the axis shows an increasing dorsal angulation in the developing infant. This phenomenon is considered to correlate with the functionally dependent establishment of the cervical lordotic curvature. During one period in the development of the odontoid, an exaggerated dorsal inclincation has been observed.

A variety of trabecular systems which correlate with the varying position of the articular facets on the odontoid and with its varying angle of dorsal inclination can be observed.

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# Cytostatic Treatment of Spinal Tumors

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## Introduction

Recent statistical reviews have revealed that the number of brain and spinal metastases is increasing, even in cases of autochthonic tumors of the brain and spinal cord in neurosurgical specimens (1, 2, 9). This raises the question as to what significance, alongside surgical and radiological therapy, cytostatic treatment may have in the interdisciplinary treatment strategy for primary and secondary spinal tumors.

## Problems in Cytostatic Treatment of Spinal Tumors

1. Spinal tumors are rare. It is therefore especially difficult to obtain a large number of treatment statistics relating to one group of tumors.

2. Spinal tumors are almost always discovered relatively late, mostly when they are over 1 cm in diameter and causing neurological disorders. This equates to a tumor size of $10^{10} - 10^{11}$ cells. This high cell number renders it less likely that cytostatic treatment will provide a cure.

3. A problem in the cytostatic treatment of brain tumors and autochthonic spinal tumors is tumor genetics. These tumors have a very low proportion of tumor cells in the DNA synthesis phase; rather they are almost all in the $G_0$ phase. This means that cytostatic drugs whose main mechanism of action is at the DNA synthesis phase – and these are the majority of those we know of – are of no use.

4. Just as important as the mode of action of the cytostatic in the cell cycle is the fact that the cytostatic must be transported to its place of action and then also act for a certain length of time. Most of the cytostatics used in oncology pass the blood-brain barrier only with difficulty. Systemic application using common dosages will therefore cause little or no level of reaction at the site of the tumor. How is it then possible to increase the cytostatic level at the tumor among patients with brain and spinal tumors? Several ways of increasing dosages which result in additional toxic side effects are conceivable and of consequence for the future:

a) Application of high dosages of methotrexate with subsequent application of a folic acid antagonist. This plays a role in the treatment of meningiosis leucaemica, intracerebral lymphomas, and brain tumors (8). There have as yet been no published reports of this regimen in the treatment of spinal tumors.

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b) Direct application of methotrexate or another cytostatic intrathecally, that is, bypassing the blood-brain barrier. An increase in the cytostatic dosage in the spinal fluid is thereby possible. For intramedullary tumors this method is, however, of no essential importance (7).

c) Application of excessively high amounts of cytostatic and subsequent transplantation of previously obtained autologous bone marrow. The very high technical expenditure and the risk involved during the aplastic phase seem to result in only very slight median prolongation of survival (3.5 to maximally 7 months) after bone marrow transplant (3).

d) Reversible alteration of the blood-brain barrier by use of physical or chemical means. NEUWELT (4) using mannitol infusions, was able to modify the blood-brain barrier experimentally and clinically. In a latest study from 1984 he described three cases in which this method was employed in subsequent combination with cytostatics. The diseases in these three cases were a central glioma, a metastasizing breast cancer with brain metastases, and a central lymphoma. The survival chances are very slight so that these results must be evaluated very critically. Results concerning spinal tumors are hitherto not known.

e) New cytostatics with increased lipophilic activity and thus an ability to pass the blood-brain barrier more easily. Unfortunately such drugs are difficult to develop. In spite of the large number of new cytostatics developed each year, only a fraction attain clinical relevance so that no breakthrough is to be expected in the near future.

## Present State of Cytostatic Therapy for Autochthonic Spinal Tumors

The most common spinal tumors are the meningiomas and neurinomas, and these are still a domain of the neurosurgeon. Cytostatic therapy is of no consequence (8, 9).

Only among medulloblastomas does chemotherapy have a definite place in the strategy of treatment. With spinal medulloblastomas this is usually a case of contact metastases. For these relatively rare tumors, current treatment protocols involve the cytostatic vincristine, CCNU, and methotrexate, intrathecally applied and in special sequential dosages. These are the most often used cytostatics, and they are applied postoperatively and/or as adjuvant therapy after operation and radiation (8).

For astrocytomas, glioblastomas, ependymomas, and the remaining rare malignant tumors of the spinal cord, cytostatic treatment does not play any special role. Those results reported pertain to tumors in the brain area. Successful cytostatic treatment of spinal gliomas has only been registered in isolated cases and reports have revealed rather discrepant results. Cytostatic therapy in these cases is still at an experimental stage. The real value of cytostatic treatment of these tumors can only be verified by larger cooperative studies (6, 8).

## Cytostatic Treatment of Metastatic Processes in the Spinal Cord

The situation concerning metastatic processes in the region of the spinal cord is a different story. Whether the metastases are located intradurally, extradurally, intramedullary, or extramedullary plays an important role. For these types of tumor an oncologist should be

consulted when planning treatment since this is usually complex and the primary tumor in most cases also has to be treated. According to statistical reviews (9) 43.1% of all spinal tumors are caused by metastases. Bronchial carcinomas, breast carcinomas, thyroid carcinomas, prostatic carcinomas, osteogenic and soft tissue sarcomas, hypernephromas, and systemic diseases such as Hodgkin and non-Hodgkin lymphomas and plasmacytomas are therefore of prime importance. Other, rare tumors can, however, also give rise to metastases in the spinal cord. As far as spinal metastases from solid tumors are concerned, it is safe to assume that the metastases will respond to systemic cytostatic treatment only when the primary tumor and its metastases also do so. It is known that among solid tumors breast, small-cell bronchial, ovarian, and prostatic carcinomas and among sarcomas osteogenic and soft tissue sarcomas basically respond well to cytostatic treatment. There is, however, a whole series of solid tumors on which systemic cytostatic treatment has practically no effect, and systemic therapy for the occurrence of metastases also fails. Here may be noted colonic carcinomas, hypernephromas, hepatic carcinomas, pancreatic carcinomas, bile duct carcinomas, and also the non-small-cell bronchial carcinomas.

By contrast, for systemic disorders such as leukemias, lymphomas, and plasmacytomas there exist cytostatic combinations with which good to very good and long-term remissions can be achieved, even in advanced stages. In such cases it is necessary, depending on the tumor size and extent of spread in the spinal region, to consider cytostatic treatment when planning treatment. In some cases it can prove very useful to consider cytostatic treatment prior to surgery or irradiation. Three paraspinal tumors (histologically defined as an osteogenic sarcoma, Ewing sarcoma, and an embryonic rhabdomyosarcoma) successfully treated with preoperative cytostatics were described by SUNDRESAN (7) in 1983: Because of the large and extended tumor mass, all three patients were treated primarily with cytostatics and then later operated on and subjected to radiation. For many years they have been "disease free".

## Summary

Cytostatic treatment of primary tumors, excepting contact metastases of medulloblastomas, is a form of therapy which is still at an experimental stage. General directions for cytostatic therapy of astrocytomas, gliomas, ependymomas, and other serious spinal tumors cannot be provided by the oncologist.

The therapeutic procedure for treatment of metastatic processes in the spinal region – whether they are caused by metastases of a solid tumor, a sarcoma, or a systemic disease – should definitely be discussed in an interdisciplinary manner by the surgeons, radiologists and oncologists involved. In some cases chemotherapy can, despite the many side reactions, prove successful, and it thereby has a place, however modest, in the palliative interdisciplinary treatment of spinal tumors.

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# Malignant Lymphomas and Spinal Cord Compression

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## Introduction

Extradural compression of the spinal cord is the most frequent neurological complication of malignant lymphomas (10). It also occurs in other hematoblastomas and can cause a rapidly progressive neurological deficit. Although these tumors are mostly radiosensitive (8, 9) and chemotherapy has made remarkable progress (2, 6, 7, 10, 13), surgical excision often remains absolutely necessary. Probably nowhere is palliation more justified than in malignant spinal cord compression, in order to relieve intolerable pain and to avert the catastrophic consequence of threatening paraplegia (12).

The aim of this retrospective study in cooperation with hematologists and neurosurgeons is to demonstrate the possibilities as well as the limits of combined surgical and conservative treatment.

## Clinical Material and Methods

Between 1973 and 1984 we operated on 44 patients with spinal cord compression due to malignant hematoblastomas. This represents about 17% of all patients operated on by us for malignant epidural tumors. The sex distribution was 1:1, with an average age of 54 years (19 - 77).

In 61% of our patients the disease was diagnosed before the occurrence of neurologic deficit; in 39% the spinal involvement was the initial manifestation, and in some cases it was the sole manifestation.

### *Clinical Features*

Local pain – sometimes radiating over the dermatome level – was almost invariably the first complaint, occurring months before spinal cord or cauda equina compression (1, 3, 10). The subsequent course was rapid, many patients losing ambulatory function within days. On neurosurgical admission 66% of the patients were unable to walk, whereas the average duration of motor deficiency was only 4.8 days (and less than 24 h in three patients). In one patient complete paraplegia followed a lumbar puncture (3, 4, 5).

### *Diagnostic Investigations*

On admission emergency myelography was carried out, through lumbar puncture in the event of simple lumbar symptoms or through descending

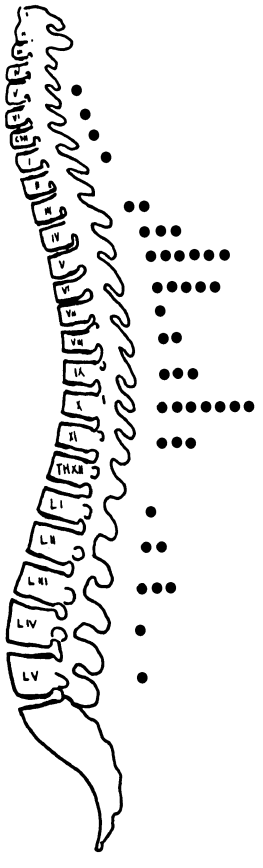

Fig. 1. Localization of spinal cord compression in 44 patients

myelography when signs of spinal cord compression were present (5), in order to avoid spinal impaction. The most common localization was the thoracic spine, followed by the lumbar and cervical regions (Fig. 1).

Space-occupying lesions in the cervical and thoracic area were seen as a complete block; however, in the lumbar region they sometimes caused incomplete obstruction. To enable prompt surgery, further preoperative diagnosis (tomography, osteoscintigraphy, sternal puncture, etc.) was only done in exceptional cases.

*Treatment*

Of all patients, 54% (62% with complete myelographic block) were operated on within hours of admission (5). In each case a dorsal decompressive laminectomy was carried out. In only four patients was a total removal possible (simple epidural spreading (11). In two other patients anterior vertebral body extirpation with spinal stabilization was performed in a second session.

Histological findings showed 15 Hodgkin's lymphomas, 13 non-Hodgkin's lymphomas, 13 plasmacytomas, and 3 leukemias. Depending upon the histological findings and the preoperative therapy, almost all patients then received chemo- and/or radiotherapy.

Table 1. Summary of early results

| After 10 days | | After 6 months | |
|---|---|---|---|
| Considerable improvement | 73% | Good | 52% |
| | | Deteriorated | 5% |
| | | Dead | 16% |
| Unchanged | 11% | | |
| Deteriorated | 16% | | |

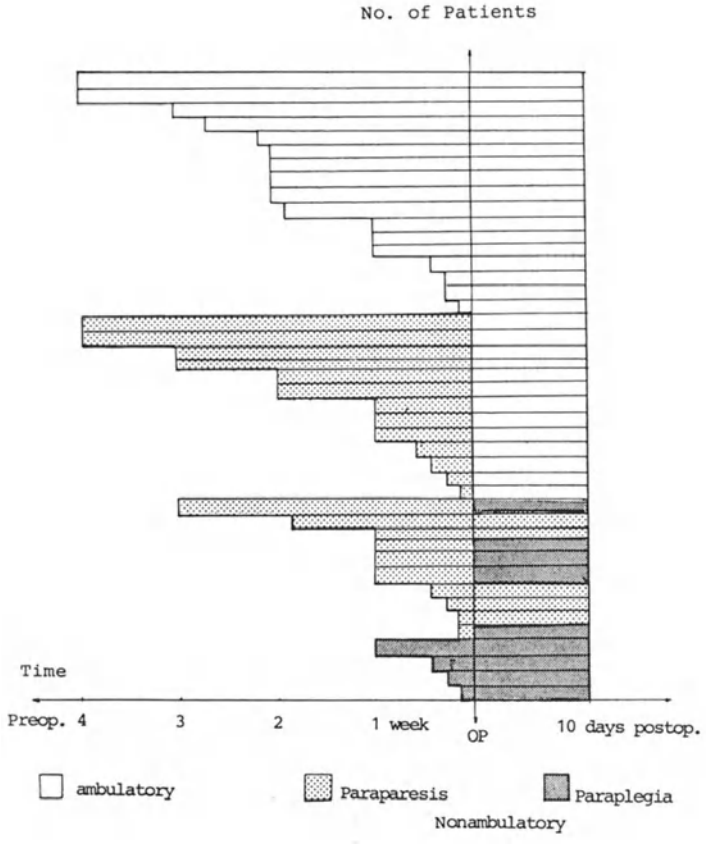


Fig. 2. Early results of ambulatory function correlated to the duration and extent of preoperative neurological deficit

## Results

Ten days after the operation surgical results were compiled and divided into three groups (Table 1). Thirty-two patients (73%) had a considerable improvement of their neurological deficits; five (11%) were unchanged; and seven (16%) had deteriorated further despite surgery. During the first posoperative week 41% regained ambulatory function (Fig. 2), and altogether 75% were able to walk.

Table 2. Postoperative complications[a]

| | | |
|---|---|---|
| Epidural hemorrhage | 3 | |
| Wound infection (sepsis) | 2 | (2) |
| Myelomalacia | 1 | |
| Pulmonary embolism | 2 | (2) |
| Pneumonia | 1 | (1) |

[a]Numbers in parentheses represent deaths

Table 3. Correlation of histological findings with survival rates

| | No. of patients | Survival rate (months; median) |
|---|---|---|
| Hodgkin's lymphoma | 15 | 46 |
| Non-Hodgkin's lymphoma | 13 | 10 |
| Plasmacytoma | 13 | 16 |
| Acute myelocytic leukemia | 1 | 6 |
| Chronic myelocytic leukemia | 2 | 1.5 |
| | 44 | 26.3 |

While there was no intraoperative mortality, we had many postoperative complications (Table 2), in fact the highest rate of complication as far as all spinal surgical interventions are concerned. We had to re-operate on three patients because of epidural hemorrhage; nonetheless all became paraplegic. In one patient myelomalacia developed on the third postoperative day and caused irreversible paraplegia. Three patients had wound infections, two of which ended after weeks in lethal sepsis. Finally, four paraplegics had severe pulmonary complications (pulmonary embolism and pneumonia), three of them dying within the first month.

In our long-term results only 37 of the 44 patients could be taken into consideration. Six months postoperatively 62% were still alive; but after two years only 35%. Altogether 8 patients (18%) are still alive, in six cases more than 6 years postoperatively. The median survival time is 26.3 months and is very dependent on the histological findings. Hodgkin's lymphoma has the best prognosis, at 46 months (Table 3).

## Discussion

The best treatment of spinal cord compression due to malignant lymphomas has not been definitively established (2, 6, 7, 13). No doubt the progress in chemo- and radiotherapy has diminished the role of surgery (2, 9). We regarded surgery as indicated in cases of unknown histology (39%), in patients with neurological deficits who failed primary conservative treatment (43%), and when there was extremely rapid progression of paralysis (18%).

Acute deterioration of malignant spinal space-occupying lesions occurs through vertebral body collapse with direct pressure on the medulla or

through compression of the vascular supply to the cord. Hemodynamic disorders in connection with venous insufficiency are usually irreversible. Prompt neurosurgical intervention therefore can be essential in preventing this pathomechanism (3, 5, 12), even when the patient is in a poor condition.

Our results show that the main danger is not the surgery itself but the high rate of postoperative complications, brought about by the impaired body defense system and the week-long bed confinement. Although improvement of paraplegia has been reported following decompression or radiotherapy (9, 11), it is our experience that no significant recovery can be expected. The functional restitution depends on the extent and duration of neurological symptoms. Further progress of the disease is not so much determined by radical surgery as by the postoperative response to chemo- and radiotherapy.

## Conclusions

1. In 39% the extradural spinal spreading was the first manifestation of the hematoblastoma.

2. Most of our patients showed neurological deterioration in spite of conservative therapy, thus requiring neurosurgery.

3. Our favorable immediate postoperative results (49% ambulatory improvement) were partly offset by rapid progression of the hematoblastomas.

4. The best survival rates were obtained in cases of Hodgkin's lymphoma, followed by plasmacytoma, non-Hodgkin's lymphoma, and leukemia. Our longest survival at this time is 12 years.

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# Aspects of Neurosurgical Intervention for Spinal Manifestations of Malignant Lymphomas

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## Introduction

Lymphatic diseases play an important role in tumor statistics. According to De VITA (4), 30 000 patients suffering from a disease of the lymphatic system were reported in the U.S.A. in 1980. In talking about lymphomas, Hodgkin lymphoma stage I-IV has to be differentiated from non-Hodgkin lymphoma with a lower or higher degree of malignancy and from chronic lymphatic leukemia. According to the latest literature spinal lymphatic manifestations are seen in 3% - 8% (3, 5, 8). Neurologic deficits are observed when one of the following pathogenetic factors is present:

1. A mechanical factor, e.g., compression of nervous tissue
2. A hemodynamic factor, e.g., circulatory disturbance
3. An inflammatory factor, e.g., radiculitis, myelitis

## Material

Of 428 patients with malignant lymphoma, 7% showed spinal manifestations. Neurosurgical intervention was necessary in ten patients (2.3%). Previously three of the ten patients had undergone radiotherapy, two chemotherapy, and five combined radio- and chemotherapy.

## Results

At the time of operation the patients had a history of lymphatic disease lasting on average 2 1/2 years. Neurologic signs and symptoms occurred on average 14.5 days preoperatively. In one case neurologic deficits which might have been due to an inflammatory lesion had been known for 3 years.

The segmental localization of malignant lymphomas was compared with that of the benign and malignant spinal tumors. The thoracic segments are the site of predilection for spinal lymphomas (Fig. 1). Follow-up of patients with radicular symptoms or incomplete paralysis revealed the following results: After 4 weeks five patients were found to be in the stage of recovery, and three did not show a positive or negative alteration in the course of their disease. After 1 year three patients had completely recovered, two patients showed neither progress of the disease nor any recovery, and one patient had died because of generalized metastasis. Two patients with a history of complete paralysis of a few hours' duration died within 4 weeks of their underlying disease.

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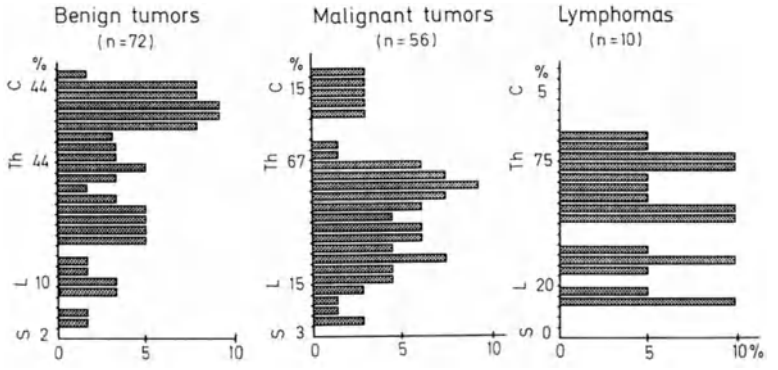


Fig. 1. Segmental distribution of spinal tumors ($n$ = 138)

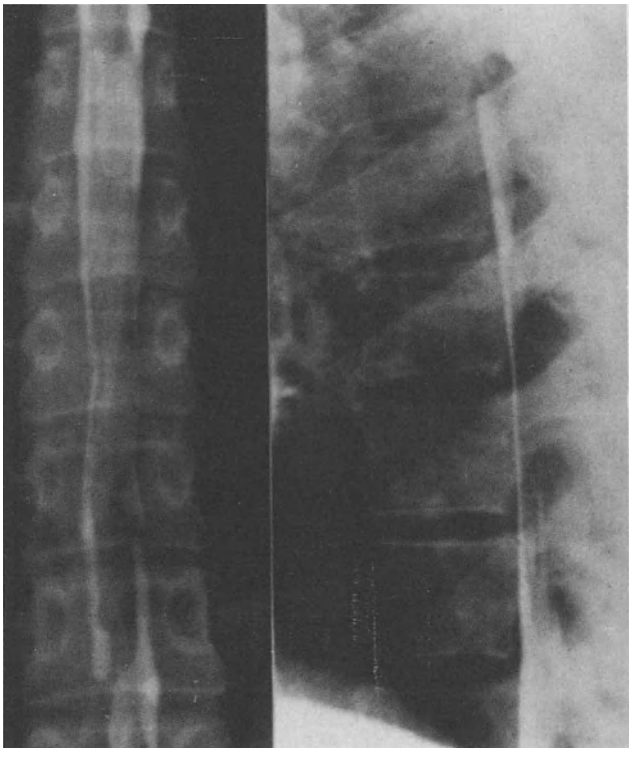

Fig. 2. Female, 30 years old, with Hodgkin disease. Epidural tumor growth in the lower thoracic spinal canal with dorsal compression of the dural sac

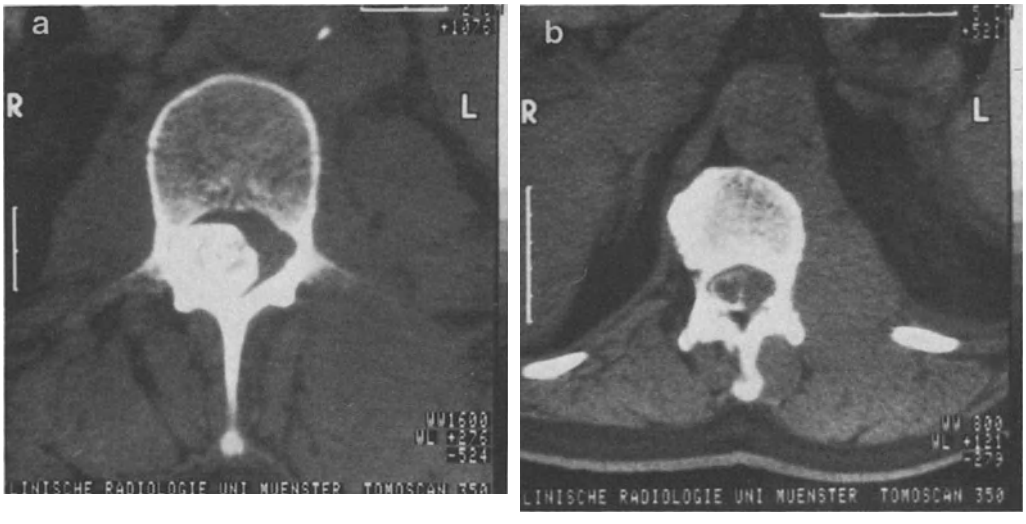


Fig. 3a,b. Male, 76 years old, with non-Hodgkin lymphoma. Postmyelography CT of the thoraco-lumbar spine. Extensive left paraspinal tumoral growth with infiltration of the muscles and invasion of the spinal canal from L2 (a) to D11 (b)

In all patients undergoing neurosurgery the spinal lymphomas were located in the epidural space (Figs. 2, 3). Six out of ten patients had bone manifestations. The procedure of choice was a laminectomy with radical removal of the tumor. Up to now we have not seen any new tumor growth in any of the operated patients.

## Conclusions

According to the literature (6, 7), the treatment of choice for spinal metastasis of lymphomas is primary radiotherapy, which is limited by the tolerance dose of the spinal cord. Therefore if patients who have undergone primary radiotherapy for lymphomas do manifest signs and symptoms of spinal metastasis, early surgical intervention is indicated.

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# Clinical and Neuropathological Aspects of Rare Semimalignant Spinal Tumors: Case Reports of a Giant Cell Tumor (Osteoclastoma) and an Atypical Osteoblastoma

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Among a variety of vertebral tumors that can damage the spinal cord and nerve roots by compression and/or infiltration, the group of primary bone tumors is very small. Between 1977 and 1984, 231 patients underwent operations for spinal tumors in our clinic, of whom only 3% had primary bone tumors.

We present two such unusual cases with semimalignant features which were classified between the benign bone tumors (osteoblastomas, osteochondromas) and the malignant osteosarcomas. These tumors caused special diagnostic and therapeutic difficulties.

## Case 1

The first case is that of a 15-year-old boy who suffered from a bone-destroying lesion of the lumbar vertebral body L5 (Fig. 1A). A biopsy taken from this lesion showed a cell-rich, pleomorphic tumor consisting of polygonal and spindle-shaped cells. The predominant feature of the tumor was multinucleated cells with up to 40 - 50 nuclei of equal structure as the stromal cells (Fig. 1B). Mitotic activity was moderate. There was no osteoid formation. Hemosiderin deposition could be seen. There were abundant reticulin fibers and collagen. No regressive changes could be seen.

Diagnosis of semimalignant osteoclastoma of the bone was made, which was confirmed by a bone tumor register (Prof. GRUNDMANN, Knochengeschwulstregister Nord-Rhein-Westfalen). Two months later a second operation with bony replacement of the fifth lumbar vertebra was performed. Histology showed the same features as in the first operation, and in addition extensive infiltration of spinal ganglia, nerve roots, and soft tissue. The patient died soon after the operation of circulatory complications.

## Case 2

The second case is that of a 22-year-old man who had suffered from a slowly progressive spastic tetraparesis from the age of 15. Myelography revealed an incomplete block at the cervical level C6/7. Laminectomy was performed and a tumor, destroying the right arch of C6, could be partially removed. Histological diagnosis was that of an osteoblastic osteosarcoma (Prof. GERHARD, Neuropathologie, Universität Gesamthochschule Essen), which was confirmed by a bone tumor reference center (Prof. Dahlin, Mayo Clinic, USA). One year later the first recurrence occurred with destruction of the arches C5/6 as well as the vertebral

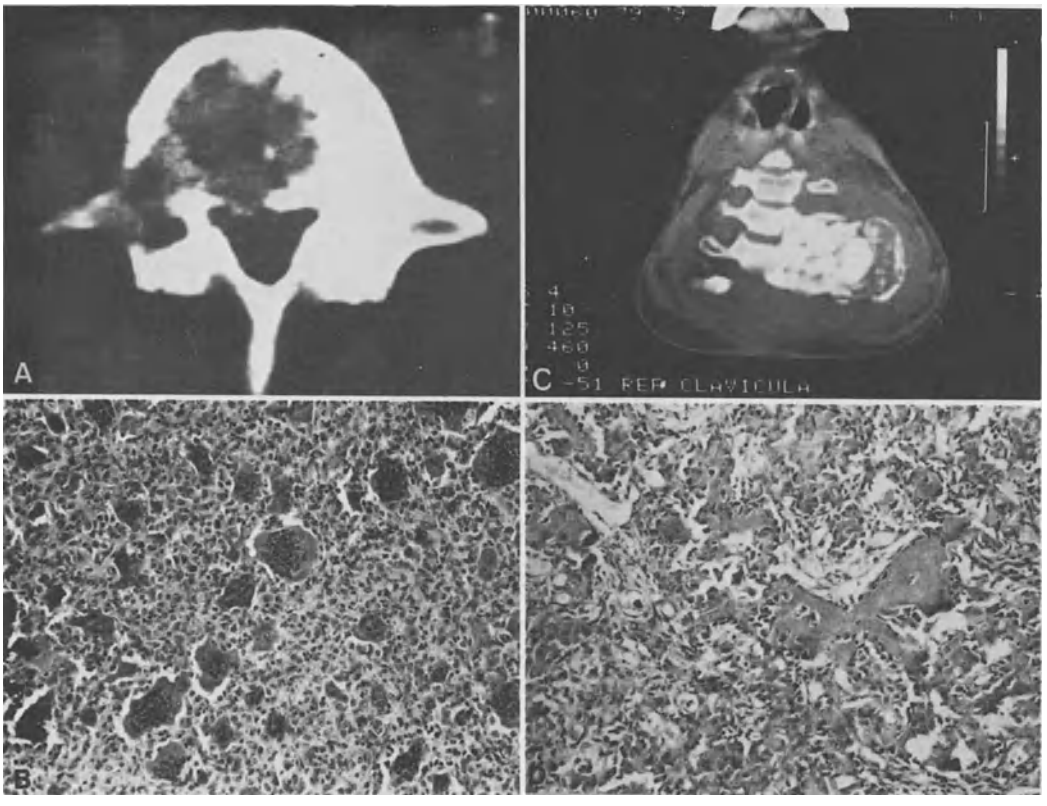


Fig. 1A-D. *Case 1:* Computed tomography of L5 showing extensive destruction of body, lamina, and transverse processus by osteoclastic tumor (A). Osteoclastoma with abundant multinucleated giant cells (B). *Case 2:* Computed tomography of cervical spinal column showing a large second recurrence of calcified mass with extension into soft tissue (C). Histopathology of a semimalignant proliferating osteoblastoma with numerous osteoblasts and osteoid formation (D)

body C6 and extension into the soft tissue of the neck. Due to the invasive nature we thought this tumor to be consistent with the first recurrence of an osteoblastic osteosarcoma. Two years after the onset of symptoms a third operation was performed. Due to widespread infiltration of the soft tissue (Fig. 1C), the posterior mediastinum, and the upper thoracic aperture, radical surgery was again impossible. Histologically a cell-rich tumor with different cell populations consisting predominantly of spindle cells was found. Primitive osteoid formation by numerous osteoblastic cells was present (Fig. 1D), as was an intense osteoclastic reaction by polynuclear giant cells. Mitotic activity was moderate to high. No regressive changes could be detected. Histological diagnosis was difficult. Due to the numerous osteoclastic cells and the abundant osteoblastic activity the diagnosis of proliferating (semimalignant) osteoblastoma was made by another bone tumor reference center (Prof. UEHLINGER, Zürich). A third recurrence occurred 2 years later. The histological picture had not changed. There were no metastases either by lymphogenic or by hematogenic spread. Tetraparesis slowly progressed and the patient died of subacute ileus 5 years after the first symptoms.

## Discussion

Both from a pathological and a clinical viewpoint these very rare bone tumors arising in the spinal column cause considerable difficulties in terms of differential diagnosis, classification, grading, and therapy.

Osteoclastomas are rare primary bone tumors that affect the major tubular bones in more than 70% of all cases (7). Although several cases of uncommon localization have been reported (1, 4, 20, 21), this tumor is rarely encountered by the neurosurgeon. In cases of involvement of the spine the lumbar area seems to be slightly more commonly affected than cervical or thoracic areas (8, 12, 23). The preferential age group is the second or third decade. The therapeutic results after radical excision and autogenous bone grafts are not bad (23). If radical excision and anterior or posterior arthrodesis cannot be achieved, local excision and radiation therapy seems to be of value. Among the 31 patients of DAHLIN (8), 15 survived more than 5 years (the follow-up was up to 17.5 years after operation). Some histologically diagnosed osteoclastomas have been treated by radiotherapy alone (8, 13). In smaller lesions there seems to be some effect, so that this kind of treatment should be applied if major surgical procedures are unsuitable.

Our second case is extremely unusual in terms of both the clinical course and the histomorphological features. Among the primary bone tumors of the spine, osteoblastoma (benign osteoblastoma) is a common, vascular osteoid and bone-forming tumor containing numerous benign-appearing osteoblasts (17). By contrast, osteosarcoma is extremely rarely encountered in the vertebral column, the only cases being described arising from transformed bones on the basis of PAGET's diseases of bone (2). In our second case the diagnosis of the primary tumor and the first recurrence was that of an atypical osteoblastic osteosarcoma, mainly due to the moderate mitotic activity, the hyperchromaticity, and the bizarre appearance of some osteoblasts around and within the osteoid and bone. From a clinical point of view, this tumor did not metastasize and recurred four times at the same site, which is suggestive of a rather semimalignant tumor. In addition, numerous multinucleated giant cells, typical osteoclasts, were seen, a feature which one would not expect in osteosarcoma. The pattern of osteoid formation showed areas of higher differentiation, as in classical osteoblastomas. These are the reasons for classifying this unusual tumor as "proliferating osteoblastoma". It has to be emphasized, however, that this diagnosis does not meet the widely accepted classification of the Armed Forces Institute of Pathology (25) or other bone tumor classifications. Only three other cases have been published showing local recurrence or malignant degeneration of a documented benign osteoblastoma (17, 18, 19), and all three were in sites other than the spine.

We think it justified to draw attention to these very rare, semimalignant primary bone tumors of the spine, which do not metastasize but instead tend to recur locally, hence having a rather doubtful prognosis. Close collaboration between surgeons, oncologists, and pathologists is required to monitor the biological development of these tumors and to apply the most adequate therapy.

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# Experimental Neurosurgery

# Microsurgical Anatomy of the Transoral Approach for Anterior Processes of the Upper Cervical Spine

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The main problem in surgical treatment of ventral processes of the upper cervical spine is the operative access. The transoral approach (TOA) allows direct exploration of this region (1, 2, 3, 8, 9, 13) and has been used for particular malformations of the atlanto-occipital junction (2, 11), for atlanto-axial dislocations (10), and for epidural lesions (8, 10). The aim of this anatomical study is to investigate the possibilities and limits of the TOA for extra- and intradural operations in the cervical region.

## Material and Methods

The study was carried out in ten cadavers (six female, four male) without pathological alterations of the cervical spine. In five unfixed specimens the vertebral artery was exposed bilaterally in the lateral cervical trigone and injected with 5 - 15 ml of dye (Epoxydred). The preparation was performed in the operative position using microtechniques. The prevertebral soft tissue was dissected layer by layer according to FRANKE and CLARISSE (4). After diskectomy of C2/3 and exposure of the posterior longitudinal ligament, a spondylectomy of C1-C3 was performed using a microdrill. The approach was enlarged cephalad by a vertical incision of the soft palate and a window of 20 × 20 mm was cut in the clivus above the tuberculum pharyngeum according to KUHN (7). The dura was incised longitudinally between C1 and C3 and Y-shaped behind the clivus. In every specimen the distances between the surgically important landmarks were measured and documented by photographs.

## Results and Discussion

Relevant distances are summarized in Tables 1 and 2. As a rule the TOA allows the exploration of the cervical spine from C1 to the upper half of C3 without splitting of the soft palate. The intervertebral disk C3/C4 and the upper part of C4 could be removed transorally only in two of the ten specimens. Due to the above-mentioned anatomical limits, sagittal tomography through the open mouth with hyperextension of the neck is mandatory for planning the operative approach. The extent of the operative field between C1 and the middle of C3 measures 36 - 44 mm (M: 40). The width of the bony window depends on the level, the minimum values always being measured at the C1 level (10 mm). As the mean working distance during the operation is 12.2 cm, a 320-mm objective and bayonet-shaped instruments of at least 20 cm length are required. The landmark of the TOA during the operation is the anterior tubercle of the atlas (TA), which can be palpated easily above the retrolingual region.

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Table 1. Relevant distances of the TOA to the upper cervical spine (mm) in ten specimens

| N | LL | TA/LL | WOF | DOF | | | | | D | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C1 | C2 | C3 | C1 | C2 | C3 | C1 | C2 | C3 |
| 1 | C4 | 44 | 11 | 13 | 12.5 | 98 | 102 | 107 | 6.5 | 21 | 18 |
| 2 | C3 | 36 | 7 | 11 | 11 | 91 | 96 | 99 | 6 | 19 | 17.5 |
| 3 | C3 | 37 | 10 | 12.5 | 13 | 94 | 98 | 102 | 7 | 19.5 | 18 |
| 4 | C3 | 41 | 9 | 11 | 12.5 | 93 | 99 | 100 | 6 | 22 | 16.5 |
| 5 | C3 | 39 | 8 | 12 | 12.5 | 101 | 104 | 109 | 5.5 | 21 | 17 |
| 6 | C3 | 37 | 8 | 11.5 | 12 | 99 | 103 | 107 | 6.5 | 22.5 | 17 |
| 7 | C4 | 44 | 10 | 12.5 | 12.5 | 94 | 99 | 104 | 5 | 19.5 | 17.5 |
| 8 | C3 | 42 | 11 | 12 | 11.5 | 93 | 98 | 105 | 6.5 | 19 | 18 |
| 9 | C3 | 39 | 10 | 11.5 | 12 | 97 | 102 | 104 | 7 | 20 | 18.5 |
| 10 | C3 | 42 | 10 | 12.5 | 12.5 | 98 | 103 | 107 | 7 | 19.5 | 18 |

*Abbreviations:* LL, lower limit of the operative field; TA/LL, distance between the anterior tubercle of C1 and the lower limit of the operative field; WOF, width of the operative field; DOF, depth of the operative field; D, distance

Table 2. Relevant distances, with clival enlargement of the TOA, to the upper cervical spine (mm) in ten specimens

| N | DS/LC | TA/TP | TP/LC | K(TP) | SPI(TP) | SPID | PB/LC |
|---|---|---|---|---|---|---|---|
| 1 | 45 | 20.5 | 14 | 8.5 | 2.5 | 28.5 | 24 |
| 2 | 41 | 19.5 | 12 | 8 | 3 | 29 | 22 |
| 3 | 44 | 19.5 | 12.5 | 8 | 2.5 | 26 | 21 |
| 4 | 43 | 23 | 15 | 6 | 2.5 | 24 | 23 |
| 5 | 37 | 21 | 15 | 10 | 3 | 26 | 21 |
| 6 | 41 | 18 | 11 | 6.5 | 2 | 25 | 19.5 |
| 7 | 50 | 18.5 | 12.5 | 7.5 | 2.5 | 29 | 22.5 |
| 8 | 46 | 20 | 13 | 7.5 | 3 | 26 | 22 |
| 9 | 43 | 18.5 | 11 | 6 | 2 | 25 | 18.5 |
| 10 | 44 | 21 | 13.5 | 7 | 3 | 26.5 | 21.5 |

*Abbreviations:* DS/LC, distance between the dorsum sellae and the lower edge of the clivus; TA/TP, distance between the tuberculum anterius atlantis and the tuberculum pharyngeum; TP/LC, distance between the tuberculum pharyngeum and the lower edge of the clivus; K(TP), depth of the clivus at the level of the tuberculum pharyngeum; SPI(TF), diameter of the inferior petrosal sinus at the level of the tuberculum pharyngeum; SPID, distance between the right and left inferior petrosal sinus 20 mm above the lower edge of the clivus; PB/LC, distance between the basilar plexus and the lower edge of the clivus

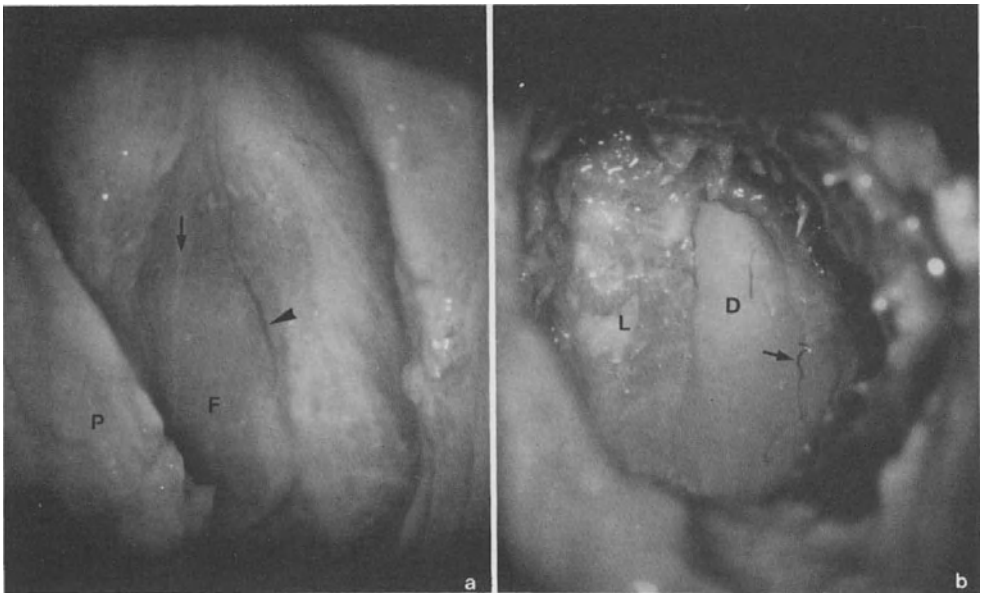


Fig. 1a,b. Transoral approach to the upper cervical spine. a Prevertebral soft tissue. *P*, pharynx wall; *F*, deep cervical fascia and muscle layer (mm. longus capitis and colli); *arrow*, intermuscular septum; *arrowhead*, branch from the vertebral artery. b View of the upper cervical region after removal of the vertebral body C2. *L*, posterior longitudinal ligament; *D*, spinal dura mater; *arrow*, dural branch from the vertebral artery

A 40-mm midline incision caudally from TA splits the posterior wall of the pharynx down to the deep cervical fascia (Fig. 1a). The soft parts (mucosa, mm. contrictores pharyngis and adventitia) can be separated easily from the retropharyngeal space and are retracted laterally on both sides. In this layer we only found very small muscle branches (Ø 0.3 - 0.5 mm) from the ascending pharyngeal and palatine arteries. Oozing from these arterial branches can be stopped by retraction and cottonoids. Bipolar coagulation, which may cause shrinking of the posterior pharyngeal wall, is not necessary. After splitting of the deep cervical fascia, the mm. longus capitis and colli are exposed. The muscle layer is cranially adherent to the anterior atlanto-occipital membrane and caudally to the anterior longitudinal ligament. It can be pushed away laterally with sharp instruments. Two vascular systems become endangered by this manipulation: (a) the prevertebral vascular network from the vertebral and inferior thyroid arteries, and (b) the venous plexus surrounding the vertebral artery at the C1/C2 level. This venous plexus was found about 8 - 14 mm from the midline in our material.

Spondylectomy of C1-C3 is only possible after diskectomy of C2/C3. Osseous branches from the vertebral artery are always found; however, hemostasis can easily be achieved with the electrodrill. Adherence of the posterior longitudinal ligament to the ventral dura behind the vertebral body is variable. On the other hand no adherences could be found at the level of the intervertebral disc. In this layer the ligament forms a small fold which can be incised without injury to the

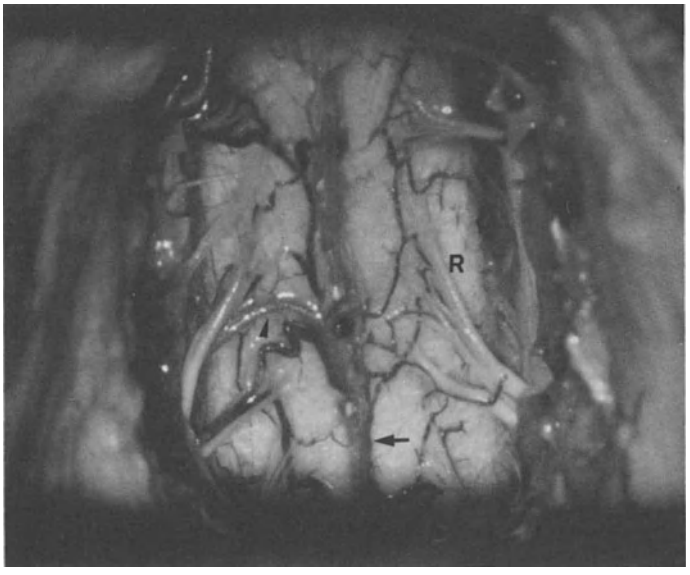


Fig. 2. The spinal dura and arachnoidea have been opened to expose the cervical spinal cord. *R*, ventral nerve root; *arrow*, anterior spinal artery; *arrowhead*, nerve root artery

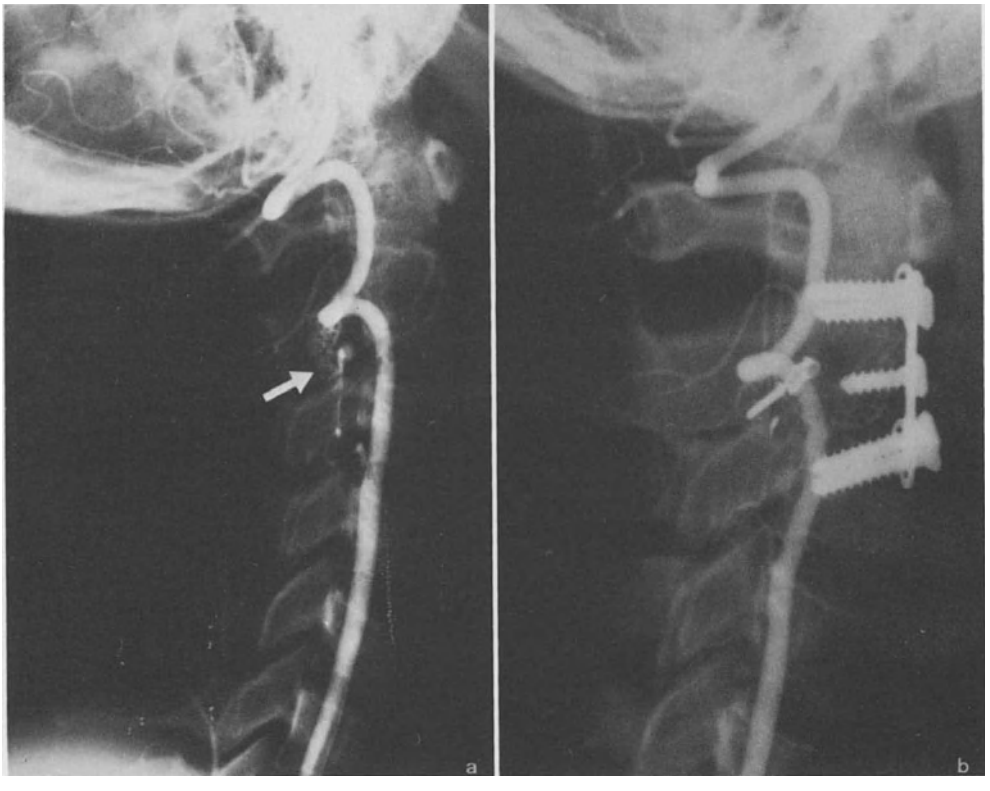


Fig. 3a,b. Intramedullary arteriovenous malformation and paramedullary aneurysm at C2/3 in a 30-year-old man with recurrent subarachnoid hemorrhage. Transoral operation (further text see next page)

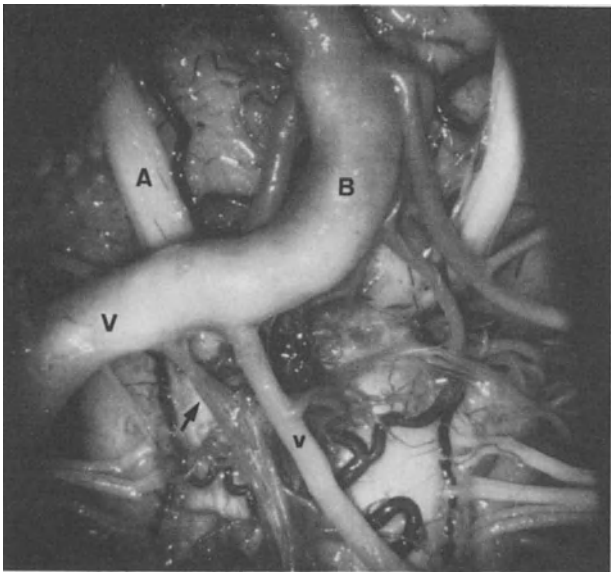


Fig. 4. The clivus has been removed above the tuberculum pharyngeum and the dura has been opened to expose the bulbopontine region. *V*, right vertebral artery; *v*, left vertebral artery (hypoplastic); *A*, sixth cranial nerve; *arrow*, anterior spinal artery

dura (Fig. 1b). The ventral dura is very tough and has to be dissected sharply. In eight of ten specimens a tough arachnoidal septum was found, fixing the anterior spinal cistern at the inner layer of the dura in the midline. To preserve this cistern, the dura has to be opened 1 mm lateral of the midline. The arachnoid covering the anterior spinal artery was rather strong in all specimens and could be opened from lateral only with sharp instruments. Dissecting along the anterior septum, the anterior spinal cistern can be opened without difficulties. The anterior spinal artery lies uncovered in the anterior sulcus (Fig. 2). Figure 3 shows a typical clinical case.

The cranial enlargement of the TAO is obtained by drilling a bone window of 20 × 20 mm above the tuberculum pharyngeum (TP). This is situated 18.5 - 23 mm ($\bar{M}$: 19.7) cephalad of the TA and can hardly be palpated through the soft tissue. To expose the trephination site exactly, it is advisable to follow the m. longus capitis to its origin lateral of the TP. After opening the dura in a Y-shaped manner the prebulbar and prepontine cisterns with their neurovascular contents are reached (Fig. 4).

Closure of the dura after the transoral exploration is problematic. Most authors have abandoned dural closure (2, 6, 16), because even with fascial grafts (5) it remains insufficient. We think closure with fibrin glue is the most simple and effective way. After dural closure with fibrin glue in three specimens, the operative field remained water-tight even after rinsing the cervical region with 200 ml water from behind. In our opinion, stabilization of the cervical spine is only necessary when spondylectomy of two levels with removal of the facets

Fig. 3. a Preoperative angiography; *arrow*, arteriovenous malformation and paramedullary aneurysm at the level C2/3. b Control angiography after transoral spondylectomy of C2 and C3, clipping of aneurysm, partial thrombosis of angioma, and stabilization of the cervical spine

is performed. The deep cervical fascia can be released by two lateral incisions, thus allowing the median closure. The pharyngeal wall is closed with single sutures in one layer; fixation in the region of TA is to be recommended to avoid a retropharyngeal pouch.

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# CT Absorption Analysis in Intracranial Tumor Diagnostics

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At the beginning of the 1970s a new era began in the diagnosis of compressive processes with the development of computerized tomography by G.N. Hounsfield (5). This diagnostic aid made direct topographical findings possible for the first time, and, within particular limits, differential diagnoses could be achieved which approached the possibilities of macroscopic pathology. Although approaches to absorption analysis have indeed been found, even in textbooks (6) the images provided by computerized tomography are presently assessed only by visual means. In connection with this, it should be borne in mind that the human eye is capable of differentiating only about 10 gray and 15 color shades. For this reason, an attempt was made by an interdisciplinary working group (consisting of neurosurgeons, neuropathologists, biomathematicians, and computer scientists) to analyze the actual information medium of the CT image: the absorption, or density, values of the pictures obtained. Primary interest was initially directed to intracranial pathological processes and to the search for characteristic absorption value distribution in meningiomas ($n$ = 40), glioblastomas ($n$ = 30), and cerebral abscesses ($n$ = 36) in unmodified images and in those featuring contrast enhancement.

Reference (4) discusses the problems encountered in the planning of the experimentation, including the following areas: inclusion and exclusion criteria for patients and CT sections, analyses of normal brain structures, localization and form of the so-called regions of interest, partial volume effects, and picture artifacts.

The central question was posed as follows: "Can a reliable model of classification for the pathological processes be found for various tumors by means of density value determination of CT images?" And further: "Is such a procedure possible in the differentiation of the two ring structures represented by glioblastomas and cerebral abscesses?" The so-called corresponding regions of interest seemed suitable as analysis structures. Meningiomas, glioblastomas, and cerebral abscesses were sectioned from the inside outward in a central analytical circle (or portions thereof), in a middle ring, and in an outer ring (or in portions of these two). In addition to the parts represented by tumor, interest was directed to the density values in the perifocal areas of edema (center and edge of the edema).

Surely it would not be without significance to achieve a means of comparing the contrast agent concentrations for the various pathological processes. In an effort to find an objective parameter here, the suggestion has been made that the sinus rectus be utilized – a structure which in any case would normally be found on one of the standard slices of the computer-assisted tomogram. Without knowledge of the degree of

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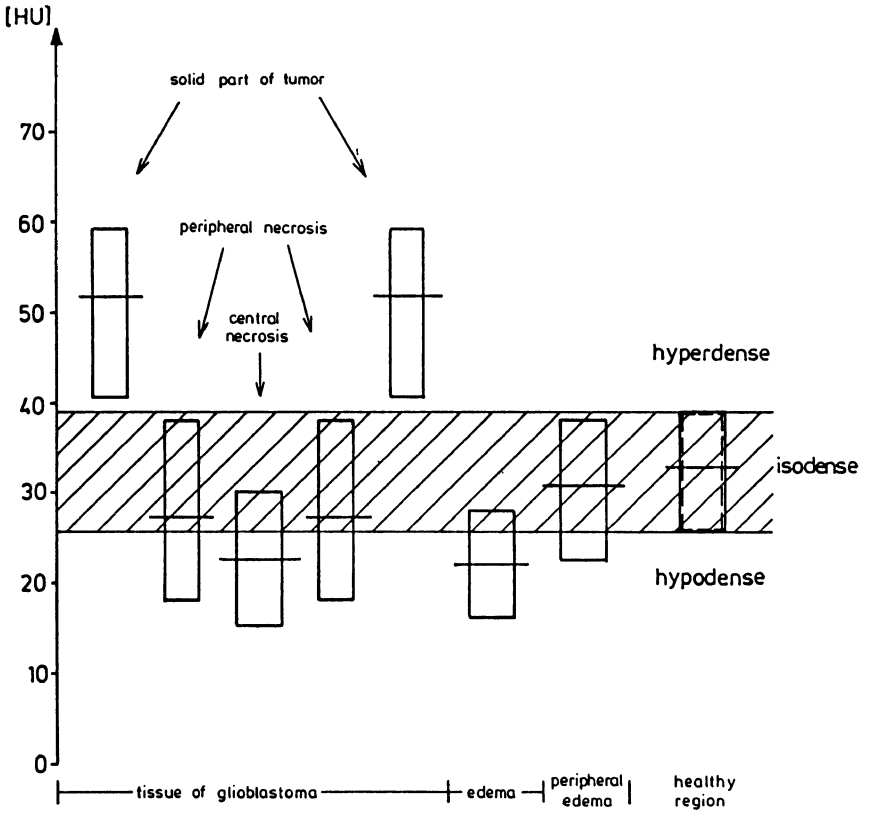


Fig. 1. Glioblastoma: density of the regions of interest after contrast enhancement (median, 80% interquantile range)

contrast-agent concentration in the sinus rectus, exact determination of the density values of a tumor after contrast enhancement would surely not be feasible for an absorption analysis assessment.

In order to make optimal use of the possibilities offered by absorption analysis, it is absolutely necessary to connect the scanner to a mainframe computer. As a matter of course, this renders necessary the development of numerous new computer programs (2, 3). Among a great number of other programs associated with this work, I would like to emphasize one certain item of software which can perform the positioning of so-called windows on the Hounsfield axis. In this way, it becomes possible to obtain on the screen certain data on the state, degree, or morphology of pathological change. In particular, it is possible to evaluate the degree of central necrosis in the case of a ring-shaped glioblastoma. In respect of this, it can be observed that for glioblastomas the first density reductions occur in the center, and that the absorption values increase towards the edge of the necrosis. In the case of cerebral abscesses, however, the initial density reductions are found at the inner capsule edges: a fact confirmed by the two figures showing contrast enhancement (Figs. 1, 2).

In general, such results promote understanding of content and satisfy scientific curiosity. Despite statistical significance and levels of error at $P < 0.01$, however, support cannot be expected from univariate

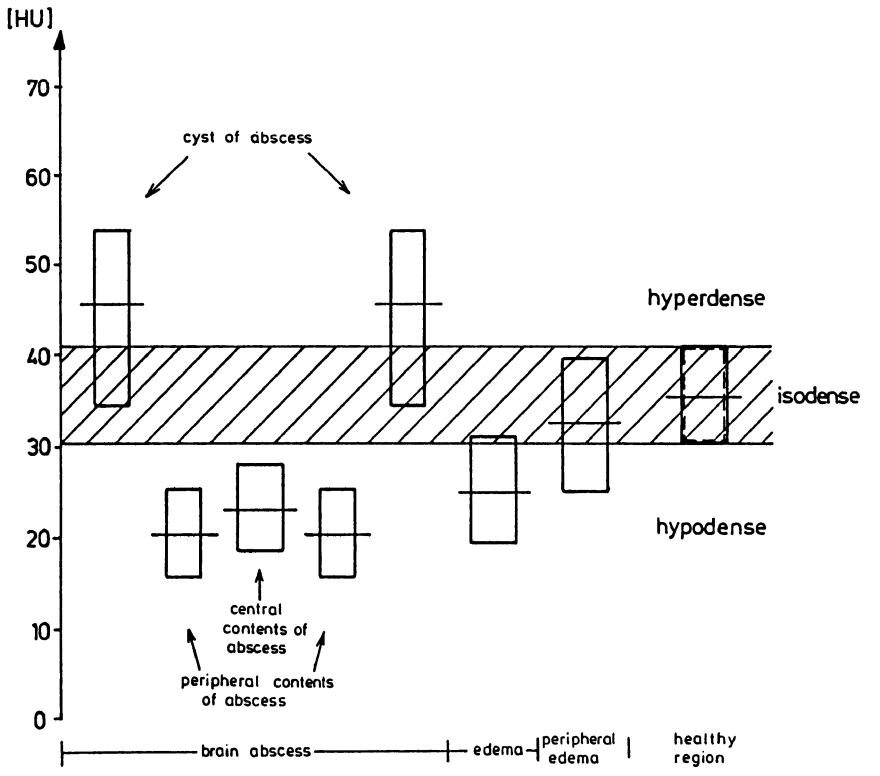


Fig. 2. Brain abscess: density of the regions of interest after contrast enhancement (median, 80%, interquantile range)

methods when the task involves providing the proper diagnosis in the next patient. Medical diagnostic judgments are based on multivariate systems of thought which in this connection must be transposed to the corresponding multivariate mathematical processes. The assumption is made here of different types of tumor – i.e., of different entities – each with their respective and comparable constant values (absorption values in the region of interest). A rule for decision is required which would allow observations from unknown group membership to be assigned with sufficient probability to the correct basic entities. This is the concept that serves as a basis for statistical discriminant analyses (1, 7). Figure 3 provides a schematic representation for centroids and the range of discriminant function values for six different $n$-dimensional discriminant processes.

Subsequent to each analysis, classification is performed by means of the leaving-out-one method. As can be easily understood, glioblastomas and abscesses can readily be differentiated from meningiomas (1, 2). In the classification of abscesses ($n$ = 36) and glioblastomas ($n$ = 30), the already very low rates of mistaken classification are further improved with increase of the measured variables (3, 4, 5). In case 5 on Fig. 3, without faulty classification, the 80% interquantile areas are also incorporated into the discriminant analysis, in addition to the density medians of the tumor and edema regions. Also worthy of mention is the last finding (case 6), for which the absorption values of the perifocal edema sufficed for us to correctly recognize approximately

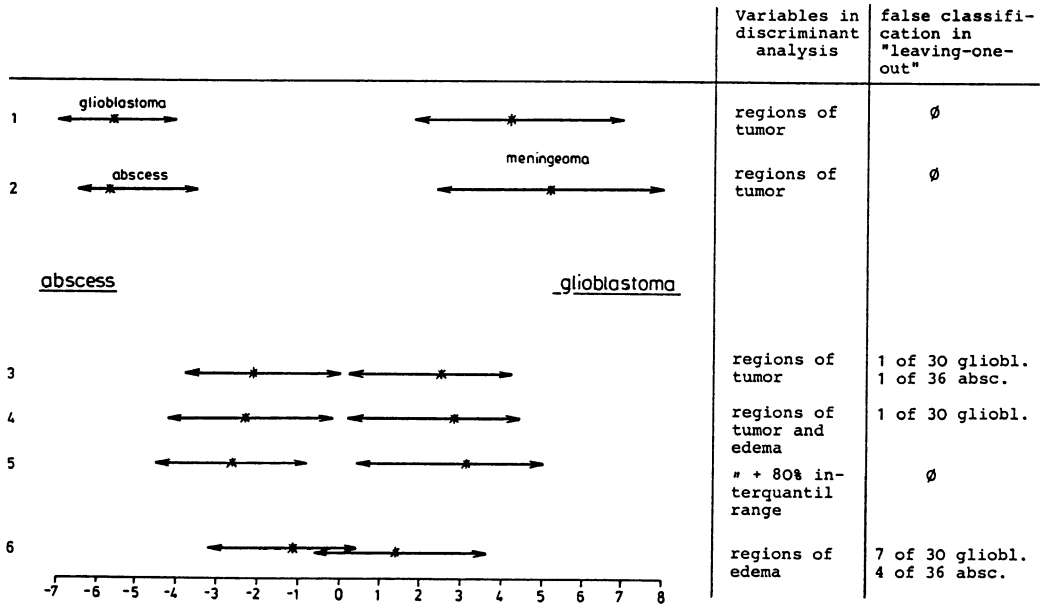


Fig. 3. Mean (*) and range of discriminant function for 2-groups analysis

83% of the diagnoses. This result shows in impressive fashion that carefully conducted absorption analysis should be made a constituent part of CT diagnostics.

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# Impulse Cytophotometry and the Biological Behavior of Gliomas*

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## Introduction

Monometric DNA impulse cytophotometry (ICP) is a valuable tool in obtaining data on tumor kinetics, such as the ploidy state (diploid versus aneuploid stemline, polyploidy) and the proportion of DNA synthesizing cells (S-phase rate), by analyzing about $10^4 - 10^5$ tumor cells (for review see GOERTTLER and STÖHR 1982). This method has been applied in neuro-oncology, too, in order to obtain information on various types of brain tumor regarding diagnosis, degree of malignancy, and prognosis (1, 5, 6).

In the present paper, ICP data on biopsy specimens of 50 human gliomas, including glioblastomas, are reported and correlated to brain tumor tpye and grade as well as to the clinical follow-up, especially to the recurrence-free interval and/or survival rate.

## Material and Approach

Biopsy specimens of 50 surgically removed brain tumors (October 1982 to December 1984) from the Neurosurgical Department, University of Heidelberg were examined. Tumor *classification* followed the WHO proposals (1979), and KERNOHAN's scale (4) was used for tumor *grading* on routinely processed tissue.

The glioma series comprised six astrocytomas (grades I and II), four pilocytic astrocytomas, three oligodendrogliomas, six oligoastrocytomas, three low-grade ependymomas, one high-grade ependymoma, and 27 glioblastomas.

For ICP measurement, small samples of native brain tumor tissue were fixed in 96% ethanol, minced into small pieces using scissors, and digested in 0.25% pepsin solution, resulting in a cell suspension (about $10^4 - 10^5$ cells per millimeter).

Nuclear DNA was labeled by a solution containing ethidium bromide, ribonuclease, and 4'-6-diamidino-2-phenylindole (DAPI) as fluorochrome. DNA-specific fluorescence was measured by an ICP 22 pulse cytophotometer (PHYWE AG, Göttingen, FRG).

*This work was supported by a grant from the Tumorzentrum Heidelberg/ Mannheim ("Neuroonkologie")

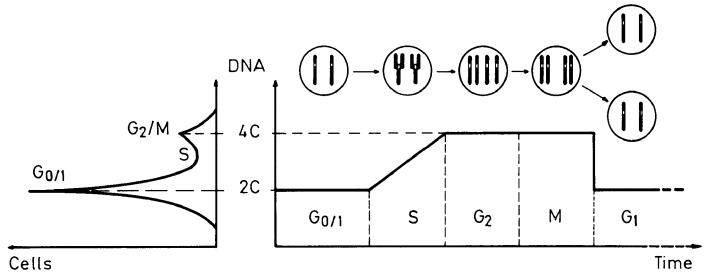


Fig. 1. Correlation between cell cycle fractions and integral histogram

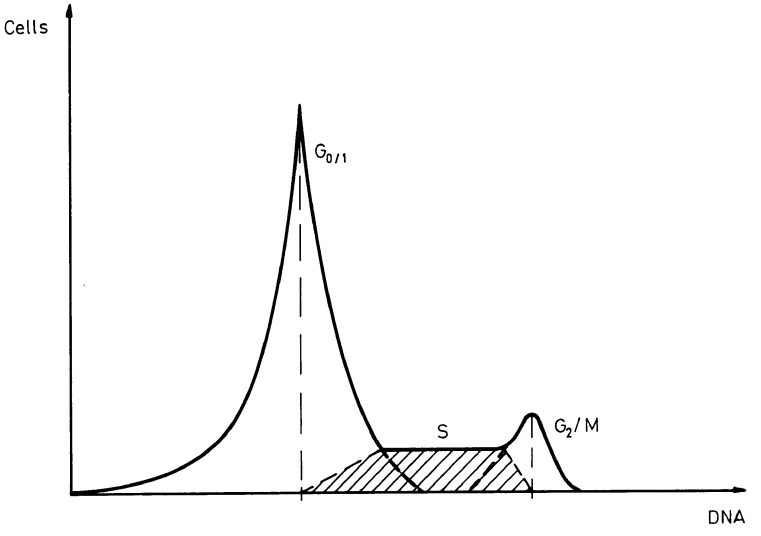


Fig. 2. Integral histogram demonstrating the $G_{0/1}$, and $G_2/M$ phases

Pulse height determination was performed by a multichannel analyzer (MCA 8100, Canberra Ind., Meridan, CT, USA) displaying the distribution in 256 channels. The principle of the method is graphically shown in Fig. 1. ICP data are transferred to a graphic computer system, where a primary logarithmic histogram is converted into a second arithmetic histogram after appropriate background corrections (3). A plotter prints the arithmetic histograms as well as an integral curve (Fig. 2). This outline provides the base for calculating the relative cell cycle phase fractions (for details see 3 ). Clinical follow-up was performed at 6-monthly intervals after surgery and included physical examination and/or CT scan controls, if indicated.

## Results

ICP data of 50 gliomas and glioblastomas were separated into five groups on the basis of ploidy state (diploid versus aneuploid stemline) and S-phase rate: diploid stemline with low (group I) or high (group II) S-phase fraction, aneuploid stemline with low (group III) or high (group IV) S-phase fraction, and gliomas with tetraploid stemline.

Table 1. ICP data, recurrence, and survival rate in relation to glioma type

| Glioma type | IPC | Group I | II | III | IV | V | Recurrence | Survival rate |
|---|---|---|---|---|---|---|---|---|
| | Number | Diploid, low S | Diploid, high S | Aneuploid, low S | Aneuploid, high S | Tetraploid, low/high S | | |
| Astrocytoma I/II | 6 | 5/6 | 1/6 | 0/6 | 0/6 | 0/6 | 0/6 | 0/6 |
| | % 100 | 83.3 | 16.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Pilocytic | 4 | 4/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 |
| astrocytoma | % 100 | 100 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.4 |
| Oligodendroglioma | 3 | 1/3 | 0/3 | 2/3 | 0/3 | 0/3 | 2/3 | 0/3 |
| | % 100 | 33.3 | 0.0 | 66.6 | 0.0 | 0.0 | 66.6 | 0.0 |
| Oligoastrocytoma | 6 | 3/6 | 0/6 | 2/6 | 0/6 | 1/6 | 0/6 | 0/6 |
| | % 100 | 50.0 | 0.0 | 33.3 | 0.0 | 16.6 | 0.0 | 0.0 |
| Ependymoma, | 3 | 1/3 | 0/3 | 1/3 | 0/3 | 1/3 | 1/3 | 0/3 |
| low grade | % 100 | 33.3 | 0.0 | 33.3 | 0.0 | 33.3 | 33.3 | 0.0 |
| Ependymoma, | 1 | 0/1 | 0/1 | 1/3 | 0/1 | 0/1 | 0/1 | 0/1 |
| high grade | % 100 | 0.0 | 0.0 | 100 | 0.0 | 0.0 | 0.0 | 0.0 |
| Glioblastoma | 27 | 12/27 | 3/27 | 3/27 | 5/27 | 4/27 | 14/27 | 6/27 |
| | % 100 | 44.4 | 11.1 | 11.1 | 18.5 | 14.8 | 51.8 | 22.2 |
| Total | 50 | | | | | | | |

*Explanatory notes:* S, synthesis rate; low S: < 6%; high S: > 6%. All deaths were due to the brain tumors

Table 2. Polyploidies, recurrence, and survival rate in the five groups of glioblastomas

| ICP data | *n* | % | Polypl. % | R % | Months | SR % | Months |
|---|---|---|---|---|---|---|---|
| Diploid, low S | 12 | 44.4 | 66.6 | 75.0 | 6.8 | 42.0 | 12 |
| Diploid, high S | 3 | 11.1 | 33.3 | 33.3 | 6.0 | 33.3 | 13 |
| Aneuploid, low S | 3 | 11.1 | 33.3 | 0.0 | - | 0.0 | - |
| Aneuploid, high S | 5 | 18.5 | 20.0 | 100.0 | 7.6 | 0.0 | - |
| Tetraploid, high S | 4 | 14.8 | 0.0 | 0.0 | - | 25.0 | - |
| Total | 27 | 99.0 | | | | | |

*Explanatory notes:* Polypl., Polyploidies; R, recurrence; SR, survival rate; S, synthesis rate

Astrocytomas of low malignant potential (grades I and II according to KERNOHAN) exhibited a diploid stemline and low synthesis rate (< 6%); recurrence of tumors was not observed. Aneuploidy in oligodendrogliomas (2/3) and oligoastrocytomas (2/6) was seen in four of nine cases. In two oligodendrogliomas, recurrence was observed after 12 and 39 months, respectively. ICP data regarding ependymomas were heterogeneous, but one malignant ependymoma showed an aneuploid stemline (Table 1).

Table 2 shows the breakdown of the 27 glioblastomas into the five ICP groups, and polyploidies, recurrence, and survival rate in each of these groups. Tumor relapse was noticed in 8 of 14 glioblastomas whose postoperative course was observed for at least 8 months. The recurrence rate of glioblastomas of group I was 75%, while it was 100% in aneuploid glioblastomas with a high synthesis fraction.

## Discussion

Our data indicate that the main criterion in the estimation of probable tumor dignity is the histological tumor type. ICP data correlated well with the tumor type. This correlation seems better in low-grade gliomas (I and II) than in glioblastomas, which show a high heterogeneity in terms of ploidy state and S-phase fraction. This fact is obviously explained by different morphological patterns of glioblastomas within the same tumor. On the other hand, even in morphologically uniform areas of a tumor, ICP parameters can vary considerably. These data illustrate tumor kinetics and growth behavior to be potentially independent of tumor morphology.

Aneuploid stemline is not necessarily a parameter of malignancy. This is suggested by the ICP data in oligodendrogliomas and oligoastrocytomas, where four of nine cases showed an aneuploid DNA distribution. Whether aneuploidy in these gliomas, however, indicates more malignant future behavior, as suggested by tumor recurrence in two cases of aneuploid oligodendrogliomas, has to be evaluated in a larger number of patients. The statistical significance of differences in the recurrence

rate in diploid glioblastomas with a low S-phase fraction (75%, 9/12 cases) and aneuploid glioblastomas with a high S-phase fraction (100%, 5/5 cases) also has to be studied in a larger group of patients.

In the correlation of biological behavior and therefore tumor prognosis with kinetic ICP parameters, determination of postsurgical tumor recurrence seems superior to absolute survival rate, because the latter is influenced by many tumor-related and/or -unrelated factors, while recurrence directly corresponds to the proliferative potential of a tumor.

## Conclusions

The biological behavior of gliomas depends on the morphologically determined tumor type. Interpretation of ICP should be based on tumor morphology. ICP data correlate well with the tumor grade in low-grade gliomas.

Glioblastomas are heterogeneous; aneuploid stemline with a high synthesis rate (about 18% of glioblastomas) characterizes malignant gliomas. Aneuploidy per se does not indicate malignancy, as it is shown in oligodendrogliomas. Because of the limited number of cases, statistically relevant conclusions cannot be drawn. However, our data demonstrate the trend for ICP to assist in histological tumor grading and to give additional information on clinical follow-up and prognosis.

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# Swelling Behavior of C6 Glioma Cells During Shutdown of Energy Metabolism

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## Introduction

Swelling of nerve and glial cells (cytotoxic brain edema) is a common feature in cerebral ischemia, anoxia, and other metabolic derangements of the brain. Analysis of mechanisms involved in cytotoxic edema of the living brain is impeded by the diversity and complexity of factors which are simultaneously subjected to change in pathological conditions. The availability of stable cell lines of cerebral origin as well as of novel flow-cytometric techniques for cell volume determination has enabled us to establish an in vitro model for the study of swelling mechanisms of defined cells under defined conditions (2, 5).

## Material and Methods

C6 glioma cells were cultured under conventional conditions by employment of Dulbecco's minimal essential medium (DMEM) and addition of fetal calf serum (FCS). The cells were harvested upon reaching confluence in the culture vessel by using trypsin. Single cell suspensions obtained after several washes for removal of FCS were then transferred to a gastight Plexiglas chamber. The test chamber allowed control of pH, $pO_2$, and temperature by a thermocouple and electrodes. A gas-permeable silicone-rubber tube in the chamber served as a membrane oxygenator for supply of the medium with $O_2$, $N_2$, and $CO_2$ in any mixture desired. After a control period of 60 min of isotonic suspension the C6 glioma cells were exposed to a hypotonic environment by dilution of the medium from 300 mOsm/liter to 150 mOsm/liter under maintenance of normal potassium, calcium, and magnesium concentrations. Cell volume changes were flow-cytometrically (Metricell) assessed (2). The experiments were conducted in normoxia (controls) or in anoxia, with or without inhibition of glycolysis by addition of iodoacetate (2.5 mm). Intra- and extracellular $Na^+$ and $K^+$ concentrations were determined by atomic absorption spectrophotometry and correction of a contamination with medium using $^3$H-inulin. In parallel experiments with C6 glioma cells plated in the culture dishes, unidirectional flux studies with radioactive $^{22}Na^+$ and $^{42}K^+$ ions were conducted, either in isotonic DMEM as control, or after hypotonic dilution.

## Results

As in previous studies (4, 5), hypotonic suspension of glial cells was associated with a normalization of cell volume, after initial swelling, within 60 min (Table 1). Regulatory volume decrease (RVD) of hypotonically suspended glioma cells failed, however, after complete shut-

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Table 1. Volume of C6 glial cells (% control ± SEM) after hypotonic dilution in normoxia (A) and during complete inhibition of energy metabolism (B)[a]

| Time (min) | A | B | |
|---|---|---|---|
| 3 | 143.36 ± 3.27 (6) | 140.82 ± 4.23 (5) | - |
| 10 | 127.44 ± 5.73 (6) | 132.54 ± 3.93 (6) | NS |
| 20 | 121.80 ± 1.35 (6) | 132.66 ± 3.95 (6) | $P < 0.05$ |
| 30 | 115.92 ± 2.41 (6) | 140.89 ± 3.92 (6) | $P < 0.001$ |
| 60 | 110.10 ± 3.28 (6) | 142.31 ± 4.98 (6) | $P < 0.001$ |

[a]Number of measurements is given in parentheses

Table 2. Intracellular $K^+$ and $Na^+$ concentrations (mmol/liter cell mass) of hypotonically suspended C6 glial cells in normoxia (A) and after inhibition of energy metabolism (B) (mean ± SD; $n = 6$).

| | | Isotonic control | Time after hypotonic dilution | |
|---|---|---|---|---|
| | | | 30 min | 50 min |
| $(K^+)_{ic}$ | A | 133.11 ± 32.72 | 48.98 ± 17.41** | 50.43 ± 15.81 |
| | B | 122.92 ± 17.78 | 36.35 ± 5.47** | 40.64 ± 9.42* |
| $(Na^+)_{ic}$ | A | 23.17 ± 7.89 | 20.16 ± 11.59 | 19.07 ± 8.58 |
| | B | 13.96 ± 3.56 | 36.36 ± 2.56** | 48.66 ± 5.92** |

*$P < 0.005$; **$P < 0.001$; paired t-test vs isotonic controls

down of energy metabolism by anoxia in combination with inhibition of glycolysis by iodoacetate. Yet anoxia or iodoacetate alone did not suffice to prevent the regulatory cell volume recovery. In normoxia intracellular potassium fell upon hypotonic exposure to less than 50% of the control level, whereas intracellular sodium remained virtually unchanged (Table 2). Similar results were obtained in experiments with anoxia or iodoacetate alone (data not shown). In experiments on hypotonic exposure together with complete inhibition of energy metabolism (anoxia + iodoacetate), intracellular potassium again decreased to less than 50% of the control level found under isotonic conditions (Table 2), while, contrary to the situation with normoxia, intracellular $Na^+$ concentrations were found to be significantly increased.

During the first 3 min after hypotonic exposure, cellular efflux of $^{42}K^+$ was approximately five times that observed in isotonic medium. Between 10 and 15 min later, efflux of $K^+$ became linear. In normoxia $^{22}Na^+$-influx reached a maximum at 10 min after hypotonic dilution and decreased thereafter (7).

## Discussion

Complete inhibition of cellular energy metabolism by anoxia and blocking of glycolysis by iodoacetate in vitro does not cause swelling of

C6 glial cells suspended in isotonic medium (8). This may indicate that cytotoxic cell swelling in brain in vivo cannot directly be attributed to the shutdown of the cellular energy supply. In normoxia C6 glial cells normalize volume after osmotic stress, like lymphocytes or nucleated red blood cells (1, 3, 6). However, the current results demonstrate clearly that recovery of cell volume after hypotonic swelling is prevented by a total inhibition of respiration and of anaerobic energy production.

Release of intracellular potassium during RVD can be considered a major mechanism of volume adjustment. Calculations of net potassium flux across the cell membrane demonstrate surprising agreement with that of cell water during RVD. Intracellular $Na^+$ concentrations remained nearly unchanged not only in normoxia but also in pure anoxia or during inhibition of glycolysis by iodoacetate without anoxia, while they increased significantly when energy metabolism was completely blocked. Failure of the regulatory volume normalized in hypotonic medium after shutdown of energy metabolism may have resulted – at least in part – from an incapacity of the cells to actively extrude increased intracellular $Na^+$.

## Conclusions

The current findings demonstrate the high priority that normal cell volume has in glial cells, even under pathological circumstances, and the presence of active mechanisms providing for volume regulation. A better understanding of the molecular mechanisms involved in cell volume control processes is essential for the development of specific and more effective treatment of cytotoxic brain edema.

*Acknowledgments.* The technical and secretarial help of SYLVIA SCHNEIDER, ULRIKE GOERKE, RUTH DEMMER, and ISOLDE JUNA is greatly appreciated.

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# Treatment of Vasogenic Brain Edema by Inhibitors of the Kallikrein-Kinin System

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## Introduction

The evidence identifying the kallikrein-kinin system as a mediator of vasogenic brain edema is almost complete (BAETHMANN et al. 1980). Kinins, the active peptides of the system, open the blood-brain barrier for small molecules (UNTERBERG et al. 1984b); this is regarded as a mechanism inducing brain edema (UNTERBERG et al. 1984a). Moreover, formation of kinins was found in acute cerebral lesions associated with vasogenic brain edema (MAIER-HAUFF et al. 1984). However, one important piece of evidence required for identification of a substance as a mediator in cerebral lesions has not yet been provided in the case of the kallikrein-kinin system: this is whether specific inhibition of release, or of the pathological function of kinins, is therapeutically beneficial.

The objective of the current study was therefore to analyze whether inhibition of the kallikrein-kinin system by aprotinin or soybean-trypsin inhibitor (SBTI) influences the formation of cold injury-induced vasogenic brain edema. Inhibition of the activating enzyme kallikrein is considered to specifically prevent formation of kinins (ERDÖS 1979; FRITZ and WUNDERER 1983).

## Materials and Methods

In rabbits of $3.3 \pm 0.6$ kg b.w. anesthetized with ketamine and xylacine, craniotomy was performed over the left hemisphere. Cold injury was induced by attaching a copper cylinder cooled with dry ice/acetone for 60 s to the intact dura. Starting 15 min after trauma the animals were continuously infused intravenously with a given inhibitor until termination of the experiment 24 h after induction of trauma. Fourteen rabbits infused with aprotinin received 150 mg/kg per day, nine animals received soybean-trypsin inhibitor (SBTI) in a dose of 150 mg/kg per day, and a third group ($n = 10$) received aprotinin + SBTI (75 mg/kg each per day). Twelve control animals received physiological saline. During the experiment, arterial blood pressure, partial thromboplastin time (PTT), and plasma aprotinin concentrations were monitored at different intervals before and after trauma.

Twenty-four hours after cold injury the animals were anesthetized and exsanguinated for removal of the brain. The experimental (left) and control (right) hemispheres were meticulously separated in the median plane. Hemispheric swelling was quantitatively assessed as the increase of weight of the traumatized cerebral hemisphere over that of the con-


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Table 1. Weight increase of injured hemispheres, in grams or percent (mean ± SD), of the corresponding contralateral hemispheres of treated and untreated animals

| | Weight increase | |
|---|---|---|
| | (%) | (g) |
| Controls ($n$ = 12) | 13.0 ± 2.6 | 0.47 ± 0.10 |
| SBTI ($n$ = 9) | 11.7 ± 1.6 | 0.43 ± 0.05 |
| Aprotinin + SBTI ($n$ = 10) | 10.4 ± 2.1** | 0.39 ± 0.08 |
| Aprotinin ($n$ = 14) | 10.1 ± 2.5*** | 0.37 ± 0.09* |

***$P < 0.01$ vs controls; **$P < 0.02$; *$P < 0.05$

tralateral hemisphere. Simultaneously, brain water and electrolytes were studied.

## Results

In untreated controls, cold injury edema led to an increase in weight of the affected hemispheres of 13.0 ± 0.8% (mean ± SEM). Treatment with aprotinin alone reduced hemispheric swelling to 10.1 ± 0.7% ($P < 0.01$), aprotinin in combination with SBTI to 10.4 ± 0.7% ($P < 0.02$). Rabbits receiving SBTI only had a hemispheric swelling of 11.7 ± 0.5%, which was, however, not significantly different from the untreated controls (Table 1). In all groups the traumatized cerebral hemispheres had a significant increase of the tissue water content, an increase of $Na^+$ content, and a decrease of $K^+$ content.

Infusion of aprotinin or of SBTI did not significantly affect the systemic arterial blood pressure. On the other hand, the coagulation potential was markedly altered by treatment. SBTI led to a considerable retardation of coagulation. The partial thromboplastin time increased from 20 to 72 s 24 h after trauma, whereas PTT rose to 38 s only during administration of aprotinin. Thirty minutes after the start of infusion with aprotinin, aprotinin concentrations in plasma approached a level which was sufficient for effective inhibition of the kallikrein-kinin system. Concentrations found in plasma were always above 120 kallikrein-inactivator units per milliliter (FRITZ and WUNDERER 1983).

## Discussion

Reduction of posttraumatic brain edema by specific inhibition of formation of kinins can be considered final proof for a role of kinins as mediators in vasogenic brain edema. Attenuation of edema by aprotinin was independent of changes of arterial blood pressure. This rules out involvement of hemodynamic mechanisms in the reduction of brain edema. However, it has not yet been studied whether administration of aprotinin or SBTI in fact prevents or reduces formation of kinins in edematous cerebral tissue. Nevertheless, effective inhibition of the kallikrein-kinin system can be assumed from the level of aprotinin found in plasma or in cerebral tissue samples. The therapeutic failure of

SBTI may be explained by an interference of the inhibitor with coagulation. A marked increase of the partial thromboplastin time by SBTI might have enhanced development of edema. It has been reported that platelet inhibition enhances formation of cold-induced cerebral edema (SEGAWA and PATTERSON 1981).

## Conclusions

The results demonstrate clearly that traumatic vasogenic brain edema can be efficiently mitigated by specific inhibition of the kallikrein-kinin system. Moreover, the data provide final proof for a mediator role of kinins in vasogenic edema. Although it remains to be shown whether formation of kinins in cerebral tissue was indeed prevented, the findings provide a solid experimental basis for therapeutic trials under clinical conditions.

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# Neurotransmitter Contents in Low-Grade Gliomas and Glioblastomas

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## Introduction

Neurotransmitters in brain tumors have already been examined both experimentally and in vivo (2, 3, 4, 8). Up to now, concentrations of various neurotransmitters have received little attention when gliomas and glioblastomas have been compared directly. By means of the study reported here, a solution was to be found to the problem regarding concentrations of neurotransmitters in various glial brain tumors. In addition, the behavior of certain neurotransmitters was looked into with respect to the altered metabolism in the case of brain tumors.

## Material and Methods

Samples of low-grade gliomas (astrocytomas, oligodendrogliomas, all tumors grade II, $n = 6$), glioblastomas ($n = 9$), and corresponding peritumoral tissue were fixed intraoperatively with liquid nitrogen, and quantitative measurements of glutamate, dopamine, and 5-hydroxytryptamine (5-HT) contents of the biopsy material were taken using high-performance liquid chromatographic (HPLC) techniques. Tissue was weighed and dried, homogenized by means of ultrasonification, and extracted either for 5-HT and dopamine or for total brain amino acids. Briefly, amino acids were derivatized with dansylchloride and separated on a reversed-phase u Bondapak $C_{18}$ column (Waters Assoc.) with 254 mm wavelength detection by HPLC as described elsewhere (1). Dopamine and 5-HT were separated on Ultrasphere ODS (Du Pont) in 66% of 0.02 M potassium phosphate containing 1 g/liter heptanesulfonic acid sodium salt (pH 3.3) and 34% methanol:water (3:2) according to PEAT and GIBB (6). Excitation wavelengths of 290 nm and emissions at 330 nm were employed for fluorescence detection. Chromatography peaks were quantified on account of standard concentration curves for each of the compounds. The concentrations of glutamate, dopamine and 5-HT were expressed per gram brain tissue, fresh weight.

## Results

The glutamate concentrations obtained in this study were compared with the values PERRY et al. (7) gained from autoptic material (owing to the fact that there was no control group). Both in the case of gliomas ($10.53 \pm 1.22$ µmol/g w.w.) and in that of glioblastomas ($10.76 \pm 1.18$ µmol/g w.w.), the concentrations in the peritumoral tissue corresponded to the "standard value" of 10.16 µmol/g w.w. Clearly increased concentrations were to be found in the tumors, but without any significant

Table 1. Neurotransmitters in tumor and peritumoral tissue of the human brain

| | Glutamate (µmol/g w.w.) | Dopamine (ng/g w.w.) | 5-HT (serotonin) (ng/g w.w.) |
|---|---|---|---|
| *Glioblastomas:* | | | |
| Tumor | 23.60 ± 6.34 ($n$ = 9) | 1204 ± 376 ($n$ = 7) | 494 ± 170 ($n$ = 7) |
| Peritumoral | 10.76 ± 1.18 ($n$ = 6) | 107 ± 36 ($n$ = 6) | 67 ± 23 ($n$ = 6) |
| *Gliomas:* | | | |
| Tumor | 18.09 ± 5.31 ($n$ = 6) | 832 ± 175 ($n$ = 6) | 454 ± 72 ($n$ = 5) |
| Peritumoral | 10.53 ± 1.22 ($n$ = 4) | 60 ± 15 ($n$ = 4) | 50 ± 20 ($n$ = 3) |

All values represent mean ± SD

difference between the gliomas (18.09 ± 5.31 µmol) and the glioblastomas (23.6 ± 6.34 µmol/g w.w.) if the mean variation of the individual value was taken into consideration.

Compared with the peritumoral tissue, dopamine had also clearly increased in all of the glial tumors. In some gliomas located near the basal ganglia there were exceptionally high concentrations of dopamine, with values of 2.5 - 3.0 ng/g w.w. These data were not included in the study.

Compared with the standard 540 ng/g w.w., the level of 5-HT in all the tumors was slightly lower, but without any differences worth mentioning between gliomas and glioblastomas. There was a significant difference, however, when compared with the peritumoral tissue. Details of all of the values obtained can be found in Table 1.

## Discussion

On the whole the results did not show any substantial difference between gliomas and glioblastomas in the case of those neurotransmitters examined. In particular cases, however, there were some interesting changes in concentration, the increased level of glutamic acid, for instance, indicating a disorder in the metabolism of glutamate. As an intermediary product in the GABA shunt process, this is also important for resynthesizing γ-aminobutyric acid. A further aspect of this is that the effect of increased concentrations of glutamate – which encourages edema – should be taken into account; this has been proven by KEMSKI and BAETHMANN (4, 9) in tests carried out in vitro on a glioblastoma cell culture.

LOWRY (5) found a distinct depression in metabolism in the case of glial brain tumors, which could be recognized owing to the low activity of the hexokinase and phosphorylase. With a high level of lactate at the same time, he noticed slight indications of ischemia. This might also explain the lowered 5-HT level, since lowering the $PO_2$ can result

in the latter occurring before significant changes in the level of lactate and in the high-energy phosphates become detectable.

If one disregards the high concentration of dopamine with some brain tumors – which depends on where they are located – the total number of increased values obtained still cannot be interpreted satisfactorily, which means that they require further clarification.


## Summary

The study that was carried out indicated distinct differences in the concentrations of neurotransmitters examined between the tumoral and the peritumoral tissue; these differences can be partially interpreted within the framework of tumoral metabolism. There were no characteristic changes that were relevant for differentiating between gliomas and glioblastomas.


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# The Influence of Acutely Increasing ICP upon Diuresis and Water-Electrolyte Balance and Its Modification by Neurohypophysectomy (An Experimental Study)

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## Introduction

Lesions of the hypothalamo-hypophyseal system and the brain stem occur through direct primary or indirect secondary involvement and are caused in neurosurgical patients mostly by head injury, cerebral stroke with brain edema, and acute space-occupying lesions.

Our previous clinical and pathomorphological studies indicated that vegetative disturbances connected with these lesions are combined with water-electrolyte balance (WEB) disturbances (2, 3, 5). The latter were observed in patients with supratentorial lesions as well as in patients with infratentorial lesions, e.g., primary brain stem damage. In this study the effect of experimentally produced supra- and infratentorial brain compression upon the function of the hypothalamo-hypophyseal antidiuretic system (HHAS) and subsequent changes of diuresis and WEB were investigated. Furthermore, the response of the HHAS to supratentorial brain compression was evaluated after performing neurohypophysectomy, which abolishes the release of ADH into the bloodstream.

## Material and Methods

Eighteen cats (weighing 2.5-3.5 kg) were used. The animals were anesthetized with pentobarbital-$Na^+$ (3.0 mg/kg) and tracheotomized. In six cats (group I) an epidural balloon was placed in the parietal region via small craniectomy. In seven animals (group II) the balloon was placed in the midline over the posterior fossa. In five animals (group III) transoral neurohypophysectomy (NHE) was performed prior to the inflation of the supratentorial balloon. The balloon was inflated at the rate of 1.6 ml/h. Intracranial pressure (ICP), mean arterial pressure (MABP), central venous pressure (CVP), respiratory frequency (RF), rectal temperature (RT), EEG, and ECG were monitored continuously. The animals were catheterized and the diuresis was measured continuously and expressed in ml/kg/h. Artificial ventilation was started when respiratory arrest occurred.

At 15-min intervals samples were drawn for estimation of plasma antidiuretic hormone (p-ADH) (RIA, Bühlmann, Basel), serum and urine osmolality (freezing point depression, Gonotec-Osmomat 030), serum and urine electrolytes (flame photometry, Eppendorf FCM 6341), serum glucose (glucose oxidase method), and serum creatinine concentration (Beckmann BUN Analyser).

Water loss was substituted by continuous infusion of Ringer's solution (5 ml/kg/h) and the hematocrit was kept in the normal range.

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## Results

Progressive inflation of the balloon caused typical ICP increase and MABP, EEG, and pupillary changes which enabled us to divide the experiments into three phases. The end-point of phase I (pI) was the fall in MABP and respiratory arrest occurring at increased ICP.

The end-point of phase II (pII) was the complete loss of EEG activity and maximal pupillary dilatation. Phase III (pIII) could be equated with brain death. These phases were present and were identical in all groups of animals. Phase I was subdivided into a and b in accordance with whether the ICP was below or above 30 mmHg.

### *Groups I and II*

No significant differences at the 95% confidence level were disclosed for changes of p-ADH in any phase of the experiment between groups I and II (Wilcoxon test, $P < 0.05$). There were also no significant differences in the diuresis, osmolality, and electrolytes in serum and urine. The cumulative data for groups I and II are shown in Table 1.

The steady-state value of p-ADH after completing surgical prodecures and before inflation of the balloon was 37±30 pg/ml (mean ± SD). With ICP increase up to 30 mmHg (pIa) there was a significant increase of p-ADH to 61±61 pg/ml ($P < 0.01$) which continued with the further increase of ICP (pIb). In this phase the highest values of p-ADH were found, with a mean of 89±66 pg/ml. The next phase (pII) is characterized by a marked decrease of p-ADH, which continues into pIII and in which p-ADH attains lower values than during the steady state (10±10 pg/ml).

The diuresis increased during pIa, returned to steady-state values with further increase of ICP during pIb and pII, and subsequently increased after brain death (see Table 1).

Concomitant with the increase in p-ADH, serum osmolality decreased in pIb; in the subsequent phases serum osmolality increased, corresponding to the decrease in p-ADH.

With the exception of an increase during pIb corresponding to the maximal increase in p-ADH, urine osmolality showed a progressive diminishing tendency (see Table 1).

There were no significant changes in serum $Na^+$ concentration throughout the experiments. Urine $Na^+$ concentration increased parallel to the p-ADH increase and dropped considerably in the last two phases.

There was a progressive rise in serum glucose concentration throughout all phases.

### *Group III*

There was a considerable fall in p-ADH following NHE.

Maximal diuresis was present in pIb; no values of p-ADH in pII and pIII were, however, connected with decrease in the diuresis (see Table 2). Serum osmolality increased continuously with a fall in p-ADH. Urine osmolality, however, decreased in all phases, parallel to the decrease in p-ADH. Similarly to groups I and II, there were no significant changes in serum $Na^+$ concentration (Fig. 1). Urine $Na^+$ concentration

Table 1. Cumulative data for groups I and II[a]

| | Plasma | | | |
|---|---|---|---|---|
| | ICP (mmHg) | CPP (mmHg) | MABP (mmHg) | ADH (pg/ml) |
| Steady state | 5± 3 $n$=48 | 132±22 $n$=48 | 138±22 $n$=69 | 37±30 $n$=18 |
| Phase Ia | 11± 7 $n$=77 | 125±25 $n$=76 | 136±25 $n$=76 | 61±61 $n$=24 |
| Phase Ib | 56±32 $n$=41 | 84±27 $n$=41 | 140±35 $n$=41 | 89±66 $n$=15 |
| Phase II | 49±26 $n$=67 | 57±32 $n$=67 | 106±31 $n$=67 | 58±52 $n$=19 |
| Phase III | 84±27 $n$=142 | 1±27 $n$=142 | 83±25 $n$=143 | 10±10 $n$=36 |

| | Serum | | | | | |
|---|---|---|---|---|---|---|
| | Osmol. (mosmol/kg) | $Na^+$ (mmol/l) | $K^+$ (mmol/l) | $Ca^{++}$ (mmol/l) | Gluc. (mg %) | Crea. (mg %) |
| Steady state | 326±11 $n$=19 | 150±5 $n$=19 | 4.2±1.1 $n$=19 | 2.5±0.2 $n$=19 | 136± 50 $n$=17 | 0.7±0.1 $n$=17 |
| Phase Ia | 324± 9 $n$=26 | 150±4 $n$=25 | 3.8±0.6 $n$=25 | 2.3±0.2 $n$=25 | 190± 69 $n$=25 | 0.6±0.1 $n$=25 |
| Phase Ib | 315±11 $n$=15 | 147±4 $n$=14 | 4.0±0.9 $n$=14 | 2.1±0.2 $n$=14 | 218± 76 $n$=14 | 0.5±0.2 $n$=14 |
| Phase II | 325± 6 $n$=20 | 151±3 $n$=20 | 3.7±0.6 $n$=20 | 2.2±0.1 $n$=20 | 299± 96 $n$=19 | 0.7±0.2 $n$=17 |
| Phase III | 330±11 $n$=42 | 153±4 $n$=42 | 3.8±0.7 $n$=42 | 2.3±0.2 $n$=40 | 281±104 $n$=42 | 0.9±0.2 $n$=37 |

| | Urine | | | |
|---|---|---|---|---|
| | Diuresis (ml/kg/h) | Osmol. (mosmol/kg) | $Na^+$ (mmol/l) | $K^+$ (mmol/l) |
| Steady state | 2.6±2.0 $n$=103 | 1797±582 $n$=107 | 237± 88 $n$=110 | 94±42 $n$=110 |
| Phase Ia | 3.7±2.1 $n$=72 | 1256±473 $n$=72 | 274± 75 $n$=71 | 73±47 $n$=72 |
| Phase Ib | 2.6±1.8 $n$=35 | 1503±466 $n$=35 | 283± 68 $n$=35 | 91±42 $n$=35 |
| Phase II | 2.2±2.1 $n$=51 | 1070±379 $n$=47 | 172±116 $n$=46 | 81±52 $n$=46 |
| Phase III | 3.5±3.3 $n$=139 | 774±507 $n$=132 | 86± 84 $n$=131 | 68±68 $n$=131 |

[a]CPP, cerebral perfusion pressure; phase Ia: ICP <30 mmHg; phase Ib: ICP ≧30 mmHg; $n$ = number of data during one phase

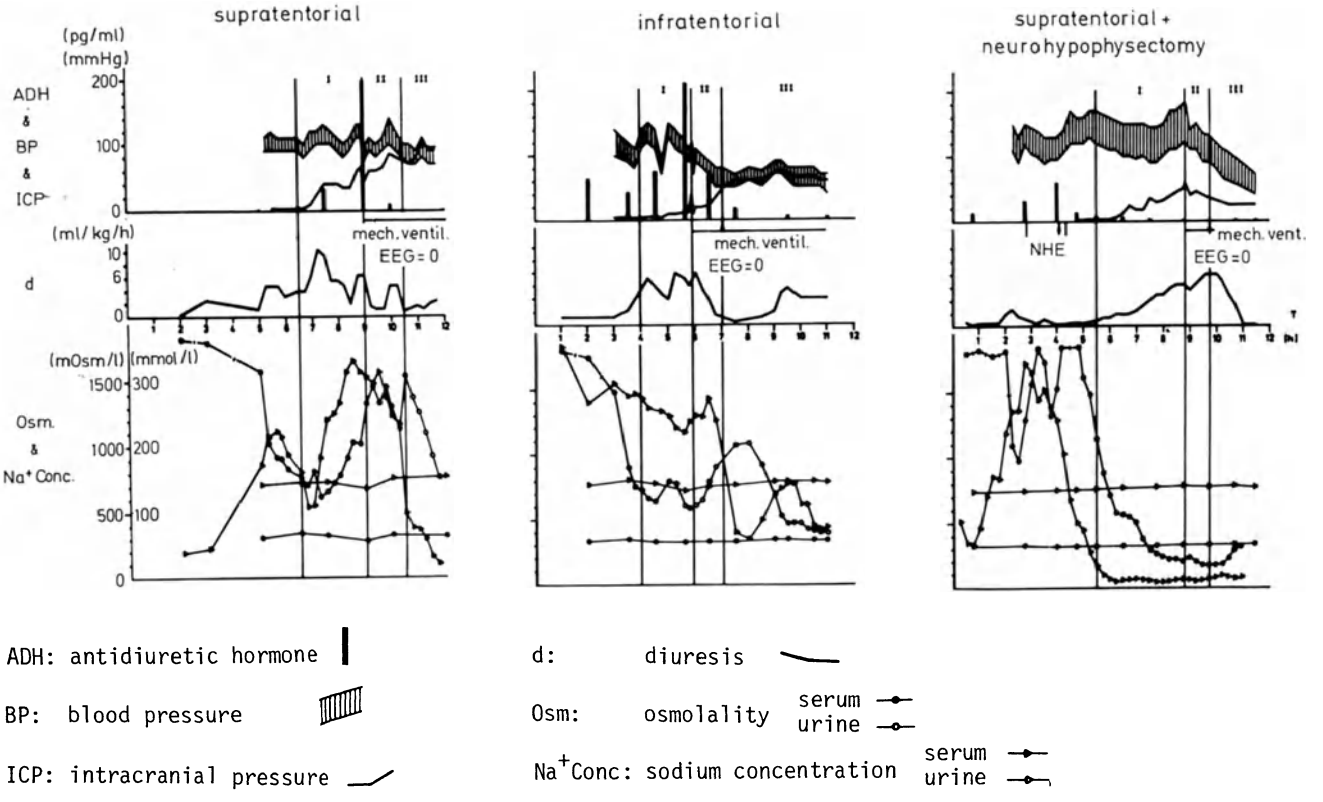


Fig. 1. Three courses, one representative animal in each group

Table 2. Cumulative data for group III[a]

| | Plasma | | | |
|---|---|---|---|---|
| | ICP (mmHg) | CPP (mmHg) | MABP (mmHg) | ADH (pg/ml) |
| Before NHE | | | 123±25 $n$=44 | 67±71 $n$=13 |
| After NHE | 4± 2 $n$=25 | 121±18 $n$=25 | 125±18 $n$=25 | 16± 5 $n$= 6 |
| Phase Ia | 10± 7 $n$=34 | 112±18 $n$=34 | 122±18 $n$=34 | 8± 4 $n$= 9 |
| Phase Ib | 51±22 $n$=19 | 94±18 $n$=19 | 145±25 $n$=19 | 5± 4 $n$= 5 |
| Phase II | 38±16 $n$=19 | 69±31 $n$=19 | 107±33 $n$=19 | 5± 3 $n$= 5 |
| Phase III | 33±14 $n$=21 | 37±19 $n$=21 | 70±24 $n$=21 | 4± 2 $n$= 4 |

| | Serum | | | | | |
|---|---|---|---|---|---|---|
| | Osmol. (mosmol/kg) | $Na^+$ (mmol/l) | $K^+$ (mmol/l) | $Ca^{++}$ (mmol/l) | Gluc. (mg %) | Crea. (mg %) |
| Before NHE | 318± 7 $n$=13 | 151± 5 $n$=13 | 4.1±0.6 $n$=13 | 2.2±0.1 $n$=13 | 106± 62 $n$= 13 | 0.7±0.2 $n$=13 |
| After NHE | 319±21 $n$= 7 | 153±13 $n$= 7 | 3.7±0.4 $n$=7 | 2.0±0.2 $n$=7 | 129± 62 $n$= 7 | 0.9±0.3 $n$=7 |
| Phase Ia | 321±11 $n$= 9 | 151± 6 $n$= 9 | 4.3±0.8 $n$=9 | 2.1±0.2 $n$=9 | 166± 50 $n$= 9 | 0.7±0.3 $n$=9 |
| Phase Ib | 326±20 $n$= 5 | 151± 7 $n$= 5 | 3.6±0.3 $n$=5 | 2.2±0.1 $n$=5 | 205±105 $n$= 5 | 0.7±0.3 $n$=5 |
| Phase II | 330±20 $n$= 5 | 153± 7 $n$= 5 | 4.0±0.7 $n$=5 | 2.1±0.2 $n$=5 | 278± 98 $n$= 5 | 1.0±0.4 $n$=5 |
| Phase III | 336±17 $n$= 4 | 153± 5 $n$= 4 | 4.9±2.5 $n$=4 | 2.1±0.3 $n$=4 | 271±104 $n$= 4 | 1.4±1.0 $n$=4 |

| | Urine | | | |
|---|---|---|---|---|
| | Diuresis (ml/kg/h) | Osmol. (mosmol/kg) | $Na^+$ (mmol/l) | $K^+$ (mmol/l) |
| Before NHE | 1.9±1.3 $n$=64 | 1500±630 $n$=72 | 261±118 $n$= 71 | 73±34 $n$=71 |
| After NHE | 2.5±1.4 $n$=36 | 956±476 $n$=35 | 139± 68 $n$= 35 | 75±50 $n$=34 |
| Phase Ia | 3.8±2.1 $n$=33 | 478±223 $n$=33 | 28± 25 $n$= 33 | 45±32 $n$=33 |
| Phase Ib | 5.3±1.8 $n$=14 | 304±140 $n$=14 | 35± 40 $n$= 14 | 25±11 $n$=14 |
| Phase II | 4.7±3.5 $n$=17 | 327±154 $n$=16 | 43± 38 $n$= 16 | 29±15 $n$=16 |
| Phase III | 1.7±2.2 $n$=19 | 420±180 $n$=12 | 26± 16 $n$= 12 | 49±35 $n$=12 |

decreased extremely, and the mean values for all three phases ranged between 26 and 43 mmol/l.

Changes in glucose concentration showed the same pattern as in groups I and II.

## Discussion

Acute supra- and infratentorial increase in ICP was reflected by the same pattern of p-ADH excretion corresponding with changes of blood - and urine - osmolality as well as of blood - and urine - $Na^+$ concentration. The activation of the HHAS during the elevation of ICP under experimental conditions has been described previously (1, 5).

In our experiments the maximal excretion of p-ADH appeared at the end of pIb (at the moment of circulatory breakdown with hypotension); afterwards p-ADH decreased continuously. In pIII, together with the brain death symptoms, the lowest p-ADH concentrations were seen.

The amount of p-ADH correlated with the diuresis and other parameters of water-electrolyte metabolism only during pIa, pIb, and pII. In pIII urine $Na^+$ concentrations and osmolality were drastically decreased in both the experimental groups I and II, corresponding to the increase in diuresis. The same pattern was noted in animals of group III.

After NHE during the phases of ICP increase (pIa, pIb, pII) p-ADH was low, with low urine $Na^+$ concentrations and osmolality.

The data of these experiments showed that vasopressinergic centers of the hypothalamus with their brainstem projections – when deprived of the neurohypophysis – could not compensate the disturbances of the water-electrolyte metabolism during intracranial hypertension.

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[a] NHE, neurohypophysectomy; phase Ia: ICP <30 mmHg; phase Ib: ICP ≥30 mmHg; $n$ = number of data during one phase

# Noninvasive Measurement of Local Cerebral Blood Flow (nl-CBF) with Stable Xenon Enhanced Dynamic CT - Description of Method and Analysis of Flow Data

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## Introduction

After the Fick principle was modified by KETTY and SCHMIDT in 1945 (6) and applied to the measurement of global cerebral blood flow in 1948, many attempts were made to develop different invasive (2, 4) and non-invasive (9, 13, 16) methods, mainly using xenon-133 as a free diffusible indicator whose radioactivity was measured by scintillation counting. Due to the large diameter of the collimators, spatial resolution was coarse and there was no anatomically correlated display of flow data, no differentiation of flow data at the surface of the brain from that in structures below, and no possibility of determining $\lambda$. To reach subcortical structures tomographic imaging of regional CBF was generated in the form of single photon emission tomography (SPECT) (7, 8) and positron emission tomography (PET) (14, 15, 17).

Estimation of l-CBF and $\lambda$ with CT scanning during inhalation of stable xenon was proposed by KELCZ and HILAL (5) and DRAYER et al. (1) in 1978; besides the free diffusibility and lipid solubility of xenon, other physical characteristics, *such as high atomic number (54), high atomic mass (131, 30), and high electron density (5th period, VIIIth group in periodic table of elements),* should be used, which are demanded for sufficient contrast enhancement. At first, however, CT scanners *with dynamic scan programs and improved density resolution* had to be developed, so that the concentration of inhaled xenon could be reduced to 30%-35%, i.e., to subanesthetic levels.

In collaboration with General Electric, the CBF study group around GUR (3) designed a xenon-CBF imaging system, which we received as a research package for clinical evaluation additionally to our GE 9800 CT scanner in November 1984.

## Method and Material

The *xenon-CBF device* consists of three parts:

1. Gas delivery system with pulmonary function bag (contents = max. 60 liters); tube with one-way valve at its end leading to face-mask or mouthpiece.
2. $pCO_2$ and xenon probe at the expiratory leg of the valve for monitoring $pCO_2$ exp. and end-tidal xenon concentration by a precalibrated thermal conductivity analyzer.
3. Special software to create the blood flow map.

After provision of detailed information about the *course of the examination* and the typical xenon side effects – paresthesia in the fingers and

toes and a certain "high feeling" – the patient is positioned on the scanner table. The gas delivery system, i.e., face mask, is attached to the patient, who continuously breathes room air. After the patient is instructed to remain completely motionless, two so-called baseline scans are taken from each level at which flow data acquisition is de-

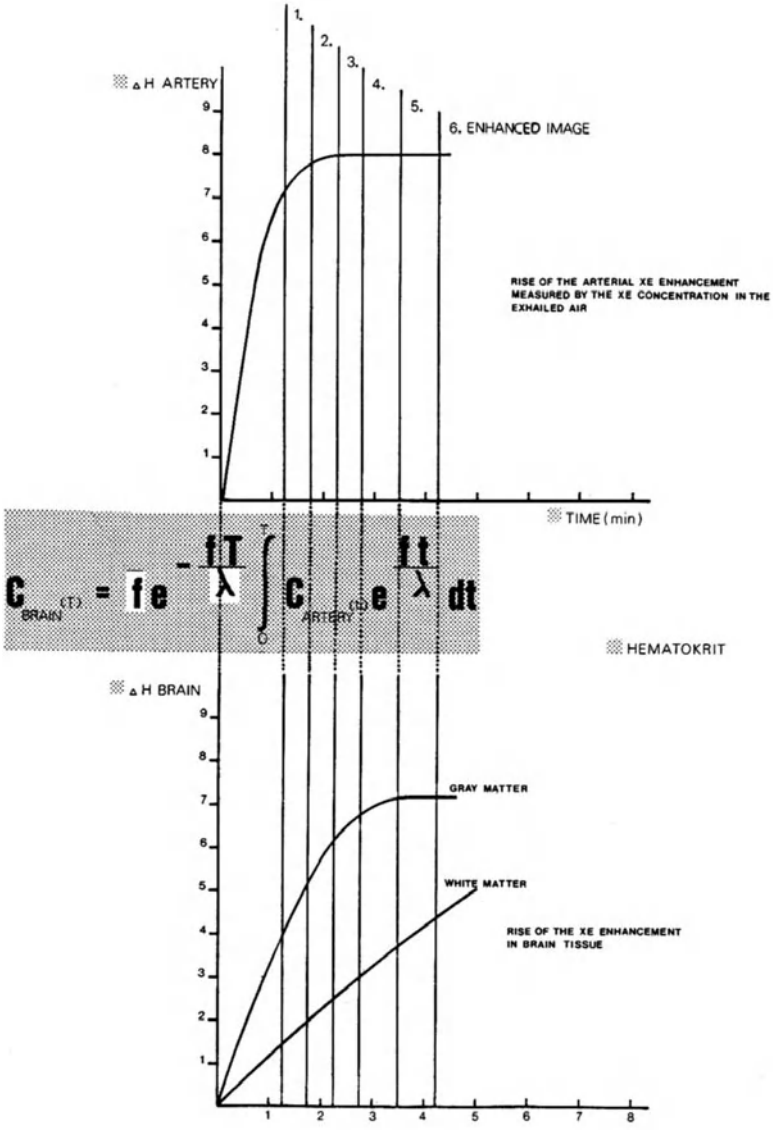


Fig. 1. Principle of simultaneous calculation of flow and $\lambda$ for each individual voxel. Dynamic scan sequence during xenon uptake (no wash-out curve analysis!). Measurement of end-tidal volume (at the end of expiration). Xenon concentrations were measured by thermal conductivity gas analyzer (GOW-MAC gas leak detector). Measurement of xenon enhancement in brain tissue was by CT during inhalation of a xenon/oxygen mixture (33%/67%). With such a xenon concentration, maximum xenon enhancement in gray matter will reach 7-9 HU (near saturation); enhancement in white matter is lower

sired (max. = three levels). Then inhalation of a xenon-oxygen mixture (33%/67%) is started, and after a preparation delay of 70-80 s a series of six xenon-enhanced images is initiated (Fig. 1).

For the *creation of the flow-map*, the two baseline images are first averaged to reduce noise levels and then subtracted from the enhanced images; consequently each voxel is defined by a series of enhancement values ($\Delta H$) as a function of time. This series is used together with end-tidal xenon measurements, which are assumed to be proportional to xenon concentrations in arterial blood, to solve a monocompartmental KETY-SCHMIDT equation (3) (equation in Fig. 1). Owing to a high pixel-to-pixel variation the flow-map has to be smoothened by a so-called bell-shape filter with two options – a high resolution option with 7 times 7 pixels and one with 9 times 9 pixels (we mainly use the latter). The unit of measurement is 100 ml blood/100 g brain/minute, as is usual in all other methodologies. With a window width of 100 HU and a window (center) level of 50 HU, flow values correlate directly to the gray scale at the left margin of the maps (Fig. 4). This means that completely white spots will have a flow of 100 ml/100 g br./min or more, while completely black areas will have no flow.

Before extensive evaluation for clinical purposes (see indications in Table 1) we first had to set up a topographic scale of reference for flow values. We reviewed the flow-maps of 71 patients, including nine healthy volunteers (Table 1), and measured l-CBF in 2021 regions of interest, with special attention to the circulation areas of the anterior, middle, and posterior cerebral arteries (ACA, MCA, PCA) as well as to superficial ("cortical") and subcortical gray and white matter. The scan level used for analysis is demonstrated at the top of Fig. 3 and includes the above-mentioned circulation areas, frontal, temporal, and occipital cortex and medulla, lenticular and caudate nucleus, thalamus, and internal capsule (Figs. 2, 3).

Table 1. Xenon-l-CBF CT examinations in 71 patients (mean $pCO_2$ exp. = 36±4 mmHg)

| Diagnosis | Number of patients | | |
|---|---|---|---|
| | Male | Female | Total |
| Cerebrovascular insufficiency | 24 (56 years) | 9 (47 years) | 33 |
| Subarachnoid hemorrhage (SAH) due to aneurysmal rupture | 5 (48 years) | 8 (51 years) | 13 |
| Angioma (AVM) | 2 (23 years) | 2 (42 years) | 4 |
| Craniocerebral trauma | 5 (26 years) | - | 5 |
| Tumor (perifocal edema) | 3 (51 years) | 2 (58 years) | 5 |
| Intracerebral hematoma | - | 2 (51 years) | 2 |
| Normal healthy volunteers | 5 (34 years) | 4 (43 years) | 9 |
| Total | 44 (49 years) | 27 (50 years) | 71 |

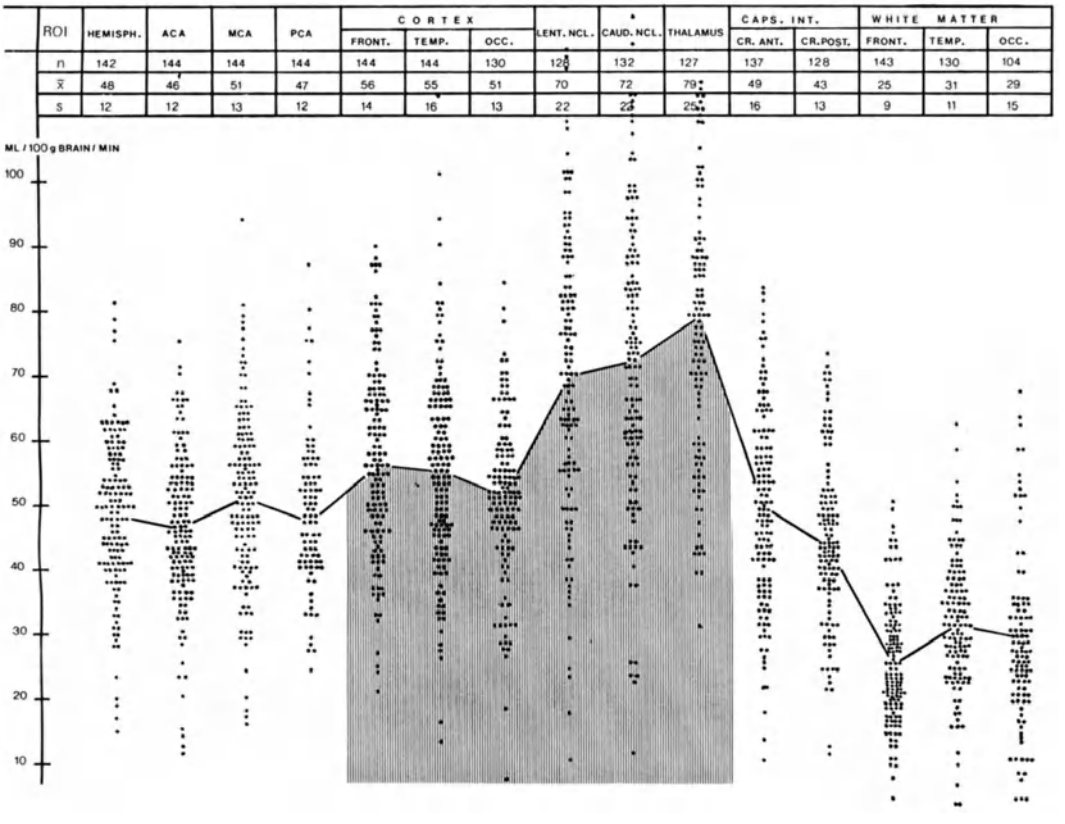


Fig. 2. l-CBF values of 2021 regions of interest (ROIs) in 71 patients

## Results

Topographical distribution of averaged flow values is demonstrated in Fig. 2, where each point represents an l-CBF measurement in a defined area, the so-called region of interest (ROI). In addition, regions with pathologically increased and reduced l-CBF were measured for each of the diseases listed in Table 1; subsequently achieved mean flow values can be expected to be somewhat lower than "normal" values. Furthermore with a growing number of examinations, which means a higher statistical reliability, a flow monogram in respect of age groups will be prepared.

## Discussion

MEYER et al. (12), who are working with a similar technique of xenon-enhanced CT, presented a list of l-CBF values gathered in seven normal healthy volunteers (mean age = 41 ± 9.6 years) (Table 2). For frontal, temporal, parietal, and occipital cortex they found extremely high values which we cannot accept despite the fact that in our l-CBF measurements especially cortical or, better, superficial structures are distinctly underestimated. This is due to the impossibility of measuring completely homogeneous brain tissue (dimension of voxel = 1 × 1 × 5 mm; smoothing option). In the case of the cortex even a small subarachnoid space which definitely has no flow can superimpose on flow measurement and artificially reduce the flow. As far as subcor-

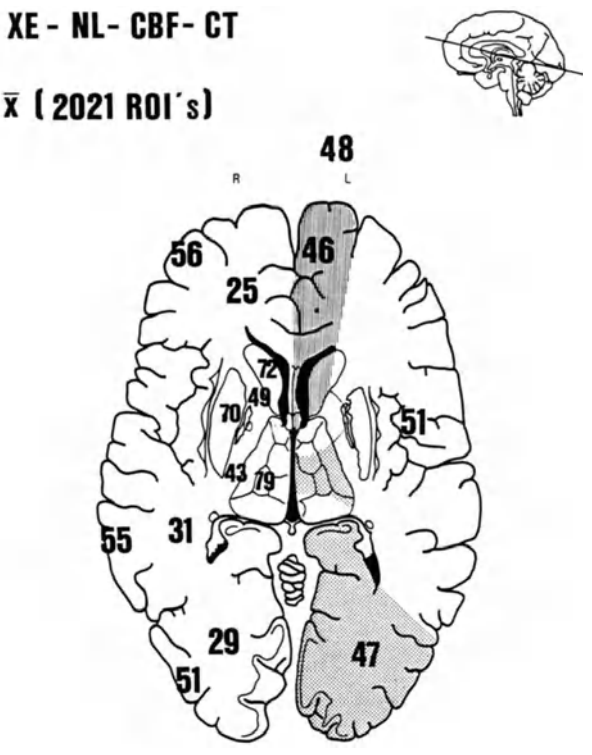


Fig. 3. Scan level used for l-CBF study, including area of circulation of ACA, MCA, and PCA, frontal, temporal, and occipital cortex and medulla, basal ganglia, and internal capsule. Distribution of averaged flow values

tical structures (17) and gray and white matter in general (fast and slow compartment) (4, 13, 16) are concerned, our averaged topographical l-CBF data are in line with those in the literature.

As evidence of the capabilities of xenon-CBF CT in clinical diagnosis, a case of flow reduction after subarachnoid hemorrhage due to aneurysmal rupture which we followed up with l-CBF mapping is reported in brief (Fig. 4): A 58-year-old man suffered from SAH two days before he entered our hospital. He presented with grade II according to HUNT and HESS. Angiography showed aneurysm on the right internal carotid artery (ICA) and vasospasm of the right middle cerebral artery (MCA) (Fig. 4, top left). Five days after SAH the first CBF study (Fig. 4., top right) showed significantly reduced flow values for the right MCA territory, with an averaged value of 33 ml/100 g br/min. Contralaterally we found an averaged flow of 59 ml/100 g br./min. At this point we decided to adopt temporarily a conservative attitude with Nimodipin therapy, but after five days l-CBF increased in the right hemisphere nearly to the same level as on the left side (Fig. 4., middle left). Because of the excellent clinical condition of the patient, surgery was performed 14 days after SAH. Three days after the operation the patient developed a left-sided hemiparesis. CT scan only showed a small edematous area in the right internal capsule, but the flow-map offered a generalized decrease of flow down to averaged values of 33 ml/100 g br./min in the right and 36 ml/100 g br./min in the left hemisphere (Fig. 4, middle right). Under hypervolemic infusion therapy, controlled

Fig. 4. Follow-up of subarachnoid hemorrhage due to aneurysmal rupture with stable xenon-l-CBF CT. See text for explanation

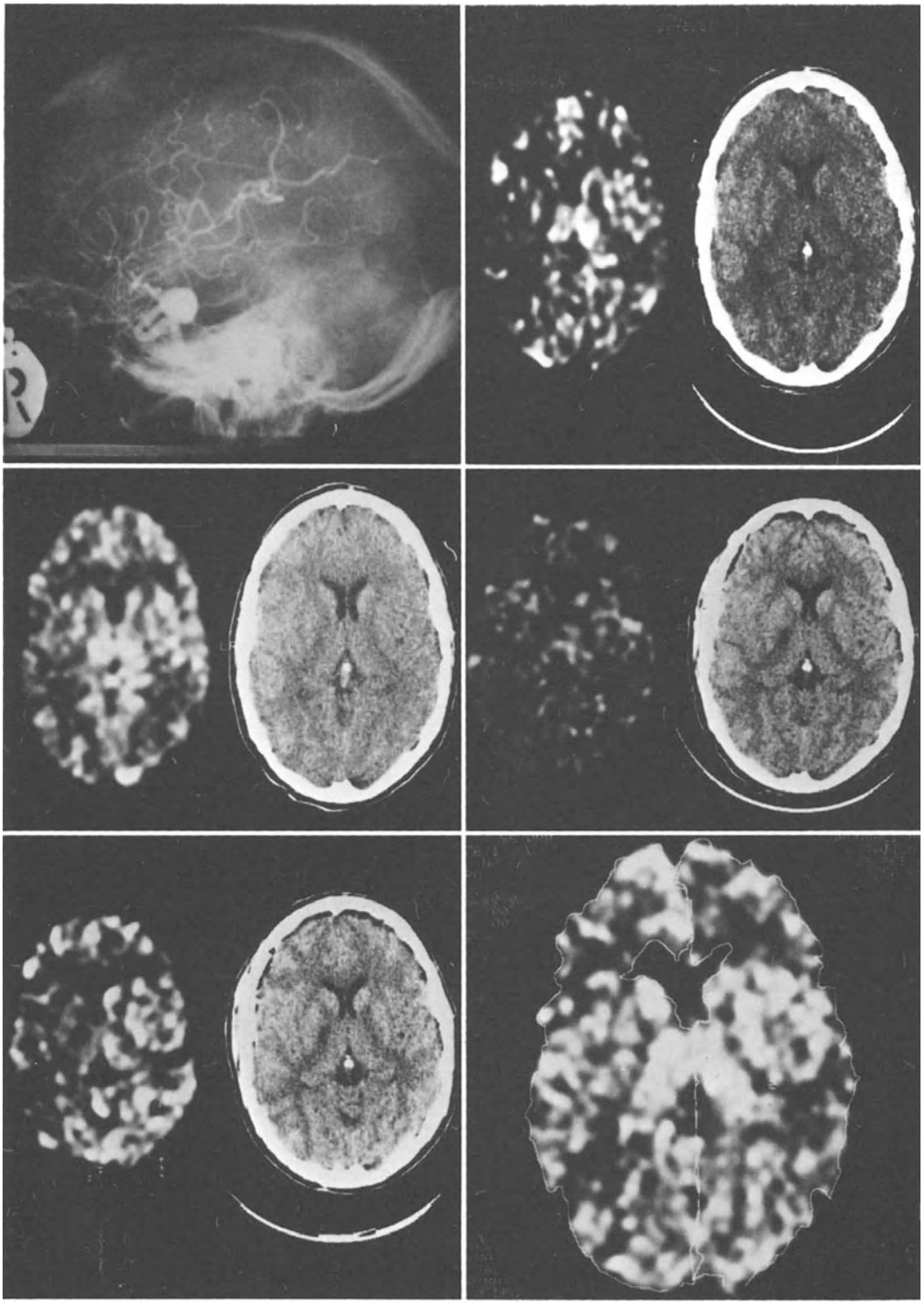

Table 2. Topographical regional and local CBF measured by different techniques (unit of CBF = ml/100 g/min)

| Method | Fast compartment | Slow compartment |
|---|---|---|
| Xenon-133 intracarotid injection (INGWAR et al. 1965) (4) | 79 ± 10 | 21 ± 3 |
| Xenon-133 inhalation (OBRIST et al. 1975) (13) | 71 ± (2-compartmental)<br>75 ± (3-compartmental) | 14 ± 6<br>22 ± 7 |
| Xenon-133 inhalation (WILSON et al. 1977) (16) | 74 ± (2-compartmental) | 16 ± 4 |
| Krypton-77 PET (positron emission tomography) (YAMAMOTO et al. 1981) (17) | Frontal cortex 74 ± 10<br>Parietal cortex 76 ± 10<br>White matter 3 ±<br>Caudate nucleus 71 ± 5<br>Putamen 74 ± 6 | |
| Stable xenon-enhanced CT (MEYER et al. 1981) (10-12) | Frontal cortex 81.3 ± 9<br>Temporal cortex 78.4 ± 11<br>Parietal cortex 83.3 ± 9.9<br>Occipital cortex 95.0 ± 25.2<br>Thalamus 84.4 ± 16.8<br>White matter 42.4 ± 8.3 | |
| Stable xenon-enhanced CT (LERCH et al. 1985) | Frontal cortex 56/14[a]<br>Temporal cortex 55/16<br>Occipital cortex 51/13<br>Lenticular nucleus 70/22<br>Caudate nucleus 72/23<br>Thalamus 79/25<br>Internal capsule 46/14<br>White matter 25/9 | |

[a]Standard deviation

hypertension and Nimodepin flow could be increased but mainly on the left hemisphere. There was still misery perfusion in the right MCA territory (Fig. 4, bottom left). One month after SAH his CBF study was normal, except for a local flow reduction in the right internal capsule (Fig. 4, bottom right). At discharge the patient presented with slight weakness of the left upper extremity.

## Conclusion

Stable xenon-1-CBF CT offers a topographical display of flow data with the highest spatial resolution currently available. The low radiation dose allows important follow-up studies in aneurysmal surgery, for example. In general our mean flow data correlate well with those gained with competing methodologies by other authors.

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# Perioperative Chemiluminescence of Polymorphonuclear Leukocytes and Monocytes in Brain Tumor Patients

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Different aspects of the involvement of the immune system in the defense against brain tumors have been investigated in the past. MAHALEY (5) found a decrease in delayed hypersensitivity reactions in patients with primary malignant brain tumors. PALMA et al. (9) reported data on the prognostic value of lymphocytic infiltration in glioblastoma. They correlated the outcome with the increase in lymphocytic infiltration and found that patients with glioblastoma and high lymphocytic infiltration had an increased survival time. The study by MORANTZ et al. (6, 7) has disclosed that a significant number of the cellular components represent macrophages.

Activated macrophages and granulocytes are important effector cells in the host defense system against malignant tumors. After stimulation, activated phagocytes show a massive respiratory burst, which is characterized by increased nonmitochondrial oxygen consumption. This stimulation results in the activation of oxidases which catalyze the production of activated oxygen species (1, 2). The oxygen species are microbicidal and tumoricidal (1-3). They generate chemiluminescence (CL) after relaxation and photon emission (1, 2).

The aim of this study in neurosurgical patients with benign and malignant diseases was to investigate whether there is a correlation between CL of phagocytes and tumor grade. Consequently the question arises as to whether or not the change in CL after operation correlates with the radicalness of the operation.

## Material and Method

Eighty-six patients were included in this study who had been admitted to the Neurological or the Neurosurgical Clinic of the University of Heidelberg. Patients were divided into several groups according to their histological tumor grade and the radicalness of operation. Four patients with AV malformations were not included in the histological tumor grade groups, and two patients were not operated upon.

### *Histological Tumor Grade*

Controls: vertebral disc operation ($n = 19$)
I. Meningioma and pituitary tumor ($n = 33$)
II. Oligodendroglioma, astrocytoma Kernohan grades I and II ($n = 17$)
III. Glioblastoma, astrocytoma Kernohan grades III and IV ($n = 13$)

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*Radicalness of Operation*

1. Controls: vertebral disc operation ($n = 19$)
2. Curative tumor operation ($n = 27$)
3. Palliative tumor operation ($n = 23$)
4. Biopsy or shunt procedure ($n = 15$)

Of 67 tumor patients 23 had received corticosteroid treatment before operation. All tumor patients received corticosteroids after the operation.

*Method*

Venous blood was drawn in all patients before the operation and 8 days postoperatively, and the white cells, monocytes, granulocytes, and erythrocytes were counted. Blood (0.1 ml) was mixed with 1 IU heparin, 0.4 ml Dulbecco's modification of Eagle's medium (DMEM), and 0.02 mg luminol and then incubated for 10 min at 37°C. The CL reaction was started by adding 0.5 mg nonopsonized zymosan or 0.5 mg latex (0.8 µm latex beads). The integral of the dynamic 40 min CL measurement with the Biolumat 9505 (Berthold, Wildbad) was related to 1000 phagocytes (monocytes and granulocytes) and termed CLA. Quenching of CL by erythrocytes was corrected using the formula described by HEBERER (4). Statistical analysis was performed with Wilcoxon 1 and 2 tests. Significance was set at $P < 0.05$.

Results

As stated above, 23 tumor patients had had short-term corticosteroid treatment before the operation and 44 tumor patients had not. There was no statistically significant difference between the two groups, neither in the zymosan-stimulated group (CLA with corticosteroid: 50.5, 95% confidence interval: 38.0-63.0; CLA without corticosteroid: 53.0, 95% confidence interval: 45.1-60.8), nor in the latex-stimulated CL group (CLA with corticosteroid: 87.8, 95% confidence interval: 50.5-125.0; CLA without corticosteroid: 76.3, 95% confidence interval: 58.5-94.2). The median dosage before CL measurement was 20 mg dexamethasone.

All histological subgroups had markedly elevated CLA levels after latex stimulation and slightly elevated CLA levels after zymosan stimulation compared with the controls (Table 1). There was a significant differ-

Table 1. Preoperative phagocyte CL (CLA = counts/1000 phagocytes per 40 min) of patients with brain tumors of different histological grade and controls (shown as mean and 95% confidence interval). Wilcoxon 2 test, NS: $P \geq 0.05$

| Histological tumor grade | $n$ | Zymosan stimulation | $n$ | Latex stimulation |
|---|---|---|---|---|
| Controls | 19 | 44.8 (38.6-51.0) | 19 | 51.7 (31.5- 72.0) |
| Group I | 33 | 52.3 (42.1-62.5) NS | 32 | 82.2 (55.7-108.7) $P = 0.04$ |
| Group II | 17 | 47.6 (38.4-56.7) NS | 17 | 77.8 (38.1-117.5) NS |
| Group III | 13 | 53.2 (32.2-74.3) NS | 13 | 70.9 (38.2-103.7) NS |

ence between group I after latex stimulation and the control group. When the pre- and postoperative CLA values were compared, there was no significant difference except in the biopsy and shunt operation group. The CLA changes did not correlate with the radicalness of operation. The lowest preoperative CLA levels increased, while the highest levels decreased after operation (Table 2).

## Discussion

Several immunological parameters were correlated with the outcome after brain tumor operation. Increased lymphocytic infiltration in and around malignant brain tumors was found to correlate with a longer survival time (9). The decreased delayed cutaneous hypersensitivity reaction (DHR) was proportional to the presence and extent of anaplasia of the brain tumors (5). DHR is also significantly diminished in patients with malignant extracranial tumors (10). In contrast to the depression of specific immune reactions, the reaction of the phagocytic cell system (macrophages, granulocytes) is markedly increased after stimulation in brain tumor patients, as shown in this study. Similar results have been obtained in patients with metastasizing malignant extracranial tumors (11).

Activation of macrophages has been shown to result in an increased production of activated oxygen species after stimulation (8). Phagocytes are involved in tumor defense against brain tumors (6, 7) and may be activated in brain tumor patients. It is desirable to correlate these data with the lymphocytic and phagocytic infiltration of the brain tumors, the postoperative survival rate, and long-term observations on CL.

## Conclusion

In conclusion, increased phagocytic cell CL was found after stimulation with zymosan and latex using the whole blood method. This may be the result of an increase in the activation of phagocytic cells in brain tumor patients. The radicalness of the operation did not correlate with the postoperative changes in CL 8 days after operation since the trauma of the operation may be predominant at this time.

Investigations of mononuclear cell infiltrations of brain tumors in correlation with the survival rate and long-term postoperative CL are ongoing.

Table 2. Pre- and postoperative phagocyte CL of patients with brain tumor operations of varying degrees of radicalness and controls (shown as mean and 95% confidence interval). Wilcoxon 1 test, NS: $P \geq 0.05$

| Radicalness of operation | | $n$ | Zymosan stimulation | | Latex stimulation | |
|---|---|---|---|---|---|---|
| Curative tumor operation | Preoperative | 27 | 52.4 (40.7-64.2) | NS | 81.2 (50.5-112.0) | NS |
| | Postoperative | | 56.2 (44.1-68.4) | | 74.5 (51.9- 97.0) | |
| Palliative tumor operation | Preoperative | 23 | 52.1 (41.0-63.1) | NS | 68.0 (43.7- 92.3) | NS |
| | Postoperative | | 60.9 (50.1-71.7) | | 70.6 (44.3- 96.9) | |
| Shunt or biopsy | Preoperative | 15 | 49.6 (36.1-63.0) | NS | 78.7 (39.2-118.2) | $P = 0.03$ |
| | Postoperative | | 49.5 (35.0-64.1) | | 41.2 (13.5- 68.9) | |
| Controls | Preoperative | 19 | 45.0 (38.4-51.5) | NS | 53.4 (32.1- 74.6) | NS |
| | Postoperative | | 49.9 (40.7-59.2) | | 61.8 (36.3- 87.3) | |

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# Experimental Hypertensive Intracerebral Mass Hemorrhage in Cats*

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## Introduction

About two-thirds of all patients with spontaneous intracerebral hemorrhage suffer from systemic hypertension. Additionally systemic hypertension is the main factor indicating a poor prognosis of intracerebral hemorrhage. This has been shown in our statistical evaluation of 117 cases of conservatively treated spontaneous intracerebral hemorrhage. More than 48% of the hypertensive patients died, but only 30% of the normotensive patients (Fig. 1). In an experimental study we investigated the influence of systemic hypertension and normotension on epidural pressure and on the formation of brain edema during the first 12 h after artificial intracerebral hemorrhage.

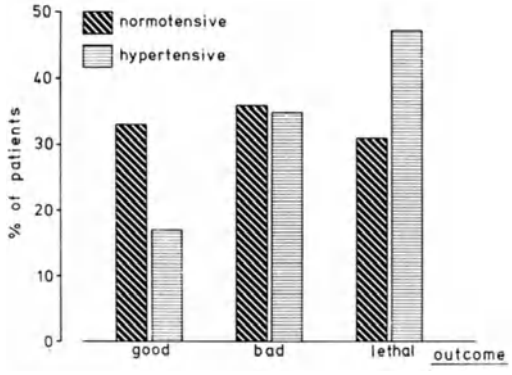


Fig. 1. Outcome of normotensive and hypertensive patients

## Methods

Nineteen randomized cats of either sex (2.8-3.6 kg body weight) were anesthetized (chloralose 40-50 mg/kg body weight; 1% solution), tracheotomized, relaxed (Imbretil 0.6 mg initially, 0.3 mg every 30 min), and normoventilated under steady-state conditions. Intracerebral hemorrhage was produced by stereotactic injection of 2 ml of freshly drawn autologous, arterial blood into the capsula interna of the right hemisphere (Fig. 2). In the normotensive group ($n = 9$) mean arterial blood pressure (MABP) was 110 mmHg. In the hypertensive group ($n = 10$) MABP

*This work contains parts of the theses of Mr. J. Bayer and Mr. G. Fries


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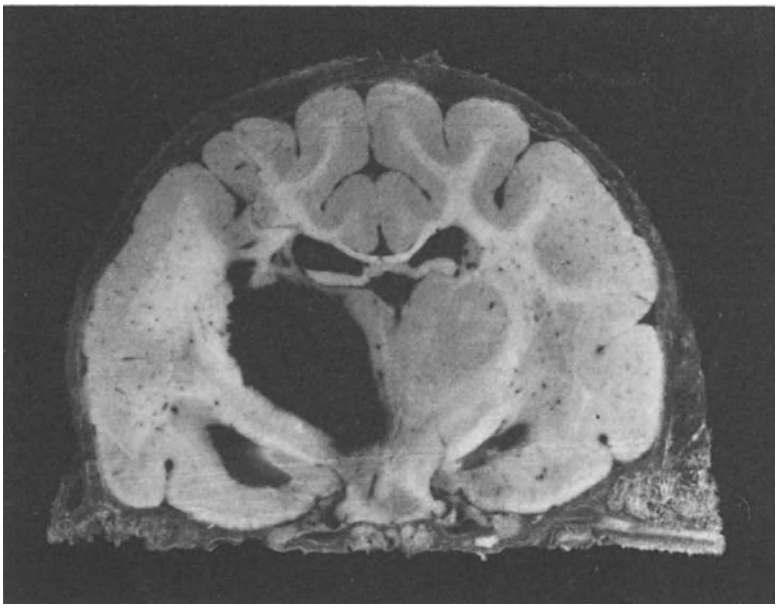

Fig. 2. Coronary brain section in the region of experimental intracerebral hemorrhage. Note the slight vasogenic edema in the perifocal area (normotensive animal)

was elevated to 165 mmHg for 13 h by a continuous infusion of angiotensin (Hypertensin CIBA, 3-60 µg/h).

Six cats with the same operative procedure but without intracerebral hemorrhage served as a control.

Immediately after the intracerebral injection of the blood, all animals received 2 ml of Evans-Blue 2% intravenously as a marker of extravasated plasma albumin.

MABP and epidural pressure were recorded continuously for 12 h after the intracerebral blood injection. Thereafter the brains were removed and the following investigations were performed: Water content and Evans-Blue content of the white matter of both hemispheres, adjacent and remote to the lesion (1). Coronary brain sections in the vicinity of these samples were examined microscopically for plasma protein extravasation using an immunofluorescence technique described by WILMES and HOSSMANN (6).

## Results

During the first 12 h after the intracerebral hemorrhage both groups, normotensive and hypertensive animals, presented only slight differences in epidural pressure, which was moderately elevated to 20 mmHg. However, during the phase of blood injection into the capsula interna, all hypertensive animals demonstrated an extreme increase of epidural pressure. To provide a sufficient cerebral perfusion pressure during this phase, the time of injection had to be doubled in most of the hypertensive animals. Nevertheless, three hypertensive animals developed cerebral decompensation, whereas none of the normotensive animals

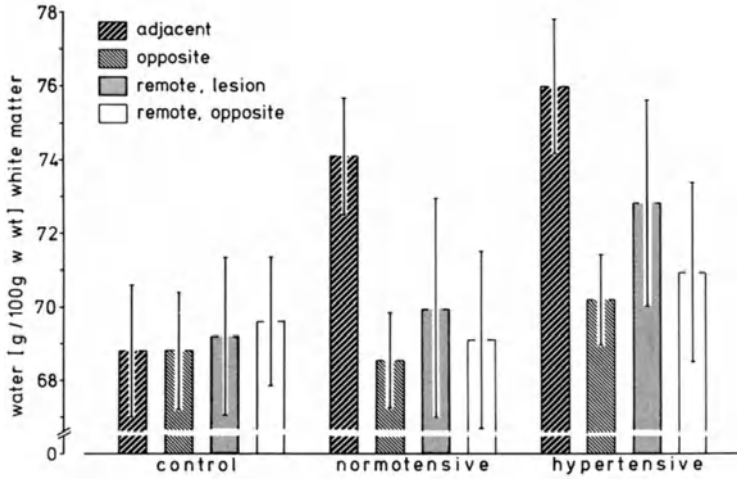


Fig. 3. Water content of the white matter in the control group, in the normotensive group, and in the hypertensive group. Values are $\bar{x} \pm Sx$

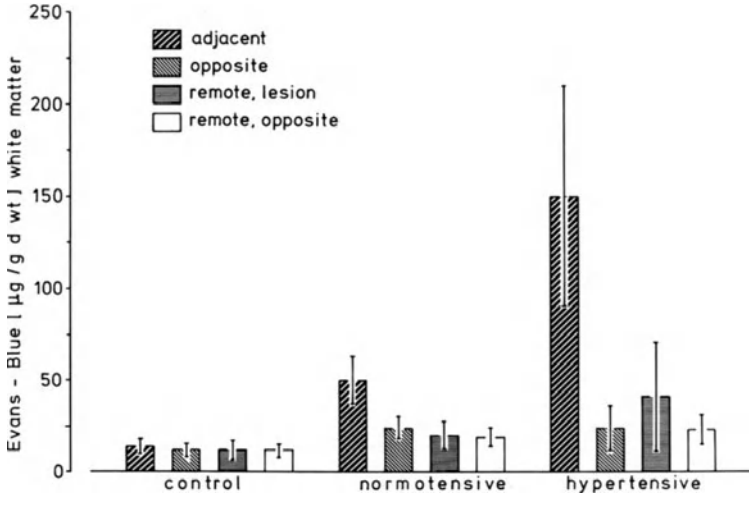


Fig. 4. Evans-Blue content of the white matter in the control group, in the normotensive group, and in the hypertensive group. Values are $\bar{x} \pm Sx$

decompensated. After 12 h perifocal white matter water content had increased to about 75 g/100 w. wt. in both the normotensive and the hypertensive group (Fig. 3). The white matter of the opposite hemisphere and of the control group offered normal values of water content (68-70 g/100 g w. wt.).

In contrast to these findings, the Evans-Blue content of the perifocal white matter in hypertensive animals (150 µg/g d. wt.) was three times higher than in normotensive animals (50 µg/g d. wt.) and ten times higher than in control animals (15 µg/g d. wt.) (Fig. 4). Though the


Fig. 5. Immunofluorescence microscopy in a normotensive animal ( x 60). Plasma fluid (*P*) has been filtered from the hemorrhage (*H*) into the perifocal white matter. There is no vasogenic edema around perifocal cerebral vessels (*V*)

increase of perifocal white matter water content was almost identical in the normotensive and the hypertensive group, we could observe a marked disturbance of the blood-brain barrier in the perifocal area only in the hypertensive group, identified by the massive concentration of Evans-Blue.

The immunohistochemical investigation demonstrated that within 12 h after the intracerebral hemorrhage under systemic normotension most of the plasma fluid of the hemorrhage was filtered into the perifocal white matter, leaving fine spots of fluorescence in the cerebral tissue (Fig. 5). Vasogenic edema could not be seen (3).

Due to the obviously reduced compliance of the cerebral tissue under systemic hypertension, most of the plasma fluid remained trapped in the hemorrhage.

Parallel to the increase of perifocal Evans-Blue content, intense perivascular fluorescence indicated vasogenic brain edema resulting from blood-brain barrier disruption in perifocal vessels.

## Conclusion

The prognosis of intracerebral hemorrhage is impaired by systemic hypertension. Our findings in experimental intracerebral mass hemorrhage in cats revealed two main causes of this impairment:

1. Systemic hypertension leads to an increased tension of cerebral vessels. As a consequence the cerebrovascular compliance is reduced

(5). The increase of cerebrovascular rigidity which contributes to the intracranial compliance provokes a pronounced rise of the intracranial pressure during the phase of bleeding (4).

2. Under normotensive conditions the plasma fluid of the hemorrhage is drained through the interstitial space into the cerebrospinal fluid. Thereby the initial space occupation due to the hemorrhage is reduced, whereas systemic hypertension may cause further disruption of the blood-brain barrier in the perifocal vessels (2). The developing vasogenic edema under systemic hypertension forms an additional space occupation besides the hemorrhage.

These factors have to be considered in the clinical therapeutic management.

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# Cerebrospinal Fluid and Serum Levels of the Arachidonic Acid Metabolites 6-keto-$PGF_{1\alpha}$ and Thromboxane $B_2$ in Patients with Subarachnoid Hemorrhage

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## Introduction

The development of cerebral angiospasm following rupture of an intracranial aneurysm is considered to be one of the major causes of morbidity and mortality in patients with subarachnoid hemorrhage (SAH) (20, 22, 29). Despite many clinical and experimental studies there is still no generally accepted treatment or prophylaxis of cerebral vasospasm. The complicated pathophysiological events which occur during the pre- and postoperative course of SAH and which may lead to fatal arterial narrowing are only partially understood. Recent investigations have elucidated the important role of metabolites of arachidonic acid, especially prostacyclin ($PGI_2$) and thromboxane $A_2$ ($TXA_2$), in the genesis of cerebral vasospasm after aneurysm rupture (1-6, 13, 18, 26) (Fig. 1). The delicate balance between $PGI_2$, a potent vasodilator and inhibitor of platelet aggregation, and $TXA_2$, a substance with strong vasoconstricting and platelet aggregating properties, is thought to be essential for the preservation of the tonus of the cerebral vasculature under physiological circumstances. During the course of SAH several pathological events lead to a decreased synthesis of $PGI_2$. Thus the relationship between $PGI_2$ and $TXA_2$ is changed to a disproportionate concentration of $TXA_2$ with consequent platelet aggregation and cerebral vasospasm.

The data which represent the basis for this hypothesis are almost all derived from in vitro studies and animal experiments. Therefore it was the aim of our study to clarify whether these alterations in $PGI_2$-$TXA_2$ homeostasis can be demonstrated after SAH in humans, too.

## Material and Methods

Eighteen patients with SAH who were admitted to our department within 1-5 days after aneurysm rupture and who had not taken any medication known to interfere with prostaglandin synthesis for at least 1 week prior to SAH, were included in the study. The patients were graded after the HUNT and HESS scale (14). Fifteen patients had their aneurysm verified by cerebral angiography. In three patients no aneurysm was found angiographically. In another three patients no operation was attempted because of their severe clinical condition. An initial CT scan was used to demonstrate the extent and degree of the SAH, which was graded after the proposed scale of HIGUCHI and co-workers (11), and to exclude any additional space-occupying lesion (Table 1). CSF was obtained preoperatively by lumbar puncture or postoperatively either by lumbar puncture or from continuous ventricular drainage. Venous blood was obtained via direct puncture of a vein or (in most cases)

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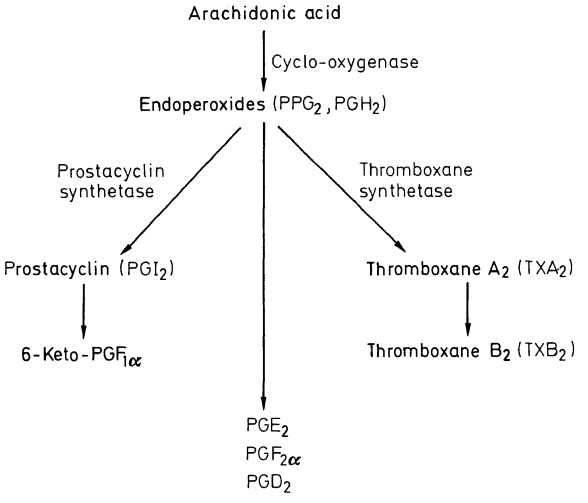



Fig. 1. Arachidonic acid metabolism: the cyclo-oxygenase pathway

by withdrawal of blood from an intravenous catheter. The CSF and blood samples of ten patients who had to undergo lumbar puncture because of a myelographic examination served as a control group.

Prostacyclin and $TXA_2$ are unstable metabolites with half-lives of 3 min ($PGI_2$) and 30 s ($TXA_2$), respectively. Therefore the $PGI_2$ and $TXA_2$ levels in CSF and serum were measured as a function of their stable hydrolysis products 6-keto-$PGF_{1\alpha}$ and $TXB_2$, which were assayed utilizing a highly specific radioimmunassay developed in the department of molecular pharmacology.

## RIA Procedures

6-keto(5,8,9,11,12,14,15 (n)-$^3$H)$PGF_{1\alpha}$ (spec. act. 120-180 Ci/mmol) and (5,6,8,9,11,12,14,15 (n)-$^3$H)$TXB_2$ (spec. act. 5-20 Ci/mmol) used as tracers in the specific radioimmunoassays were purchased from Amersham Buchler, Braunschweig, F.R.G. Prostanoid standards were from Upjohn, Kalamazoo, MI, U.S.A. and goat antirabbit $\gamma$-globulin antibody was from Behring-Calbiochem, Frankfurt, F.R.G. Venous blood or cerebrospinal fluid was collected together with sodium citrate (final concentration $10^{-2}$ M) and diclofenac (final concentration $10^{-4}$ M) as inhibitor of cyclooxygenase activity. Plasma was rapidly separated from blood cells by centrifugation at 4°C and samples were kept at -20°C until use.

6-keto-$PGF_{1\alpha}$ and $TXB_2$ were coupled to bovine serum albumin (BSA) using 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide (Sigma, München, F.R.G.) (9). Aliquots of the immunogens (300 µg in terms of BSA) were freshly emulsified with equal volumes of complete Freund's adjuvant (Difco, Detroit, MI, U.S.A.) and antisera were raised in white New Zealand rabbits by repeated booster injections (i.c.) at multiple sites of the animals' backs.

Radioimmunoassays were performed with minor modifications as described by PESKAR et al. (21) using a goat antirabbit $\gamma$-globulin antibody to separate free and antibody-bound prostanoids (19). Briefly, 0.1 ml labeled ligand (5000-10 000 cpm) and 0.1 ml antiserum diluted in char-

Table 1. Clinical characteristics, initial clinical and CT grades, and initial $TXB_2$ concentrations in 18 patients with SAH

| Patient | Sex | Age | Aneurysm | Grade | CT grade | Initial $TXB_2$ concentration in CSF (pg/ml) |
|---|---|---|---|---|---|---|
| 1 | m | 74 | Carotid | III | V | 63 |
| 2 | f | 59 | Carotid | IV | II | 46 |
| 3 | f | 63 | Carotid | I | IV | 4440 |
| 4 | f | 51 | Ø | II | II | 60 |
| 5 | m | 50 | Carotid | I | I | 133 |
| 6 | f | 68 | Ø | II | IV | 1224 |
| 7 | f | 61 | Ant. communic. | II | IV | 9832 |
| 8 | f | 57 | Carotid | II | II | 25 |
| 9 | f | 46 | Carotid | II | III | 26 |
| 10 | f | 43 | Middle cerebral | II | IV | 1412 |
| 11 | f | 22 | Carotid | III | II | 44 |
| 12 | f | 33 | Middle cerebral | III | II | 22 |
| 13 | f | 62 | Carotid | III | IV | 2486 |
| 14 | f | 39 | Middle cerebral | I | III | 299 |
| 15 | f | 50 | Middle cerebral | II | II | 43 |
| 16 | f | 55 | Basilar | I | II | 129 |
| 17 | f | 65 | Ø | III | IV | 792 |
| 18 | m | 61 | Middle cerebral | II | II | 29 |

coal-adsorbed normal rabbit plasma (final dilution 1:175) were incubated with samples or standards in a total volume of 0.6 ml (final dilution of anti-6-keto-$PGF_{1\alpha}$ antiserum 1:170 000) for 2 h at 4°C. After addition of goat antirabbit $\gamma$-globulin antibody (0.5 units in 100 ml) the incubation was continued overnight at 4°C. The antibody-prostanoid complexes were separated from unbound tracer by centrifugation and dissolved in sodium hydroxide solution (0.1 M). Radioactivity was determined by liquid scintillation counting and prostanoid levels were calculated in comparison with calibration standards ranging from 2.4 to 2500 pg. Radioimmunoassay for both prostanoids were highly sensitive, with detection limits of about 20 pg/ml of blood or cerebrospinal fluid. The intra-assay coefficients of variation were below 10% and exogenously added prostanoid standards (500 pg each) were recovered to 106 ± 5.7% ($TXB_2$) or 94.3 ± 2.2% (6-keto-$PGF_{1\alpha}$), respectively ($n = 4$). Relative cross-reactivities of various prostanoids with the specific antibodies were determined by comparing the amount of compound required to produce label displacement. A cross-reactivity below 0.1% was thereby found for $TXB_2$ in the 6-keto-$PGF_{1\alpha}$ radioimmunoassay and vice versa.

## Results

In eight out of ten patients of the control group the CSF level of $TXB_2$ was below the detection limit of 20 pg/ml. One patient had a $TXB_2$ concentration of 70 pg/ml, while in the other it was 117 pg/ml. The serum $TXB_2$ levels showed a wide distribution, ranging from below 20 pg/ml in four patients up to 394 pg/ml in one patient. Except in one patient (64 pg/ml), the CSF and serum levels of 6-keto-$PGF_{1\alpha}$ were below the detection limit (Table 2).

The $TXB_2$/6-keto-$PGF_{1\alpha}$ levels of the nonoperated patients are summarized in Table 3. Figure 2 shows the pre- and postoperative $TXB_2$/6-keto-$PGF_{1\alpha}$ levels of the 12 operated patients. The mean preoperative $TXB_2$ concentration was 58.4 pg/ml (<20-143 pg/ml), the mean postoperative $TXB_2$ being slightly lower at 46.6 pg (<20-145 pg/ml). The 6-keto-$PGF_{1\alpha}$ levels were significantly higher, with a mean preoperative level of 90.0 pg (20-542 pg/ml), while the mean postoperative value was 211 pg (<20-1303 pg/ml).

Table 2. Control group: $TXB_2$ and 6-keto-$PGF_{1\alpha}$ levels in patients with lumbar myelography

| | $TXB_2$ (pg/ml) | | 6-keto-$PGF_{1\alpha}$ (pg/ml) | |
|---|---|---|---|---|
| | Serum | CSF | Serum | CSF |
| 1 | 108 | 117 | 28 | <20 |
| 2 | < 20 | < 20 | <20 | 64 |
| 3 | 53 | < 20 | <20 | <20 |
| 4 | < 20 | < 20 | <20 | <20 |
| 5 | < 20 | < 20 | <20 | <20 |
| 6 | 394 | < 20 | <20 | <20 |
| 7 | < 20 | < 20 | <20 | <20 |
| 8 | 234 | < 20 | <20 | <20 |
| 9 | 125 | 70 | <20 | <20 |
| 10 | 52 | < 20 | <20 | <20 |

Table 3. $TXB_2$ and 6-keto-$PGF_{1\alpha}$ levels from nonoperated patients or patients without aneurysm

| Patient | Sex | | $TXB_2$ | | 6-keto-$PGF_{1\alpha}$ | |
|---|---|---|---|---|---|---|
| | | | Serum | CSF | Serum | CSF |
| A.K. | m | No operation | 430 | 74 | < 20 | 55 |
| U.R. | f | No operation | 52 | 46 | < 20 | 47 |
| B.P. | f | No operation | 149 | 22 | 69 | 57 |
| A.S. | f | No aneurysm | < 20 | 1224 | 683 | < 20 |
| I.W. | f | No aneurysm | 66 | 40 | < 20 | 267 |
| E.D. | f | No aneurysm | < 20 | 398 | 129 | < 20 |

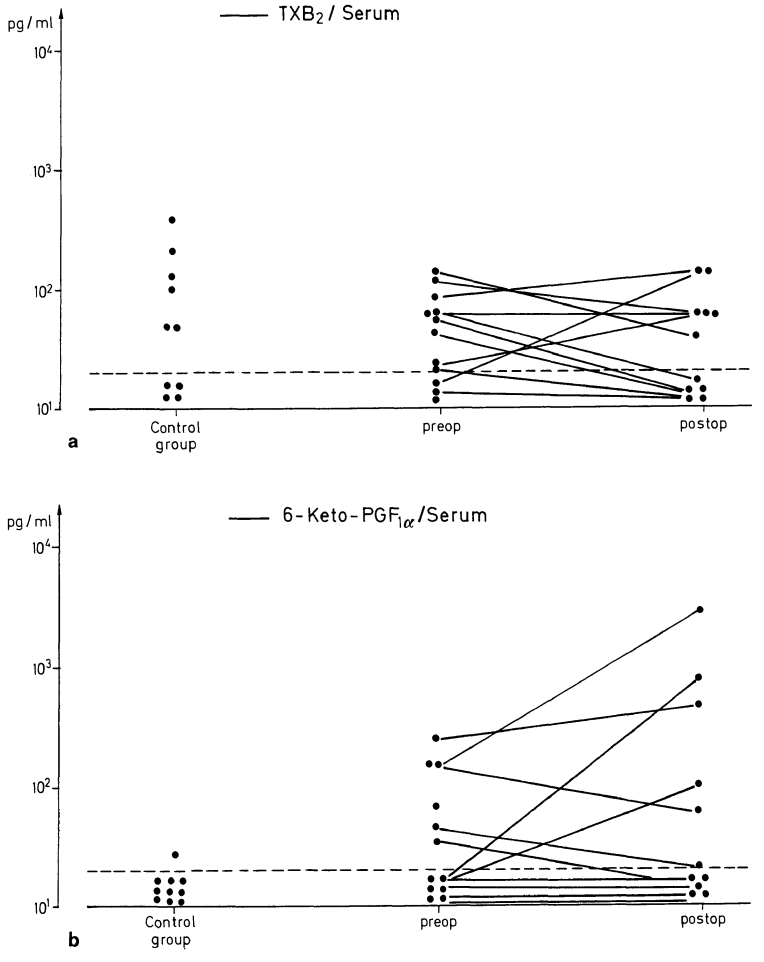



Fig. 2a,b. $TXB_2$ and 6-keto-$PGF_{1\alpha}$ levels in serum of 12 operated patients

As demonstrated in Fig. 3, the CSF level of both substances showed a different course. The mean preoperative value of 6-keto-$PGF_{1\alpha}$ was 62.4 pg (<20-143 pg/ml), with only one patient being below the detection limit in contrast to nine patients out of ten of the control group. The mean postoperative concentration was only slightly higher, at 73.1 pg/ml.

In contrast, the $TXB_2$ levels were exceedingly elevated. The mean $TXB_2$ level was 1582 pg, with a range from 26-9832 pg/ml. While eight out of ten patients of the control group were below 20 pg/ml, none of the patients with SAH were below the detection limit. Additionally, as demonstrated in Table 1, there was a good correlation between the initial $TXB_2$ CSF level and the grade of the SAH as demonstrated in the CT scan. The postoperative $TXB_2$ levels were significantly lower, with a mean value of 96.4 pg (<20-607 pg/ml).

The postoperative course of the CSF levels of $TXB_2$ and 6-keto-$PGF_{1\alpha}$ is even more informative. This will be demonstrated in the following four examples:

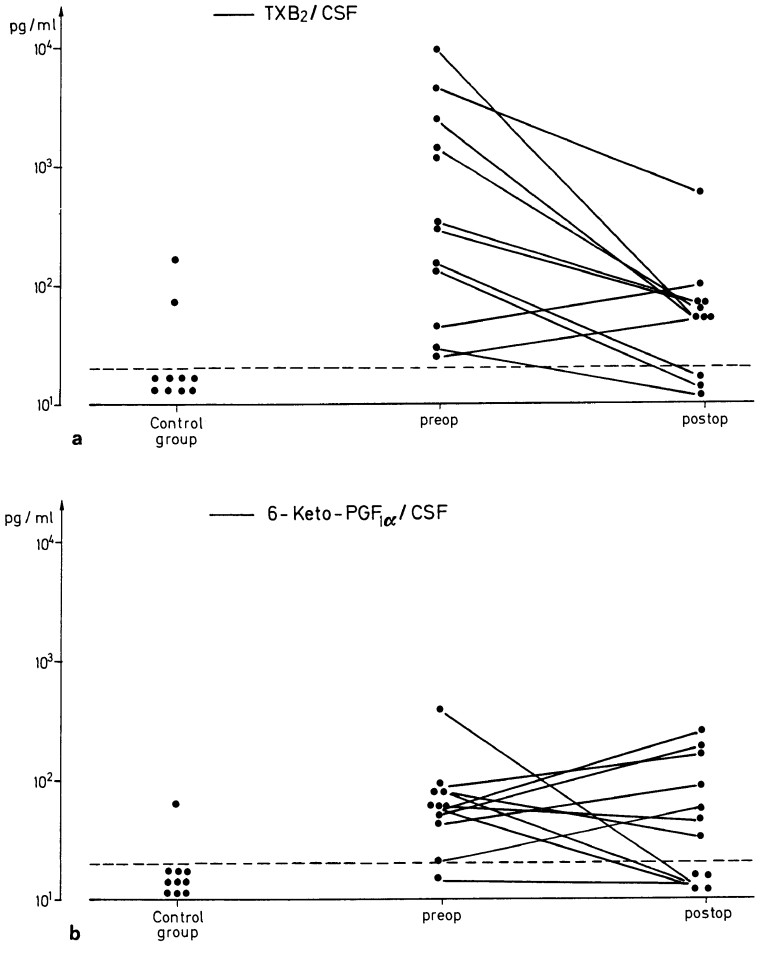



Fig. 3a,b. $TXB_2$ and 6-keto-$PGF_{1\alpha}$ levels in CSF of 12 operated patients

*Case 1:* A 39-year-old female with an aneurysm of the middle cerebral artery. SAH grade 3, initial $TXB_2$ level 299 pg/ml. Following operation and routinely performed cleavage of the basal cisterns, the TXB level fell to 74 pg and later to 40 pg/ml. The patient made an uneventful recovery (Fig. 4a).

*Case 2:* A 57-year-old female with an aneurysm of the carotid artery. SAH grade 2, low initial $TXB_2$ level of 25 pg/ml, slight elevation to 114 pg/ml at the third postoperative day without change in the clinical condition. Uneventful recovery (Fig. 4b).

*Case 3:* A 43-year-old female with an aneurysm of the middle cerebral artery. SAH grade 4, initial TXB level of ↑412 pg/ml. After operation and cleavage of the cisterns the $TXB_2$ level dropped to 63 pg/ml. Six days after SAH the $TXB_2$ level rose again, with clinical deterioration of the patient from grade 2 HUNT and HESS (14) to grade 3-4. The patient recovered slowly, paralleled by a decline of the $TXB_2$ levels (Fig. 4c).

*Case 4:* A 61-year-old female with an aneurysm of the anterior communicating artery. SAH grade 4. Highest initial $TXB_2$ level of all patients, with 9832 pg/ml. After operation and cleavage of cisterns the $TXB_2$ level dropped below detection limit. Secondary rise of $TXB_2$ level on the seventh postoperative day. Clinical deterioration from grade 2 to grade 4. The patient died after further deterioration. (Fig. 4d)

In cases 3 and 4 the control CT scans demonstrated marked hypodense areas of cerebral infarction.

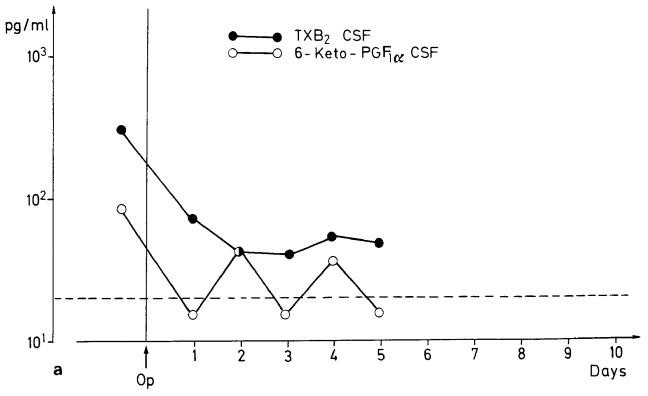
## Discussion

The homeostasis between the two arachidonic acid metabolites prostacyclin and $TXA_2$ is thought to be essential for the maintenance of the cerebrovascular tone. In recent studies it has been demonstrated that during experimental SAH there is a significant deficiency of prostacyclin concentration (16, 18, 26). This is considered to be a sequela of, on the one hand, the ultrastructural damage of the endothelial cells of the cerebral arteries (7, 17, 27, 28), which are considered to be the main location of prostacyclin production, and, on the other, the inhibition of prostacyclin synthetase by specific inhibitors synthesized during the course of SAH following lysis of the subarachnoid blood clots in the basal cisterns. The decline of the prostacyclin concentration leaves the cerebral vessels unprotected against the combined action of spasmogenic substances. The enzyme essential for the synthesis of $TXA_2$ is not affected during SAH (10, 23, 25). Additionally, the damaged endothelium is an ideal condition for adhesion and aggregation of circulating platelets with release of $TXA_2$. Thus the elevation of $TXA_2$ and the decreased concentration of $PGI_2$ may lead to prolonged cerebral vasospasm following SAH.

The above-mentioned data are almost all derived from experimental investigations.

The main finding of our clinical study is that the alteration of $TXA_2$/$PGI_2$ homeostasis which has been postulated is demonstrable during the clinical course of SAH in humans, too. However, the serum levels of both $TXB_2$ and 6-keto-$PGF_{1\alpha}$, although being elevated in half of the patients pre- and postoperatively in comparison to the control group, do not provide any informative data concerning the degree of SAH or the clinical course of the patient (Fig. 2a,b). In contrast to other vascular diseases like angina pectoris or Prinzmetal's angina (12, 15, 16), it seems unlikely that alterations in prostaglandin metabolism and especially $TXA_2/PGI_2$ homeostasis which take place in the vicinity of the cerebral vessels within the blood-brain barrier can be detected in the peripheral venous blood. The possibility of artifacts from the venous puncture make interpretation of the serum levels even more difficult.

In contrast, measurement of $TXB_2$ and 6-keto-$PGF_{1\alpha}$ in the cerebrospinal fluid provides important additional information. Firstly, there seems to be a close correlation between the amount of blood demonstrable by CT and the degree of the initial preoperative $TXB_2$ level (Table 1). As the frequent association of vasospasm with the presence and especially the amount of subarachnoid blood has been verified by CT scan and clinical studies (8, 11), it can be speculated that the preoperative $TXB_2$ level in the CSF may be an additional important factor for the detection of patients at risk of developing cerebral vasospasm. Secondly, although the role of intraoperative cleavage of the basal cisterns is generally accepted (24) and its importance can be demonstrated by the postoperative fall in $TXB_2$, it cannot totally prevent a secondary



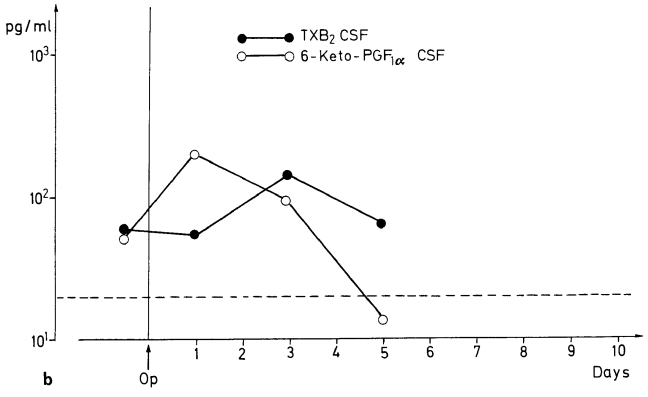
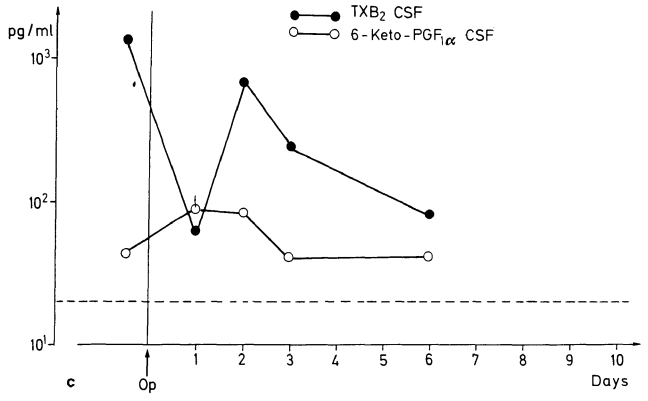
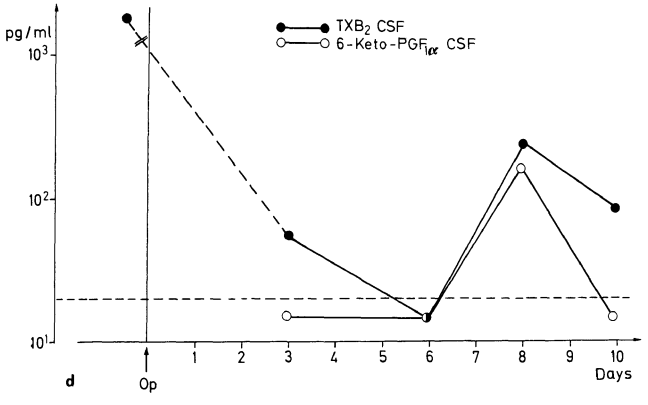




Fig. 4a-d. Cases 1-4

rise in $TXB_2$ and consequent worsening of the clinical condition. The degree of alteration of the $TXA_2/PGI_2$ relationship during SAH is obvious when comparing the CSF levels of $TXB_2$ and 6-keto-$PGF_{1\alpha}$ (Fig. 3). The slight to moderate elevation of 6-keto-$PGF_{1\alpha}$ or prostacyclin which, according to general opinion, exerts an important protective effect on the cerebral vasculature is significantly surmounted by the elevation of $TXB_2$. As a nearly normal pre- and postoperative course of $TXB_2$ at low CSF levels seems to be associated with a benign clinical course, the secondary rise in $TXB_2$ may be even more important for the development of cerebral vasospasm, as demonstrated in cases 3 and 4 discussed above. As the rise in $TXB_2$ level seems to occur before the clinical deterioration of the patient, the detection of postoperative elevated $TXB_2$ concentration in the CSF may possibly serve as a biochemical indicator of incipient cerebral vasospasm.

Further studies concerning the important role of arachidonic acid metabolites in bigger patient groups are warranted.

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# The Effect of the Cleavage Peptide C3aDesArg of the Third Complement Component on the Accumulation of Leukocytes in Cerebrospinal Fluid (CSF) and on the Permeability of the Blood-CSF Barrier

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## Introduction

Complement is an important humoral effector system of the immune response (5, 8). It is a set of nine serum proteins which can be triggered by antigen-antibody complexes to initiate an exactly defined cascade of proteolytic and protein-binding reactions (Fig. 1), so-called complement activation (5, 8). This finally leads to phagocytosis and lysis of foreign cells. Apart from this main pathway an alternative pathway (Fig. 1) of complement activation by endotoxins is known (5, 8). The fact that its activation can also be triggered by plasmin and Hageman factor fragment (Fig. 1) links complement to other important humoral effector systems, the fibrinolytic, coagulation, and kallikrein-kinin systems. During complement activation C3a arises as a cleavage peptide of the third complement component and is rapidly transformed into C3aDesArg by a serum carboxypeptidase (8). Like C3a, C3aDesArg increases vascular permeability and causes chemotaxis of leukocytes (1, 2, 4). These properties make both peptides potent mediators of inflammation. It had not yet been demonstrated that the experimental application of complement-derived polypeptides to the CSF caused an inflammatory response including the increase of cell counts and an increase of the permeability of the blood-CSF barrier. We studied this using the more stable polypeptide C3aDesArg.

## Materials and Methods

Highly purified C3aDesArg[1] of the hog was used. Cats of both sexes with body weights of about 3 kg (2.7-3.2 kg) were anesthetized with xylazine and ketamine, tracheostomized, and ventilated. Arterial pressure was continuously monitored by a Statham device. Intracranial pressure (ICP) was continuously monitored by an epidural Statham device. The ventilation was supervised by arterial blood gas analyses. The cisterna magna was punctured, 0.5 ml of CSF was taken, and 4 mg C3aDesArg in 0.5 ml saline was injected in eight animals. Eight control animals received saline without C3aDesArg. Initial cell counts of the sampled CSF were performed to make sure that all animals had normal cell counts at the beginning. Ten minutes later all 16 animals received 2 ml/kg body weight of a 2.5% solution of Evans' blue by intravenous injection.

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[1]The authors wish to thank Prof. Dr. med. W. Vogt and PD Dr. med. B. Damerau, Department of Biochemical Pharmacology, Max-Planck Institute for Experimental Medicine, Göttingen, West Germany, for preparation and purification of C3aDesArg

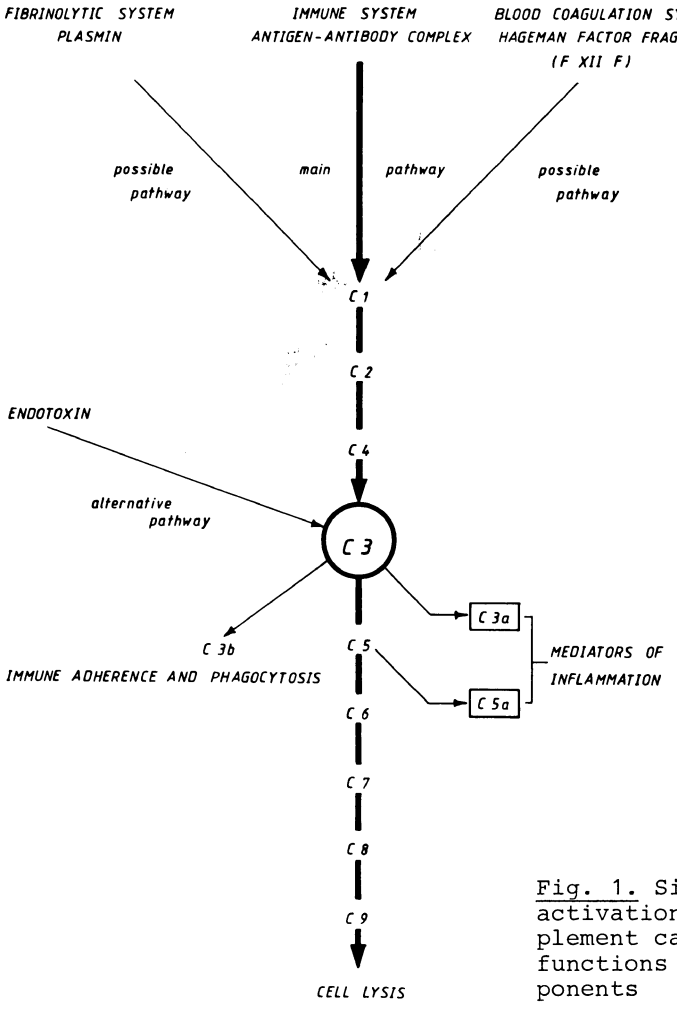


Fig. 1. Simplified diagram of the activation pathways of the complement cascade and physiological functions of the complement components

Three hours later CSF was sampled. The white blood cells (WBC) were counted and the dye concentration was measured photometrically. The animals were sacrificed and the choroid plexus of the fourth ventricle was taken for electron microscopic examination.

## Results

There was only a slight increasing effect of C3aDesArg on the ICP.

Figure 2 shows the WBC counts of the CSF. There was a highly significant increase of WBC in the CSF of C3aDesArg-treated cats. The number is approximately 15 times higher in the C3aDesArg group than in the control group.

Figure 3 shows the concentration of Evans' blue. The dye concentration was 6 times higher in the C3aDesArg group than in the control group. The difference is highly significant.

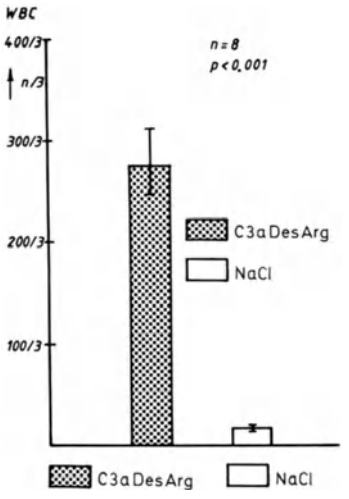


Fig. 2. The accumulation of white blood cells (*WBC*) in CSF after application of C3aDesArg or NaCl to the cisterna magna. The difference is significant ($P < 0.001$) in Student's $t$-test and the Whitney U-test

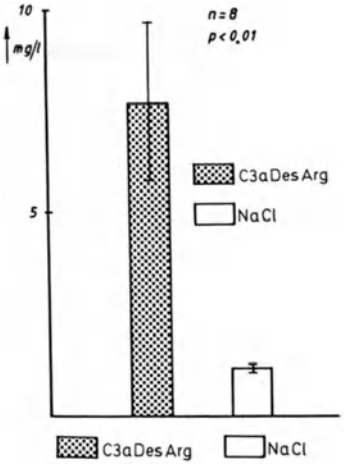


Fig. 3. The accumulation of Evan's blue in CSF after application of C3aDesArg or NaCl to the cisterna magna. The difference is significant ($P < 0.01$) in Student's $t$-test and the Whitney U-Test

Electron microscopic examination of the choroid plexus revealed a large number of leukocytes in the plexus capillaries of the C3aDesArg-treated cats but only sporadic leukocytes in the control animals (Fig. 4).

## Discussion

The role of complement-derived polypeptides as mediators of inflammation has been established, as already stated in the introduction. We were able to demonstrate that the cleavage peptide of the third complement component C3aDesArg can play a role in inflammatory processes in the central nervous system. The increase of the CSF cell counts to a 15 times higher level is unequivocal. The dye concentration was significantly increased, too.

The probable site of the effect is the choroid plexus, as may be suggested by the electron microscopic findings showing a significant accumulation of WBC in the plexus capillaries. It is interesting that not only polymorphonuclear granulocytes but also macrophages and lymphocytes were found.

The mode of action of complement-derived polypeptides is not fully clear. The chemotactic effect of polymorphonuclear leukocytes can be shown in vitro (1). It has also been established that the C3-derived polypeptide C3b is indispensable for phagocytosis by macrophages (5, 8).

Recent investigations show that macrophages and rabbit peritoneum can be stimulated by C3-derived polypeptides to release prostaglandins (3, 6, 7). Further investigations will be necessary to find out whether the effect of C3aDesArg is due to a stimulation of the prostaglandin

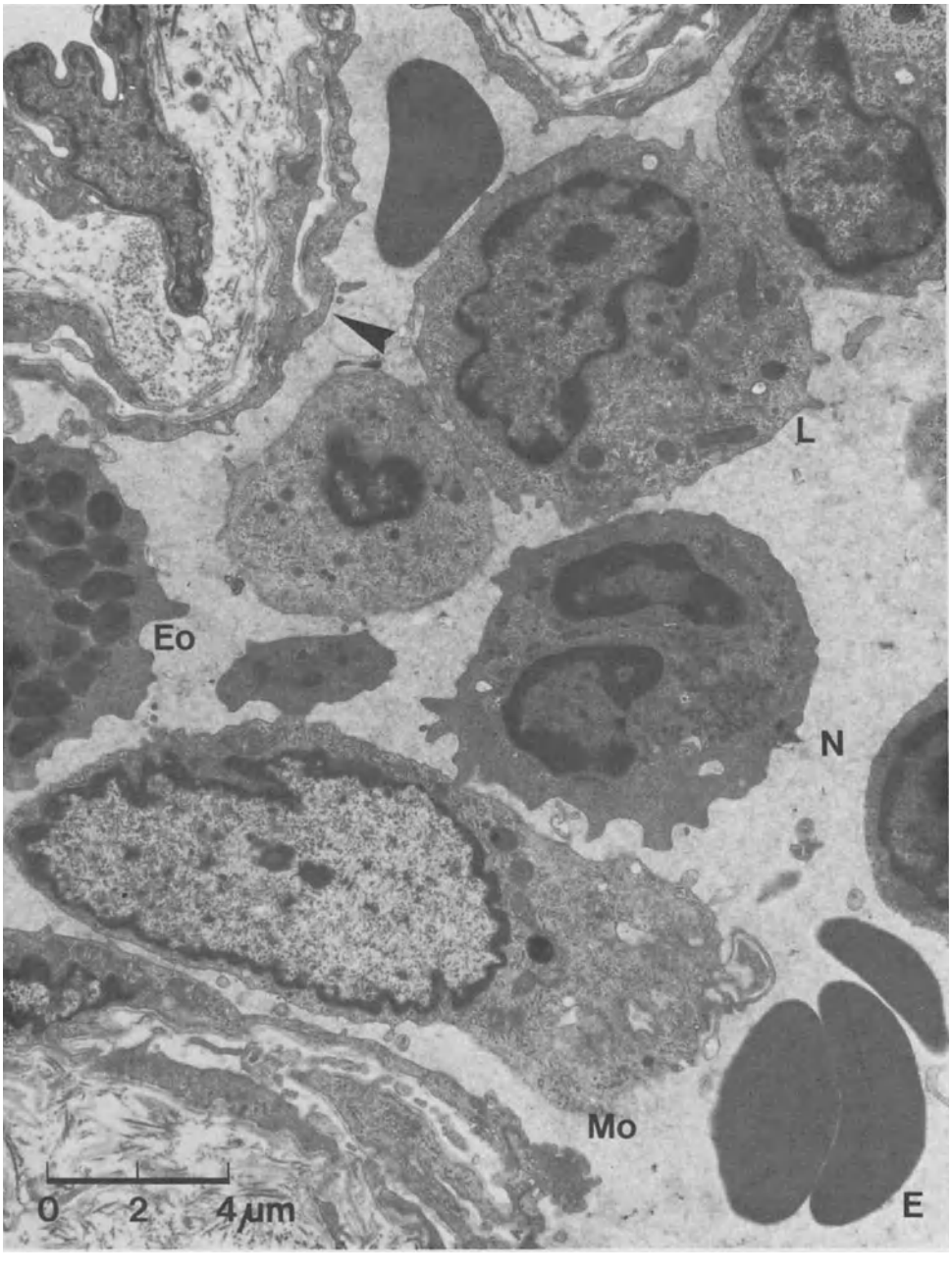


Fig. 4. Electron microscopic examination of a plexus capillary of a C3aDesArg-treated cat reveals a large number of white blood cells in the lumen, including neutrophilic granulocytes (*N*), eosinophilic granulocytes (*Eo*), lymphocytes (*L*), and monocytes (*Mo*). Homogeneously dark cells are erythrocytes (*E*). The capillary wall is marked by an *arrow*

synthesis or not. DAMERAU et al. (2) could not find a significant effect of indomethacin, an inhibitor of prostaglandin synthesis, on the C3a-induced inflammatory response of the guinea pig pleura.

As complement cannot only be activated by antigen-antibody complexes but also by endotoxins, plasmin, and Hageman factor fragment, it plays an important role in all processes of infection, inflammation, and tissue repair. We were able to show that it is efficacious in the CNS, too.

## Conclusions

From our results we conclude that we found a new experimental model for inflammatory processes of the CNS which may imitate the factual pathophysiological mechanisms.

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# Rostral Spread of Epidural $^3$H-Labeled Morphine

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## Introduction

Since BEHAR (1) first introduced epidural morphine for treatment of pain, morphine solution has generally been administered in a high injection volume. Yet epidural morphine in low injection volumes is also effective in the treatment of acute (3, 7) and chronic (4, 8) pain, as we were able to prove in 1984 (6). Recently we have demonstrated that cisternal cerebellomedullary CSF concentrations of morphine are dependent on the volume of the epidural injection; this suggests that the risk of respiratory depression might be reduced with low-volume injections of epidural morphine (5), as HUG et al. demonstrated in 1981 that there is an evident relationship between cisternal cerebellomedullary CSF concentrations and end-tidal $CO_2$ (10).

The aim of the present study was to obtain further information on the rostral spread of epidural morphine using various bolus volumes in both large and small dogs.

## Materials and Methods

For ethical reasons, we obtained permission from the Committee for Animal Investigations to carry out our investigations on dogs. Three dogs anesthetized with pentobarbital were kept lying on their left side throughout the course of the experiment. Dog I (12 kg) and dog II (33 kg) received 2 mg morphine in 10 ml saline into the epidural interspace at T7 and L3, respectively. The solution administered to dog I contained 0.25 mCi $^3$H-morphine; that of dog II contained 1 mCi $^3$H-morphine. Dog III (32 kg) received 2 mg morphine in 1 ml saline (+ 1 mCi $^3$H-morphine) prior to an epidural infusion of 8 mg (+ 5 mCi $^3$H-morphine) over 48 h at T7. Cisternal cerebellomedullary CSF samples (Fig. 1) were taken at various intervals to determine the counts per minute (cpm) by the Packard Tricarb liquid scintillation spectrometer, model 574.

Six large dogs, with a mean weight of 33 kg, and three small dogs, with a mean weight of 15 kg, received an epidural bolus injection of 10 ml Iohexol (300 mg/ml, Schering) to evaluate rostral spread by radiography.

## Results

In small dog I, peak cisternal cerebellomedullary radioactivity of 24 000 cpm was reached within 30 min after the bolus epidural injection of morphine. Radioactivity subsequently declined to 70 cpm after 48 h (Fig. 2).

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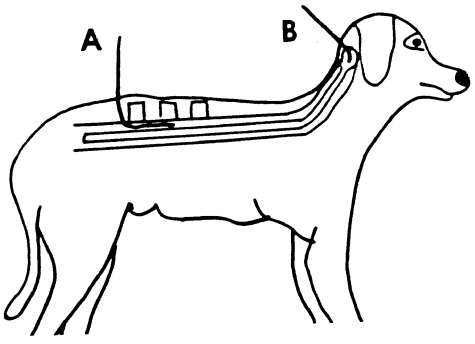


Fig. 1. The catheter position. *A*, epidural space; *B*, cerebellomedullary cistern

Figure 3 shows cisternal cerebellomedullary CSF radioactivity in large dog II. Peak radioactivity of only 2800 cpm was reached within 40 min after the bolus epidural injection. Radioactivity subsequently declined to 20 cpm after 48 h. In large dog I, which weighed 32 kg, peak radioactivity of 990 cpm was reached within 50 min after the administration of the low-volume epidural bolus (Fig. 4). The counts were significantly lower than after the high-volume bolus (Fig. 3), although the epidural catheter tip at T7 was placed far higher in dog III than in dog II (Fig. 3)

These differences of CSF morphine concentrations in large and small dogs led us to investigate the distribution of a contrast agent, Iohexol, in large and small dogs. The mean rostral spread of Iohexol was 12±0.7 spinal segments in larger dogs (mean weight 33 kg) and 17±1 spinal segment in smaller dogs (mean weight 15 kg).

## Discussion

Respiratory depression due to the rostral spread of epidural morphine (2) has until now prevented the widespread use of the method in treatment of postoperative pain (9). The relationship between morphine concentrations near the respiratory center and the risk of respiratory depression has already been established. However, our cerebellomedullary CSF morphine concentration measurements gave, for the first time, evidence that the injection volume of epidural boluses is of major importance for the occurrence of this side effect (5). Epidural morphine in high injection volumes produced far higher cisternal cerebellomedullary CSF morphine concentrations than epidural morphine in low injection volumes.

Our morphine measurements by radioimmunoassay confirmed the results stated above. Moreover, these results showed that the position of the epidural catheter tip plays a role in the risk of respiratory depression, because the morphine concentration near the respiratory center is inversely related to the distance from the site of injection to the cerebellomedullary cistern. The size of the epidural space has also proved to be of great importance for the extent of rostral spread of epidurally administered solutions. Thus it would be interesting to inspect cases of respiratory depression following high volume bolus epidural injections of morphine with regard to the size of the catheter tip and the age of the patients.

At any rate, our results indicate that epidural infusions of morphine do not appear to pose a serious risk of respiratory depression and are therefore preferable to intermittent high-volume bolus epidural injec-

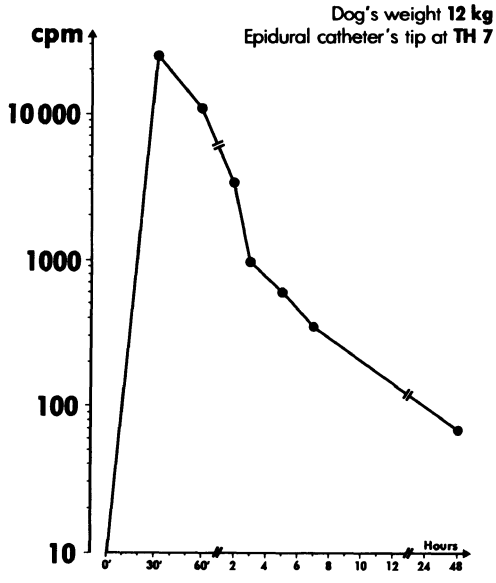


Fig. 2

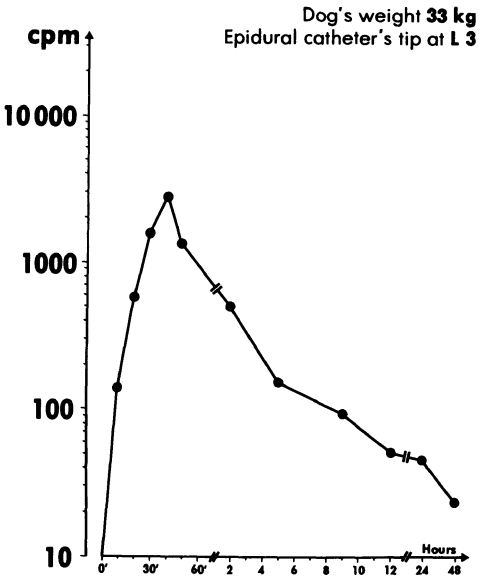


Fig. 3

Figs. 2, 3. Cisternal cerebellomedullary CSF radioactivity after an epidural morphine bolus of 2 mg (+ 0.25 mCi $^{3}$H-morphine)/10 ml saline

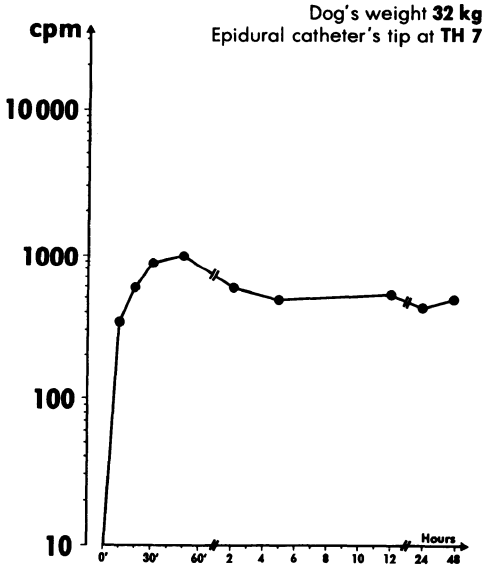


Fig. 4. Cisternal cerebellomedullary CSF radioactivity after an epidural morphine bolus of 2 mg (+ 1 mCi $^{3}$H-morphine)/1 ml saline prior to a morphine infusion of 8 mg (+ 5 mCi $^{3}$H-morphine) over 48 h

tions, which should be abandoned in postoperative pain treatment, provided the epidural catheter tip is placed in the area with the maximum nociceptive input.


## Summary

Rostral spread of contrast agent in the epidural space and of epidurally administered, radioactively labeled morphine was evaluated in dogs. It was established that the rostral spread of a bolus epidural injection of contrast agent depends on the size of the epidural space. The level of radioactivity of CSF samples taken near the respiratory center was shown to be inversely related to the distance from the site of injection to the cerebellomedullary cistern and to be directly related to the volume of the epidural injection. High-volume bolus epidural injections should therefore be abandoned in pain treatment in order to reduce the risk of respiratory depression.


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# Subdural Implantation of RG2 Glioma Spheroids in Rat Cerebellum: A New Experimental Brain Tumor Model*

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## Introduction

In experimental oncology multicellular tumor spheroids (MTS) serve as an in vitro model which simulates avascular three-dimensional solid tumor growth adequately (13). We succeeded in growing the malignant RG2 glioma clone as MTS. The RG2 clone is derived from a transplacentally N-nitrosourea induced tumor of the central nervous system in inbred CDF rats, morphologically characterized as malignant glioma and established in tissue culture (4).

Previous transplantation brain tumor models depend on direct implantation of tumor cells into the brain, by stereotactic or other techniques, necessarily traumatizing the nervous tissue and causing primary mechanical disruption of the blood-brain barrier (1, 6, 11, 12). The use of intracerebral transplantation tumors has advantages and also distinct limitations with regard to the evaluation of tumor growth and of disturbances of the blood-brain barrier (3), so that chemotherapy or irradiation effects have to be determined in terms of changes in the mean survival time (1, 5).

In order to avoid the problem of primary mechanical disruption of the blood-brain barrier and to check tumor growth with ease by direct visualization, we developed and standardized a new transplantation model in syngeneic rats, by implantation of RG2 glioma spheroids into the subdural space of the cerebellum.

## Materials and Methods

### *Multicellular Glioma Spheroids*

For the MTS production, RG2 clonal neoplastic cells (4), routinely growing as monolayer in DMEM cell culture medium, were grown as spheroids according to the simplified method of YUHAS et al. (15). The kinetics of RG2 MTS growth in vitro and the light and electron microscopic characteristics of this MTS are described elsewhere (7).

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*Technique of MTS Transplantation*

Multicellular glioma spheroids of the RG2 clone were transplanted under the dura of cerebellum of syngeneic Fischer CDF rats. Forty inbred adult rats (male and female) were anesthetized by i.m. injection of 0.10-0.15 ml Hypnorm (Jansson Pharmaceutics Beerse, Belgium) and fixed in a stereotactic head holder (David Kopf Instruments, USA). After disinfection with alcohol the scalp was opened and the superior sagittal suture and parieto-occipital sutures exposed. A craniotomy above the cerebellum of about 6 × 6 mm was performed. With the aid of a needle and a microsurgical hook, the dura overlying the cerebellar vermis was carefully incised and slightly elevated. In this subdural space, about five to ten RG2 MTS were deposited by means of an 18-gauge lumbal puncture needle. The spheroids were implanted 3 mm in front of the dural incision. Immediately after transplantation, the superficial extension of deposited MTS (length/width) was measured using a stereoscopic microscope. There was no bone replacement and the scalp was closed with single sutures. As a control, five animals were submitted to the same operative technique, but without MTS implantation. The mean value of cells implanted as spheroids in one implantation was approximately 450 000 ($SD = \pm 1.17 \times 10^5$).

*Tumor Growth Observation*

Tumor growth was determined by oculometry on the surface of the cerebellum after sacrifice of animals at intervals of 3, 5, 7, 10, 12, 14, and 21 days. Tumor size was expressed as mean diameter (length plus width in mm, divided by 2). Moreover, a cross-median-area morphometric study of a representative frontal tumor section was performed by means of the Videoplan image analysis system (Kontron, FRG).

*Histology*

The brains were fixed in buffered 4% formalin, embedded in paraffin, and the resulting sections were stained with HE, Masson trichrome stain, silver impregnation for reticulin fibers by the method of Tibor-Pap, cresyl violet, and Sudan black.

*Tracer Studies*

To investigate vessel permeability and barrier functions, especially of the tumor vessels, two animals in each experimental group were intravenously injected with an aqueous solution of 2% Evans blue (Merck, Darmstadt, FRG) for 1-2 h before sacrifice.

## Results

The 40 animals implanted with vital RG2 MTS, taken in the exponential phase of growth (4th-6th day of culture), all revealed solid tumors (100% take rate). Clinically, the animals appeared normal up to 10 days postimplantation (p.i.). Later, most animals had ataxia, impairment of walking, and apathy. The mean survival time was 16 days. Up to 7 days p.i., the tumor noduli could be observed within a trepanation window under in vivo conditions. After sacrifice of animals the tumors were easily found on the surface of the cerebellum, appearing as tumor mass covered by the meninges (Fig. 1a). In animals injected with Evans blue, only this area was deeply blue stained (Fig. 1b). Before formalin fix-

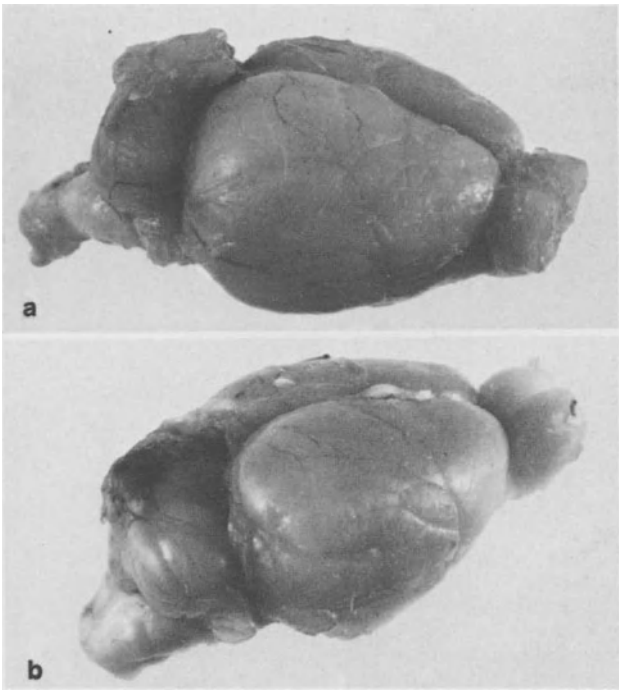


Fig. 1. a Subdural cerebellar tumor 7 days post RG2 MTS implantation. Magnification, × 3.4. b Evans blue-stained subdural cerebellar tumor 5 days post RG2 MTS implantation. Magnification, × 3.2

ation, the abnormal tumor area was measured superficially and the mean values were plotted to obtain the sequential growth curve presented in Fig. 2a. The implanted RG2 MTS grew exponentially. Only up to 7 days p.i. was the tumor growth limited to the trepanation window. Later, intracerebellar and epicranial expansion of the tumor occurred. The median cross-section measurements of representative tumor section are an adequate method both for extra- and intracerebellar growth evaluation. The mean values, called relative tumor area, are demonstrated in Fig. 2b, showing the same exponential growth tendency of tumors as is observed in superficial measurements.

*Morphology of RG2 Subdural Tumors*

After 3-19 days of growth in vivo, tissue specimens from 40 syngeneic RG2 subdural tumors were sequentially studied by light microscopy. As soon as 3 days after MTS implantation, a slight invasion of tumor cells occurred into the cerebellar cortex along the leptomeningeal vessels (Fig. 3a). In the following days, a nodular or spherical growth of tumor was observed in the space between the dura mater and the cerebellum (Fig. 3b). Beginning from the 5th day of MTS growth in vivo, the RG2 tumors showed a fairly stable morphology of malignant anaplastic glioma, similar to that described elsewhere (4). The tumors were highly cellular and composed of round, ovoid, and spindle shaped glioma cells, with frequent mitotic activity (Fig. 3c). New tumor vessels were scarcely distributed. After 9 and 10 days p.i., three different regions of tumor growth could be distinguished: subarachnoidal, intra-

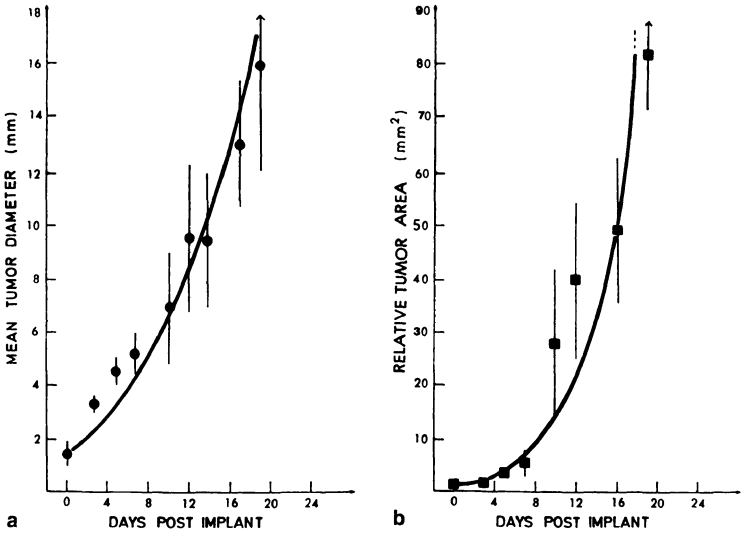


Fig. 2. a Subdural growth of RG2 spheroids in rat cerebellum. Growth curve of syngeneic transplanted RG2 MTS under dura of cerebellum, evaluated by superficial morphometry in vital or nonfixated stages. Mean values of growth differences of 40 subdural tumors are plotted. b The same tumors evaluated by cross-median area morphometry of paraffin sections by Videoplan image analysis system. Note the similar exponential growth character of implanted MTS as compared to Fig. 2a

cerebellar, and epicranial. Proportionally to tumor size, there was an increase in the number of small slit-shaped coagulation-type tumor necrosis, which were irregularly distributed in the tumor tissue (Fig. 3d). In a few cases large, frequently hemorrhagic tumor necroses were found in the center of intracerebellar or intermediate parts of tumors. By 14 or 19 days p.i. the tumors had invaded the whole cerebellum and reached the fourth ventricle so that the cerebral CSF circulation was disturbed, causing hydrocephalus occlusus of third and lateral ventricles. In this last period, the final tumor growth was directed frontally to the basal ganglia. In all phases of tumor growth there were moderate signs of perifocal tumor edema.

*Tracer Investigation*

All tumor-bearing animals demonstrated macroscopically a strong blue coloration of the tumor and a weak staining of the adjacent cerebellar tissue. In all cases the strongest tracer luminescence was found microscopically in tumor vessels, which were frequently dilated, in tumor interstitial tissue, in necroses, and in the narrow rim of cerebellum surrounding the tumor. The blood supply of tumor tissue seemed to originate firstly from leptomeningeal and in the second line from cerebellar parenchymal vessels. There was no Evans blue staining in the operated areas of control rats submitted only to the same operative procedure, either 3 or 12 days after operation.

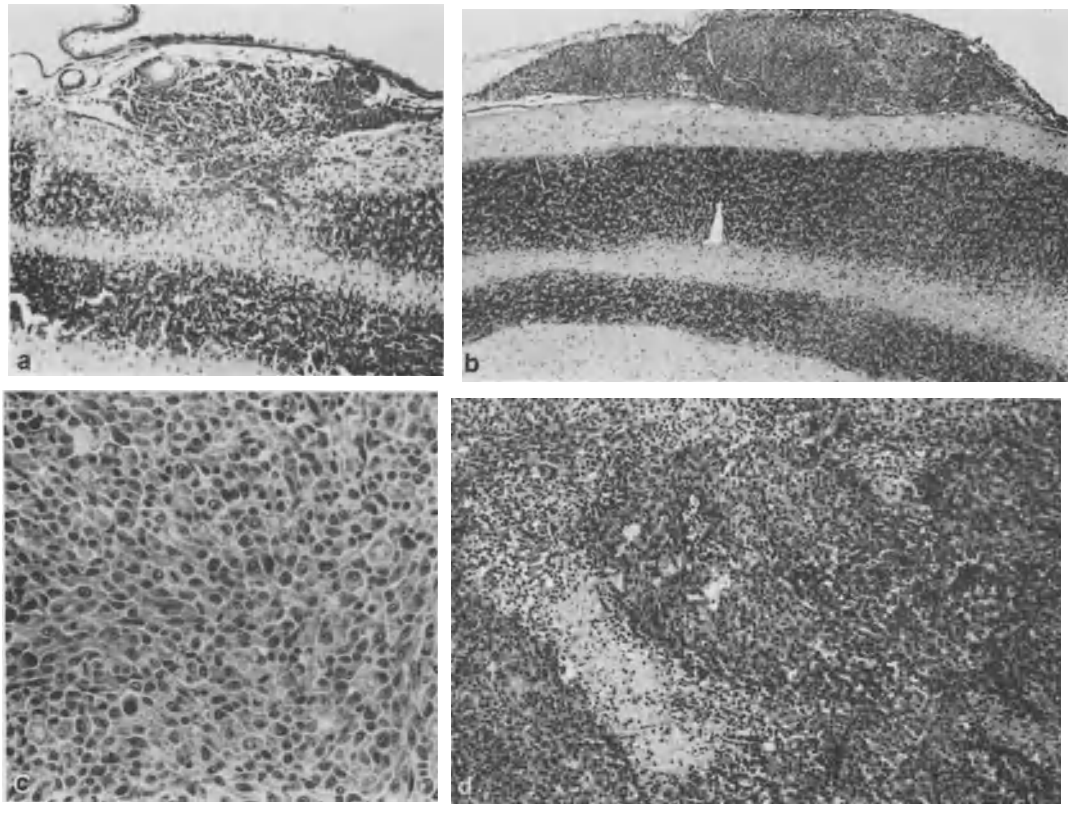

Fig. 3a-d. Morphology of subdural cerebellar tumors. a Cerebellar invasion of RG2 cells from implanted MTS along leptomeningeal vessels 3 days p.i. HE, × 200. b Spherical RG2 tumor, 7 days p.i. in subarachnoid space of the cerebellum. HE, × 150. c Highly mitotic RG2 subdural tumor 7 days p.i. HE, × 300. d Slit-like necroses in the intracerebellar and intermediate *(arrow)* part of tumor 12 days p.i. HE, × 100

## Discussion

The successful development of three-dimensional spheroids of RG2 glioma cell clone in our laboratory gave birth to the development and standardization of a new transplantation brain tumor model, with well comparable growth of glioma cells in vitro and in vivo. Implantation of vital RG2 spheroids resulted in a solid, spherical, and nodular growth with progressive cerebellar infiltration within a period of 5-10 days, the take rate being 100%. The early and deep infiltration of cerebellum reveals the strong invasiveness of cells from RG2 MTS, which easily cross the membrane limitans of glia. This ability of tumor cells is of great scientific and clinical importance with regard to resulting tumor growth, as studied by MAREL and DE METS (9), in vitro and in vivo. In the next 7 days, the large extracranial extension was accompanied by neurological complications such as atactic gait disturbances or stupor, thus making the self-feeding of animals impossible. After sacrifice of animals after 14 and 21 days p.i., we observed approximately 15 mm to 20 mm large intracerebellar tumors with extension to extracranial structures.

Both morphometric methods were proper for tumor growth evaluation. The superficial position of the tumors, similarly as in subrenal capsule assay (8, 14), offers the advantage of easy and adequate measurements even in the first days p.i. The superficial morphometric method, especially employed for the checking of MTS growth during the first 7 days, is quicker and therefore seems superior to morphometry of representative tumor sections. However, when deep invasive tumor growth later occurs, the second method may be more adequate.

The new tumor vessels were well permeable to the Evans blue-albumin complex, which had already been observed macroscopically as a deep blue staining of tumor area on frontal sections and as intensive red luminescence of tumor interstitial tissue, especially tumor necrosis in fluorescent microscopy. The same results were observed in other tumor models as to the breakdown or lack of blood-brain barrier in the tumor vascular net (2, 10).

In the developed model, with gentle implantation of the glioma spheroids in the subdural space of cerebellum, we achieved well reproducible and statistically significant data. This experimental brain tumor model provides an excellent opportunity for radiation and chemotherapeutic trials or surgical as well as laser-assisted removal of the tumors.

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# Testing of Hydrocephalus Shunt Systems*

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## Introduction

The operative treatment of hydrocephalus with recent shunt systems frequently leads to a too high rate of complications. This is due to biological factors as well as to the mechanical properties of the systems.

## Measuring Methods

Preclinical testing of the shunt systems nowadays is generally done according to the regulation F647-79 of the American Society for Testing and Materials (ASTM) (1). According to this regulation flow is kept constant and after a period of stabilization the pressure is measured immediately before the valve, once it has become stable. The physiological condition that the flow is dependent on a given pressure or suction is not kept. Kind and dimensions of the catheter are not considered. Within our *flow-measuring method*, however, shunt systems with both valves and catheters were tested, the heights of the inlet and the outlet columns were present, and the flow measured (Fig. 1).

When the valve is closed the heights of the columns determine the inlet and the outlet pressure of the valve. When assessing antisiphon systems it is particularly necessary to make measurements with distal catheters. In various kinds of typical shunt systems according to the flow-measuring method, the flow was determined as a function of the heights of inlet and outlet columns. The heights were changed stepwise. Hysteresis, opening, and closing pressures were determined.

## Results

### *Shunt Systems with Distal Slit Valves*

In shunt systems with distal slit valves the flow increased nearly linearly to the pressure. There were considerable differences in the measuring curves of the individual items tested where the catheters were of equal length. The opening and closing pressures showed large discrepancies (Fig. 2). One or two weeks after installation of the valves, the pressure values were below the range of closing pressures given by the manufacturer.

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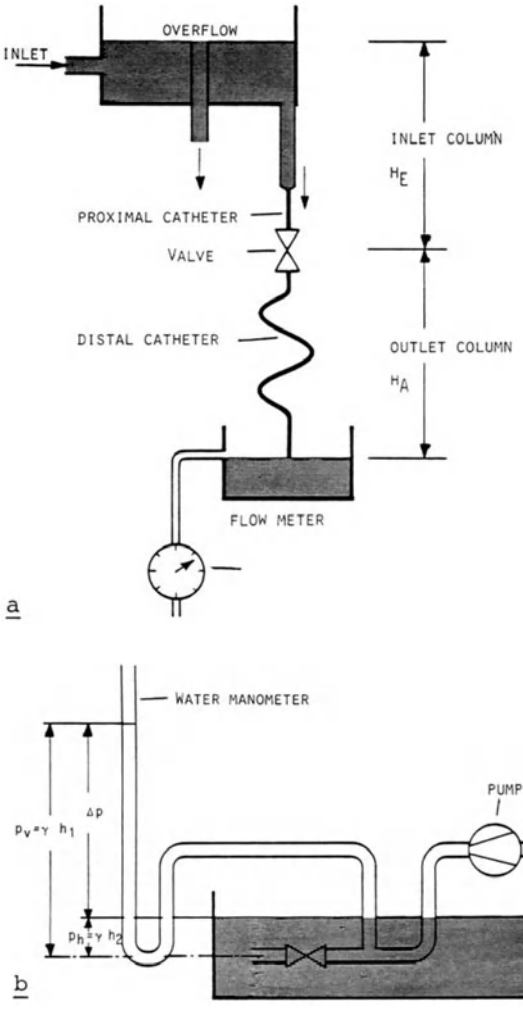



Fig. 1. a Flow-measuring method. Measuring the flow as a function of the heights of the inlet column and the outlet column $\dot{V} = \dot{V}(H_E, H_A)$. b Pressure-measuring method according to ASTM: Measuring the pressure difference $\Delta p = p_v - p_h$ as a function of the flow controlled by a variable speed pump. $\Delta p = \Delta p(\dot{V})$

The flow values increased with the pressure so much that within the normal pressure range the flow exceeded the physiological CSF production rate. There is a high risk of overdrainage, because when the patient stands, the pressure caused by the fluid column in the catheter has an influence on the flow corresponding to the ventricular inlet pressure and must therefore be added to that pressure value.

*Shunt Systems with Spring Ball Valves*

In the spring ball systems the flow increased linearly with one exception. There was no hysteresis (Fig. 3) in the tested pediatric medium pressure valves, in contrast to the earlier tested standard systems (2). Opening and closing pressures were identical but were, however, not always in the range given by the manufacturer.

The increase in flow with the pressure is so high that in the patient no CSF pressures noticeably higher than the actual opening pressure could be attained. The opening pressure in the tested systems fluctu-

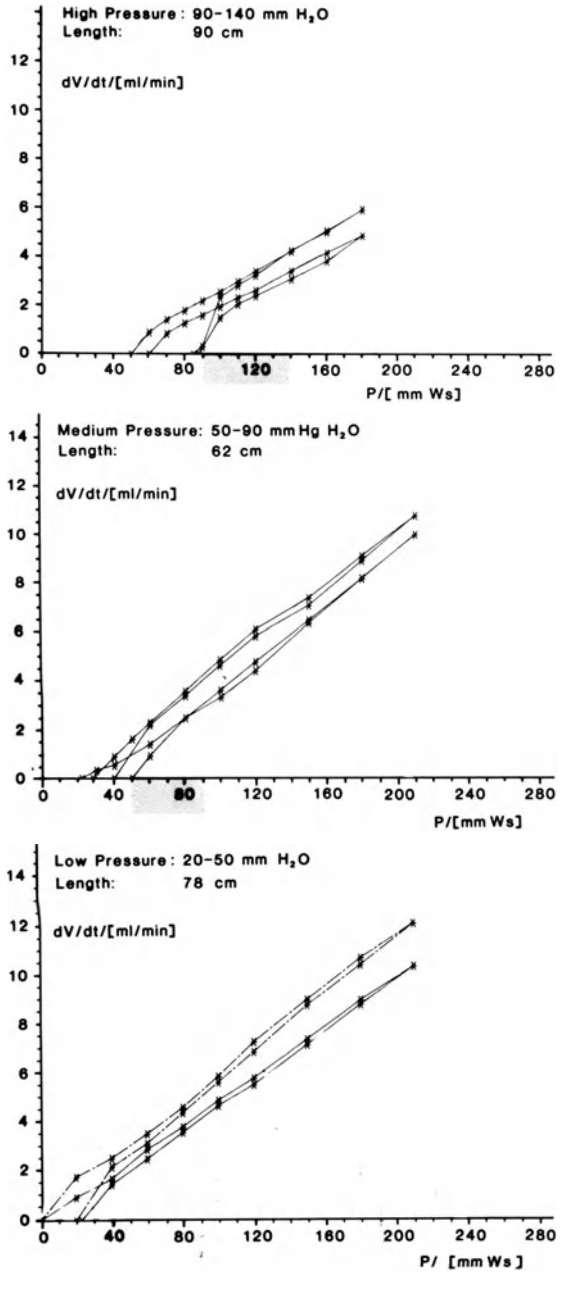



Fig. 2. Flow as a function of the heights of the fluid column in *distal slit valve* assemblies ("Uni shunt"). *Bottom:* low pressure valves ($n = 2$); *center:* medium pressure valves ($n = 2$); *top:* high pressure valves ($n = 2$)

ated between 33 mm and 98 mm $H_2O$. Again, as in the distal slit valve system, suction pressure of the fluid column in the distal catheter has to be added to the inlet pressure valve.

If the patient is in a sitting or a standing position, an overdrainage develops and unphysiologically low pressures are built up.

*Shunt Systems with Cross Slit Valves*

In all tested cross slit valves the opening and closing pressures were above the range given by the producer (Fig. 4). In the medium pressure valves the flow increased less with the pressure than in the low pressure valves. In the medium pressure system the values had a distinct hysteresis.

The hysteresis is especially striking if the flow is determined before and after a high pressure loading (Fig. 4b). Thus, the flow not only depends on the actual pressure but also on the height and the duration of a preceding pressure load. The smaller the pressure in the preceding measurement, the less was the flow when the pressure was set again to 3.8 kPa (≈ 380 mm $H_2O$). This phenomenon was less distinct or not present in the other shunt systems. For the patient it could be advantageous, if after short-term pressure fluctuations – for example in coughing – the flow changes are smaller.

*Shunt Systems with Membrane Valves*

There are not yet sufficient test results for membrane valve systems. In some of these shunt systems assigned for testing bubbles appeared both in the valve and in the catheters. They could only partly be removed from the valve region by complicated means. They led to such dysfunctions that we must clarify this phenomenon before further testing.

*Special Results*

Since the flow-measuring method was introduced, much more can be said about the influence of length and diameter of the catheters and about the formation of the outlet slits on the flow through a shunt. As expected, the flow decreases with the length of the catheter (Fig. 5).

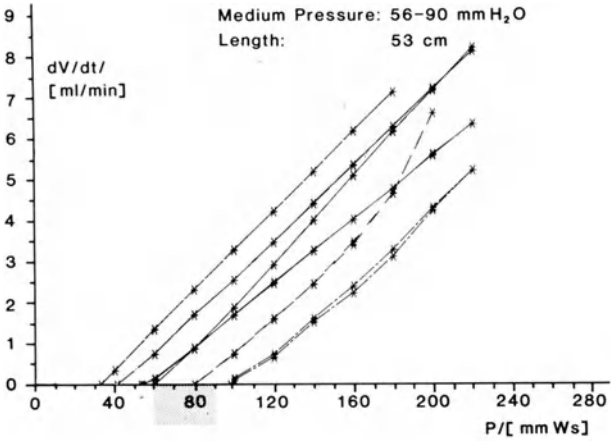
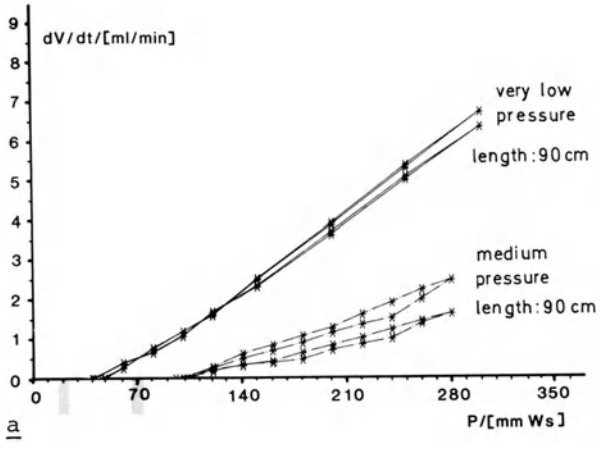



Fig. 3. Flow as a function of the heights of the fluid columns in *pediatric spring ball valves* (medium pressure, $n = 6$)



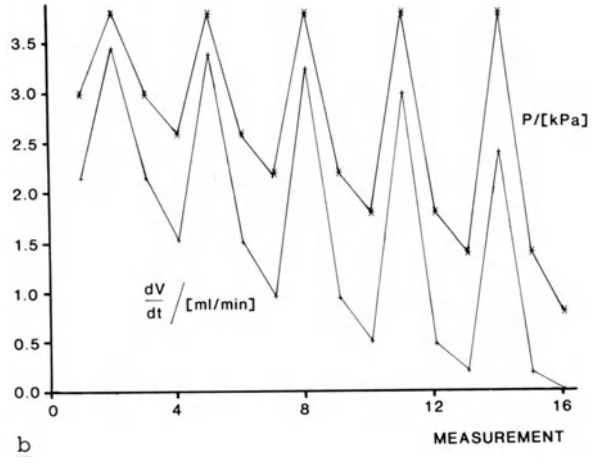




Fig. 4. a Flow as a function of the heights of the fluid columns in *cross slit valve* assemblies: very low pressure valves ($n = 2$), medium pressure valves ($n = 2$).
b Flow $\frac{dV}{dt}$(ml/min) as a function of the heights of the fluid columns and of the preload p/(kPa)

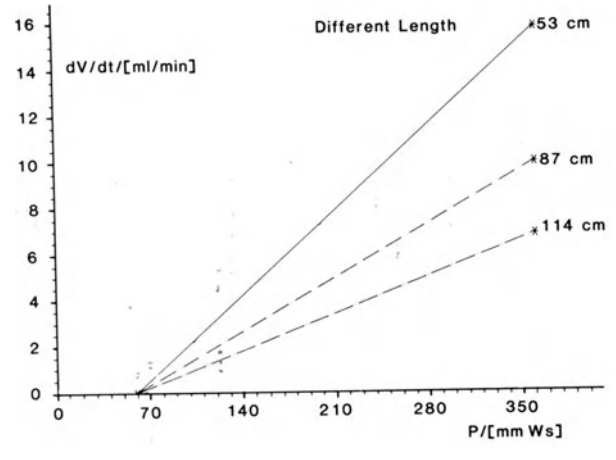



Fig. 5. Flow as a function of the heights of the fluid column in *spring ball* assemblies with varying lengths of catheters

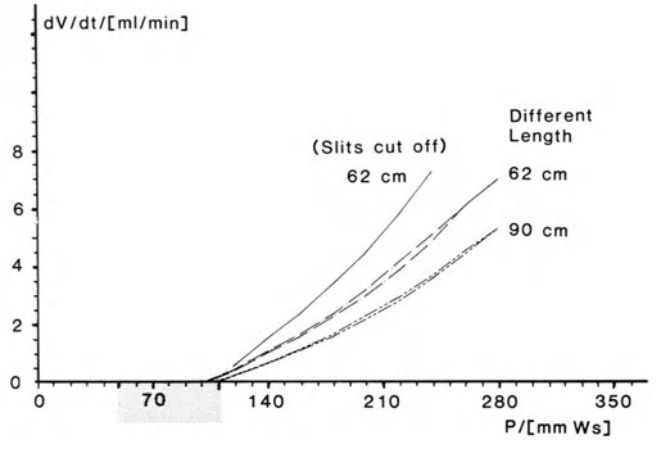



Fig. 6. Flow as a function of the heights of the fluid columns in *membrane valve* assemblies with varying lengths of catheters

Outlet slits of a catheter can hinder the flow considerably (Fig. 6). Obstruction of the flow by bubbles can be detected, which is not possible with the pressure-measuring method according to ASTM, since in this test system the flow is maintained by force; bubbles which form are washed out. By contrast, with the flow-measuring method these bubbles settle in the catheters as well as in the valves. They hinder the flow considerably. In an extreme case, the flow is completely interrupted.

We must study this phenomenon and its causes more closely in further tests. This problem is particularly important, since gas bubbles can be the origin of a dysfunction of the implanted shunt systems.

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# Vessel Repairs of the Carotid Artery of the Rat Using the Modified Nd: YAG Laser

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Vascular defects of very small brain vessels can be repaired by microsurgical suture. This method is time consuming and requires temporary clipping off of the vessel to be repaired. The organ to be supplied with blood (in neurosurgery, the central nerval system) is thus cut off from the brain circulation for a considerable length of time. Moreover, suturing very tiny brain vessels is technically difficult and hardly possible in the case of vessels under 0.5 mm in diameter. Bipolar coagulation appears to be unsuitable for repair of very tiny brain vessels. JAIN (1979) has described repairs of very tiny arterial vessels (0.8-0.5 mm) by means of the Nd:YAG laser. He used the Nd:YAG laser with a wavelength of 1.06 µm as well as a light conductor of 600 µm and a focal point of 0.3-0.5 mm diameter.

The 1.32-µm Nd:YAG laser[1] which we used for the repair of very tiny vessels has a maximum output power of 35 W and is fitted with an He-Ne laser as pilot light.

The desired focal diameter of 200 µm can be attained with a 1:3 optical system, but the depth of field is very much less and the working distance is reduced to one-third. For this purpose, a special 200-µm focusing light conductor was developed which results in sufficient depth of field at a focal diameter of 200 µm with a 1:1 optical system. However, the maximum output power of the 1.32-µm Nd:YAG laser had to be restricted so that the laser power in the focus is a maximum of 15 W.

## Methods

In the rat carotid artery emptied of blood, a vaporization and a discrete carbonization effect could be demonstrated at the tissue surface from 14.0-W laser power at 200 µm and a duration of irradiation of 0.1 s. In seven further experiments, the carotid artery was temporarily clipped off and a stab-like lesion was produced with a 26 1/2-G needle. In the application of 1 × 14.0 W within 0.1 s, there was likewise a prompt sealing of the lesion site. After opening the microclip, a brownish staining could be detected merely in the irradiated area. The vessel showed normal pulsation without constriction of the vessel circumference.

In eight further experiments the carotid artery was incised transversely to the course of the vessel after the artery had been shut off from the blood circulation with two clips. After transverse incision, it

[1] Nd:YAG laser-medilas provided by MBB-AT, GmbH, D-8000 München 80


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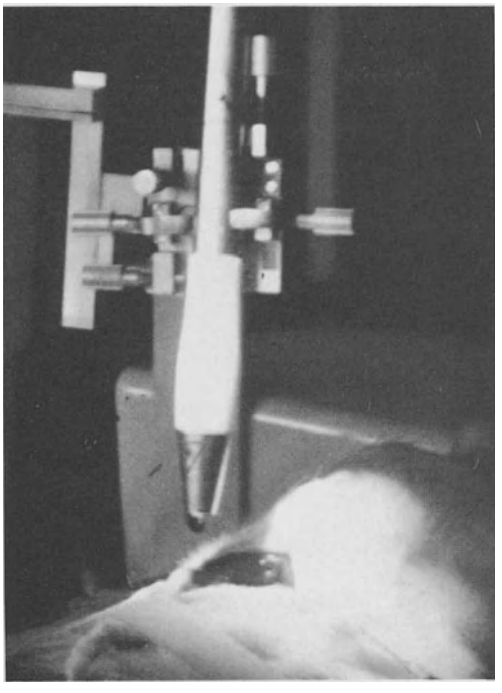

Fig. 1

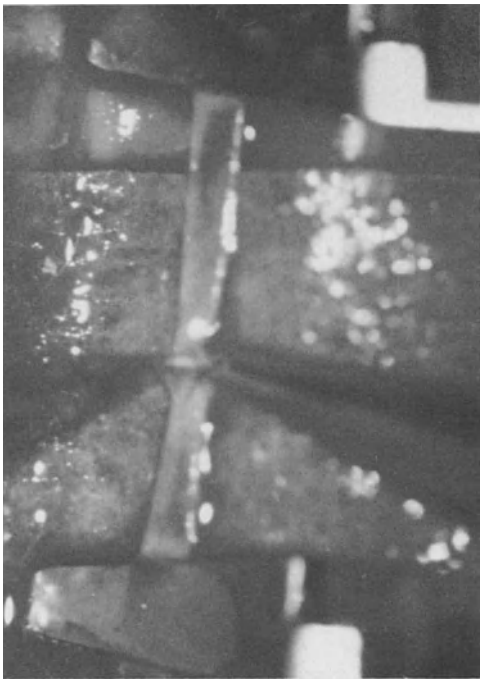

Fig. 2

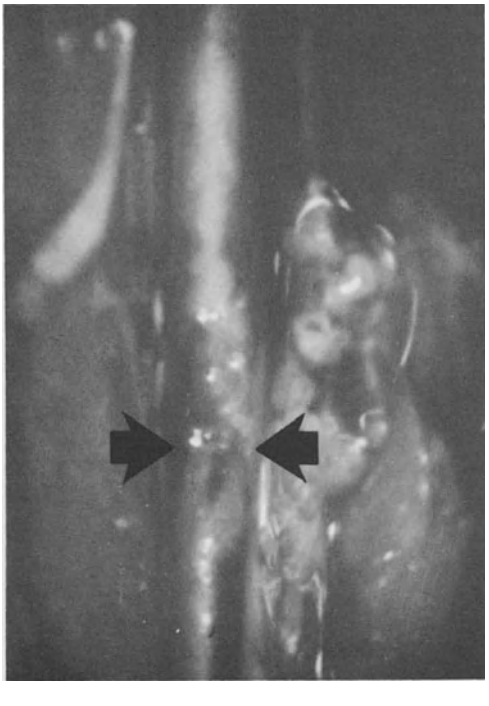

Fig. 3

could be seen that a slightly rhomboid cut surface resulted from the elastic forces in the vessel wall. For precise aiming of the laser beam, the light conductor was brought up to the vessel with a micromanipulator. In three animals a good closure of the incision-like lesion could be achieved by application of 4 × 14.0 W/0.1 s. After opening the clip, the vessel was sealed and showed a normal proximal and distal pulsation. In the region of the fusion suture, there was no constriction, but a slight protrusion of the vessel wall. In three cases the defective transverse cut surface could only be closed by application of 6 × 14.0 W/0.1 s. In one case the distal portion seemed to be slightly constricted.

In a further trial series of ten experiments, the carotid artery of the rat was incised longitudinally over a length corresponding roughly to the width of the vessel. Closure of the longitudinal vascular lesions proved to be more problematic than repair of transverse lesions. In four animal experiments in which fusion points of less than 12.6 W were applied, adaption and sealing of the longitudinal vascular incisions were insufficient. On the other hand, a relatively good sealing of the vascular lesions could be attained in three further experiments by application of 4 × 14.0 W/0.1 s. Compared with fusion of the transverse sections, it was noticeable that the fusion suture did not appear to be raised, but rather indented. The cut surface was likewise brown in color after application of the laser. After opening the clip, the carotid showed good pulsations proximally and distally. In three further experiments the vessel wall defect was closed by application of 6 × 14.0 W/0.1 s. A good repair was possible macroscopically. The vessels remained free after opening the clip, and showed good proximal and distal pulsation (see Figs. 1-3).

## Results

It could be shown that vessel repairs of the carotid artery of the rat can be performed with the modified Nd:YAG laser. This prototype with a wavelength of 1.319 µm possesses the advantage of a lower depth of penetration of the laser beam into the tissue compared with the conventional Nd:YAG laser with a wavelength of 1.06 µm. The especially developed 200-µm focusing light conductor ensures an adequate depth of field with a 1:1 optical system.

Punctiform, transverse, and longitudinal vascular lesions of the rat carotid artery can be closed with an application of 14.0-W laser power for 0.1 s with a light conductor of 200 µm. The radiation intensity per fusion point corresponded to more than 300 W/mm$^2$. It was shown that at the beginning of the irradiation, water vaporized at the tissue surface and a slight carbonization occurred which could be discerned from the brownish-black discoloration of the surface. In punctiform lesions, no constrictions of the vessels could be detected. The fusion sutures of the transverse incisions tended to be raised and were not indented, in contrast to the longitudinal fusion sutures.

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# Neurosurgical Intensive Care

# Legal Problems of Intensive Care

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## Basic Considerations

While representing extraordinary efforts, intensive care has nevertheless to be considered as medical treatment. The usual conditions for diagnosis and therapy therefore apply. The ethical and legal conditions likewise do not differ from the considerations in respect of regular therapy, but are modified due to the greater extent of medical care. This care involves extraordinary steps about which the patient generally needs to be informed and to which he has to consent. As a consequence of his condition, however, the patient frequently will not be able to express his consent explicitly. The physician has to use his professional and ethical judgment to decide upon the extent to which the extraordinary steps to be taken are indicated and justified.

## The Start of Intensive Care

Intensive diagnostics and treatment in an intensive care unit basically require the consent of the patient. Informing the patient of the steps planned has to precede this consent. Usually the patient will, however, have a general idea of what intensive care involves. The patient may also conclusively consent to treatment by not opposing his transfer to an intensive care unit.

For patients who are unconscious or otherwise unable to express their consent the following applies: If the patient has a legal guardian, e.g., still being a minor, the guardian will decide. Nevertheless, such a guardian can only act within a certain framework of duties and obligations. If consent is therefore arbitrarily refused, the court relating to matters of guardianship should be referred to.

If the patient has no guardian, e.g., being an unconscious adult, the principles of expected consent should apply. Prime considerations should be the objective interests of the patient and his subjectively evaluated actual or presumed wishes. These conditions usually coincide in a pressing situation: Usually it is assumed that to receive the best medical treatment is in the interest of the normal patient and simultaneously corresponds to his wishes.

The patient has a right to reject intensive care. If this rejection is expressed while his mental capacities are not impaired, compliance with his wishes is obligatory. Likewise a patient is entitled to cancel an earlier consent to intensive care, and the physician, as well as the hospital, is under obligation to comply with such a wish.

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The so-called "last will" of the patient involves special problems. We all know that within the last 10 years many patients, particularly at an advanced age, have stated in writing that they do not wish to receive intensive care in the event of a serious disease. If the "last will of the patient" corresponds to the wishes of the patient at a given time, both are binding and have to be fulfilled. Difficulties may arise, however, if the patient has filed a "last will" at an earlier time and is now unconscious. The physician then has to evaluate whether the statements made earlier still apply in the face of the present circumstances. Many patients will have a different opinion about their condition during good times than later, in the hospital. For this reason a "last will" filed earlier cannot be absolutely binding on a physician. If, however, the physician thinks that the patient would still express the same wish, he is justified in refraining from intensive care. To verify such an assumption by the physician, the opinion of close relatives or friends of the patient is usually sought. Such persons may furnish information to help determine the probable wishes of the patient, but should not contribute their own decisions.

A fairly recent concept in this context is the "power of the attorney for health care". On 1 January 1985, California became the first U.S. state in which the so-called Durable Power of Attorney for Health Care Act became law. Accordingly, persons living in California are now entitled to designate an adult who can make decisions in matters pertaining to health in their stead. If the patient should be unconscious or otherwise incapacitated, the person authorized may instruct the physician to comply with the wishes of the patient specified at an earlier date. In emergency cases the person with "power of attorney for health care" may also make his own decisions affecting the patient. In the Federal Republic of Germany so far such stand-ins in the area of highly personal decisions have not been approved. It is true that parents or legal guardians may make decisions with respect to incompetent persons in matters pertaining to their health, that parents or legal guardians need to be kept informed, and that their consent is required. As mentioned before, however, persons acting for an incompetent patient can only decide in favor of the patient, not against him. Accordingly, German courts dealing with matters of guardianship routinely intervene and limit the legal power of the parents if the legal guardians should not permit the execution of a medically indicated procedure. Similarly in other fields legal guardians are not allowed to perform certain highly personal transactions for the persons entrusted to them. As examples, a guardian can neither enter a contract of marriage nor file a last will for his ward. On the other hand, the authorization to publish diaries after the death of the author can be transferred to close relatives according to current legal practice. Acceptance of special stand-ins for patients in matters pertaining to health would concur with this train of thought in legal affairs.

## Limits of Therapy

The patient may combine his consent to intensive care with certain limitations. In particular, he may exclude specific procedures. Borderline cases, where such limits substantially reduce the effectiveness of medical efforts, merit special attention. The physician cannot be forced to perform treatment in such a fashion that the results could be considered as substantial malpractice. From this standpoint selective limitations to the consent of the patient are unacceptable. At a large university hospital in the Federal Republic of Germany the staff recently refused to perform a surgical intervention for a good reason,

namely that owing to religious convictions the patient refused to accept blood transfusions that might have proved necessary. In the face of the extensive surgery expected, the necessity for voluminous blood transfusion had to be considered. Without the preparation of such transfusion an attempt to perform the intervention would have represented a severe case of malpractice. Within the context of these precautionary considerations refusal of therapy complied with current law and medical ethics.

Passive euthanasia is presently practiced as "therapy in which no life-prolonging steps are used". If a patient is terminally ill, his treatment can be restricted to regular procedures within the scope of his assumed wishes. Prolongation of his sufferings via intensive care is then no longer indicated.

The problem of transition from passive to active euthanasia is much harder to resolve. All responsible persons rightly reject active euthanasia. Borderline areas exist, however. If, for example, a patient is suffering from excruciating pain or has extreme respiratory difficulty, his condition may be alleviated by the administration of potent pain killers or other steps that may simultaneously shorten his life. Such a practice is presently generally accepted, but only if the patient does not object by his expressed wish to hang on to life. A patient, even when mentally ill, who expresses a will to live should receive any medical assistance, even by intensive care.

## Death

Much has been written about the change in the criterion for death over the last 15 years – from the cessation of the action of the heart and the circulation to brain death. It is nowadays generally acceptable to use the death of the brain as the conclusive criterion for the decision to discontinue intensive care or to start explantation of organs. Starting with the regulations published in 1968, a considerable change has therefore taken place as compared with earlier practice. In the context of termination of intensive care or explantation of organs, however, other legal considerations in Germany still refer to the cessation of the action of the heart and of the circulation, since this criterion can be determined more precisely and more simply. This is true, for example, of the laws concerning inheritance, family status, or insurance policies. There are no objections to this practice since different definitions of death may be applicable for different purposes. Such differences in definition are known in other legal fields also, e.g., negligence is distinguished as being criminal or civil.

Precise determination of the instant of death constitutes the principal problem in the use of brain death as the criterion of death. I will not deal here with the criteria formulated first in 1968 by the ad hoc committee of Harvard University, presided over by BEECHER, which have been defined in more detail since. At the present time discussions are taking place on whether or not a commission should decide upon brain death of a specific patient. Most likely an ethics commission assembled for a different task will not be in a position to make or to confirm a diagnosis of brain death. On the other hand, one might argue that it should not be the physician currently in charge of a patient who has to bear sole responsibility. This question is still very much open. At least for the time being it is still the physician responsible for the patient's treatment who specifies whether brain death has occurred. Whether such sole responsibility is in his best interests will only be resolved by further discussion.

## Liability

Liability cases in the area of intensive care are relatively rare. In earlier times they were discussed in the light of the emergency nature of such treatment. Today, however, we are of the opinion that emergencies must be inspected more closely. One must differentiate between the expected emergency, for which one must be prepared when working in an intensive care unit, and the unexpected emergency, where conscientiousness is not evaluated quite so strictly. As a rule the doctor's actions in an intensive care unit are expected to correspond to those of a specialist in this field. Legal judgment in this area is also very cautious. In one case before the Bundesgerichtshof (VersR 1985, 338), an anesthetist faced with the emergency of a hemorrhagic shock had decided to leave a subclavian catheter in an unfavorable position in order to infuse plasma substitutes. This led to severe irreversible damage. The Bundesgerichtshof analyzed whether there might have been a medical error during the preparations for the operation. During the anesthetist's preparations, he had punctured the vertebral artery by mistake, rather than the subclavian vein. In emergencies one can count on the fact that unusual or erroneous measures may be tolerated by the judges, but they may ask whether a mistake occurred at an earlier point in time, i.e., before the emergency materialized.

Courts have had special problems with the culpability of a person whose victim has later died in the intensive care unit. An English court pronounced the verdict of guilty of planned murder in the following case: A man had attacked a young girl and inflicted such severe injuries that she needed intensive care. After 2 days of treatment the doctors arrived at the conclusion that the girl had suffered cerebral death from the beginning; thereupon the reanimator was turned off. The court agreed with this decision. Turning off the reanimator did not interrupt the causal relationship between the planned deed and the death of the girl (Regina v. Malcherek – 1981 – 1 W.L.R. 690). Death is far more difficult to evaluate when the person concerned has not wanted treatment. In another English case, a Jehovah's witness was stabbed. She refused a blood transfusion, although her chances were not bad providing she received adequate medical treatment. She was also informed of the fact that her refusal of the transfusion would mean her death. The jury pronounced the man who stabbed her guilty of planned murder after she had died. In this case, too, the supreme court confirmed the verdict since the knife wound was responsible for the death (Regina v. Blaue – 1975 – 1 W.L.R. 1411). Of course, the question remains open as to whether the unusual denial of the transfusion by the patient did not interrupt the causal relationship between the deed and the death.

In summary it may be said that the legal problems of intensive care are those of medicine in general, seen through a magnifying glass. This magnifying glass not only magnifies the problems, it also distorts them to a certain degree. The reticence of courts and legal opinion about liability in the area of intensive care shows that the peculiarities of this field are known, and that is a good sign.

# Computer-Aided Neuromonitoring: Conditions, Techniques, and Clinical Applications*

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## Introduction

To date, neurological monitoring in the intensive care unit has only been possible at relatively infrequent intervals (10). Continuous monitoring of the biosignals of the brain is not, in contrast to monitoring of the cardiac, circulatory, and respiratory systems (1), a routine measure in the ICU. This is related in part to the difficulty of recording and displaying continuous EEG and ICP data in this artifact-ridden environment. Continuous EEG and ICP monitoring generate an enormous amount of data. This makes long-term presentation of data with simple video screen or printed paper techniques difficult (5, 8).

To counter these difficulties we have developed a bedside monitoring computer. We have also studied the optimal conditions for computer-aided monitoring of neurological biosignals.

## Methods of Signal Recording and Evaluation

### *Cerebral Biosignal and Recording Techniques*

As a parameter of brain function, we continuously follow a two-channel (right and left) bipolar EEG ($F_3/P_3$; $F_4/P_4$). EEG artifacts are minimized by using adhesive silver/silver chloride electrodes (3M/Arbo or corresponding adhesive ECG electrodes) and *insulated* leads.

We also simultaneously record ICP and arterial pressure (SAP) as (8) cerebral *"warning parameters"* (calculation of the cerebral perfusion pressure CPP = SAP-ICP, 8). We have thoroughly tested both in vitro and in vivo (8) the characteristics of different methods of measuring SAP and ICP. Pressure measurements over *fluid-filled catheters* (e.g., intraventricular catheters, arterial cannulae) lead to large signal distortions (dampening in thin "microcatheters" and resonance in normal silicon catheters). Optimal signal reproduction is obtained with intracranially implanted (for ICP) and intravascularly introduced (for SAP) *microtransducer catheters* (MTC), if these microtransducers operate on strain gauge or piezo-electric principles.

Double checking the entire measurement system must always be done prior to a computerized evaluation of the pulsation transfer function SAP ⟶ ICP (3, 12).

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*Measuring SAP and Calculating CPP*

Intracranial pressure measurements are standardized against the height of the foramen of Monro (8). With intracranially implanted pressure transducers, hydrostatic errors secondary to varying patient position are minimal (<3 mmHg). Measurements of central *arterial* (femoral/iliac) or peripherial (radial/dorsalis pedis) pressures for the calculation of CPP, on the other hand, pose problems. Cerebral perfusion is dependent not on the blood pressure in any of these arteries but rather on the pressure of the blood entering the base of the brain. This pressure in turn can vary with elevation of the upper body or other maneuvers. To verify this, we cannulated the external carotid artery via the superficial temporal artery (2) in ten patients and placed central and peripheral arterial catheters as well. Due to large differences in the pulse wave, systolic and mean pressures differed even in the supine position by up to more than 40 mmHg from one another! With elevation of the upper body, the pressure in the external carotid artery sank, while the pressures in the central and extremity arteries rose (Fig. 1). We therefore utilize catheterization of the external carotid via the superficial temporal artery (4) for the critically important control of the CPP. We thus measure at roughly the same level at which the internal carotid artery enters the skull. Also, the pulse form in this artery offers the best agreement with ICP (Fig. 1).

*Computerized Neuromonitoring*

*Hardware.* Based on preliminary work with larger computers (4, 6), we have developed a bedside "Neuromonitor" computer (Dr. Richard Weiss "Neuromonitor"). It continually evaluates four analog or (RS 232) digital inputs (2X EEG, ICP, SAP, see Table 1). The sampling rate of 1 kHz/channel is much faster than necessary but is designed for expansion of the system to include measurement of evoked potentials and EMG. A multiple microprocessor system with a one MB main memory allows for an *online* analysis of all channels in *real time* (5). The actual current signals can be displayed on a color screen at all times and printed on one of two integrated four-color printers. In addition, simultaneous displays of both graphic and numerical data are possible (Figs. 2-4). All data are stored on a "patient" floppy disc and can later be re-evaluated with a number of different programs. Via a second floppy disc drive, the various operating systems are loaded.

Programming is done by menu-directed dialog. A color-coded function keyboard simplifies this process, and programming can be done by individuals without specialized training. The "Neuromonitor" can store manually entered data in addition, like history data, physical findings, or other remarks.

*Programs.* The data are analyzed with quantitative statistics for independent variables (14) and also with frequency analysis (Tables 2, 3). Additional programs (7, 8) allow for the calculation and depiction of an intracranial pressure-volume (P/V) curve with its derived *compliance* variables as well as data for *cerebrospinal fluid dynamics* (e.g., resistance, conductance, Table 4). ICP, SAP, and the CPP can be evaluated for trends (i.e., time plot), in histogram form, or after pulse-amplitude analysis (Tables 2, 3). A *time plot* shows what has occurred over a desired and preselected period of time. Reasonable alarms (heights and durations) can also be set. In addition, the time axis can be extended up to 16-fold (Fig. 3). A *histogram* reveals the pressure distribution over a certain period of time (Figs. 2-4) and yields *quantitative statistical data* (Table 2, Figs. 2-4). The intracranial pulse amplitude

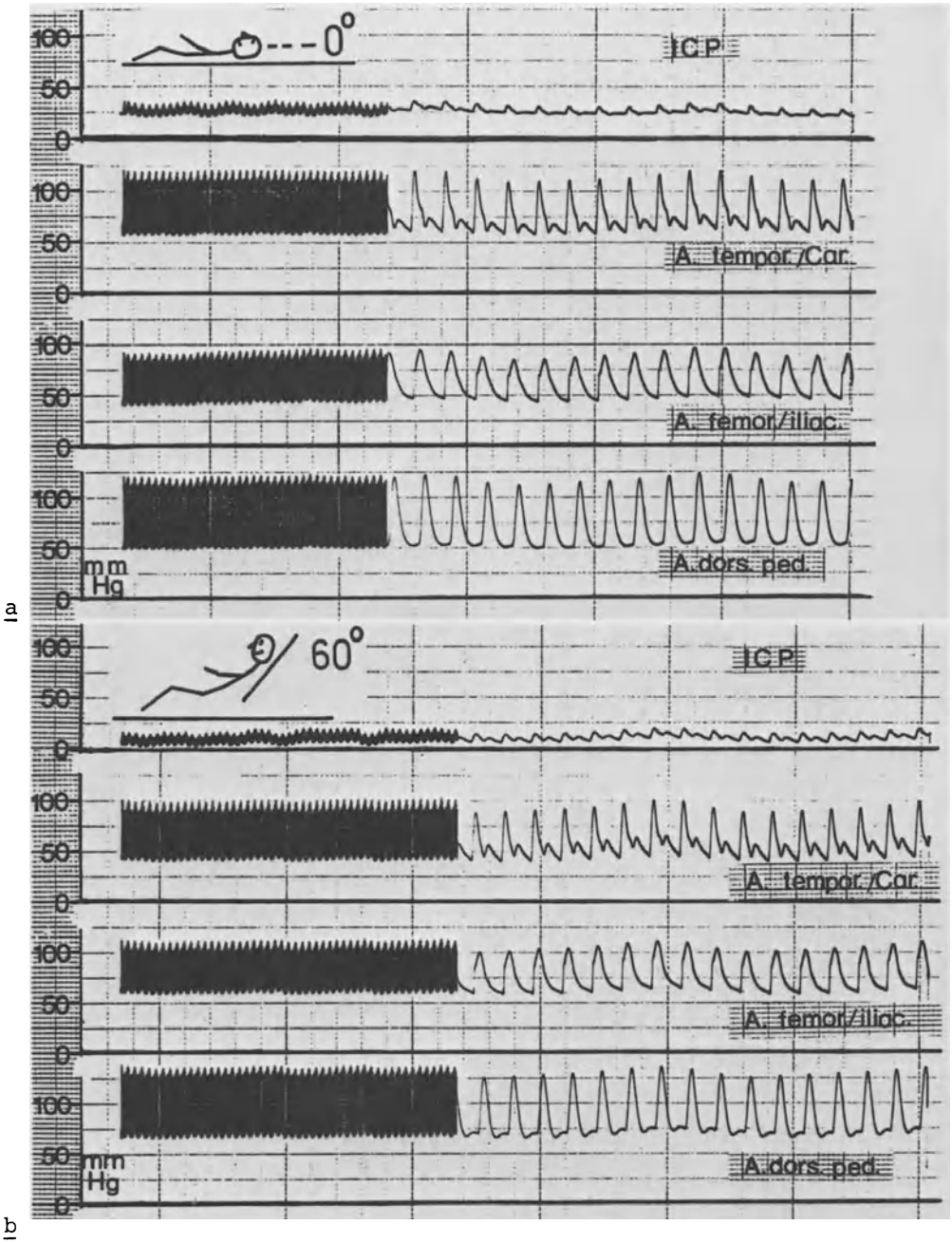
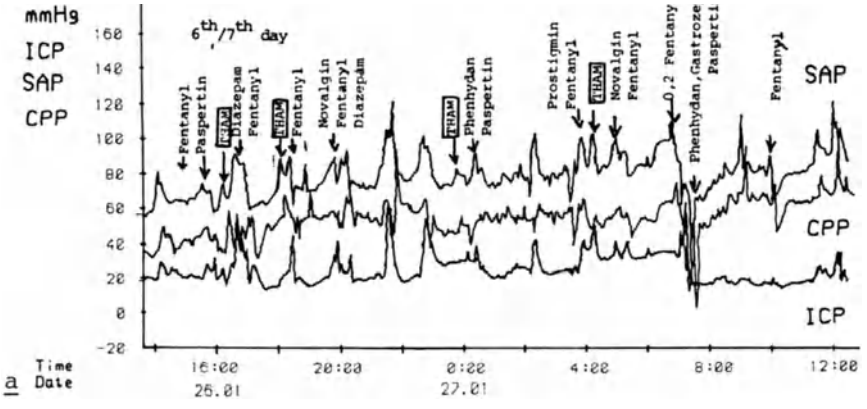
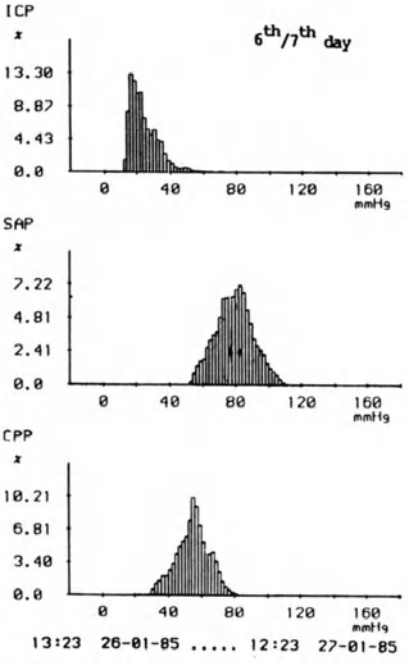



Fig. 1a,b. ICP and different modes of arterial blood pressure registration. Already in the horizontal position, there are differences between the arterial approaches of up to 40 mmHg (a); with head elevation (b), there is a decrease of pressure in temporal artery/external carotid, similar to ICP decrease; other arterial pressures increase. Important for CPP calculation!




a

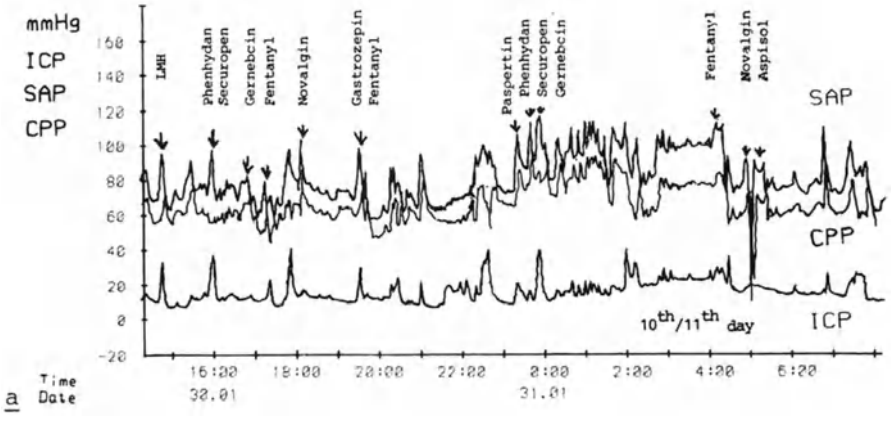



STATISTICS

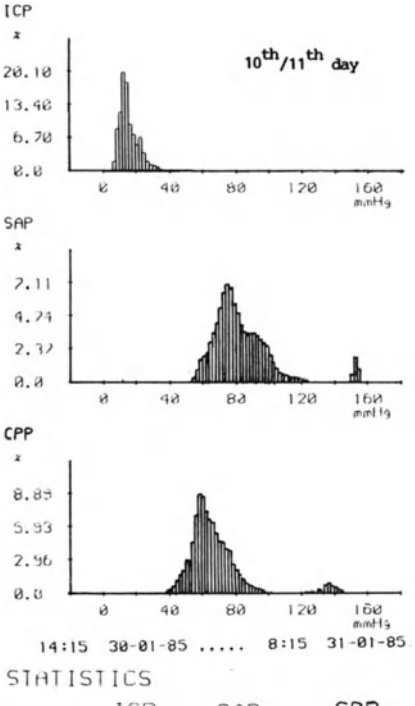
| | ICP | SAP | CPP |
|---|---|---|---|
| ARITHM. MEAN | 25 | 79 | 55 |
| MEDIAN | 22 | 79 | 55 |
| MODUS | 17 | 82 | 55 |
| VAR.-WIDTH | 11 | 13 | 16 |
| STAND.-DEV. | 8.874 | 14.239 | 13.269 |
| SKEWNESS | 1.50 E 0 | 1.27 E 0 | 1.51 E 0 |
| KURTOSIS | 3.26 E 0 | 2.56 E 1 | 3.40 E 1 |

b

Fig. 2a,b. ICP, SAP, and CPP after head injury. Frequent ICP waves on 6th day due to edema; controlled therapy of ICP/CPP with THAM (a, time plot). Pathological shifting of pressures – ICP to the right, CPP to the left (b, histograms, with statistical values)




a




b

STATISTICS

| | ICP | SAP | CPP |
|---|---|---|---|
| ARITHM. MEAN | 16 | 84 | 66 |
| MEDIAN | 14 | 79 | 64 |
| MODUS | 13 | 75 | 59 |
| VAR.-WIDTH | 59 | 97 | 71 |
| STAND.-DEV. | 6.795 | 20.968 | 19.418 |
| SKEWNESS | 2.42 E 0 | 1.81 E 0 | 2.16 E 0 |
| KURTOSIS | 1.08 E 1 | 9.76 E 0 | 1.38 E 1 |

Fig. 3a,b. Improvement of ICP, SAP, and CPP head injury. Same patient as in Fig. 2; ICP and CPP normalized, no specific therapy required (a, time plot); note normal histograms (b). Fully rehabilitated

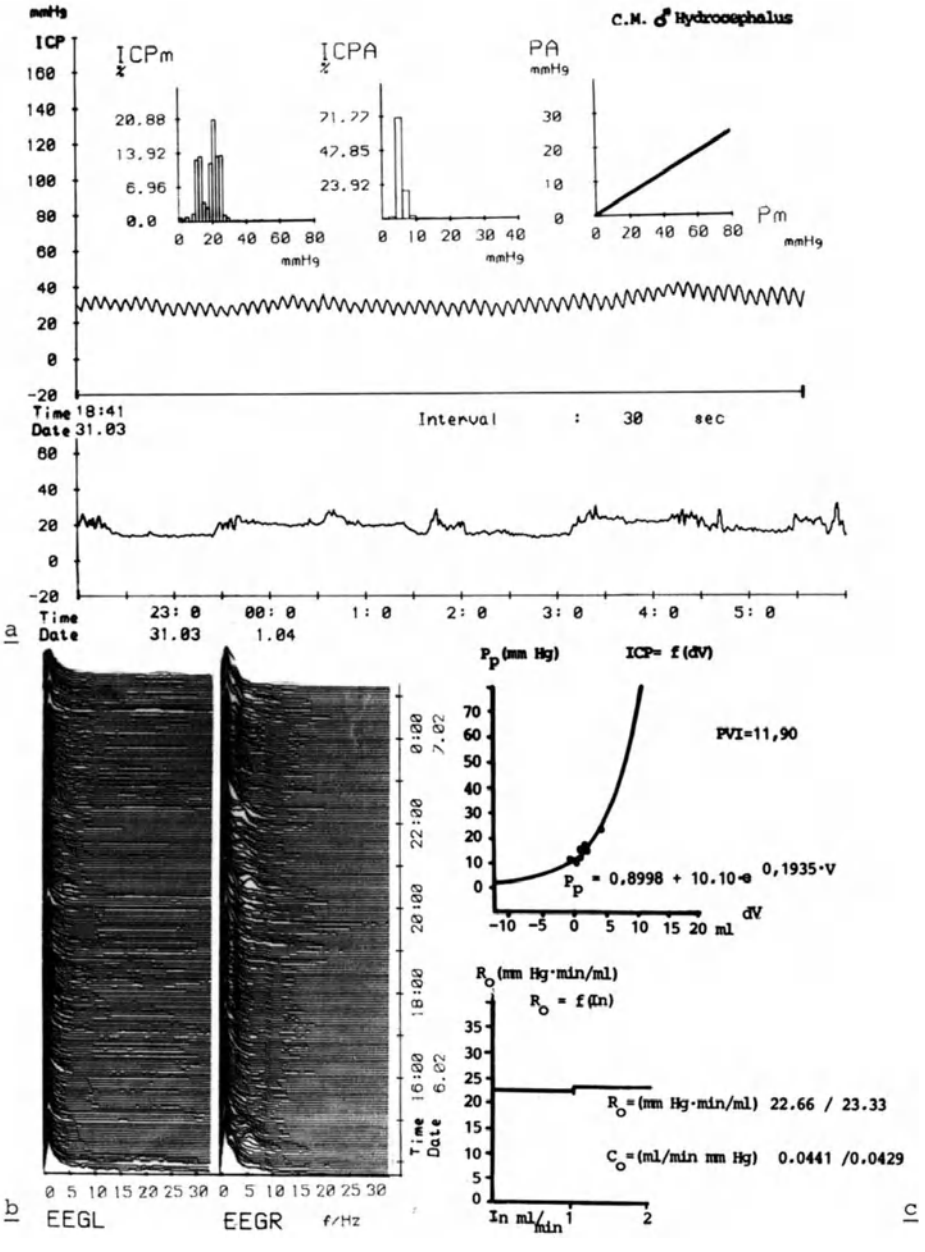



Fig. 4a-c. ICP, compliance, resistance, and EEG in infant with large ventricles. Clearly active hydrocephalus-B-waves in time plot, and ICP histogram skewed to the right; steep PA/Pm regression (a). Compliance reduced – steep P/V diagram; resistance increase (b). Predominant left hemispheric damage in EEG (CSA spectrum, c)

Table 1. Cerebral biosignals used for "computerized neuromonitoring": two-channel EEG for neuronal function; evoked potentials supplemented 1985/86. ICP, SAP, and derived CPP as "warning parameters". Principles of evaluation (graphics/statistics) with the "Neuromonitor"

| | | |
|---|---|---|
| a) Parameter of *neuronal function*: | | |
| *EEG*: | Sample at ≥128 Hz (Neuromonitor: 1 kHz) | |
| | Evaluate by frequency analysis (Fourier transform, FFT) | |
| | Graphics: | CSA-Spectra or "Chronospectra" |
| | Statistics: | Dominant frequency |
| | | Spectral edge frequency (95%) |
| | | Total EEG power |
| | | % power in different frequency ranges |
| *EVP*: | Graphics and statistics: | Interpeak, latency, amplitudes, form, standard deviation |
| b) Intracranial *"warning parameters"*: | | |
| *ICP, SAP*: | Sample at ≥15 Hz (Neuromonitor: 1 kHz) | |
| | Derivate the *CPP* (= SAP - ICP), evaluate by histogram statistics | |
| | Graphics: | Time plot with magnification (16 ×) |
| | | Histogram (single and serial) |
| | | Amplitude-mean ICP-regression (PA/Pm) |
| | | Fourier-spectrum of ICP (FFT) |
| | Statistics: | Arithmetic mean, mode, median range, variance, standard deviation coeff, skewness, kurtosis regression slope, and R of PA/Pm |
| | | % ICP power in different frequency ranges |
| *Autoregulation*: | Frequency transfer from SAP to ICP | |
| *Off line* (manual data input): | | |
| | Compliance after bolus test: k-slope, PVI, P/V diagram | |
| | CSF dynamics-resistance, conductance, $I_{form}$ | |

can be depicted as a histogram and correlated with the mean pressure by regressions analysis (Fig. 4). A *frequency analysis* of ICP pulsation is also possible, and a *transfer function* of SAP on ICP can be constructed. All calculations are performed and stored even when they are not being displayed at the bedside. The *EEG* is graphically shown either as a CSA spectrum or as a "chronospectrum" after FFT (Fig. 4). This is done simultaneously to the graphic or numeric printing of pressure data. A program of multimodal evoked potential (with associated hardware) is being developed.

Table 2. Statistical parameters derived from histogram statistics (ICP, SAP, CPP). Terms and basic mathematical equations

| Parameters | Equations |
|---|---|
| Arithmetic mean pressure (m) | $m = \frac{1}{n} \sum_{i=1}^{n} x_i$ |
| Median (M) | $M = x_g + \frac{\frac{n}{2} - s_o}{z_o} \cdot d$ |
| Mode ($m_o$) | $m_o = x_g + \frac{n_o - n_{-1}}{2n_o - n_{-1} - n_{+1}} d$ |
| Range (R) | $R = P_{max} - P_{min}$ |
| Variance ($s^2$) | $s^2 = \frac{\sum_{i=1}^{n} (x_i - x_m)^2}{n - 1}$ |
| Standard deviation (s) | $s = \sqrt{\frac{\sum_{i=1}^{n} (x_i - x_m)^2}{n - 1}}$ |
| Coefficient of skewness (S) | $S = \frac{\Sigma z_i (x_i - x_m)^3}{n \cdot s^3}$ |
| Coefficient kurtosis (K) | $K = \frac{\Sigma z_i (x_i - x_m)^4}{n \cdot s^4} - 3$ |

## Clinical Applications and Results

The computer-aided analysis of biosignals has two primary indications: "neuromonitoring" in the ICU and the diagnosis of intracranial pathology.

### *Neuromonitoring in the ICU*

Neuromonitoring assists in the recognition of complications and in prognostic and scientific patient evaluations. We use as automatic alarm setting the following: ICP >25 mmHg, mean SAP <80 mmHg or >150 mmHg, and CPP <60 mmHg. Alarms are activated when one of the above settings is exceeded for at least 3 min (Fig. 2).

Table 3. Principles of frequency analysis of EEG and ICP. Fourier transformation and derived graphics with basic equations

*EEG or ICP Fourier analysis*

$$E(fk) = \underbrace{\sum_{n=0}^{249} e_a(nT)w(nT)\cos(2\pi\frac{kn}{N}) - \ldots}_{a(f_k)}$$

$$\ldots - j \underbrace{\sum_{n=0}^{249} e_a(nT)w(nT)\sin(2\pi\frac{kn}{N}).}_{jb(f_k)}$$

*CSA-Spectra: amplitude intensities*

$$J(f_k) = \sqrt{[a(f_k)]^2+[b(f_k)]^2}\ .$$

*Chronospectra: power densities*

$$P(f_k) = [a(f_k)]^2+[b(f_k)]^2 = [J(f_k)]^2$$

Table 4. Off-line analysis of intracranial compliance and CSF dynamics: Data provided from the "Neuromonitor and basic equations

| | | |
|---|---|---|
| *Compliance data:* | from bolus test: | |
| | P/V diagram: | $P_p = P_{eq} + (P_o - P_{eq})\ e^{k \cdot \Delta V}$ |
| | Pressure-volume index (PVI): | $PVI = \ln \frac{10P_o - P_{eq}}{P_o - P_{eq}}\ k^{-1}$ |
| | k-slope: | $k = \ln \frac{P_p - P_{eq}}{P_o - P_{eq}}\ \Delta V^{-1}$ |
| *CSF dynamics:* | from infusion test: | |
| | Resistance ($R_o$) | $R_{So} = \frac{P_{ss} - P_o}{\ln} = 1/C_o$ |
| | Conductance ($C_o$) | $C_o = \frac{\ln}{P_{ss} - P_o} = 1/R_o$ |

The *"time plot"* replaces the use of continuous paper recording. Either time plot or current data can be displayed on the video screen. Alarm activations and other remarks can be added to the visual display and their time of occurrence and nature noted.

With this system, the converse courses of ICP and CPP and the reaction of these parameters to therapy are easily recognized. Continuous monitoring of ICP, CPP, and EEG has shown THAM treatment of post-traumatic brain swelling to be quite effective (Figs. 2, 3).

The effects of interventions can be mathematically determined and quantified by analyzing the parameters of amount and duration of therapy (Figs. 2, 3). This is particularly easy to see in *histogram* form (Figs. 2, 3). An increase in the ICP leads to a rightward shift and a flattening of the histogram. After successful therapy, the histogram is "normally" distributed, narrow, and under 20 mmHg throughout (Fig. 3). With standard statistical methods (Table 2), the effect of a particular therapy on a number of different patients can be statistically calculated.

The *EEG* provides prognostic information. A poor prognosis, for example, is indicated by sustained δ/sub-δ-EEG without recognizable modulation (13). EEG monitoring helps to prevent overdoses in patients treated with barbiturates (11). Digitalized storage of EEG as well as ICP and CPP allows for statistical expression of these parameters for groups of patients and quantification of the effects of therapy on EEG as compared with the effects on ICP/CPP (6).

*Diagnosis of Intracranial Pathology*

In addition to the above uses, the "Neuromonitor" is often used to further investigate instances of abnormal intracranial pressure of unknown origin, such as enlarged ventricles, cystic defects, and "pseudotumor cerebri" (Fig. 4).

There are certain typical patterns characteristic of different disease states. Typical *"high-pressure" hydrocephalus* is one example. In those cases where clinical and CT indications for shunting are relatively clear, the mean ICP during the day is higher than at night. The mode is lower.

In so-called *intermittent normal-pressure hydrocephalus* and in venous pressure-dependent *pseudotumor cerebri*, expansion of the time-plot curve for ICP reveals a typical pattern. Frequent "B" waves are seen (Fig. 4), especially at night. The ICP is higher at night than during the day. The histogram is quite flat and shifted markedly to the right. It is often bimodal due to the large number of "B" waves. In addition, the pulse amplitude increases markedly at night and the PA/Pm regression is quite steep (Fig. 4). After operation, the histogram normalizes completely.

The ICP was normal in a patient scheduled for shunting based on an abnormal RISA ventriculogram. The EEG in this patient, however, was strikingly abnormal. A complete neurophysiological work-up established a diagnosis of psychomotor epilepsy.

## Conclusions

The above analyses are dependent on the correct measurement of cerebral biosignal, for example through adhesive EEG electrodes, implanted minitransducers for ICP, and the measurement of blood pressure in the external carotid artery for the calculation of CPP.

The computerized evaluation of ICP, SAP, CPP, and EEG with a bedside microprocessor-based "Neuromonitor" improves recognition of complications, observation of a patient's course with time, and direction of therapy in an ICU setting. Such monitoring can also be used for the objectivation of ICP and EEG as an aid in diagnosis.

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# Present Status of Barbiturates in the Acute Stage of Cerebral Damage

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## Introduction

Barbiturates, introduced into clinical practice in 1932 by WEESE and SCHARPFF (30), still have a definite place in the practice of anesthesiology. Barbiturates are the anesthetics of choice for the induction of anesthesia in neurosurgical risk patients. The latter are all patients with decreased intracranial compliance as well as patients with functional narrowing of arterial cerebral afferent vessels.

## Effects of Barbiturates

The major effects of barbiturates are to decrease brain metabolism and brain circulation. The reduction of both these parameters can amount to 50%-65%, according to the dose given (4). The decrease of metabolism concerns solely the functional metabolism. If the EEG is isoelectric, the metabolism, i.e., the structural transformation, cannot be further decreased (3, 27). The coupling between metabolism and circulation remains intact, in contrast to the case with some volatile anesthetics. Further effects of barbiturates can partially be explained as a consequence of this, e.g., the decreases in intracranial blood volume, intracranial pressure, and body temperature. Barbiturates affect regional distribution of cerebral circulation, and especially in focal ischemia the regional distribution is most likely the decisive factor in their favorable influence. Barbiturates are antiedematous and anticonvulsive. The effects described up to now seem to improve the quotient between oxygen supply and requirement in situations of acute cerebral damage.

As regards the protective effects of barbiturates, further mechanisms are discussed which affect the cell or molecular level, such as seizing free radicals with a high membrane damaging potential, decreased release of lysosomal enzymes, reduction in the formation of free fatty acids, and decrease in intracellular potassium content. Decisive for a protective effect, in a limited sense, however, is the prevention of terminal membrane depolarization, recognized by the irreversible potassium outflow from the cells. Newer results from several centers have shown that barbiturates cannot stop the extracellular potassium increase following global cerebral ischemia; thus a protective effect in this respect applies only to hypothermia from a clinical point of view (2).

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## Experience with Barbiturates in Long-Term Therapy

Therapeutic doses of barbiturates are unsuccessful in treating global cerebral ischemia following arrest of circulation: the initial claims of their effectiveness by SAFAR's group (1978) (6, 20) have now been disproved by both animal experiments and multicenter clinical investigations (1, 10). Other individual centers have also found similar negative results (22, 25, 28). Therefore, long-term therapy with barbiturates cannot be recommended.

In the search for alternatives, some calcium antagonists have shown hopeful results in animal experiments, but only when given soon after the occurrence of global cerebral ischemia (12, 17, 26, 29). Combinations of barbiturates and calcium antagonists have not yet been reported on.

The situation in respect of focal or regional ischemia is quite different, in particular when the ischemia is not definite. Thus, barbiturates can to a certain extent play a part in cerebral circulation narrowing, in carotid surgery, cerebral aneurysm surgery, extra-intracranial bypass, and induced controlled hypotension (5, 11). In cerebral insults which cannot be cured surgically, barbiturate therapy has been of less value (21-23), although it might be that early administration of barbiturates would be of benefit.

A generally accepted indication for long-term use of barbiturates is a therapy-resistant increase in intracranial pressure, in particular in connection with severe skull-brain trauma. When all other drugs that decrease cerebral pressure have been exhausted, it has been proven by continuous measurement of intracranial pressure that barbiturates may decrease pressure (7, 8, 14, 15, 18, 19, 24, 31). Nevertheless, not all authors emphasize the use of barbiturates even for this indication (16).

Relative indications for limited treatment with barbiturates are the acute posttraumatic mesencephalic syndrome and occasional cases of posttraumatic or postoperative vegetative dysfunction when stabilization cannot be effected with sedatives (24). In addition, therapy-resistant status epilepticus is sometimes an indication for limited treatment with barbiturates (9).

## Barbiturate Therapy

Barbiturate therapy is not without problems, on the one hand because of severe side effects, on the other because of a defective dose-effect relationship. Pharmacokinetic studies revealed that administration of 100 mg thiopental per hour effected a stable blood level of about 6 µg/kg. With 500 mg/h – about 30 µg/ml – in many cases a burst suppression pattern occurs in the EEG. This is the maximal possible metabolic decrease via barbiturate. For a decrease in intracranial pressure, doses between 100 mg and 200 mg thiopental per hour seem sufficient. However, considerable acute and chronic barbiturate tolerance has been reported (13), and in all, there are no definite dose recommendations.

## Side-Effects of Barbiturate Therapy

Barbiturates lead to a spreading depression of all organic systems. Mechanical respiration of patients is a presupposition for long-term barbiturate therapy. Such therapy leads regularly to atonia of the gastrointestinal tract; spontaneous perforations may escape diagnosis. Further side effects are cholostatic hepatoses as well as hypersensi-

tive reactions; complications from infection and sepsis seem to occur more frequently.

Because of incompatibilities with other drugs, an own central-venous approach is also a prerequisite for long-term therapy with barbiturates.


## Summary

Barbiturates have not fulfilled the hopes that they would have protective effect in global cerebral ischemia; however, they are of value in focal or regional cerebral ischemia. The most important indication for long-term barbiturate therapy is an otherwise therapy resistant increase in intracranial pressure. Relative indications for limited therapy with barbiturates are the traumatic mesencephalic syndrome, postoperative or traumatic vegetative dysfunctions, and therapy-resistant status epilepticus.


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# Cerebrovascular Reserve and Brain-Protective Measures in Cases of Interruption of Carotid Artery Flow

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## Introduction

Some varieties of cerebrovascular disease, such as giant or intracavernous aneurysms and sinus cavernosus fistulas, are often unsuitable for direct operation and may require carotid artery ligation. During carotid surgery either temporary or permanent occlusion of the carotid artery may be necessary. These procedures carry a substantial risk of postoperative cerebral ischemia. According to a cooperative study performed in 1966 (3), 30% of patients who had common or internal carotid ligation suffered ischemic complications, i.e., collateral cerebral blood flow was insufficient in these cases.

Since the introduction of extra-intracranial arterial bypass procedures, it has been expected that the risk of cerebral ischemia would be reduced by combining a bypass operation with carotid ligation. But the latest multicenter study in 1984 (2) showed an incidence of ischemic complications not differing significantly from that of carotid ligation without bypass. To assess intolerance to carotid occlusion, we have performed a manual carotid compression test (MCCT) under clinical and EEG analytical observation in about 170 patients over the last 5 years. However, this test is only positive if there is absolutely insufficient cerebrovascular reserve, and cannot recognize borderline vascular reserve volumes. On the other hand, an MCCT performed under simultaneous EEG and regional cerebral blood flow (rCBF) measurements should give more information about the sufficiency of collateral cerebral blood supply.

## Method

In ten patients (five female and five male, mean age 55.1 years) with bilateral obstruction of the internal carotid artery, considered as high-risk patients for carotid endarterectomy, the carotid compression test was performed under continuous EEG analytical monitoring and rCBF measurements. During the test patients were in a lying position; they were alert and able to cooperate with neurological testing. Conventional bilateral multichannel bipolar needle electrode arrays were used and the EEG was analyzed by an interval-amplitude-analysis system (5). RCBF measurements were done by xenon-133 inhalation (1) before and during the manual carotid artery compression, which lasted 3 min. In five patients showing symptoms of insufficient cerebrovascular reserve, during operation carotid clamping was carried out and thiopental-natrium given intravenously in doses sufficient to produce 15- to 30-s burst suppression of the EEG.

## Results

Five patients did not show any significant neurological, EEG, or CBF changes during MCCT and were operated on with an uneventful follow-up.

In four other patients we found especially during the first minute of MCCT changes in EEG activity, with decreases in β-, α-, and θ-activity (Fig. 1) and recovery after decompression. In these patients CBF measurements revealed a diminished cerebral blood supply during MCCT. For example, in a 63-year-old woman with bilateral carotid stenosis during left MCCT, there was a reduction in CBF of 12% in the contralateral and of 45% in the ipsilateral hemisphere (Fig. 2).

Another 61-year-old woman with recurrent ischemic attacks caused by a right-sided internal carotid occlusion and a severe left internal carotid stenosis developed a right hemisyndrome and became unconscious after 30 s of left MCCT. The compression was immediately interrupted and she recovered fully. After 10 s MCCT the EEG showed severe changes in the left hemisphere, with increasing δ-activity (Fig. 3). Intraoperatively the EEG analytical values changed in the same way, with decreases in the α- and β-ranges and increases in the θ- and δ-ranges (Fig. 4) during a test clamping of the carotid artery. The same changes were registered even after hypertension had been induced pharmacologically. Therefore, carotid endarterectomy was done under EEG burst suppression by barbiturates. After reopening the internal carotid flow, EEG values returned to their initial levels. The patient showed no postoperative ischemic deficits and was symptom-free when last examined 7 months postoperatively.

## Discussion and Conclusion

The last case especially is an example of a patient with absolute insufficiency of the collateral blood supply in a case of carotid occlusion. The use of an intraoperative inline shunt – with its own risks – would take more time than is available before signs of cerebral ischemia appear. The fact that this patient and the other four mentioned above were at risk of postoperative ischemic complications but did not suffer such deficits speaks in favor of the therapeutic value of barbiturate therapy. It may reduce cerebral metabolism and protect the brain before an ischemic insult occurs, if it is administered early

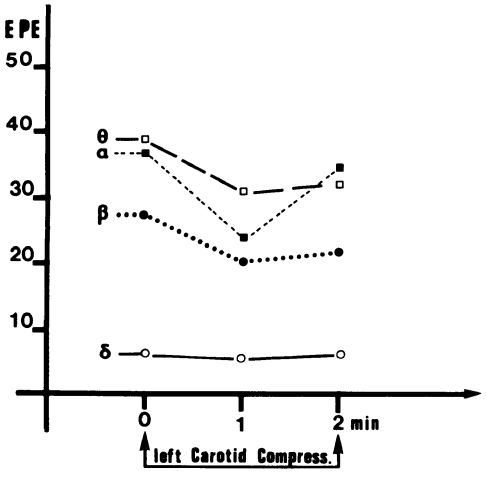


Fig. 1. EEG analytical follow-up during MCCT in a 63-year-old woman with bilateral carotid stenosis, showing decreases in β-, α-, and θ-activity, especially during the first minute (*EPE*, electrical power equivalent values)

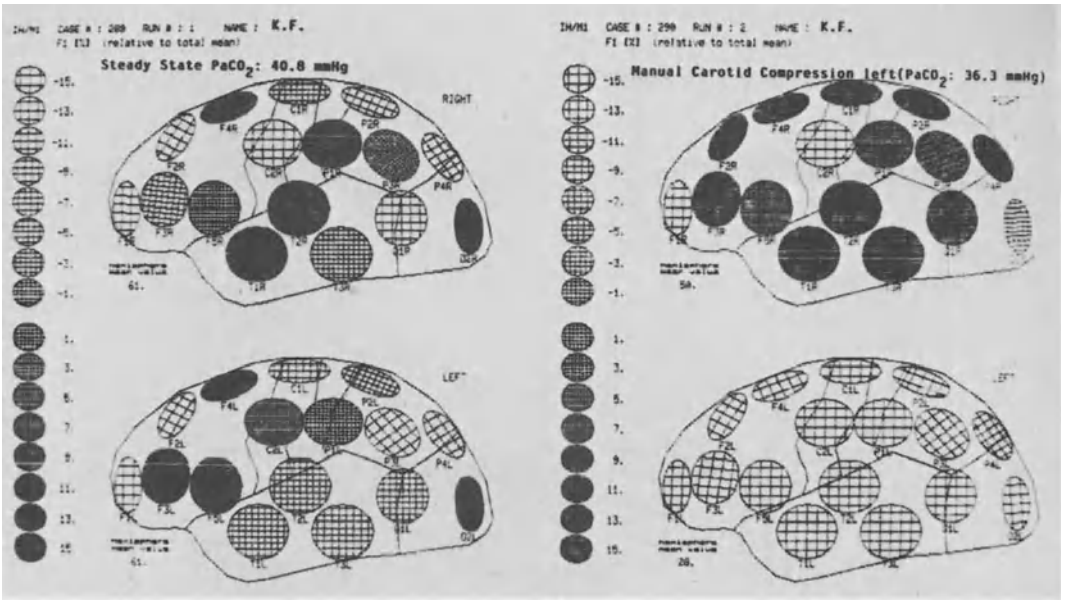


Fig. 2. RCBF measurements before *(left)* and during left carotid compression test *(right)* demonstrate a reduction in CBF of 12% over the contralateral and of 45% over the ipsilateral left hemisphere in the patient with bilateral carotid stenosis. Each regional value indicates percentage deviation of gray matter flow from the bihemispheric mean value

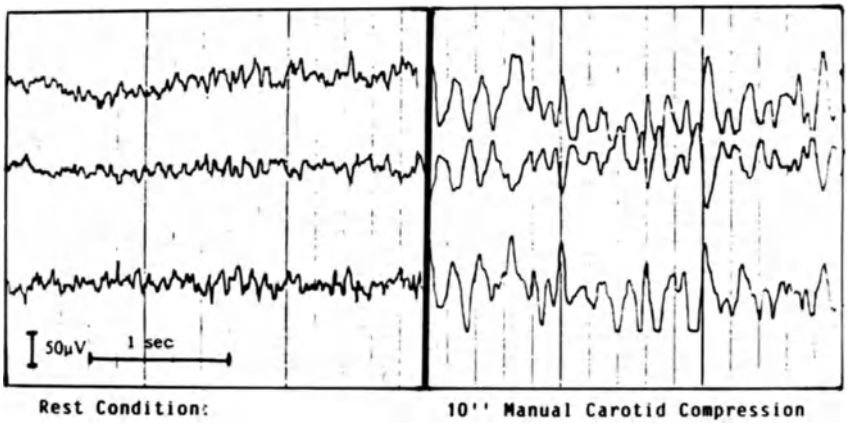


Fig. 3. EEG recordings of a 61-year-old woman with internal carotid artery occlusion on the right and severe stenosis on the left. Before left-sided MCCT *(left)* and 10 s after *(right)*. The three tracings are from the left frontal, parietal, and parieto-occipital region *(bottom)*, and show obvious δ-activity during left carotid compression

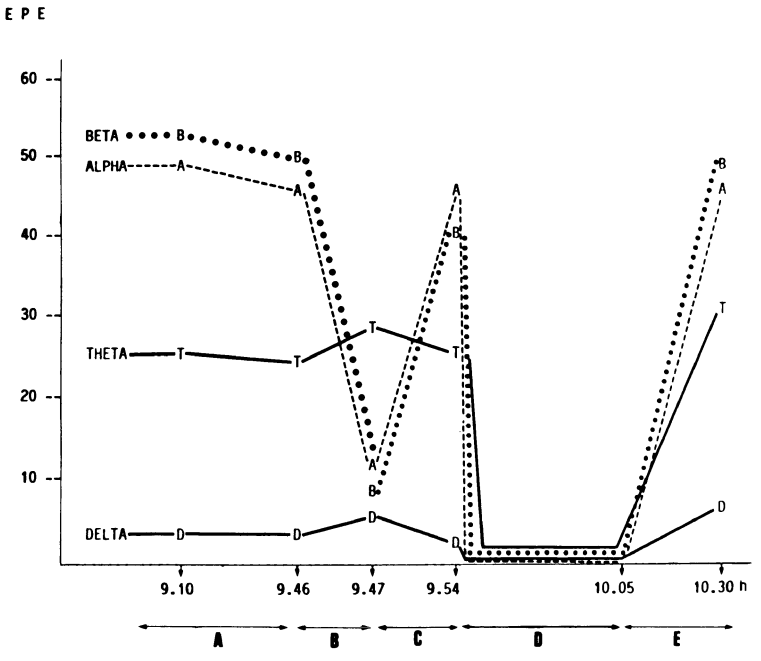


Fig. 4. Intraoperative EEG analytical follow-up of the 61-year-old woman with internal carotid artery occlusion on the right and severe stenosis on the left. Before (*A*) and during left carotid test clamping (*B*), during carotid reopening (*C*), during endarterectomy under thiopental-induced EEG burst suppression (*D*), and after restoring carotid artery flow (*E*). (*EPE*, electrical power equivalent values in the four classical ranges)

enough and ischemia is transient (4). If a permanent occlusion of the carotid artery is necessary, even an extra-intracranial bypass may not prevent a stroke in such cases, as a multicenter study has shown (2). Postoperative complications were observed in 33% of the patients, a rate not different from those who did not have a bypass, of whom two-thirds showed ischemic complications. It was found that carotid ligation on the left side showed a significantly higher incidence of ischemia (39%) compared with the right side (15%). Gradual ligation also resulted in a higher incidence of ischemia (39%) compared with abrupt ligation (20%).

We therefore prefer at this time the following procedure in patients considered for transient or permanent carotid occlusion (Table 1): MCCT is performed under EEG observation on every patient. In patients with multiple vascular lesions MCCT is performed additionally under rCBF measurement. As a result of the MCCT, we conclude:

1. If the test with all parameters is negative: collateral blood supply is sufficient to allow a carotid ligation to be carried out safely.
2. If MCCT is tolerated clinically, but EEG changes occur and CBF values decrease:
   - In cases of transient carotid occlusion: administration of brain-protective measures such as barbiturates is performed.
   - In cases of permanent occlusion: bypass surgery is first done, followed by MCCT to see if carotid occlusion is tolerated.

Table 1. Manual carotid compression test (MCCT) for evaluation of safety of carotid occlusion and brain-protective measures

| Reaction on MCCT (- = no, + = mild, ++ = distinct) | | | Brain-protective measures in cases of carotid occlusion | |
|---|---|---|---|---|
| Clinical | EEG | CBF | Transient occlusion | Permanent occlusion |
| - | - | - | Not necessary | Not necessary |
| - | + | + | Barbiturates | EC/IC bypass, later CCT control |
| - | ++ | ++ | Barbiturates | No safety |

3. If MCCT is not tolerated in all parameters:
   - In cases of transient occlusion: barbiturate protection is given.
   - *No* permanent occlusion should be carried out, as it may lead to ischemic deficits, even after establishing a bypass.

This procedure will certainly not prevent complications of an embolic nature; these had to be discussed with hematologists and treated by administration of anticoagulants or antiplatelet drugs. But in the majority (76%) of cases the probable cause of ischemia was found to be hemodynamic insufficiency (2), which we hope to reduce by this procedure.

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# Intensive-Care Aspects in the Treatment of Increased Intracranial Pressure

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## Introduction

The treatment of increased intracranial pressure (ICP) is a typical intensive-medical measure. It represents an intervention in various vital functions of the human body; on the other hand, a number of intensive-medical measures in turn lead to changes in ICP. The main topics to discuss in this context are:

- Controlled ventilation, with the dangers resulting from pulmonary infections and intrathoracic pressure changes
- Drug therapy, with its problems of interactions
- Positioning and physiotherapy
- Sedation and analgesia

It is our intention to elucidate several problems arising in the treatment of increased ICP and to point out the need for adequate continuous monitoring.

## Results

### *Controlled Ventilation*

A vital therapeutic support in patients with increased ICP is controlled ventilation. It has the aim of maintaining optimal oxygenation and reducing the $PaCO_2$ as therapeutic hyperventilation. This can also produce undesirable effects, particularly when aggressive respiratory patterns must be applied.

*Pulmonary Infections.* Patients undergoing controlled ventilation are at a high general and specific risk for pulmonary infections. Thus severe courses of infections with pulmonary failure are not seldom.

The general risk of infection arises from the disturbed clearance function of the tracheobronchial system (results of intubation: absence of the cough impulse, disturbed ciliary transport) and concomitant colonization with problem pathogens. Immunosuppression with barbiturates, corticosteroids, chemotherapeutics, and other substances used in intensive therapy is a component of the specific risk of a severe infection of the lungs and respiratory tract (CRABTREE et al. 1980). The specific risk also includes the danger of neurotraumatological patients contracting aspiration pneumonia when initial treatment is inadequate.

*Airway Pressure and ICP.* In former times, when ICP was not yet measured continuously, artificial respiration with a positive end-expiratory

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pressure (PEEP) was reputed to increase ICP. We now know that a PEEP of up to 10 cm $H_2O$ exerts only a negligible influence on ICP (AIDINIS et al. 1976). On the other hand, inversed ratio ventilation elevates the basic line of the ICP curve as an expression of an intrathoracic mean pressure increase (BAUM et al. 1980).

*Relaxation.* The measures required for cleaning the respiratory tract result in the development of acute high ICP peaks caused especially by coughing. A complete relaxation of the patient can prevent coughing and improve ventilation in extreme cases; it also reduces muscular tension with $PaCO_2$ increases, e.g., as reflex resistance associated with treatment measures. On the other hand, relaxation suppresses spontaneous coughing, and thus the remaining secretory mobilization from the peripheral bronchi, without completely preventing the ICP increases associated with suction (TSEMENTZIS et al. 1982). Even the proper suction procedure reduces functional residual capacity (FRC) of the lung; this is also true for younger people, so that airway closure occurs, and the $PaCO_2$ rises rapidly. Brief repeated inflation of the lungs is thus indispensible after suction.

We therefore restrict relaxation to a few cases – less than 5% of patients on artificial respiration. Moreover, the assessability of the relaxed patients is very limited.

*Drug Therapy*

Pharmacotherapy of increased ICP, here particularly therapy with barbiturates, can also take an undesirable course. An induction of barbiturate metabolism must be expected to occur in relation to the duration of therapy. This enzyme-inducing property of barbiturates is responsible for loss of potency at an unaltered dosage. Therefore, no prediction can be made as to the effect of a particular barbiturate dose in long-term therapy. A doubling of pentobarbital clearance can be expected after a week (Fig. 1; HEINEMEYER et al. to be published). It is necessary in determining the daily barbiturate dose to consider not only the treatment goal but also the side effects. The numerous drugs concomitantly administered during intensive therapy may produce changes

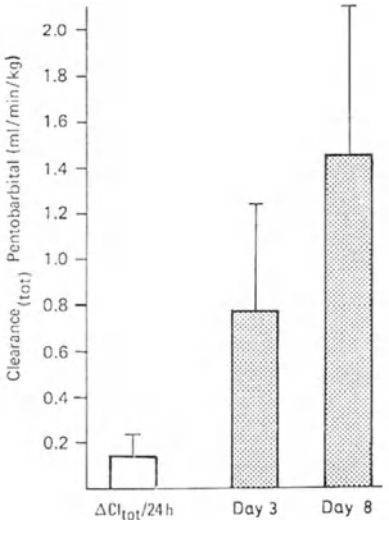


Fig. 1. Estimated pentobarbital clearance in high-dose barbiturate treatment of intracranial hypertension

counteracting the oxidative drug metabolism in the sense of inhibiting barbiturate elimination. This may in turn lead to the sudden occurrence of acute side effects, even if the patient has already shown good tolerance for the barbiturate therapy for a longer period of time.

In a 43-year-old man with increased ICP after a subarachnoid hemorrhage, both the pentobarbital plasma levels and the total plasma clearance for pentobarbital were measured in connection with the drug therapy (Fig. 2; HEINEMEYER et al. 1985). The course was typical. First, there was the above-described enzyme induction: in spite of increasing pentobarbital doses of 2.5-4.5 g/day, the plasma levels dropped from an initial value of 18 µg to 13 µg/ml. A parallel increase in plasma clearance was clearly recognizable. Despite concomitant reduction of the barbiturate dose, miconazole therapy for a mycosis on the 10th treatment day led to an increase of plasma concentrations to values exceeding 30 µg/ml. The plasma clearance decreased. With the increase of pentobarbital levels in plasma to high normal values, the patient developed cardiac insufficiency necessitating treatment. Dobutamine had to be added to the long drug list of this patient.

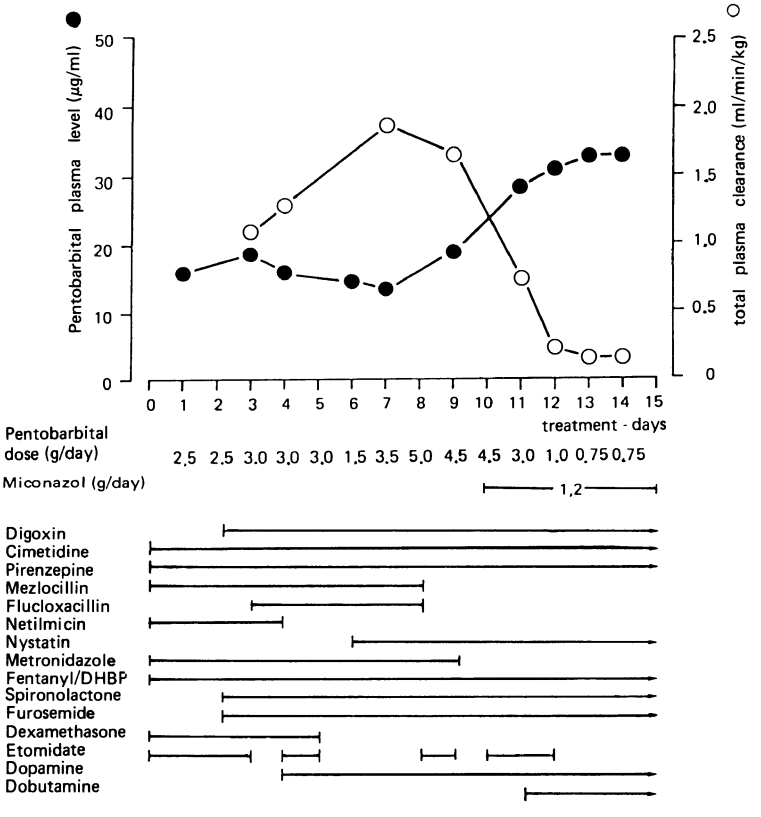


Fig. 2. Inhibition of pentobarbital metabolism by miconazole (HEINEMEYER et al. 1985)

*Positioning*

Positioning is an important means of influencing ICP. Although this relationship is known, daily routine work shows that it is easily forgotten in the course of performing the numerous other measures involved in intensive therapy. But it is also necessary to monitor ICP changes in connection with physiotherapeutic measures, nursing care, and positioning (TSEMENTZIS et al. 1982). This may be very exacting for all those concerned, particularly when patients with multiple injuries are involved. In principle, it can be said that there are no restrictions as long as the measures do not lead to an increase in ICP and the cerebral perfusion pressure is sufficient.

*Sedation and Analgesia*

Sedation and analgesia are important components of modern intensive therapy, also in comatose patients. It must be mentioned, however, that scientifically substantiated procedures for sedation and analgesic treatment are either lacking or have not yet gained general acceptance. At present, we only have useful concepts in the field of analgesic treatment. Sedation of intensive-care patients is, at best, at the experimental stage. There are two fundamental reasons for this: for one thing, the success of sedation is difficult to measure and, for another, sufficient knowledge is lacking on the drug metabolism of sedatives in connection with all other drugs applied during intensive therapy. Attention is presently being directed to two problems: the enzyme induction and inhibition that has already been mentioned and the undesirable central side effects of sedatives (central anticholinergic syndrome, states of delirium, etc.).

The gradual reduction of the barbiturate dosage necessitates sedation which, however, does not replace systemic analgesic treatment regardless of the drugs used.

In single polytraumatized patients, an analgesic treatment can also be carried out via an epidural catheter using local anesthetics or morphine derivatives. The epidural lumbar volume loading, however, can lead to significant ICP increases in patients with reduced intracranial compliance (Fig. 3), and should be avoided in these patients (HILT et al., to be published).

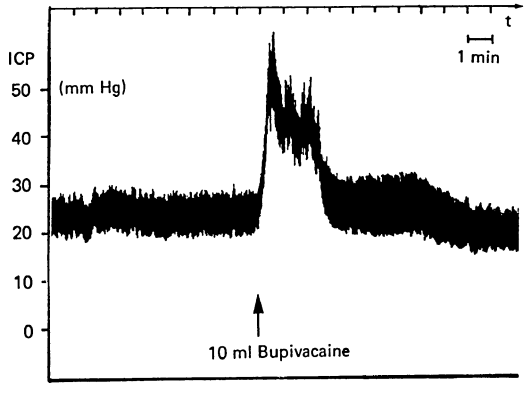


Fig. 3. ICP response to epidural volume load in a multiple injured patient. Epidural anesthesia via epidural catheter at L3/4 interspace. (ICP tracing redrawn from original)

*Monitoring*

The monitoring procedures used in our intensive care unit can be derived from what has been said so far:
- Continuous ICP recording (epidural or intraventricular)
- Continuous measurement of $P_ECO_2$ by capnometry, controlled by intermittent blood-gas analysis
- Hemodynamic monitoring: direct arterial blood pressure, central venous pressure, Swan-Ganz catheter (optimal)
- Computerized EEG (raw EEG, spectral analysis)
- Drug monitoring (barbiturate plasma level)

*ICP.* The first step comprises the continuous measurement of the ICP. All therapeutic measures must be brought in relation to the current value, the tendency, and the shape of the pressure curve.

*Capnometry.* The indirect monitoring of the arterial $PaCO_2$ by means of capnometry comes second. The $PaCO_2$ pressure is subject to various influences and can change very rapidly. Consequently continuous measurement is required for this parameter as well as for all those with similar short time constants. Although the end-expiratory partial $CO_2$ pressure ($P_ECO_2$) certainly does not constitute the actual standard value, it is easy to determine and can be brought in relation to the $PaCO_2$ by means of gas analyses establishing the alveoloarterial difference of both $PaCO_2$ and $P_ECO_2$. The random sample blood-gas analyses have therefore lost some of their significance as control procedures of controlled hyperventilation. They only serve for the control of the capnometrically measured $P_ECO_2$ as well as the determination of the partial oxygen pressure ($PaO_2$) and the saturation measurement in arterial and mixed venous blood. It must be mentioned in this connection that capnometry is an extremely sensitive measuring technique also used in the monitoring of the circulatory system. Changes in the lung perfusion directly involve changes of $P_ECO_2$. The corresponding alarm signals react even prior to those monitoring the mean arterial pressure.

*Hemodynamic Monitoring.* The determination of the cerebral perfusion pressure necessitates direct measurement of the blood pressure, since it is well known that indirect techniques for blood pressure measurement do not yield absolute values (BRUNNER 1978). The continuous blood pressure monitoring, the determination of the central venous pressure as filling pressure of the right ventricle, and the clinical examination furnish sufficient information on the cardiac output and vascular resistance in most of our patients. If it is necessary to obtain more differentiated information on these two parameters determining the blood pressure, the patients are provided with a pulmonary artery catheter. This may be necessary particularly in children and old patients under barbiturate therapy.

*EEG and Drug Monitoring.* The continuously measured EEG also reflects the tendency to replace random samples by continuous monitoring. EEG or its spectral analysis (CSA) is useful in assessing the general cerebral function or in detecting seizure activities. Moreover, in combination with intermittent barbiturate blood level determinations, once or twice a day, it is a particularly valuable parameter in determination and continuous monitoring of the highest reasonable barbiturate level (burst suppression, Fig. 4; McGILLICUDDY 1985) – especially because interindividual responses to barbiturates exist and the prediction of the metabolic rate is difficult. Here an apparatus is used that yields a derivation of both the left and the right hemisphere (e.g., $F_{p1/2}$-$A_{1/2}$) as a raw EEG. The latter is then demonstrated as a CSA in an integrated computer by means of the Fast-Fourrier analysis.

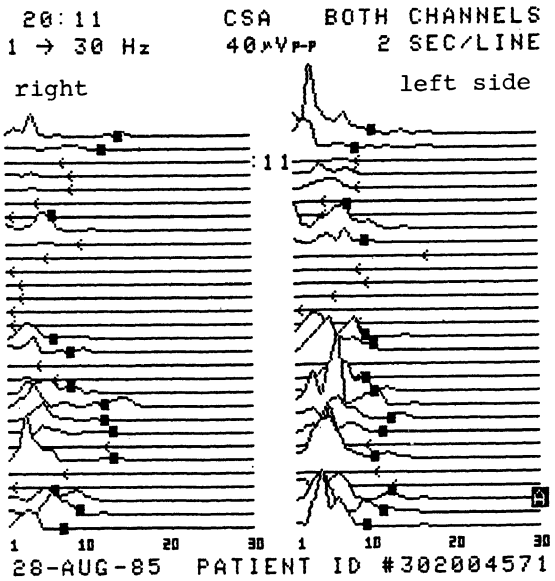


Fig. 4. EEG-spectral analysis (CSA): typical burst suppression in barbiturate coma (original print-out)

## Conclusions

It can be said that the continuous measurement of the ICP, the arterial pressure, the $P_ECO_2$, and the EEG has superseded the random sample characteristics of former procedures. The brain, with its narrow range of tolerance, requires consistent monitoring of all relevant vital functions and immediate regulative interventions whenever dysfunctions occur, especially because the aggressive treatment of increased ICP includes measures which are able to counteract their benefits by their side-effects. Thus modern intensive therapy provides the single patient with a maximum of individual treatment.

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# Possibilities and Limitations of High-Dose Barbiturate Therapy in the Management of Intracranial Hypertension

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## Introduction

Reduction of increased intracranial pressure is a well documented effect of barbiturates (1-4, 7, 8, 11, 13-15), whereas their protective effect in cerebral ischemia remains doubtful (16). But even the reliability of the drug effect on intracranial hypertension has yet to be determined, and in a first study on 34 patients (3) we found that barbiturates are less effective than previously reported (7, 8). The aim of the present study was to reconsider that conclusion on the basis of a larger population of treated patients.

## Material and Methods

One hundred and three patients entered the study, their ages ranging between 3 months and 68 years. They all were selected for high-dose barbiturate therapy because of acute intracranial hypertension which could not be controlled by conventional measures. Table 1 summarizes the origin of intracranial hypertension and the surgical care preceding the institution of barbiturate coma. Intracerebral hematomas were evacuated with the exception of one case of hemorrhage within the basal ganglia. In 29 of 42 surgically treated patients the bone flap was removed because of acute brain swelling; problems involved with this procedure will be discussed in a separate paper.

Prior to treatment all patients were comatous (Glasgow coma score 7 or less) with abnormal posturing in 68 and absence of any motor response in 11. Twenty-five presented with bilaterally fixed pupils.

Table 1. Origin of intracranial hypertension and primary surgical care

| | No. of patients | Craniotomy | Craniectomy |
|---|---|---|---|
| Contusion | 52 | - | 11 |
| Traumatic hematoma | 20 | 8 | 11 |
| Spontaneous intracerebral hemorrhage | 10 | 5 | 4 |
| Ruptured aneurysm | 11 | - | 2 |
| Hypoxic, metabolic, others | 10 | - | 1 |
| Total | 103 | 13 | 29 |

Table 2. Effect of therapeutic barbiturate coma on raised intracranial pressure (ICP)

| ICP before treatment | No. of patients | Decreased ICP | Increased ICP | Unchanged ICP |
|---|---|---|---|---|
| 21 - 30 mmHg | 36 | 28 | - | 8 |
| 31 - 40 mmHg | 24 | 17 | 7 | - |
| 41 - 60 mmHg | 26 | 12 | 14 | - |
| 60 mmHg | 17 | 3 | 14 | - |
| Total | 103 | 60 | 35 | 8 |

Treatment with barbiturates was initiated if the epidural pressure (monitored using a fiberoptic system) exceeded 20 mmHg for at least 20 min and if – in addition – clinical signs of a midbrain sydrome were present, or if the pressure exceeded the level of 30 mmHg.

The great majority of patients received pentobarbitone in a loading dose of 3 - 5 mg/kg followed by an individual dosage of 1 - 2 mg/kg per hour until electrical activity was lowered to a burst suppression pattern. During the last 2 years we used thiopentone (5 - 20 mg/kg loading dose, followed by continuous infusion at a rate of 5 - 10 mg/kg per hour) and phenobarbitone, since pentobarbitone was no longer available for clinical use.

Adjustment of the individual drug dosage was assured by daily analysis and/or continuous monitoring of the EEG, with a close view to the cerebral perfusion pressure as calculated from epidural pressure and directly measured arterial pressure, by assessment of the serum drug levels at intervals, and by careful controls of renal function.

Treatment was finished after 2 - 21 days (4 - 7 days in most cases) by gradual reduction of dosage, if the epidural pressure could be maintained below 15 mmHg for 2 days. If the pressure did not fall below this level, withdrawal of drugs was tried after 7 - 10 days while observing the neurological functions as well as the intracranial pressure.

Barbiturate therapy was considered successful if drug administration resulted in a decrease in epidural pressure of at least 10 mmHg and if this effect could be maintained by continuous treatment.

## Results

In 60 patients (58%) intracranial hypertension definitely responded to barbiturate treatment as previously defined, whereas in 20 other patients only a transient effect could be observed. While the drug effect was independent of the origin of intracranial hypertension, it was strongly dependent on the level of intracranial pressure before treatment (Table 2): Of those patients with a preexistent pressure up to 40 mmHg, 75% were responders, whereas only 35% of patients with an initial pressure above 40 mmHg responded to treatment. In the latter group failure of treatment was invariably followed by fatal decompensation of intracranial hypertension, resulting in a total of 35 deaths due to uncontrollable intracranial hypertension. In some patients in the group with an initial epidural pressure of 21 - 30 mmHg, reduction

Table 3. Outcome at 5 months in patients with head injury ($n$ = 72)

| | | |
|---|---|---|
| I | Good recovery | 16 pat. = 22% |
| II | Moderate disability | 11 pat. = 15% |
| III | Severe disability | 13 pat. = 18% |
| IV | Persistent vegetative | 2 pat. = 3% |
| V | Death | 30 pat. = 42% |

of pressure was less than 10 mmHg. Therefore they had to be considered nonresponders according to our definition of successful treatment. None of this group experienced an uncontrollable rise in intracranial pressure.

In 23 patients one or more episodes of systemic hypotension (systolic arterial pressure below 99 mmHg) were encountered. Renal failure occurred in seven patients and was responsible for lethal outcome in at least five of them. Septicemia was suspected but not proved in three cases. Hypothermia and pneumonia represented no outstanding problems in this series, whereas inhibition of gastrointestinal motility was a quite common event prohibiting oral feeding for several days.

Fifty-five of the patients (53%) succumbed, 35 of them due to decompensating intracranial hypertension, the others because of primary brain damage or various extracerebral complications, most of them reflecting their severe illness. For the group of head-injured patients Table 3 gives a more detailed analysis of outcome according to JENNETT and BOND (5). In this group the causes of death were intracranial hypertension in 21 patients, brain stem injury in three others and extracerebral complications in the remaining six: renal failure, gastric ulcer, pulmonary embolism, and others. Generally speaking the outcome was found to be adversely affected firstly by an initial intracranial pressure above 30 mmHg, but even more so by a poor neurological condition.

## Discussion

Our results indicate that induced barbiturate coma is an additional effective aid in the management of intracranial hypertension. However, the drug effect is not as reliable as has been reported by some other authors (7, 8, 11), and this is particularly true for patients with severe intracranial hypertension. Failure of barbiturate therapy has been attributed to primary brain damage in some patients and to advanced secondary ischemia in others (10). In our series the ineffectiveness of the drugs at high levels of intracranial pressure suggests that in these cases edema and ischemia have reached an irreversible state. Consequently SAUL and DUCKER (12) advocated a more vigorous treatment at an earlier stage of intracranial hypertension. However, it should be emphasized that in our series no patient who presented with an initial intracranial pressure below 30 mmHg succumbed due to decompensated intracranial hypertension. Beyond this we have to realize that in slight or moderate intracranial hypertension, differentiation between drug-induced and coincidental pressure decrease is often difficult.

The findings of this open and uncontrolled study do not permit a definite statement above the effect of barbiturates on clinical outcome. In our group of head-injured patients outcome was quite similar to that reported by JENNETT et al. (6) in patients who did *not* receive barbiturate treatment. In a recent prospective randomized trial MILLER and his group (9) could not find any overall benefit of barbiturate therapy, and they suggested that a potential benefit might have been matched by the risks of therapy.

In fact, some of the fatalities in our own series may be attributed to complications of treatment, although detailed analysis of the patients with acute renal failure revealed additional factors to be involved in most of them: preexistent latent renal failure, pancreatitis, or signs of septic shock. Nevertheless, unexpected barbiturate blood levels above 50 mg/liter were frequent findings in these cases, underlining the need for strict control of blood levels.

## Conclusion

There is unequivocal evidence that intracranial hypertension of various origin may be treated successfully by high-dose barbiturates in a number of patients. However, consistent control of intracranial pressure can be achieved in little more than half of all patients treated and in only one-third of patients with high levels of intracranial pressure. These facts, as well as the serious risks of treatment, must be taken into account whenever therapeutic barbiturate coma is to be instituted.

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# Treatment of Intracranial Hypertension Without Barbiturates

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## Introduction

Intensive care treatment of intracranial hypertension tries to counter pathophysiologically different space-occupying lesions such as cerebral hyperemia or brain swelling, brain edema of different genesis, brain shift, and disturbances in cerebrospinal fluid (CSF) circulation. Preconditions for specific and successful treatment of intracranial pressure (ICP) increases are regular control of neurological status, monitoring of vital functions, and continuous measurement of intracranial pressure. Uncontrolled treatment of presumed increased ICP is risky and of questionable effect.

## ICP Monitoring

The decision on whether ICP is to be measured epidurally or intraventricularly can be made on the basis of the computer tomographic findings (9):

- Epidural measurement is appropriate in patients with small, compressed, or shifted ventricles, such as with cerebral tumors or after severe brain trauma with acute brain swelling.
- Ventricular fluid pressure (VFP) measurement is appropriate in patients with dilated ventricles, such as those with diencephalic or cerebellar tumors or spontaneous hemorrhages into CSF spaces or with an inflammatory process with subacute CSF circulation disturbance.

The timing, extent, and kind of pressure-lowering therapy cannot be based solely on the absolute value of ICP. Cliniconeurological findings, particularly the state of consciousness, have to be taken into account. We know from experience that acute high intracranial pressures in fully conscious patients rarely determines prognosis, whereas a VFP above 20 mmHg can hardly be tolerated by the unconscious patient (13).

## General Principles of ICP Treatment (Fig. 1)

In conscious patients with normal or slightly disturbed neurological functions, pressure-lowering therapy can be restricted to prophylactic measures.

In a 56-year-old female after operative evacuation of a spontaneous intracerebral hematoma, epidural pressure peaks above 60 mmHg were repeatedly measured in the stage of edema during the first week. In this

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| | |
|---|---|
| Head | 30°-40° |
| $pO_2a$ | >70 mm Hg |
| $pCO_2a$ | 25-30 mm Hg |
| SAP syst. | 100-160 mm Hg |
| Fluid Balance | ± 500 ml |
| Sodium | 135-145 mmol/l |
| Osmolality | 270-295 mosmol / kg $H_2O$ |

Fig. 1. General principles of ICP management

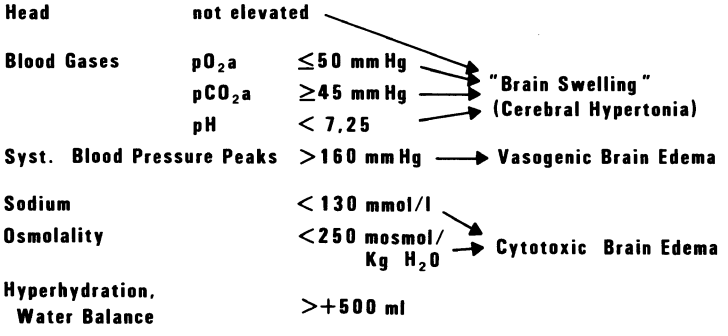


Fig. 2. Negative factors for intracranial pressure

responsive patient, pressure-lowering therapy consisted of elevation of the upper part of the body and head, careful regulation of fluid and electrolyte balance, and slight sedation.

*Sedation*

To maintain the current level of neurological functions, patients with enhanced muscular tone, tachypnea, tachycardia, and elevated blood pressure should be sedated with benzodiazepines, different anesthetics and narcoleptic agents, and, if necessary, short anesthesia. Adequate sedation will lower ICP appreciably by normalizing vegetative functions. In patients with decreased muscular tone and depression of the cardiovascular and/or respiratory system, however, sedation is contraindicated.

*Prevention of Secondary Brain Damage* (Fig. 2)

Especially important is the elimination of factors which favor the development of secondary space-occupying lesions leading to an ICP increase:

- Horizontal position of the head, hypoxia, hypercarbia, and acidosis dispose to cerebral hyperemia and brain swelling.
- Pathological increases of blood pressure or severe variations in arterial pressure and or hyperhydration with hypotonic solutions can make brain edema worse.

On the other hand, after excessive dehydration a life-threatening state of hypertonic hydropenia can develop. With low systemic blood pressure an extremely elevated head position can lower the cerebral blood flow and favor cerebral hypoxia. After a severe head injury early ICP increases within the first hour are usually due to either peracute hemorrhage or to brain swelling caused by cerebral hypoxia.

Elevation of the upper part of the body and of the head by 30 - 40° supports the cerebral venous return (11). An extreme position of the head must be avoided as it may induce compression of the venous drainage. Arterial hypoxemia or hypercapnia are indications for intubation and ventilation.

Early intubation and hyperventilation will lower the cerebral blood volume and ICP, provided that the brain vessels still respond to changes in $CO_2$ tension. Hyperventilation, however, has no longlasting effect (14). *Positive negative pressure respiration* (PNPR) will not only cause extreme hypocarbia but also effectively increase flow rate in the upper vena cava (1). It would be ideal for treatment of increased ICP, but it has some serious side effects on lung and cerebral blood flow (6, 16). Therefore, controlled PNPR must be restricted to a limited period of time, for example during intracranial operative procedures or for lowering life-threatening increases of ICP after operation or trauma.

A slight change in end-expiratory pressure will only have an influence upon the ICP if it leads to a change in respiratory minute ventilation or arterial $CO_2$ tension. By keeping the respiratory minute ventilation and the $CO_2$ tension at a constant level, a slight increase in ICP can be corrected by further elevation of the head (4).

The close correlation between optimum lung ventilation and the ICP level is particularly evident after interruption of the artificial ventilation of a comatose patient, who has lost his intracranial reserve space (8). Sufficiently long expiration is particularly important for a decrease in ICP. An inspiration-expiration ratio of 2:3 is especially effective (8).

## Specific Treatment

For the treatment of increased ICP caused by edema, specific medical treatment is available apart from the general measures mentioned above:

- Steroids
- Osmotics and oncotics
- Diuretics

That *steroids* have an effect upon tumor edema is beyond any doubt (5). The effect upon traumatic brain edema remains to be seen from specific investigations.

Today, the most frequently used *osmotically effective agents* are mannitol, sorbitol, and glycerol.

*Sorbitol* as a 40% solution with an osmolality of 3200 mosmol is especially effective. A rapid infusion of sorbitol with an immediate increase in serum osmolality leads to a prompt decrease in ICP which can even reach subatmospheric values (12). As a rule, after a severe brain injury edema is to be expected after several hours, which is similar to the interval observed after contusional hemorrhage. Therefore, osmotics are usually not indicated before hospitalization (12).

Small quantities of sorbitol applied as bolus shot proved good for ICP lowering not only in inoperable brain contusions but also generally in brain edema of different genesis. Repeated application of sorbitol should only be performed with regular control of serum osmolality, to avoid renal failure with secondary osmotic brain edema. Even today this complication is occasionally observed after uncontrolled dehydration.

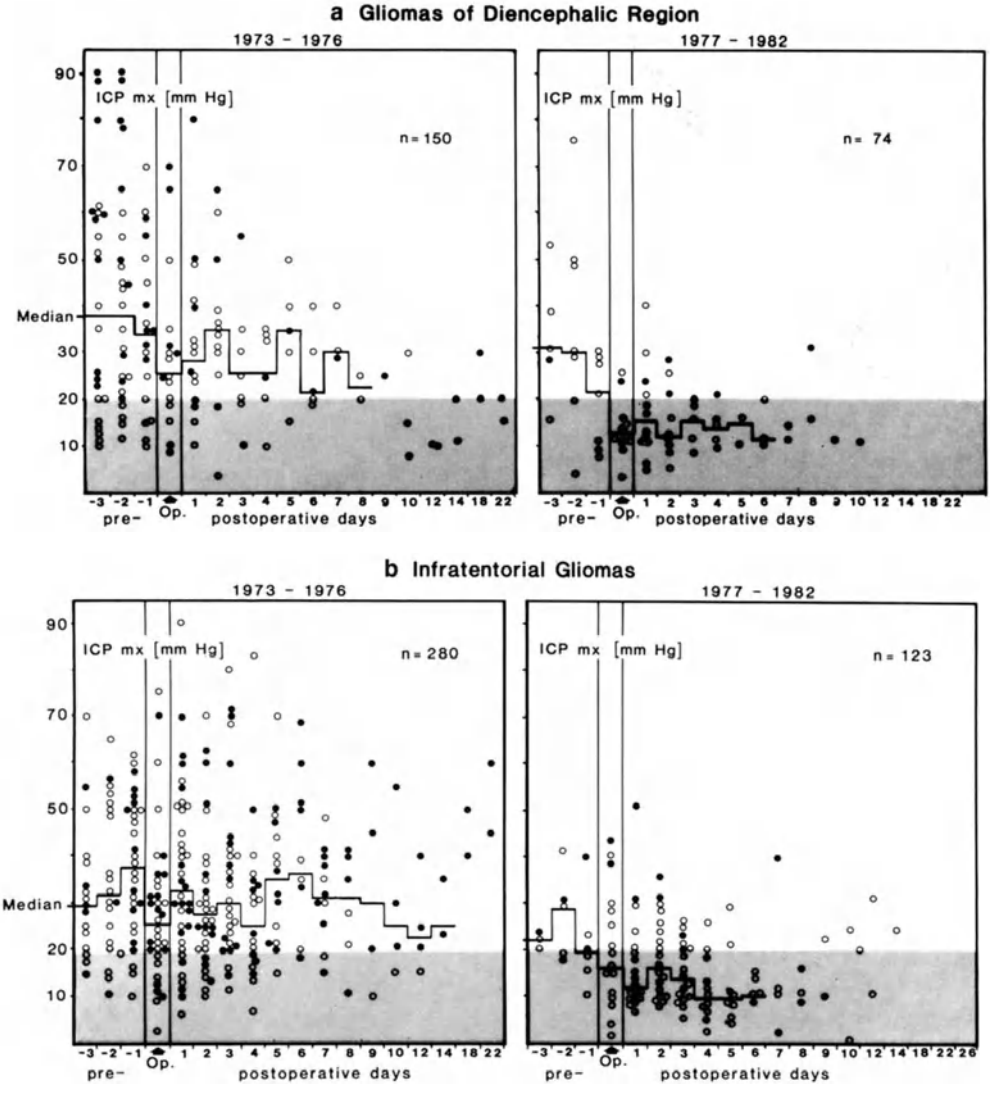


Fig. 3. a *Maximum ICP values* in the pre- and postoperative course of patients with *gliomas of the diencephalic region*, divided into two different periods of surgery. After 1977 we observed a distinct decrease in the ICP peaks on average. b *Maximum ICP values* in the pre- and postoperative course of patients with *infratentorial gliomas*, divided into two different periods of surgery. *Open circles*, ICP peaks of patients with favorable outcome; *closed circles*, ICP peaks of patients with fatal outcome

Acute vascular hypervolemia with increased central venous pressure can provoke complications such as tachyarrhythmia, particularly in patients with congestive heart failure. The metabolism requires special care, since serum lactate may increase during sorbitol infusion.

Simultaneous application of diuretics increases the ICP-lowering potential. In any case, development of electrolyte imbalance, hypovolemia, or hyperosmolality should be avoided.

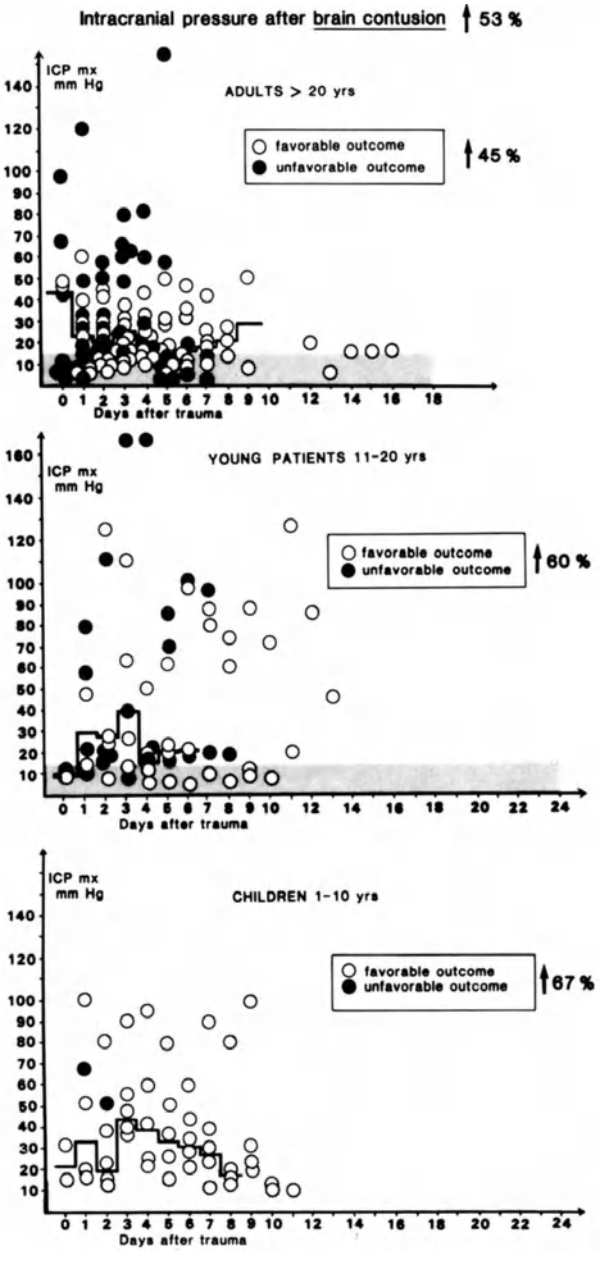


Fig. 4. *Maximum ICP values after contusional hemorrhages in children, juveniles, and adults*

*Acute CSF Circulation Disturbance*

None of the above-mentioned therapeutic measures are effective enough to achieve sufficient ICP lowering if a disturbance of the CSF circulation or absorption dominates, such as with hydrocephalus due to trauma or tumor, CSF hemorrhage, acute cerebral or cerebellar malacia, or any acute cerebral inflammatory process.

In these patients, of course, only pressure-controlled external CSF drainage is effective (7, 9).

## Results of Therapy

With improved diagnostic tools, treatment of acute intracranial hypertension could be specifically adjusted to its pathogenesis. This may be the reason why in recent years a distinctly faster normalization of postoperative/post-trautmatic ICP could be registered (Fig. 3).

As an investigation of 961 injured persons with severe brain lesions confirmed, the prognosis is not primarily dependent on the absolute value of ICP but rather on the severity of brain function disturbance, which can be estimated from coma grade and age of the patient (2, 3, 13). Out of 36 patients with contusional hemorrhages in whom ICP was measured continuously, 19 survived (53% survival rate). The survival rate in children was 67%, in juveniles 60%. In some of them a transitory epidural pressure above 100 mmHg was registered. In adults the survival rate was 45%; none of them survived ICP peaks over 60 mmHg (Fig. 4) (15).

## Conclusion

1. Intracranial pressure is an objective criterion which can be evaluated only in relation to cliniconeurological findings.
2. The underlying cause of increased ICP must be treated.
3. The most important measures are: optimum sedation, if possible without blurring the neurological condition; artificial respiration; osmotics, oncotics, and diuretics; temporary pressure-controlled external drainage.
4. Constant evaluation of all available data on the patient's condition is imperative, since all therapeutic measures are of transitory value only. Therapy must be adjusted to the current need of the patient.

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# Significance of Acute Disturbances of Pupillary Function in Postoperative Intensive Care After Operations for Craniopharyngiomas

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## Introduction

In postoperative intensive care dilated pupils without reaction to light are interpreted as an alarming sign of a bulbar or midbrain lesion. To exclude postoperative bleeding or a swelling reaction as quickly as possible, generally CT of the skull or an immediate operative revision is performed.

This study gives a report on patients with craniopharyngiomas who had acute postoperative pupillary dysfunctions without any evidence of bleeding or swelling of the brain.

## Patient Material

In the years 1971 - 1984 60 operations on 27 male and 21 female patients with craniopharyngiomas were performed. The patients ranged in age from 3 to 77 years.

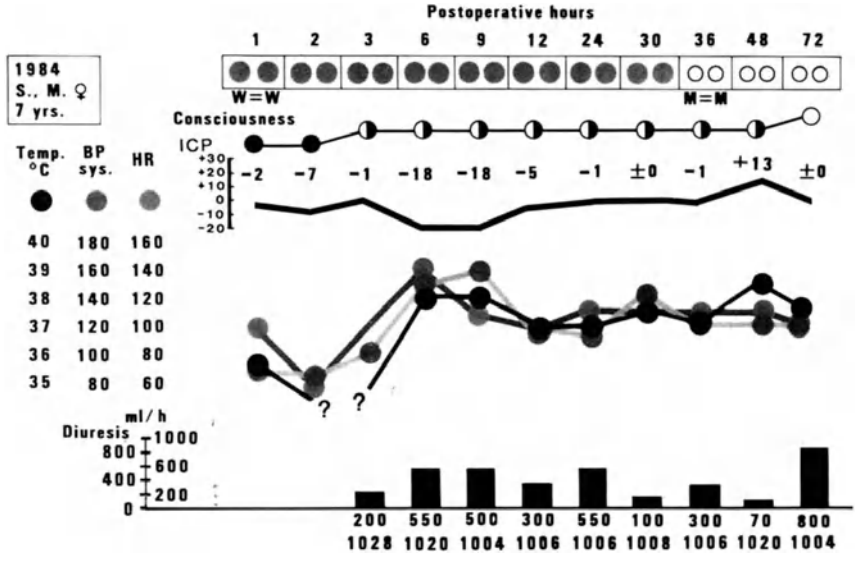


Fig. 1. Postoperative pupillary dysfunction, state of consciousness, intracranial pressure (ICP), and vegetative functions (*BP*, blood pressure; *HR*, heart rate) in a seven-year-old child following surgery of a suprasellar cystic craniopharyngioma

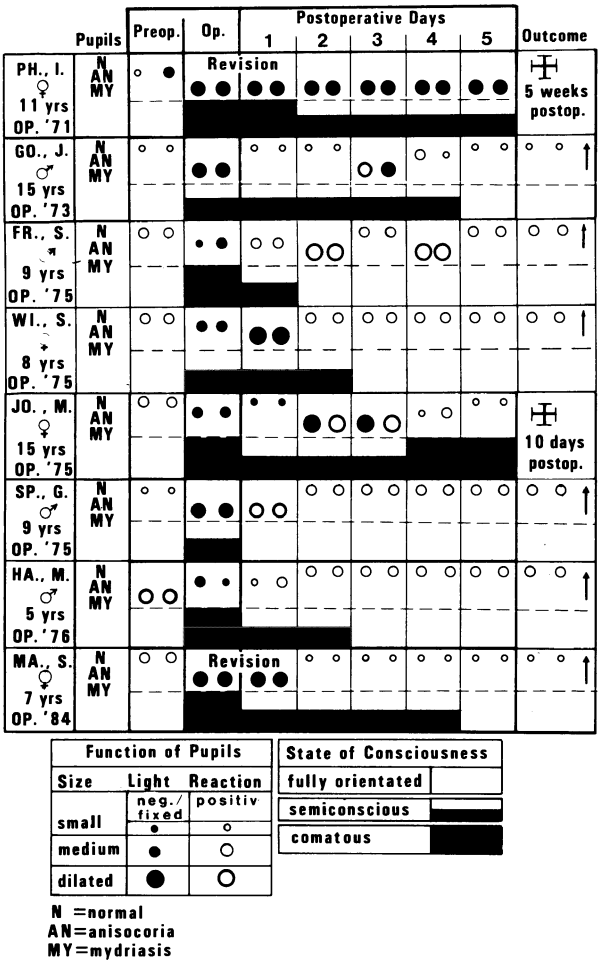


Fig. 2. Outcome of eight children with craniopharyngiomas after severe postoperative pupillary dysfunctions (anisocoria, fixed and/or dilated pupils) and disturbance of consciousness (coma/semi-coma)

## Results

A seven-year-old girl was operated on for a cystic craniopharyngioma which extended into the hypothalamic area. While the child was still in the operating room bilateral dilated and fixed pupils were observed. Consequently an operative revision was performed. No bleeding was observed, neither epidural nor subdural. The dura was flaccid. A local swelling of the brain was not noticed.

The pupils remained dilated and without reaction to light for 36 h (Fig. 1). The child became responsive after 24 h.

The ventricular fluid pressure (VFP) stayed continuously within the limits of normal. Systolic blood pressure, heart rate, and temperature increased during the first 9 h after the operation. They then normalized gradually.

Six hours after the operation a diabetes insipidus developed. One week later the child had recovered completely. The pupils were medium-sized and reacted promptly to light. Sight was bilaterally normal.

Table 1. Postoperative pupillary dysfunctions after operations for craniopharyngiomas in relationship to the patients' age

| Alarming (?) pupillary dysfunction | Patients' age (years) | | | | |
|---|---|---|---|---|---|
| | 0 - 10 | 11 - 20 | 21 - 40 | 41 - 60 | > 60 |
| + ($n$ : 8) | 5 (62.5%) | 3 (37.5%) | | | |
| ø ($n$ : 52) | 18 (34.6%) | 6 (11.5%) | 9 (17.3%) | 17 (32.7%) | 2 (3.9%) |

Table 2. Postoperative pupillary dysfunctions after operations for craniopharyngiomas in relationship to supra- and retrosellar extension of the tumor

| | Increasing supra-/retrosellar tumor extension | | | |
|---|---|---|---|---|
| Alarming (?) pupillary dysfunction | Slight suprasellar | Indented 3rd ventricle | Up to foramen of Monro | Blockage of foramen of Monro |
| + ($n$ : 8) | | 1 (12.5%) | 2 (25%) | 5 (63%) |
| ø ($n$ : 40) | 12 (30%) | 21 (53%) | 4 (10%) | 3 (7.5%) |

In the same manner five patients with postoperative dilated and fixed pupils were observed (Fig. 2). In all cases this symptom disappeared by the 8th day. A permanently changing pupillary reaction was noticed in four cases.

It is remarkable that none of these patients with pupillary dysfunctions was older than 15 years (Table 1). In five of these children, i.e., 63%, the tumor led to a uni- or bilateral blockage of the foramen of Monro (Table 2). In two other cases the lesion almost reached the foramen of Monro. With patients who had a normal pupillary reaction the tumor extended similarly in only 18%.

Also postoperative vegetative dysregulations such as hyper- or hypotonia, tachycardia, hyperthermia, and tachypnea were observed more frequently in patients with pupillary dysfunction (Table 3). In seven out of the eight cases diabetes insipidus developed.

The pupillary dysfunction had no prognostic significance. During the subsequent period two of the eight children died, i.e., 25%, compared with 30% of the patients without pupillary dysfunction. Six children recovered totally (Fig. 2). As already indicated, the pupillary function normalized 8 days after the operation at the latest.

During the same period 54 patients with other tumors in the diencephalic area underwent surgery. Similarly, severe pupillary disturbances were not observed in the postoperative course of these cases.

Table 3. Postoperative pupillary dysfunctions after operations for craniopharyngiomas in relationship to vegetative dysregulations

| | Postoperative vegetative dysregulation | | | | | |
|---|---|---|---|---|---|---|
| Alarming (?) pupillary dysfunction | Diabetes insipidus | Tachycardia (≧120/min) | Hypertension ≧160 mmHG | Hypotension ≧100 mmHg | Hyperthermia (≧38.5°C) | Tachypnea (≧30/min) |
| + ($n$ : 8) | 7 (87.5%) | 6 (75%) | 2 (25%) | 2 (25%) | 5 (62.5%) | 2 (25%) |
| ∅ ($n$ : 52) | 34 (65.4%) | 25 (48.1%) | 11 (21.1%) | 7 (13.5%) | 24 (46.2%) | 9 (17.3%) |

## Discussion

The experimental findings of W.R. HESS (1, 2) from the 1930s offer an explanation for the observed reversible pupillary dysfunctions: HESS obtained a bilateral mydriasis through electric stimulation in the central and posterior part of the hypothalamus of the cat even at the lowest level of stimulation. Thus, most probably, acute pupillary dysfunctions in connection with other vegetative disturbances after operations for craniopharyngiomas are caused by an irritation of the hypothalamic centers (1 - 5). In all observed cases the preoperative radiodiagnostics showed retro- and suprasellar tumor extension to these areas.

## Conclusion

Acute disturbances of pupillary function after operation for craniopharyngiomas with extension to the hypothalamic area are not necessarily a sign of a space-occupying complication. Especially children and juveniles with a suprasellar craniopharyngioma that has caused uni- or bilateral blockage of the foramen of Monro often showed postoperative pupillary dysfunctions. In such cases the indications for control via CT scan and an operative revision should depend not only on the state of consciousness and the pupillary function but also on continuous intracranial pressure monitoring.

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# Provisional Diagnostic Value of the Anaphylatoxin Radioimmunoassay (C3a-desArg-RIA) in the Neurosurgical Intensive Care Unit

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## Introduction

The anaphylatoxins (C5a, C3a, C4a) are cleavage products of the complement system, responsible for the modulation of several pathophysiological mechanisms. Their molecular effects have been elucidated mainly by HUGLI (4-6). (For illustration, see Table 1, modified after KÖLBLE (8).)

Our special interest with regard to the neurosurgical intensive care unit (ICU) was prompted by the observations of HAMMERSCHMIDT et al. (1) concerning the significance of complement activation in the "adult respiratory distress syndrome" (ARDS). KIRSCHFINK et al. (7) have reported similar results of C3a measurement in surgical multiple trauma patients in the context of a multicenter study in Germany. HEIDEMAN and HUGLI (2) have found a correlation between raised anaphylatoxin concentrations and the subsequent development of multiorgan failure. These and other observations suggested that especially the continuous analysis of C3a might detect jeopardized patients early: in most of the cases, plasma concentrations of C3a rose before the deterioration of the clinical, radiological, or microbiological results.

Investigations in this area have produced new methods for anaphylatoxin detection. At the moment, anaphylatoxin radioimmunoassays (RIA) by HUGLI and CHENOWETH (3, 9) are the most sensitive. The limit of detection is about 10 ng/ml. It is of considerable clinical importance to know whether these kits are able to give "predictive" C3a levels: i.e., Does a C3a peak precede the clinical deterioration, and if so, for how long? If this question could be answered positively, one would

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[a] C3a, C4a, C5a, "anaphylatoxins", i.e., the $NH_2$-terminal α-chain cleavage products of the anaphylatoxinogen components of the human complement system, C3, C4, and C5, that behave as hormonelike peptides; C5a-des Arg, Ca5 without C-terminal arginine, a cleavage product of C5a by carboxypeptidase N (synonym: kinase I, anaphylatoxin inactivator; E.C. 3.4.17.3, E.C. 3.4.12.7.); CR-1, human complement receptor 1 (C3b/C4b receptor); IL-1, interleukin-1 (macrophage-derived factor that promotes short-term proliferation of T-lymphocytes); $LTB_4$, $LTC_4$, $LTD_4$, $LTE_4$, leukotrienes $B_4$, $C_4$, $D_4$, $E_4$ (vasodilatory lipoxygenase metabolites or arachidonic acid); PAF, platelet aggregating factor; $PGE_2$, $PGF_{2\alpha}$, prostaglandins $E_2$ and $F_{2\alpha}$; SRS-A, "slow reacting substance of anaphylaxis" (a mixture of extremely potent spasmogenic and vasodilatory lipoxygenase metabolites of arachidonic acid: $LTC_4$, $LTD_4$, $LTE_4$); -, no data available; ↑, enhanced; >, more than; <, less than


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Table 1. Anaphylatoxins and their biological effects[a]

| Ligand | Receptor | Target cell/tissue | Receptor-positive cells | Receptor density ($\times 10^3$/cell) | Biological responses |
|---|---|---|---|---|---|
| C3a > C4a | C3a receptor | Mast cells/ basophils | - | - | Degranulation, autacoid release |
| | | Eosinophils | - | - | Degranulation |
| | | Neutrophils | - | - | Chemotaxis |
| | | Lymphocytes: T-helper transformed | < 5% | - | Humoral immunosuppression Cytolysis |
| | | Tumor cells | - | - | Cytolysis |
| | | Lung | - | - | $PGE_2$, $PGF_2\alpha$ release |
| C5a > C5a-desArg | C5a receptor | Mast cells/ basophils | - | - | Degranulation, autacoid release, chemotaxis |
| | | Neutrophils | 95% | 160 - 200 | Enzyme release (including PAF, $LTB_4$), aggregation, vascular permeability ↑, chemotaxis, CR1 expression ↑, superoxide radical production ↑, adherence ↑ |
| | | Monocytes | 68% | 80 - 100 | Chemotaxis, IL-1 production ↑ |
| | | Lymphocytes, T-helper | 6% | - | Chemotaxis, immunopotentiation (lymphokines) |
| | | Macrophages, alveolar | - | - | Chemotaxis, enzyme release, IL-1 production ↑ |
| | | Tumor cells | - | - | Chemotaxis? |
| | | Lung | | | "SRS-A" ($LTC_4$, $LTD_4$, $LTE_4$) $PGE_2$, $PGF_2\alpha$ release |
| | | | | | *Complex tissue reaction* with smooth muscle contraction, microemboli, postcapillary leakage, vasodilation, enhanced mucus secretion, ... |

[a]see p. 328

Table 2. Twenty-six trauma patients with coma and respiratory assistance[a]

| | Survivors (Y) | Nonsurvivors (X) | |
|---|---|---|---|
| Number | 13 | 13 | |
| Female (°) | 1 | 2 | |
| Age (yrs) | 13 - 69 | 12 - 82 | |
| Distribution | | | |
| 0-10 | Y | | |
| 10-20 | Y° X | | |
| 20-30 | Y X<br>Y X<br>Y X<br>Y X | X | |
| 30-40 | Y X | X | |
| 40-50 | Y<br>Y<br>Y | | |
| 50-60 | Y<br>Y X° | | |
| 60-70 | | Y X | |
| 70-80 | | X | |
| 80-90 | | X° | |
| Mean/median (yrs) | 36.7/35 | 43.2/30 | |
| Head injury: open | 1 | 3 | |
| Acute epidural hematoma | 7 | 1 | * |
| Acute subdural hematoma | 2 | 9 | * |
| Thoracic injury | 4 | 4 | |
| Aspiration | 4 | 7 | * |
| *Therapy* | | | |
| Steroids initially | 13 | 13 | |
| Steroids thereafter | 0 | 1 | |
| Blood substitution | 3 | 7 | * |
| Therapeutic craniotomy | 10 | 9 | |
| Respiratory assistance (d) | 6.5 | 4 | |
| PEEP of 5 mbar or more (d) | 4.5 | 4 | |
| *Mean coma duration* | | | |
| Preoperative (h) | 3 | 3 | |
| Postoperative (h) | 6 (0.5 - 16) | 7 (0.5 - 16) § | |
| Ca3 specimens (n/p) | 6.8 (2 - 18) | 6 (2 - 13) | |

[a]d, days; h, hours; n/p, number per patient; PEEP, positive-end-expiratory pressure; u/p, units per patient; X, nonsurvivor; Y, survivor; §, mean survival time; *, significant ($P < 0.05$)

be able to treat prophylactically (e.g., with steroids), before the general activation of the complement and other mediator systems. Because no information was available on C3a-RIA in neurosurgical patients, we have performed appropriate tests.

## Material and Methods

Between December 1984 and February 1985, we took plasma samples from 26 trauma patients with coma (mean: 7 days) and respiratory assistance

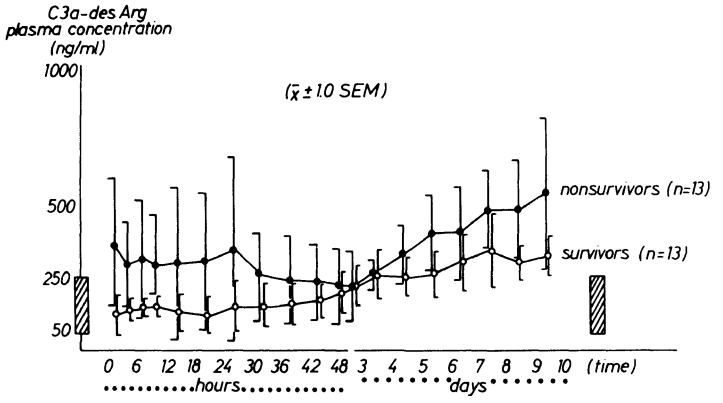


Fig. 1. Changes in plasma concentration of C3-desArg in 26 patients with head injury, coma and respiratory assistance. *C3a-desArg*, the inactive $NH_2$-terminal cleavage product of the human anaphylatoxin C3a by carboxypeptidase N (E.C. 3.4.17.3) (without C-terminal arginine on position 77); *SEM*, standard error of the mean; $\bar{x}$, mean. The *hatched bars* indicate the normal range of the C3a-desArg concentration in human EDTA-plasma: 50 - 250 ng/ml

(mean: 6 - 7 days) following head injury. There were no further exclusion criteria. We obtained two groups of survivors ("Y", $n = 13$) and nonsurvivors ("X", $n = 13$). Initially, all of them had been treated with dexamethasone (mean: 40 - 80 mg i.v.) in the emergency ambulance. This steroid treatment was interrupted by clinical admission, except for one nonsurvivor. There was no significant difference in age distribution. The nonsurvivors had been injured more seriously (more subdural hematomas) in comparison to the survivors (more epidural hematomas). This corresponded to the more extensive blood substitution for nonsurvivors (mean: 3 units for Y, 7 units for X). A more detailed description of the two groups is given by Table 2.

From some patients with external ventricular drainage, cerebrospinal fluid (CSF) aliquots were taken for comparison, in addition to plasma samples. A few plasma samples were also taken from nontraumatological patients of the ICU who seemed to be prone to develop ARDS.

Plasma and CSF were treated with $K_2$-EDTA (final concentration: 0.38 mmol/liter) according to HUGLI's recommendations (3). C3a was determined from duplicate analysis as its inactive "desArg form" (without C-terminal arginine) with the $^{125}$I-RIA from Upjohn-diagnostics (Biosigma, Munich) (9).

## Results

The C3a concentrations of groups X and Y were compared in relation to the time after trauma (see Fig. 1).

First of all, an analysis of variance was performed for all data: The C3a concentrations of nonsurvivors were significantly higher ($P < 0.001$) than those of the survivors. The twice normal level (500 ng/ml) was exceeded by 11 patients, of whom eight later died ($\chi^2 = 25$; $P < 0.001$). In a second step, the post-traumatic time period was divided into three sections: 0 - 30 h, 31 - 96 h, and more than 96 h. From 0 - 30 h,

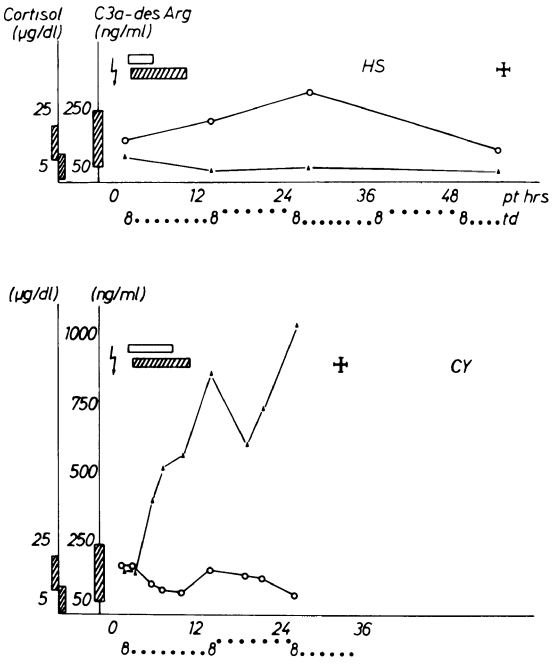


Fig. 2. Plasma concentrations of C3a-desArg (Δ) and cortisol (o) in two young males with fatal head injury. *CY*, 25 years old, open head injury, acute subdural hematoma; *HS*, 21 years old, open head injury, acute subdural hematoma; *pt hrs*, post-traumatic hours; *td*, time of day (...=day; ***=night). o, Cortisol concentration in EDTA plasma. The *hatched vertical bars* on the cortisol ordinate indicate normal concentrations: *left*: at 8 p.m., range: 8 - 20 µg/dl; *right*: at 4 p.m., range: 1 - 10 µg/dl; Δ, C3a-desArg concentration in EDTA-plasma: the *hatched vertical bar* on the ordinate indicates the normal range of 50 - 250 ng/ml; ↓, time of accident and consecutive treatment with 40 mg dexamethasone (emergency ambulance); +, exitus. *Horizontal bars: open*, operation; *hatched*, blood transfusion (10 units, both)

the C3a concentrations revealed a significant difference ($P < 0.002$) between survivors (less) and nonsurvivors (more). During this period, only one survivor showed a concentration exceeding the normal range (50 - 250 ng/ml). There was no statistically significant difference ($P < 50\%$) for the middle period (31 - 96 h). From the 4th day on (more than 96 h), the C3a concentrations were statistically significantly higher ($P < 0.002$) for nonsurvivors, though there were less data to compare because of intermittent deaths.

The subsequent results have been drawn from only a few observations. They were not analyzed statistically. All patients with C3a concentrations of more than 700 ng/ml were in coma with septic shock syndrome or lung edema or in a preterminal status. Concentrations in this range were survived by only one patient (35-year-old male). There were patients whose highly elevated C3a concentrations (<700 ng/ml) returned to normal after intravenous injections of 500 mg methylprednisolone, but only if the alterations in the C3a concentration or the clinical status had not lasted more than some days. Otherwise, the application of systemic steroids proved to be predominantly ineffective.

Respiratory insufficiency was sometimes preceded by a C3a elevation, but one could not always decide whether the clinical and laboratory status also altered simultaneously.

In one exceptional case, a C3a peak of 915 ng/ml was preceded by a generalized erythema scarlatiforme by at least 2 days.

There are variable developments of C3a concentrations in patients with fatal head injury, even in those with similar injuries, diagnostics, and therapeutics. From Fig. 2, one can see two extreme variants of C3a progress (together with the concentration of plasma cortisol), from subnormal (HS) to the very high (YC) extreme value (up to 1000 ng/ml within 24 h).

A correlation between the C3a concentrations in plasma and CSF was not found for six pairs of samples from three different patients. CSF concentrations from half to double the plasma level have been detected.

## Discussion

The patients of this investigation were divided into survivors (Y) and nonsurvivors (X), independent of intermittent complications (ARDS, septic shock syndrome). The most striking results were the initial (0 - 30 h) and secondary (over 96 h) elevations of the C3a concentrations of the nonsurvivors. One can only speculate about the causes:

Though it seems evident that extensive trauma will activate the complement system more vigorously, some patients with fatal multiple trauma (cf. Fig. 2) revealed normal or subnormal C3a concentrations. This is not explained by exogenous steroids, for these had been equivalent in the two groups. A correlation with the plasma cortisol concentration was not found. A C3a peak as described by KIRSCHFINK et al. (7) for both their groups, survivors and nonsurvivors, in the first post-traumatic hours, could not be detected, at least not for the neurosurgical survivors.

Between the 31st and 96th hour, no difference was detected in the course of the two groups. It was not surprising that the C3a concentration of the survivors showed a slight increase during the intensive care treatment (contrast media, blood transfusions). A cause of the intermittent fall of C3a for nonsurvivors in this period was not found.

After the 4th day, C3a concentrations again allowed a clear separation between the two groups; possibly because of more aggressive therapeutic interventions or the natural progress of the severe injury, and as an indicator of preterminal multiorgan failure (2).

The influence of minor blood incompatibilities are unclear. But a more detailed analysis of the individual data showed that the extent of complement activation is not uniform. This is evident from Fig. 2 and the unequal C3a changes of the two nonsurvivors: both of them had received 10 units of erythrocyte concentrates.

The time relation between anaphylatoxin increase and clinical deterioration was not found to be homogeneous. Some patients seemed to profit from steroids, even after the appearance of clinical symptoms.

Whether the favorable effects of dexamethasone after head injury that are described elsewhere are more attributable to an as yet uncharacterized specific effect counteracting brain edema, or at least partially due to a modulation of complement activation by means of an interaction with anaphylatoxin receptors or the inhibition of C5a-induced aggregation of polymorphonuclear neutrophils, remains to be shown.

## Conclusion

The possible predictive value of a longitudinal C3a analysis for neurosurgical patients was evaluated by this investigation. Further experiments are required to elucidate the definite pathophysiology on a receptor model level, and the chronological interference of C3a peaks and clinical deterioration. For more precise information, determinations of C3a, C4a, and carboxypeptidase N (E.C. 3.4.17.3) from plasma, CSF, and endobronchial lavage are in progress.

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# Investigations of Pituitary Function in Severe Head Injury by Radioimmunoassay

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## Introduction

Nowadays it is possible to determine pituitary hormones in patients with severe head injury by radioimmunoassay (14). Initially, basal serum levels are measured. Then pituitary function is analyzed using special stimulation tests. Side effects of steroid therapy should always be considered (1, 17, 20, 21, 23).

## Patients and Methods

Fourteen male patients between the ages of 16 and 56 suffering from severe closed head injury with midbrain syndrome were investigated. On the 5th to 7th posttrauma days hormone determinations were carried out at 8 a.m. on an empty stomach. Beforehand all patients had received dexamethasone 8 mg twice a day. The findings were compared with those in a control group comprising healthy men of the same age. LH, FSH, GH, testosterone, and cortisol were determined by radioimmunoassay. Evaluation was done using Student's $t$-test

## Results and Discussion

### *Basal Serum Concentrations*

Figure 1 shows the basal serum concentrations of LH, FSH, GH, cortisol, and testosterone. The results revealed a significant increase in *LH* and a significant decrease in *testosterone*. DOERR and PIRKE (6) also observed a decrease in testosterone after dexamethasone application and an increase in LH caused by a feeback mechanism. On the other hand, after surgical intervention without concomitant dexamethasone therapy we again observed a decrease in testosterone (4, 5). HACKL (11) suggests testosterone substitution in children and aldolescents with severe head injury.

*FSH* secretion does not interfere in the mechanism between testosterone and LH. In our patients the basal serum concentration was insignificantly lower than that of the control group.

In patients wie severe brain injury the basal serum concentration of *GH* was slightly but insignificantly increased.

Dexamethasone has an inhibitory effect on cortisol (2, 9, 13). On the other hand, stress, brain injury, and brain death lead to a significant increase in cortisol (8, 22). In our patients the basal serum concen-

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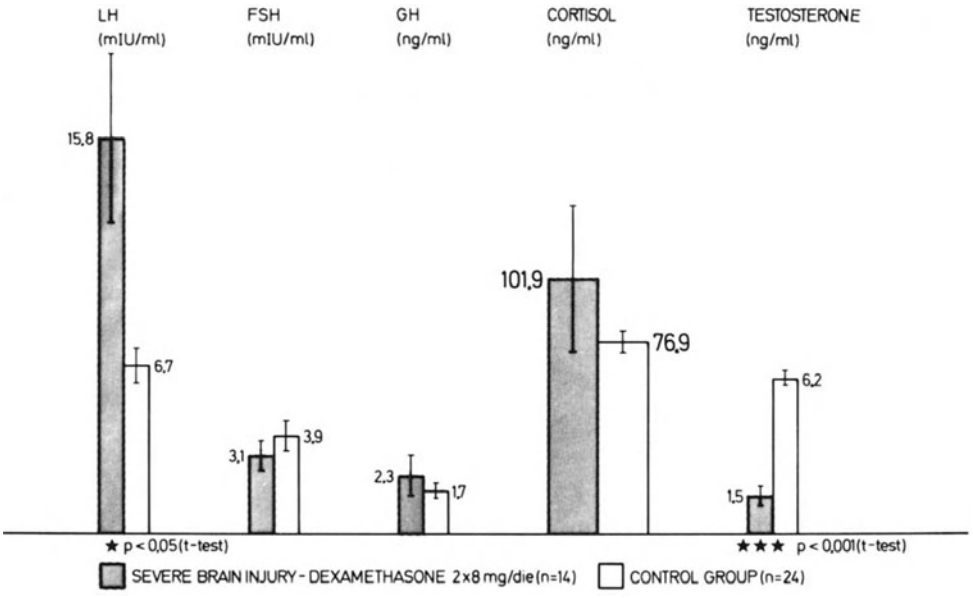


Fig. 1. Basal serum concentrations of pituitary hormones in patients with severe head injury on the 5th - 7th days after trauma

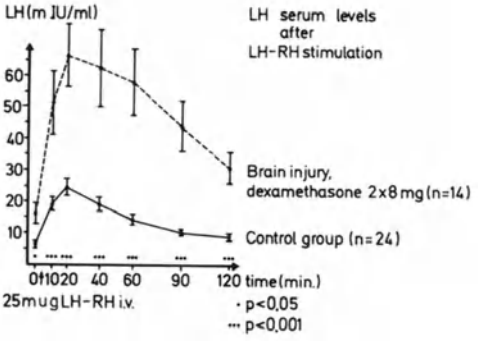


Fig. 2. LH serum levels after LH-RH stimulation in patients with severe head injury on the 5th - 7th days after trauma

tration of cortisol was insignificantly increased because of low dose dexamethasone therapy.

*Stimulation Tests*

*LH.* The secretions of *LH* was significantly increased after LH-RH stimulation compared with that of the control group (Fig. 2). Like other authors, KLINGELHÖFER and HALVES (18) reported that patients suffering from brain death caused by severe head injury showed increased LH levels after LH-RH injection.

*FSH.* After LH-RH stimulation, the FSH secretion decreased slightly in patients with brain injury. A probability value smaller than 0.02 was obtained (Fig. 3).

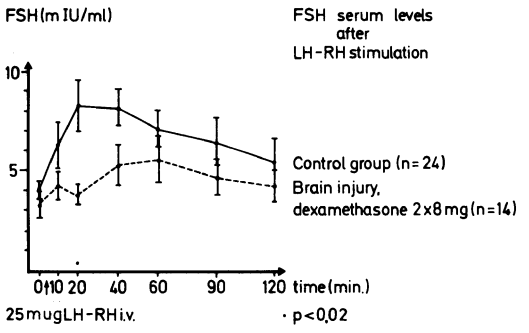


Fig. 3. FSH serum levels after LH-RH stimulation in patients with severe head injury on the 5th - 7th days after trauma

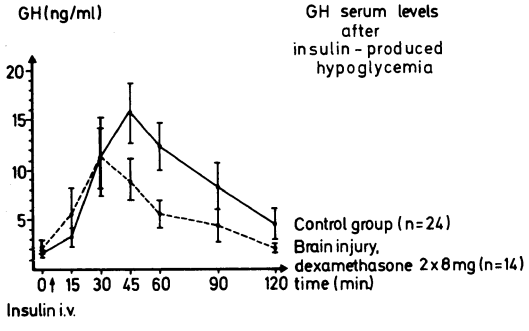


Fig. 4. GH serum levels after insulin-produced hypoglycemia in patients with severe head injury on the 5th - 7th days after trauma

*GH*. Patients with brain injury showed an insignificant decrease in GH secretion after stimulation with insulin produced hypoglycemia (Fig. 4). GH is increased after stress and multiple injury. According to GROTE (8), hypoglycemia produced by insulin does not lead to increased GH secretion after dexamethasone therapy.

HACKL (10) found a significant decrease in GH secretion in patients suffering from midbrain syndrome stage IV (7) or from bulbar cerebral syndrome. HACKL (11) put forward the hypothesis that a negative nitrogen balance, a catabolic state, is the result not only of an increased energy requirement but also of decreased GH secretion and thereby of a hypothalamic-pituitary dysregulation. HACKL (11) suggests substitution of GH in cases of severe brain injury as a therapeutic consequence. Success or failure of this therapeutic regimen still has to be studied (12, 15, 16).

Summary

If pituitary hormones are to be examined in patients with brain injury, particular attention should be paid to:

1. The effect of dexamethasone
2. Different hormone levels according to the circadian cycle (3)
3. Different levels of hormone secretion during the various post-traumatic stages, e.g., the acute post-traumatic stage, the stage of midbrain syndrome, or brain death (10, 19).

As a therapeutic consequence substitution of GH and testosterone in patients with severe head injury has to be discussed. Further investigations with patients not undergoing dexamethasone therapy are necessary.

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# Biological Rhythms of Electrophysiological and Endocrinological Parameters in Acute and Chronic Intracranial Lesions

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## Introduction

In living individuals different kinds of rhythmic organization are known, of which the 24-h "circardian" rhythm is the best known. Even in the case of missing external "Zeitgebers" (indicators of time) a free-running circadian rhythm is present (2).

Up to now, most investigations dealing with internal rhythms have been either in healthy human volunteers or in laboratory animals. As there are few publications concerning such rhythms in humans with well defined lesions, we have studied patients with acute or chronic diseases of the brain stem and the hypothalamo-hypophyseal system.

## Material and Approach

The study involved 14 patients: four cases of giant hypophyseal adenoma; one meningioma of the tuberculum sellae; one craniopharyngioma; one glioma of the optic nerve involving the hypothalamus; two giant midline tumors involving the third ventricles; two giant thalamic tumors whereby the brain stem was involved in one case; one cavernoma of the brain stem; one traumatic pontine hemorrhage; and one traumatic hemorrhage of the hypothalamus.

Cortisol, human growth hormone (HGH), prolactin, thyroid stimulating hormone (TSH), and triiodothyronine ($T_3$) were sampled every 3 h. Antidiuretic hormone (ADH), sodium ($Na^+$), potassium ($K^+$) and urine osmolarity (Osm) were analyzed once daily [$^{125}I$ radioimmunoassays: cortisol and prolactin (MAIA), HGH (DAK) all from Serono, Freiburg; TSA (MAGIC) Giessen; $T_3$ Coat-a-Count Biermann, Nauheim; osmolarity: Osmumat 030 Gonotec, Berlin].

BERG transformation of continuously monitored two-channel electroencephalography was performed as power spectra within the ranges 0.5 - 3.5 Hz, 3.5 - 8 Hz, 8 - 12 Hz, 12 - 32 Hz, 12 - 16 Hz, and 16 - 32 Hz, concurrently for both hemispheres (EEG-Trendmonitor ETM No 2264 Schwarzer, Munich).

Patients were admitted to regular wards except for three who were kept under nearly normal day-night conditions in the intensive care unit.

## Results

HGH was, as far as both absolute values and rhythmicity were concerned, normal in all patients.

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Table 1. Circadian secretion patterns of hormones and sleep-wake rhythms in neurosurgical patients

| | Pat. | Sex | Age | Diagnosis | Cortisol | | HGH | | Prolactin | | TSH | | $T_3$ | | Anti-diuretic syst. | EEG | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Abs. | Rhyt. | Abs. | Rhyt. | Abs. | Rhyt. | Abs. | Rhyt. | Abs. | Rhyt. | | s/w | sc |
| 1 | DL | F | 48 | Pituitary ad. | N | N | N | N | N | N | N | N | N | N | P | N | N |
| 2 | KG | M | 42 | Pituitary ad. (prolactinoma) | N | N | N | N | P | ? | N | N | N | N | N | N | N |
| 3 | AW | F | 61 | Pituitary ad. (prolactinoma) | P | N | ? | ? | P | N | P | P | P | P | - | N | N |
| 4 | GK | M | 50 | Pituitary ad. (postop) | N | P | ? | ? | N | N | P | P | P | P | P | P | P |
| 5 | BJ | F | 67 | Tub. sellae men. | N | N | N | N | N | N | N | N | N | N | P | N | N |
| 6 | HG | F | 44 | Craniopharyn-gioma | P | P | ? | ? | N | N | N | P | N | P | N | N | N |
| 7 | HF | M | 18 | Optic glioma | N | N | N | N | N | N | N | N | P | P | N | N | N |
| 8 | FP | M | 42 | Gangliocytoma, 3rd ventricle | N | P | N | N | N | N | P | P | P | P | P | P | P |
| 9 | GW | M | 49 | Pineocytoma | N | N | N | N | N | N | P | P | P | P | N | P | P |
| 10 | WH | M | 44 | Thalamic tumor (inc. brain stem) | N | N | N | N | N | N | P | P | P | P | - | P | P |
| 11 | GM | F | 14 | Spongioblastoma of thalamus | P | P | N | N | P | N | P | N | P | N | N | N | N |
| 12 | TO | M | 13 | Cavernoma of brain stem | P | P | N | N | N | N | P | P | P | P | - | N | N |
| 13 | SM | M | 16 | Pontine hemorr. (traumatic) | P | P | N | N | N | N | P | P | P | P | - | P | P |
| 14 | HO | M | 57 | Traumatic hemorrhage, hypothalamus | P | P | ? | ? | P | P | P | P | N | P | P | P | P |

*Abbreviations:* P, pathological; N, normal; Abs., absolute values; Rhyt., rhythmicity; s/w, sleep-wake cycle; sc, sleep cycles

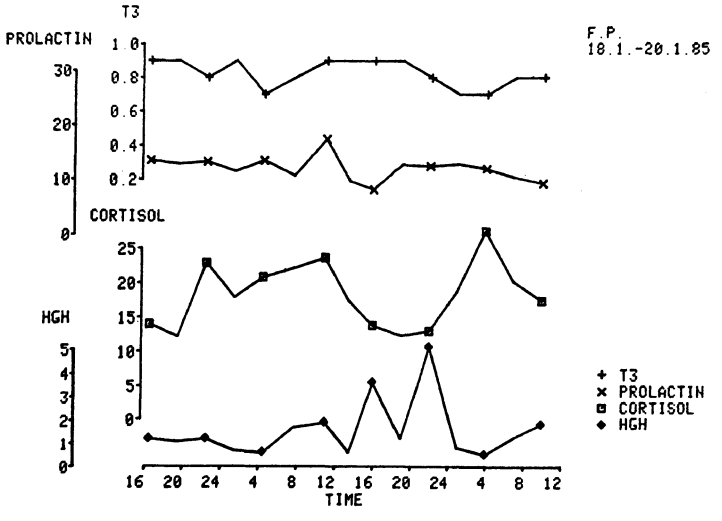


Fig. 1. Patient 8,FP. Gangliocytoma of the third ventricle. Complete loss of rhythmicity; daily values show different peaks. Cortisol reaches higher values during the early morning but there is no minimum during the night. Prolactin shows daily alternations. $T_3$ shows no cyclic fluctuation

For cortisol, pathological serum levels and disturbances of rhythm were obtained in both patients with traumatic hemorrhages, in the patient with a cavernoma of the brain stem, and in the patient with a spongioblastoma in the thalamus. Of all the patients with chronic lesions of the hypothalamo-hypophyseal region, only one (with a craniopharyngioma) showed abnormal values of plasma cortisol and rhythm. Two patients with prolactinoma presented with increased prolactin levels.

Abnormal TSH and $T_3$ levels combined with pathological rhythms could be found in most of our patients. In the craniopharyngioma case, a disturbed rhythm with physiological plasma level was obtained.

A patient with a gangliocytoma of the third ventricle showed inappropriate high secretion of ADH, whereas two patients with acute lesions and two patients with tumors of the sella region suffered from diabetes insipidus.

A disturbed sleep-wake cycle always presented with an abnormal distribution of sleep cycles within the period of sleep in our patients. There was no case of regular sleep cycles in combination with a pathological sleep-wake rhythm or vice versa. The disturbance of the sleep-wake alteration never showed an exact reversal concerning the day-night schedule, but rather a scattered pattern or completely abolished pattern.

Results obtained are listed in Table 1 (p. 341).

## Discussion

The first localized oscillator able to drive the biological clock was described by RICHTER (17), who suggested its localization was within the hypothalamus. Later investigations revealed numerous neurosecretory cell populations involved in the regulation of biological rhythms (9, 11, 12). The relationship between endocrine secretion, body temperature and sleep-wake cycle is well documented (3, 5, 7, 8, 18, 19, 20).

A dual oscillator model as rhythm generator – one responsible for body temperature cortisol, ACTH, Na, $K^+$, and REM sleep, the other for slow-

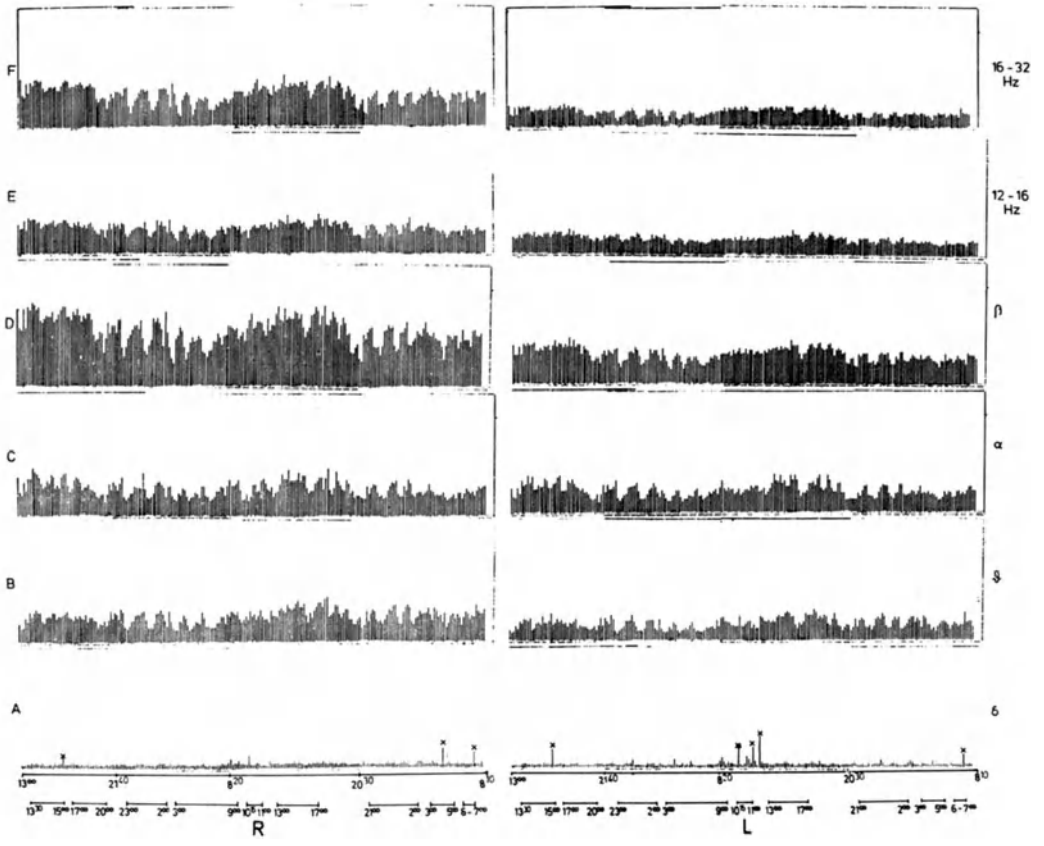


Fig. 2. Patient 8, FP. Gangliocytoma of the third ventricle. *R*, right hemisphere; *x*, artifact; *L*, left hemisphere, ⊢—⊣ , time asleep. Patient somnolent/soporous if not asleep. Continuous recording over 32 h, no distinctive sleep cycles, markedly disturbed sleep wake cycle

wave sleep, skin temperature, HGH, prolactin, TSH, and $Ca^{++}$ excretion – is presently under discussion (13).

Only a few case reports exist on clinical experiences concerning alterations of rhythmic phenomena in human diseases (1, 4, 6, 10, 14, 15, 16).

Cortisol rhythms are very stable even in the presence of dexamethasone therapy and in cases of prolonged coma (1, 14). In our cases of acute traumatic injury as well as in some of our cases of chronic disorders, cortisol rhythms were found to be disturbed. In contrast, however, giant pituitary adenomas did not effect any pathological change in cortisol rhythms.

HGH and prolactin rhythms were not markedly influenced by the lesions we investigated except in one patient with acute traumatic hemorrhage of the hypothalamus. This patient presented pathological findings in all measured parameters, except $T_3$ serum levels, which were within the normal range. The stability of HGH and prolactin rhythms was not altered in those patients who had severe disturbances of the sleep-wake

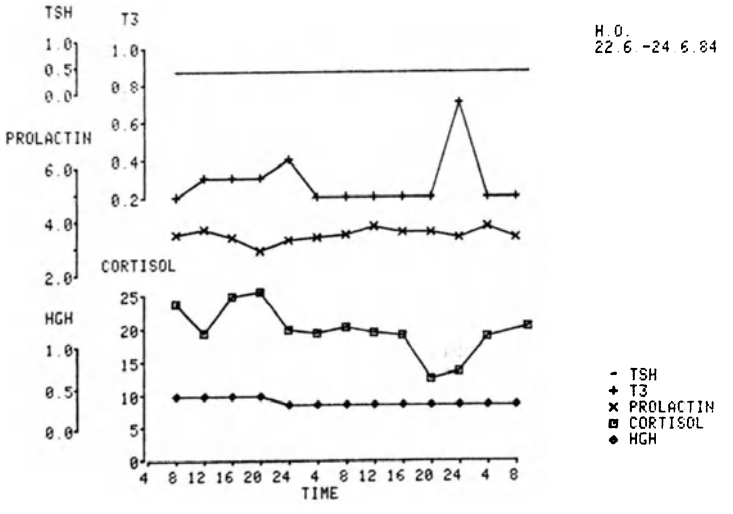


Fig. 3. Patient 14, HO. Traumatic hemorrhage within the hypothalamus, complete loss of rhythmic phenomena as regards HGH, prolactin, and TSH. Cortisol shows a daily peak but it is different from normal patterns; this is also true for the prolactin curve

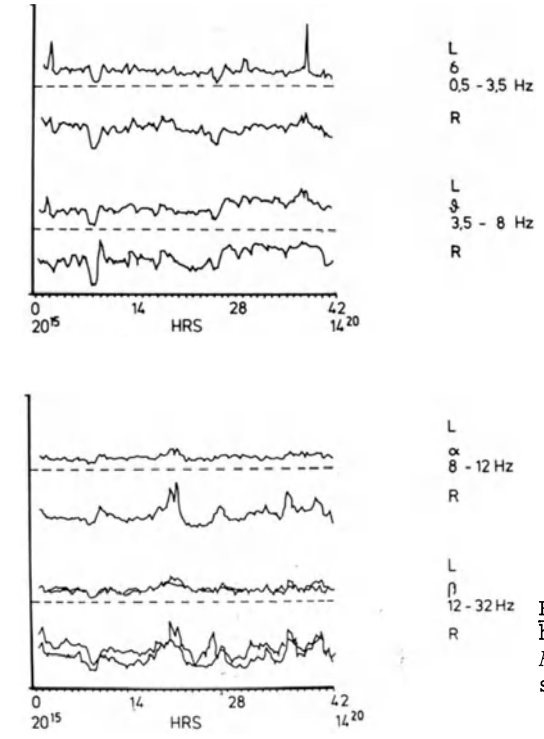


Fig. 4. Patient 14, HO. Traumatic hemorrhage with the hypothalamus. *R*, right hemisphere; *L*, left hemisphere. No rhythm, no sleep cycles

cycle. This might have been caused by too long intervals of blood sampling, so that minor abnormalities were not registered.

A great number of pathological findings of TSH and $T_3$ levels are due to the instability and high sensitivity of this test.

Pathological sleep-wake cycles in combination with altered sleep cycles were seen in all patients with acute diseases and in those patients whose lesions were located in the posterior midline [cases 8 (see Figs. 1, 2), 9, and 10]. Tumors of the hypophyseal area did not alter sleep-wake rhythms markedly. These findings are in good correlation with a group of tumors in the region of the third ventricle described by FULTON (6), whose patients presented "pathological sleep".

Acute traumatic lesions of purely the pons and hypothalamic regions (cases 13 and 14; Figs. 3, 4) led to a complete loss of rhythm.

## Conclusion

Under the same conditions and in the same locations acute lesions caused severe disturbances of endocrine rhythms as well as loss of sleep-wake regulation in comparison with chronic lesions.

The chronic lesions of the posterior midline, on the other hand, led to marked alteration of sleep-wake cycles as well as sleep regulation, the endocrine parameters showing no distinctive changes.

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# Neuromonitoring Supplemented by nrCBF

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## Introduction

Some years ago, together with REULEN, we proved that cerebral blood flow (CBF) may be significantly reduced in focal as well as in global brain edema (BE) without a significant increase in intracranial pressure (ICP) (3, 4, 8). This motivated us to supplement neuromonitoring with nrCBF as a therapeutic criterion.

## Method

rCBF was measured by a small, mobile system (NOVO Cerebrograph 10a) consisting of channel analyzers, data collection unit, processor and printer, all placed on a trolley. The 3/4 × 3/4 " NaI crystals were equipped with 17 × 20 mm lead collimators. The detectors, five per hemisphere, were fitted into two holders fixing each detector perpendicular to the scalp. 10-20 mCi xenon 133 in saline was injected into an antecubital vein in the supine patient.

The dual-artifact model (PROHOVNIK et al. 1983) employed for flow computation consisted of two tissue clearance compartments and two artifactual, linear terms. Fast flow compartment (Fg) and initial slope index (ISI) were automatically calculated by the integrated microcomputer.

## Results

nrCBF measurement in the intensive care unit provides valuable information on cerebral perfusion in various diseases and may allow a more adequate therapy.

Figure 1 shows that ICP may be increased in general brain edema. Rapid infusion of Glycerosteril did not decrease ICP, but CBF increased from 16 to 25 ml/100 g/min. In other cases, we observed a decrease in ICP, without any influence on nrCBF. Sorbitol 40% usually leads to a significant fall in ICP, while CBF is improved. Moreover, CBF measurement may enable differentiation between BE and vasoparalysis or congestion, and we are able to select those patients in whom barbiturate therapy should be tried. In cases of severe brain edema, we may obtain some additional prognostic criteria to assess chances of recovery.

Figure 2 shows a typical clearance curve of a decerebrated patient with inflow stop. The amount of xenon 133 reaching the brain is very low, whereas the air curve looks normal. Little or no brain activity is

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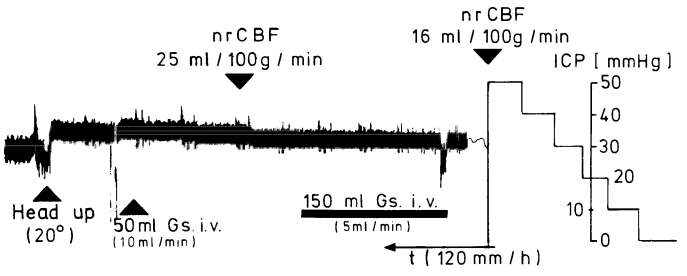


Fig. 1. ICP and nrCBF in global brain edema following head trauma during administration of Glycerosteril (*Gs.*)

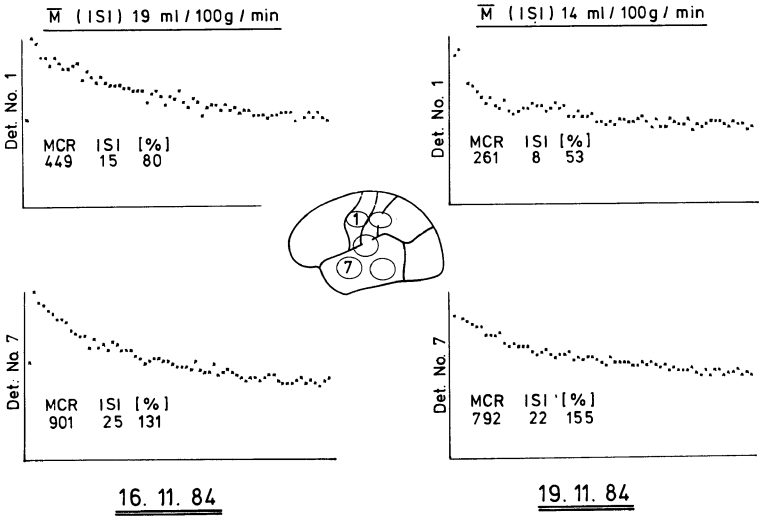


Fig. 2. Typical clearance curves of a young patient with severe head trauma in which intravital brain death is developing. The amount of xenon 133 reaching the brain (*MCR*) is rather low (the air curve of xenon 133 looks normal)

found in the EEG. With regard to such cases, we tried to evaluate prognostic criteria to recognize development to intravital brain death as early as possible. We observed eight patients with ISI values of 20 ml/100 g/min or less who developed brain death within 24 h.

In hydrocephalus or impending herniation, CBF measurement is also of some value. Figure 3 shows an extraordinary increase in CBF after CSF drainage in a patient with subarachnoid hemorrhage 10 days previously. From our limited experience, we have gained the impression that in many cases CBF rises sharply immediately after drainage, normalizing later. According to some publications (1, 2), CBF may also be helpful in chronic hydrocephalus. The shunt operation may not be indicated in cases of normal pressure, lack of pressure waves, and low CBF.

For therapeutic reasons, differentiation between BE and congestion is important. Figure 4 shows the CBF follow-up in a patient in whom a huge clivus meningioma was removed. CT did not reveal brain edema. ICP registration was not performed since there was a CSF drainage. Luxury perfusion was obvious in CBF measurements, and lasted for nearly 2 weeks after operation.

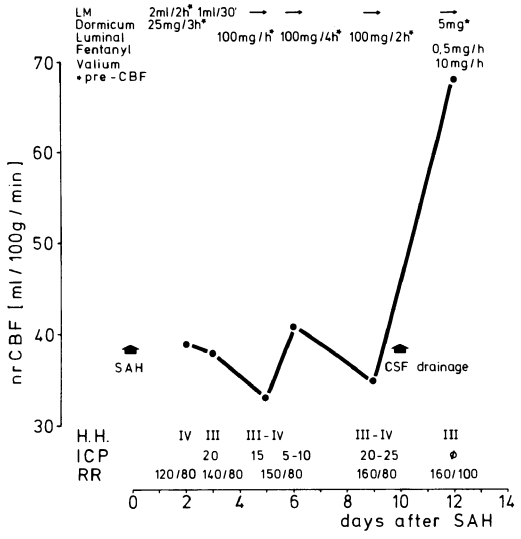


Fig. 3. nrCBF before and after CSF drainage in a patient with SAH 10 days previously

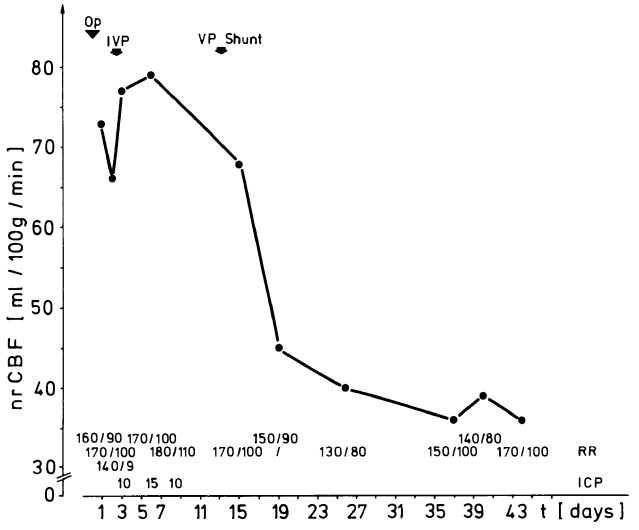


Fig. 4. nrCBF follow-up in a patient in whom a huge clivus meningioma was removed. There is a very high perfusion over 2 weeks

nrCBF is naturally valuable in cerebrovascular disease in order to estimate the risk of attempted balloon occlusion of the ICA in carotid-sinus cavernosus fistula, giant aneurysms, tumors of the neck, etc. It allows detection of changes in perfusion after permanent ligation, possibly in combination with EC/IC bypass operation (5). Figure 5 shows the follow-up CBF in a patient with a carotid-sinus cavernosus fistula which could not be occluded directly. The internal carotid artery was ligated after a balloon occlusion test. CBF increased after occlusion of the ICA on the side of the fistula, decreased on the opposite side, and then normalized within some days, although no bypass operation was performed in this patient.

The rate of CBF increase after application of calcium antagonists (nimodipine) in subarachnoid hemorrhage varied in our 23 cases, with a mean ISI of 33 ± 9 (23) before and 38 ± 12 (23) ml/100 g/min after appli-

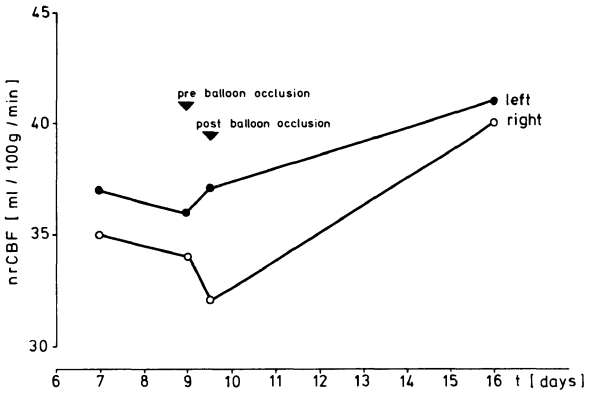


Fig. 5. Follow-up nrCBF in a patient with a left-sided carotid-sinus cavernous fistula before and after ligation of the ICA

cation of the drug with further improvement in the following days. Our first results were published in 1984 (6).

In our experience, a major problem in the evaluation of CBF data is assessment of the influence of anesthesia or sedation on nrCBF in the neurosurgical intensive care unit since every sedative reduces CBF to a greater or lesser extent. Further systematic study of nrCBF prior to and after application of various sedatives will provide more information and enable us to discriminate between drug effects and true changes in the pathophysiologic condition of a patient.

## Conclusions

nrCBF provides a valuable criterion in addition to the various data registered in neuromonitoring in the intensive care unit. It helps to differentiate between BE and brain swelling (congestion). Prognostic evaluation of severe head injury may be more accurate. We obtain more information for assessing the therapeutic effects of various drugs, e.g., calcium antagonists in cerebrovascular spasm after SAH or osmotherapy in BE. Hemodynamic changes in the course of cerebrovascular diseases such as stroke, carotid-sinus cavernosus fistula, and giant aneurysm and during probatory ICA occlusion or ligation may be monitored more accurately. The overlapping effects of sedation or anesthesia sill have to be studied in more detail in the future.

## Summary

Since intracranial pressure (ICP) does not generally correlate with cerebral blood flow (CBF) in neurological/neurosurgical patients, we introduced a small, mobile cerebrograph (NOVO Cerebrograph 10a) in our intensive care unit which allows atraumatic follow-up measurements. The CBF results provide better assessment of different pathophysiologic conditions and enable us to check the different therapeutic measures, e.g., osmotherapy, hyperventilation, barbiturate loading, vasodilatatory therapy, CSF drainage, etc.

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# Postoperative Observation at the Neurosurgical Intensive Care Unit After Surgery of the Posterior Fossa

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## Introduction

It is well known that patients undergoing surgery to the posterior fossa need to be supervised closely. To illustrate this point, Tables 1 and 2 give details regarding 500 cases of surgery within the posterior fossa and the complications in 360 cerebellopontine angle lesions (10). For comparison, a list of known postoperative complications is given:

Hematoma
Hydrocephalus
Edema of the brain stem or cerebellum
Infarction
Subgaleal hematoma (space-occupying lesion in osteoclastic craniotomy)
Aspiration (lesion of the caudal cranial nerves)
Cerebrospinal fistula
Gastrointestinal bleeding

*plus typical complications of the sitting position*[1]:

Cardiac manifestations (after air embolism or volume loading), e.g., myocardial infarction
Pneumocephalus
Spinal injuries (after Mayfield extension)
Epidural hematoma (after Mayfield extension)
Supratentorial subdural hematoma (tearing of the bridging veins)

Table 1. Surgery within the posterior fossa (500 cases, 1978-1985)

| Reason fur surgery | No. |
|---|---|
| Acoustic neurinoma | 210 |
| Meningioma | 21 |
| Vascular decompression | 130 |
| Various (angioblastoma, angioma, aneurysm, epidermoid, hematoma, metastases, tumor) | 130 |

[1] At our clinic the half-sitting position is used only in order to minimize the risk of air embolism.


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During the first few hours after surgery it is most important to detect an impending herniation which might be due to hematoma, hydrocephalus, or edema and in rare cases to a supratentorial lesion. Fast diagnosis of rising intracranial pressure is of major importance (5). By brain stem auditory evoked potentials, brain stem function can be checked while the patient is still deeply anesthetized (8, 12). Nevertheless, continuous neurological examination is still the major means of clinical observation.

Our neurological check-up examinations are listed in Table 3. Check-up is repeated at 15-min intervals for at least 24 h or until the patient is fully alert.

Early extubation while the patient is still in the operating room carries some risks, e.g., respiratory depression must be avoided. It is caused by neuroleptanalgesics, usually by the opiate component, which has a rebound effect peaking about 3 h postoperatively (2). On the other hand, coughing and pressing against the tube will give rise to intracranial pressure. In the past these problems were managed by heavy sedation and artificial ventilation (3, 4, 7, 11). Nowadays in many places this approach has changed (8). Small doses of minor tranquilizers will calm a well informed patient who easily hyperventilates himself on a modern respirator. A neurological examination is then feasible. At our clinic a postoperative flow chart guides the diagnostic evaluation of an abnormal neurological examination (8).

Table 2. Complications of 230 cerebellopontine angle tumors and 130 vascular decompressions

| | | |
|---|---|---|
| Mortality: | 2% | Myocardial infarction (1st postop. day) |
| | | Myocardial infarction (2nd postop. day) |
| | | Cardiac insufficiency (4th postop. day) |
| | | "Sudden death" (3rd postop. day) |
| | | Infarction of cer. pos. a. (28th postop. day) |
| | | Pulmonary embolism (28th postop. day) |
| | | Suppurative pneumonia (after 30th postop. day) |
| Hematoma: | <2% | Subdural hematoma (2 cases tearing of the bridging veins of the posterior fossa) |
| | | (1 case tearing of the frontal bridging veins) |
| | | Epidural hematoma (1 case med. meningeal a. – Mayfield extension) |
| | | Intracerebellar hematoma (1st postop. day) |
| Hydrocephalus: | <1% | |
| Infarction: | <1% | Infarction of cer. pos. a. (18th postop. day) |
| Gastrointestinal bleeding: | 1% | |
| Spinal injury | | 1 case of paraplegia (C6/7) after Mayfield extension and semisitting position |
| Apallic syndrome | | 1 case post intracerebellar hematoma |

Table 3. Neurological check-up

| |
|---|
| Cephalic reflexes: |
| Coughing reflex |
| Corneal reflex |
| Eyelid reflex |
| Pupils: |
| Size |
| Shape |
| Reaction to light |
| Pattern of respiration |
| *plus* |
| Glasgow Coma Scale |

If the CT scan is normal, brain stem auditory evoked potentials (BAEPs) are of special diagnostic value (8). A prolongation of the latencies III-V and I-V must then be interpreted as edema or infarction of the brain stem (Table 4).

Table 4. Diagnostic value of BAEPs

| | CT | CT and BAEPs |
|---|---|---|
| Edema | ? | + |
| Brain stem | | |
| infarction (early phase) | - | + |

## Material and Approach

If CT scan and BAEPs are within normal values, a nonsurgical complication is to be considered:

*Case 1.* A middle-aged lady was operated on for a large acoustic neurinoma. Twenty-four hours postoperatively, she could not be aroused and there was no reaction to pain. By means of CT scan and BAEPs a surgical complication could be excluded. We suspected a catatonic state since the patient was known to suffer from a psychiatric disorder. She was treated with haloperidol. Within hours she was awake and cooperative.

*Cases 2 and 3.* These two patients presented with hematoma. At the end of the operation both patients were awake. During the next 2 h, they deteriorated in performance. CT was performed (Figs. 1, 2) and proved diagnostic of subdural hematoma. In addition, acute hydrocephalus was found in one patient (Fig. 2). Ventricular drainage had to be instituted. It is to be stressed that supratentorial pressure has to be lowered before an infratentorial recraniotomy is carried out, otherwise untreated hydrocephalus might cause downward herniation. Pneumocephalus could be diagnosed from the CT scan shown in Fig. 1. Only on

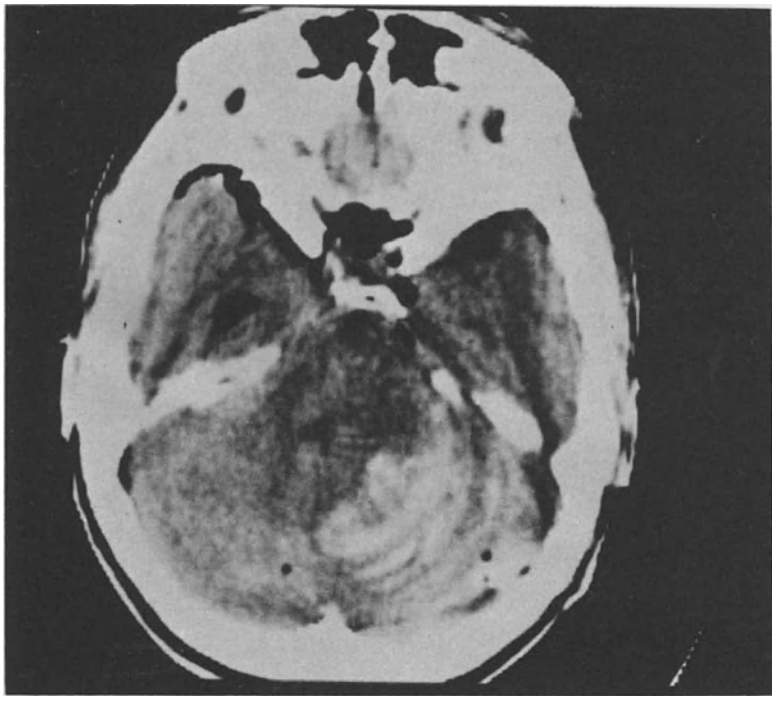

Fig. 1. A CT scan 3 h postoperatively showing a subdural hematoma

clinical grounds, i.e., by neurological findings, can the importance of this CT diagnosis be evaluated (6). Most of our patients operated on in the half-sitting position are normal upon neurological examination, but their CT scans clearly demonstrate pneumocephalus.

*Case 4.* In our series there was one "sudden death" still lacking a proper explanation. It occurred in a previously healthy middle-aged lady. She was treated for a facial spasm by vascular decompression. Her postoperative course was uneventful until the third postoperative day. Then, while eating dinner, she suddenly lost consciousness and became deeply cyanotic. The nurse, who was next to her, started resuscitation, but despite all efforts cerebral function did not recover. Brain death was diagnosed 2 days later. The immediately performed CT scan did not show a lesion, but the basal cisterns were narrow in appearance. On autopsy neither signs of raised intracranial pressure nor of infarction were found.

*Case 5.* As a very rare complication of the sitting position, a frontal subdural hematoma was diagnosed on the third postoperative day after vascular decompression. The young patient was noted for worsening psychotic condition and so a CT scan was done (Fig. 3). After surgical removal of the hematoma, which was due to a tearing of bridging veins, the patient recovered completely.

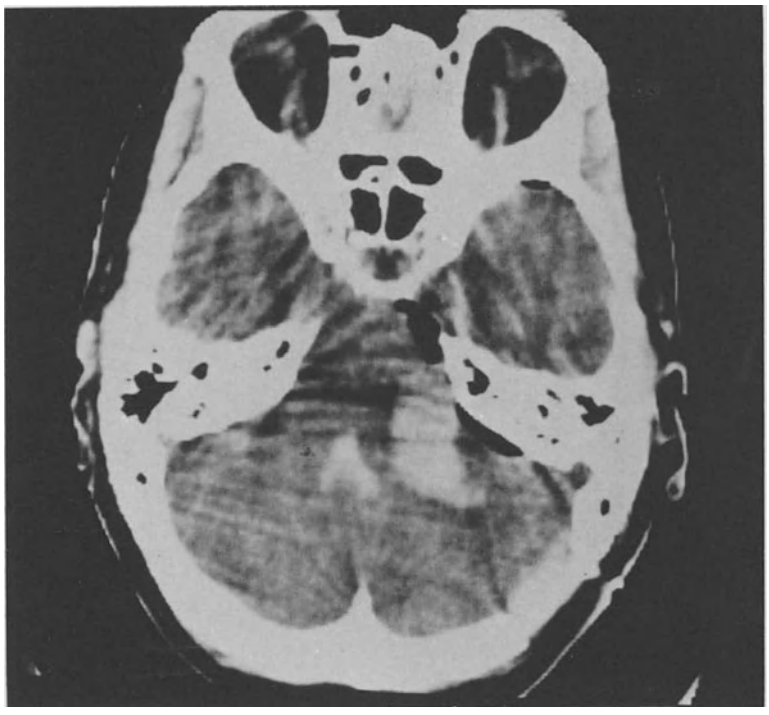

Fig. 2. A CT scan 3 h postoperatively showing a subdural hematoma and an acute hydrocephalus

## Discussion

What are the options for prevention of postoperative complications? Table 5 lists some items we have found useful.

A thorough medical check-up discloses the patient with cardiopulmonary risk who should not be operated on in the half-sitting position but lying down (routinely we already prefer to perform vascular decompression in the supine position).

Intraoperatively the monitoring of BAEPs is of major value for examining brain stem function in the deeply anesthetized patient. Prolonged latencies of peaks III-V and I-V, not returning to normal values within the first postoperative hours, are alarming. Herniation, brain stem edema, or infarction is impending.

Nevertheless, still the most important of all monitoring procedures is continuous neurological examination. And there should be a ready strategy for further diagnostic evaluation, e.g., postoperative flow chart to ensure fast detection and proper treatment of the encountered complication.

## Conclusion

A patient who has undergone surgery to the posterior fossa should postoperatively be treated by delayed extubation, little sedation, hyperventilation, and extubation after reaching full consciousness. For

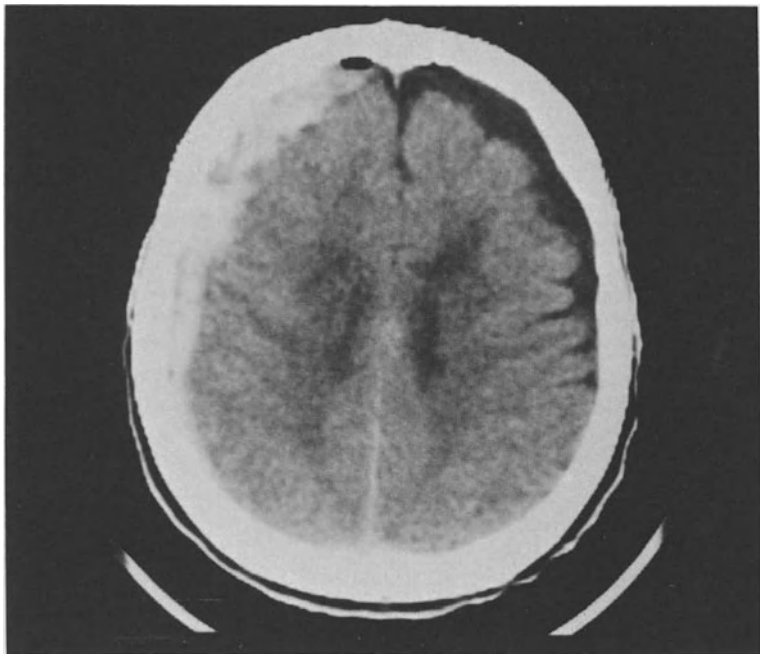

Fig. 3. A CT scan 3 days postoperatively showing a frontal subdural hematoma

Table 5. Measures for the prevention of postoperative complications

| | |
|---|---|
| *Preoperatively:* | Medical check-up (including, e.g., pulmonary function, ECG) |
| *Intraoperatively:* | Surgical measures (e.g., to use jugular vein compression and to avoid any pressure on the cerebellum by the inserted spatula) |
| | Monitoring of brain stem auditory evoked potentials |
| | Cardiorespiratory monitoring (e.g., Doppler sonography, central venous line) |
| *Postoperatively:* | Hyperventilation |
| | *Delayed extubation!!* |
| | Little sedation |
| | Continuous neurological examination |
| | Flow chart for fast diagnostic evaluation |

at least 24 h continuous neurological monitoring must be carried out, besides monitoring of the vital functions (1). A ready strategy for diagnostic evaluation of an abnormal neurological examination should exist.

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# Monitoring of Brain Stem Auditory Evoked Potentials (BAEPs) in the Intensive Care Treatment of Craniocerebral Traumata

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## Introduction

In cases of multiple cerebral injuries it may be difficult to distinguish between the clinical pictures of supra- and infratentorial traumatic lesions. Intracranial epidural pressure measurements taken in the usual fashion at certain points distributed over an entire cerebral hemisphere may not be helpful when it comes to identifying infratentorial pressure increases at an early stage. In cases of infratentorial lesion, continuous BAEP surveillance of the functions of the brain stem may furnish some reliable supplementary information.

## Material and Approach

In an intensive care unit, the monitoring of BAEPs does not present any technical difficulties. As a rule, BAEP readings will not be affected by medication, so that developments in each case can be observed intraindividually. A stimulus consisting of 1500 pressure-vacuum clicks was applied at a frequency of 10 clicks per second and a sound level of 85 dB. Potentials were monitored both ipsi- and contralaterally by needle electrodes placed between vertex and mastoid and a BASIS 8000 (Schwarzer Picker) with a filter setting of 200-2000 Hz.

By relating the histories of two cases of severe closed head injury with infratentorial hemorrhages established by CT, it will be shown that monitoring of BAEPs is indeed of diagnostic significance.

## Results

A 7-year-old girl who had been involved in a car accident was admitted in a stage II coma (Fig. 1). Her CT scan showed an asymmetrically narrowed ventricular system and a very slight blood deposit on the tentorium. At this point, the patient's auditory evoked potentials were normal. Forty hours after the accident, the BAEP readings turned pathological: waves IV and V flattened out and there was an increase in the I-V interpeak latency, but the clinical picture did not deteriorate. One day later, a bulbar syndrome manifested itself without any alteration in the total number of points on the Glasgow Coma Scale. At this point, the patient's BAEP readings also showed evidence of a pathological process; this time, components II-V lost amplitude. Intracranial pressure as measured temporally on the right hemisphere still remained within normal limits. The patient was again submitted to a CT examination which revealed unmistakable blood deposits on the right tentorium. Antiedema therapy was applied immediately, and after 2 days the BAEPs

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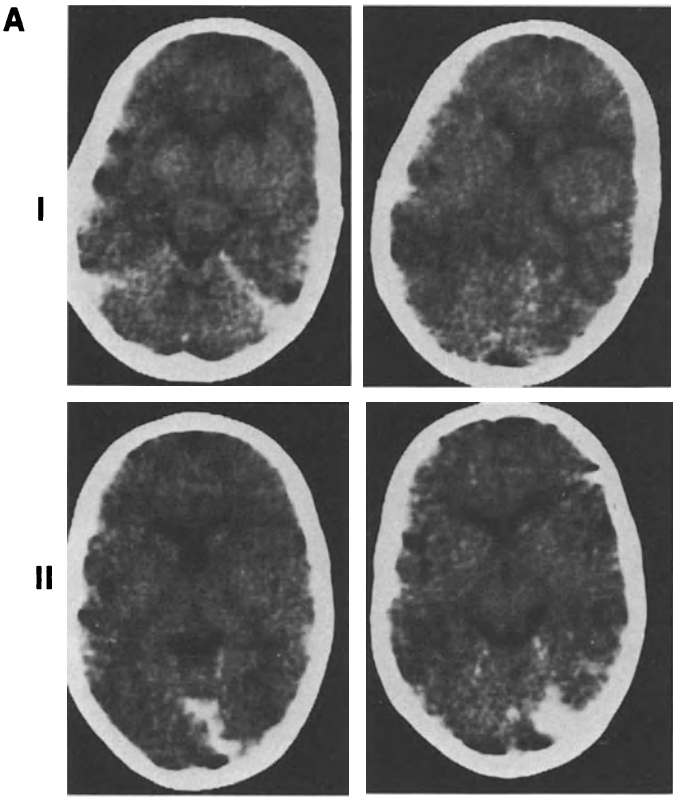


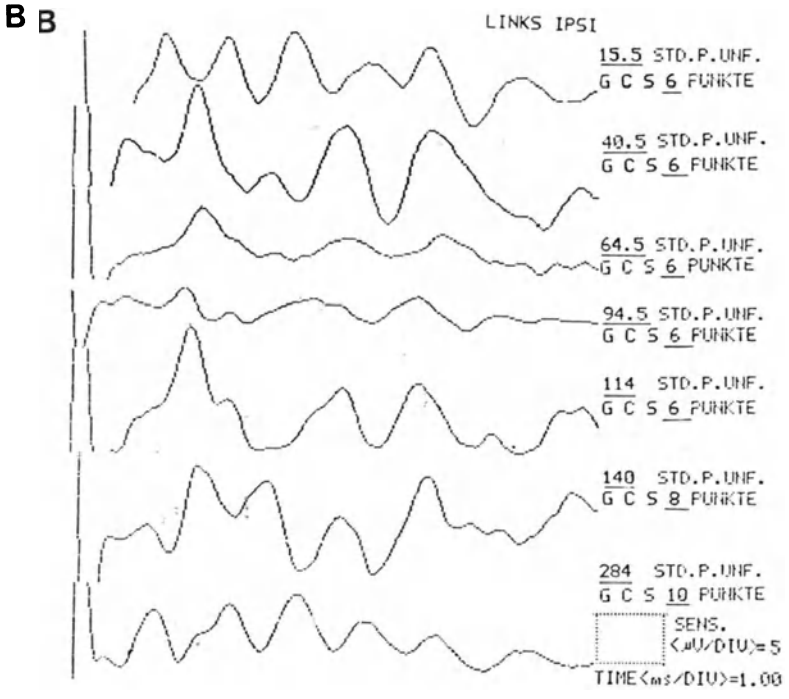




Fig. 1A,B. Seven-year-old girl suffering from hemorrhage above the tentorium. A Computer tomograms. *I*, 3 h after accident; *II*, 65 h after accident. B BAEP monitoring

began to return to normal, in parallel with an improvement in the clinical picture.

The second case is that of a 3-year-old boy who was admitted in a stage II coma after a fall from a window (Fig. 2). His CT scan showed a minor hemorrhage in the pontine region. His initial BAEP measurements indicated nothing remarkable beyond a latency delay in component V. After 2 days, the IV-V complex showed a loss of amplitude and more latency delay, and very shortly afterwards the patient had to be given artificial respiration, although his clinical picture had been improving continuously until then. Here again, intracranial pressure measured supratentorially was within normal limits. Antiedema therapy was administered, and after 2 days the clinical picture began to improve slowly but steadily, accompanied by a recovery of the patient's BAEP record. A CT examination 10 days after the accident showed no demonstrable perifocal edema.

In cases with a lethal outcome, BAEP measurements enable the diagnostician to establish the failure of brain stem functions at an early point in time. Figure 3 shows some typical BAEP readings after cerebral death. Either there is no potential at all, or there is only a wave I reading, or there is a wave I reading and a flattened wave II with delayed latency. When monitoring cases in which cerebral death was imminent, we found that these three pictures frequently manifested themselves one after the other. Until about 6 h after the onset of cerebral death, wave II remained in evidence in most cases; later on, only wave I could be found, or else there was no potential at all.

## Discussion

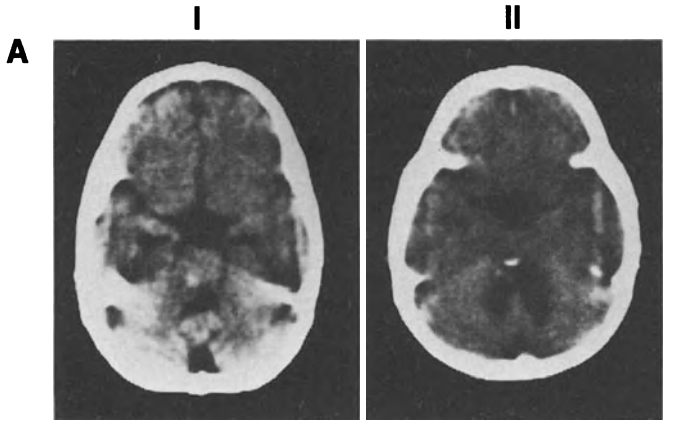
In the two cases of severe craniocerebral trauma discussed in this paper, observation revealed unmistakable potential alterations before any deterioration in the clinical picture manifested itself. Thus, antiedema therapy could begin at an early stage. Clinical improvements were always accompanied by improvements in the BAEP readings.

There is no doubt that BAEP readings are not suitable for establishing cerebral death. BAEP dysfunctions can only be safely interpreted as an indication of the loss of brain stem functions if an auditory evoked potential has been obtained from the patient at some previous time, thus excluding any chance of cochlear loss of hearing. On the other hand, a small number of cases were observed in which at one point in time all potential was lost, or wave I only remained, without any evidence of cerebral death. Auditory evoked potentials can be used to observe remaining brain stem functions until a very late point in a case history.

## Conclusion

BAEP measurements are helpful in observing brain stem functions in cases of infratentorial lesion. BAEP alterations may show up before the clinical picture deteriorates, which means that therapy can begin at an early point in time.

BAEP readings may also be helpful in diagnosing cerebral death.



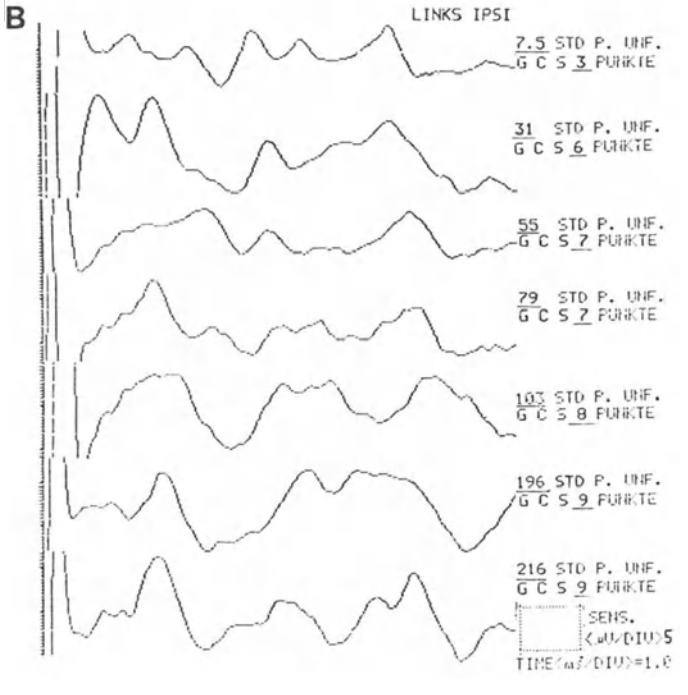




Fig. 2A,B. Three-year-old boy suffering from a pontine hemorrhage. A Computer tomograms. *I*, 4 h after accident; *II*, 10 days after accident. B BAEP monitoring

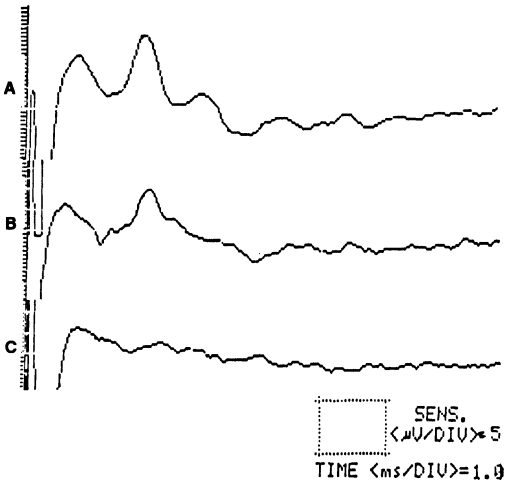



Fig. 3A-C. BAEP in cerebral death. A Wave I, wave II with delayed latency; B wave I; C no potential

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# Auditory Evoked Potentials During and After Complete Ischemia of the Brain

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In the last 6 years many clinical investigations have been published concerning evoked potentials and anoxia, evoked potentials and isoelectric EEG, and evoked potentials and brain death. Similar data have also been obtained from experiments on animals with intracranial compression by balloon inflation (5-9) or radiofrequency lesions (2).

The experiments described in the following study were performed using the method of the isolated canine head (3). In all the experiments complete ischemia was produced at a constant brain temperature of 37°C. Early auditory evoked potentials, middle latency auditory evoked potentials, and the EEG were recorded before, during, and after complete ischemia of varying duration.

Figures 1-5 show recordings from five representative experiments of averaged evoked potentials evoked binaurally by click stimuli of 0.92 Hz.

During complete ischemia, early and middle latency auditory evoked potentials disappeared 50-60 s after the onset of ischemia (Fig. 1). The EEG disappeared after 25-30 s using normal amplification (1) (Fig. 1). When amplification was increased to the maximum level at which the signal could be discriminated from background noise, the EEG was seen to persist for 40-60 s.

After the end of complete ischemia of 1 min, auditory evoked potentials reappeared earlier than the EEG: first auditory evoked potentials were discernible after 5 s, first potentials of the EEG after 20 s (Fig. 1).

With increasing duration of complete ischemia, the time from the end of complete ischemia to the first reappearance of evoked potentials and EEG potentials increased. In all experiments auditory evoked potentials reappeared earlier than the EEG.

After a complete ischemia of 5 min, only 30 s of reperfusion was required before the first reappearance of wave I of the early auditory evoked potentials (Fig. 2). The first middle latency auditory evoked potentials were discernible after reperfusion of 1 min. The first EEG potentials reappeared later, at 10 min after the end of the complete ischemia. After a reperfusion of 5 h, the evoked potentials had regained normal amplitudes and latencies, whereas the EEG was still reduced.

After a complete ischemia of 10 min, the first auditory evoked potentials reappeared after a reperfusion period of 3 min, and the first potentials of the EEG after a reperfusion period of 15 min (Fig. 3). After a reperfusion period of 11 h, evoked potentials had regained

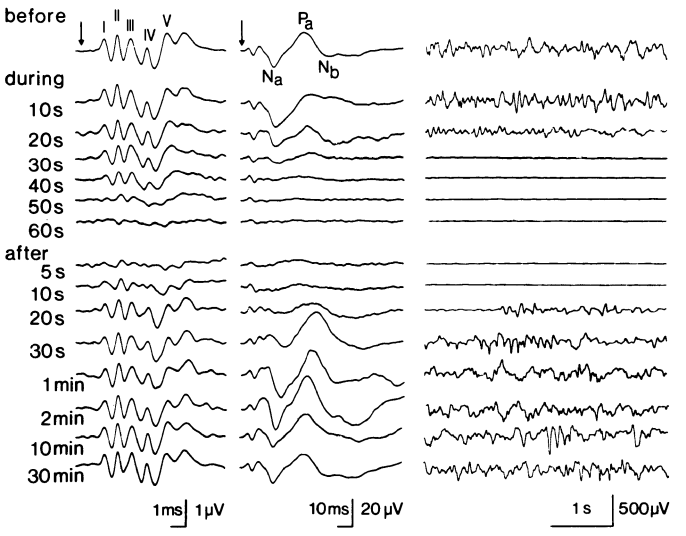


Fig. 1. Early auditory evoked potentials, middle latency auditory evoked potentials, and EEG before, during, and after complete ischemia of 1 min

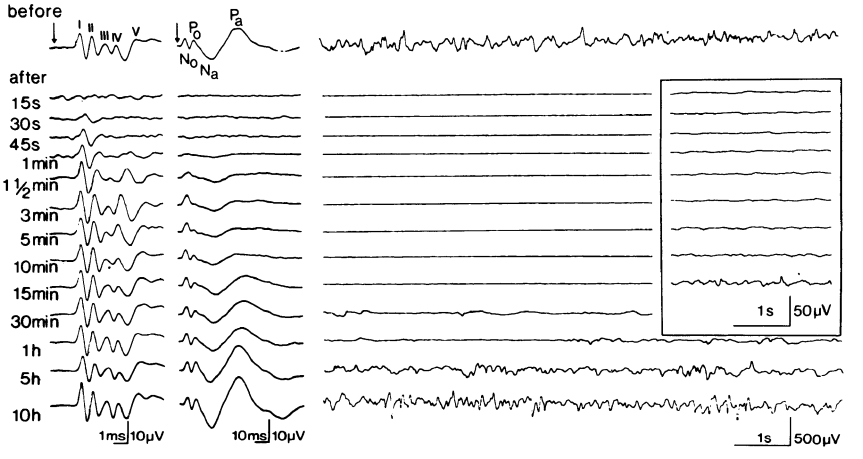


Fig. 2. Early auditory evoked potentials, middle latency auditory evoked potentials, and EEG before and after complete ischemia of 5 min

latencies and amplitudes of the control recording prior to ischemia. A complete ischemia of 10 min is the maximum duration of ischemia after which full recovery is still possible (when conditions for recovery are optimal).

After a complete ischemia of 20 min, complete recovery is not possible. Therefore it was astonishing that the early auditory evoked potentials reappeared after a reperfusion period of 8 min and the middle auditory evoked potentials after a reperfusion period of 20 min (Fig. 4). The EEG reappeared much later; first potentials were found after a reperfusion period of 45 min. In this experiment the isoelectric EEG persisted for about 1 h. The early evoked potentials were abolished for only 26 min, for 19 min during ischemia and 7 min after the end of ischemia. The middle latency auditory potentials were absent for nearly 40 min (19 min during ischemia and 19 min after the end of ischemia).

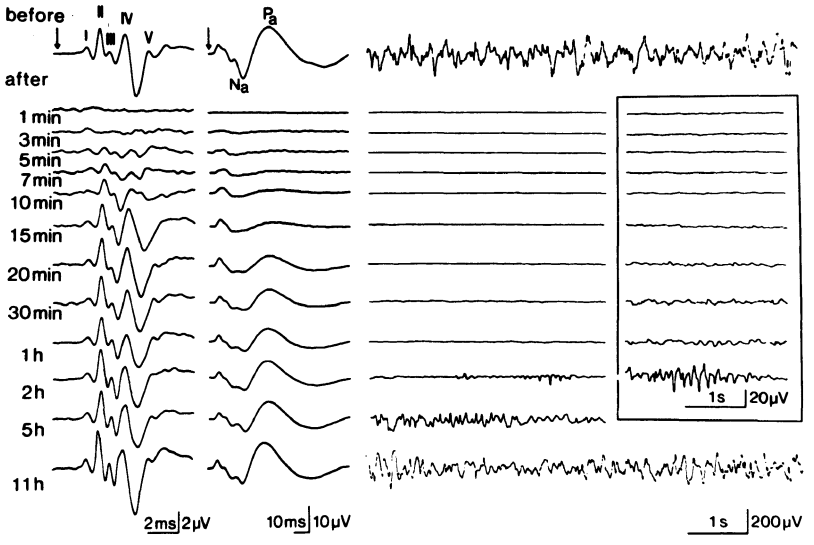


Fig. 3. Early auditory evoked potentials, middle latency auditory evoked potentials, and EEG before and after complete ischemia of 10 min

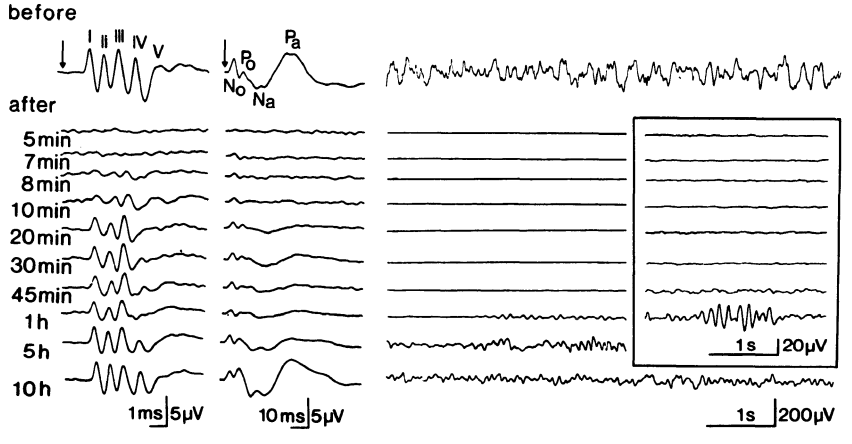


Fig. 4. Early auditory evoked potentials, middle latency auditory evoked potentials, and EEG before and after complete ischemia of 20 min

Figure 4 demonstrates that auditory evoked potentials with normal configuration can be recorded after complete ischemia, even when this is associated with incomplete recovery of all brain functions. Therefore it is impossible to ascertain the completeness of recovery of the brain from the form of the evoked potentials.

After a complete ischemia of 30 min (Fig. 5), there was only a temporary, limited recovery. The early auditory evoked potentials had a maximum amplitude after a reperfusion of 90 min and the EEG had a maximum amplitude after a reperfusion of 5 h. Middle latency auditory evoked potentials did not reappear during the reperfusion period of 8 h.

After complete ischemia of 45 min or more, auditory evoked potentials have not reappeared in any of our experiments to date. After complete

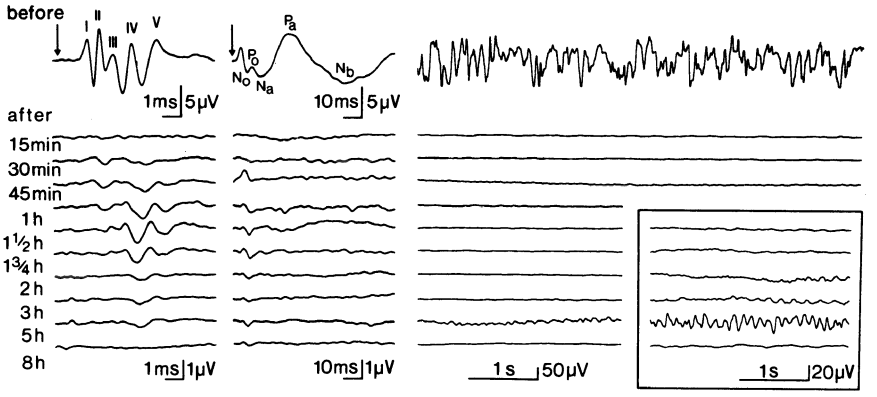


Fig. 5. Early auditory evoked potentials, middle latency auditory evoked potentials, and EEG before and after complete ischemia of 30 min

ischemia of more than 50 min, EEG was abolished irreversibly (4). If auditory evoked potentials are abolished for more than 60 min in these experiments, no reappearance of these potentials was seen.

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# Criteria for the Diagnosis of Brain Death

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## Guidelines

Since the first observation of the syndrome of "coma dépassé" by MOLLARET and GOULON in 1959, 26 years ago, a second set of criteria for the diagnosis of brain death bas been presented in recent years, especially in Great Britain (SMITH 1979), in the USA (WALKER 1981, LYNN 1981), by the Bundesärztekammer (BÄK) in Germany (WOLFF and KUHLENDAHL 1982), and in Switzerland (CHIOLERO et al. 1983).

The different codes of brain death unanimously agree on two requirements:
1. Loss of integrative brain functions
2. Irreversibility of failure

The following steps are required for proof of brain death (Fig. 1):

1. *Strict observance of prerequisites:* A clear diagnosis of either primary or secondary acute brain damage is required as well as the exclusion of other factors which cause only reversible disturbances, such as poisoning, hypothermia, and circulatory shock.
2. *Repeated examination* of essential clinical symptoms – coma, apnea, brain stem areflexia
3. *Confirmatory tests* such as isoelectric *EEG or angiography* confirming intracerebral circulatory arrest *or a suitably long observation period* depending on the individual kind of brain damage and the age of the patient.

Therefore the diagnosis of brain death is not possible at the initial examination but only after a longer period of repeated investigations.

The new sets of brain death criteria still show some variations in the details of the relevant investigations (Table 1).

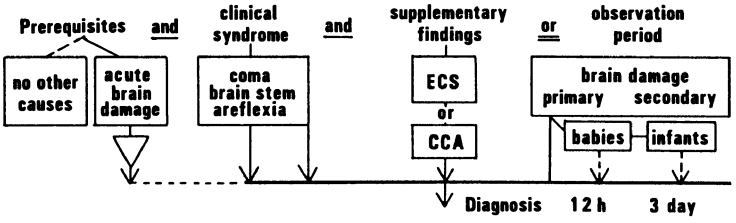


Fig. 1. Brain death criteria according to the guidelines of the Bundesärztekammer, 1982

Table 1. Synopsis of brain death criteria

| Prerequisites | U.K. 1976 | U.S.A. 1981 | BÄK 1982 | Switzerland 1983 |
|---|---|---|---|---|
| Diagnosis prim./second. BD | x | x | x | x |
| No intoxication | x | x | x | x |
| No hypothermia | x | x | x | x |
| No shock | x | x | x | x |
| **Clinical symptoms** | | | | |
| Coma | x | x | x | x |
| Apnea $PCO_2$ mm Hg | x > 50 | x > 60 | x Test | x > 50 |
| Mydriasis bil. | x | x | x | x |
| No other brain stem reflexes | x | x | x | x |
| Observation period Adults prim. BD: | hours | 12 | 12 | minim. 6 |
| second. BD: | more than | 24 | 72 | > 48 |
| Examiner | 2 | 1 | 2 | 1 |
| **Optional tests** | | | | |
| ECS | | 6 h /30' | /30' | 2x in 24 h |
| Zero BAEPs | | | (x) | |
| CCA | | Radioisotop. | Angiogr. | |
| CT | | | | |
| ICP above syst. BP | | | | 20 Min. |

*Abbreviations:* *BD*, brain damage; *ECS*, electrocortical silence; *BAEPs*, brain stem auditory evoked potentials; *CCA*, cerebral circulation arrest; *CT*, computerized tomography; *ICP*, intracranial pressure

## Apnea Test

A threshold is often recommended for the arterial carbon dioxide pressure in apnea tests: in the USA 60 mmHg (PITTS 1982), in Great Britain and Switzerland 50 mmHg, taking into account the increased tolerance of children and patients with chronic respiratory insufficiency. The BÄK recommendations do without precise figures because the carbon dioxide response curve varies from the norm after acute brain injuries and artificial respiration.

We determined in 54 apnea tests an average increase of $PCO_2$a of 2.5 ± 1.2 mmHg within 5 min after artificial respiration had been suspended. Similar findings were recorded by PITTS (1982) as well as by ROPPER et al. (1981). If blood gas levels are not available, a minimum apnea observation period of 10 min is recommended.

## EMG of Cranial Muscles – Evoked Potentials

In 1970 HIRSCH et al. stated that spinal reflexes may well persist or even reappear in a state of brain death. HAUPT (personal communication 1985) has also investigated the persistent activity of cranial muscles. In nine patients, 4-12 h after brain death, he stimulated the facial nerve and registered a normal response in the activity of the frontal and orbicularis oris muscle. By contrast, the blink reflex, being mediated by pontine structures, could not be provoked. At the same time in these cases the BAEPs and the SEPs were lost. This is in accordance with the findings of STARR (1976), STOCKARD (1980), CHARTRIAN (1980), and KLUG (1982) as well as ADELT et al. (1985).

## Electrocerebral Silence/Apnea

Electrocerebral silence (ECS) demonstrates an actual cessation of cerebral functions, but does not fully indicate loss of brain stem functions (PALLIS 1980, 1983, CHARTRIAN 1980). Therefore the onset of ECS does not always coincide with the onset of apnea (BENNETT 1978, HUGHES 1978), as illustrated by the following examples (Fig. 2).

A 14-year-old girl (S.C. 646/81) presented with coma grade IV one and a half hours after a bicycle accident. While ECS was registered, spontaneous breathing was still present with an arterial $PCO_2a$ of 39 mmHg. This situation persisted for 5 h with a positive corneal reflex, and also after 9 h with $PCO_2a$ of 37.7 mmHg. Twelve hours after the accident spontaneous respiration could no longer be elicited by the apnea test, although $PCO_2a$ had reached 52 mmHg.

The reverse condition, that is coma and apneic brain stem areflexia without ECS, was observed in cases with *infratentorial* lesions. A 51-

| | | | | | |
|---|---|---|---|---|---|
| **ECS before Apnea** | | | | | |
| Sch., C. 14 yrs Bicycle accident 646/81 | | | | | |
| CR | x | x | | ø | |
| Respiration | spontaneous | spontaneous | spontaneous | Apnea | |
| $PCO_2a$ mm Hg | 39 | 39 | 37.7 | 52 | |
| EEG | Zero | | | | |
| Time after accident | 1.50 | 5 | 9.10 | 12.20 | |
| Duration of syndrome | 0.30 | 3.10 | 7.20 | 10.30 | |
| **Apnea with Delta-EEG** | | | | | |
| Hu., A. 51 yrs 1172/82 cerebellopontine angle meningeoma | | | | | |
| CR | | ø | ø | ø | |
| Respiration | | spontaneous | Apnea | Apnea | ✝ |
| $PCO_2a$ mm Hg | | | 53 | | |
| EEG | Sub-δ | Sub-δ | | Sub-δ | |
| BP mm Hg | 110/80 | 110/70 | 110/70 | 120/70 | 0 |
| Time after operation | 12 h | 24 | 30 | 44 | 4 days |
| Duration of syndrome | 0 | 12 | 18 | 32 | |
| **Apnea with Delta-EEG** | | | | | |
| Elfg., H. 57 yrs 501/85 Cerebellar hematoma | | | | | |
| CR | ø | ø | ø | | |
| Respiration | Apnea | Apnea | Apnea | | |
| $PCO_2a$ mm Hg | 68 | | | | |
| EEG | θ–δ | interm. zero | zero | | |
| BP mm Hg | 90/70 | 90/70 | 90/? | | |
| Time after hemorrhage | 1.15 | 5.25 | 22.0 | | |
| Duration of syndrome | ~1.00 | | | | |

Fig. 2. Electrocortical silence versus apnea: see text. *CR*, corneal reflex

year-old patient (Hu., 1172/82) had delta and subdelta activity on EEG 12, 24, and 44 h after operation for a meningioma of the cerebellopontine angle. Already 30 h after operation, however, at a $PCO_2$ of 53 mmHg, no spontaneous respiration had been observed. Controlled respiration was continued until cardiac arrest occurred 4 days later.

In a 57-year-old patient with cerebellar hemorrhage, no ECS was registered until 22 h after apnea. These clinical observations of persistent EEG in the beginning of brain stem areflexia are in accordance with experimental findings by WALKER. At the Neurological Congress of Heidelberg in 1984, he demonstrated the EEG of a spontaneous seizure occurring in a rhombencephalectomized cat 4 min after the intravenous injection of 2.5 ml metrazole.

## Comparison of Time of Onset of Apnea

In Fig. 3 the onset of apnea is correlated to other disorders involved in brain death syndrome:

(1) In former investigations we have found apnea 1 h after and 1 h before circulatory arrest as proved by angiography (FROWEIN and POHL, 1970).

(2-4) ECS has been observed 3-10 h before apnea in five out of our last 93 patients with primary supratentorial cerebral lesions.

(5) Persistence of delta-EEG beyond the time of apnea was registered in primary infratentorial lesions, such as after surgery of the cerebellopontine angle or cerebellar hematoma, and in patients with basilar

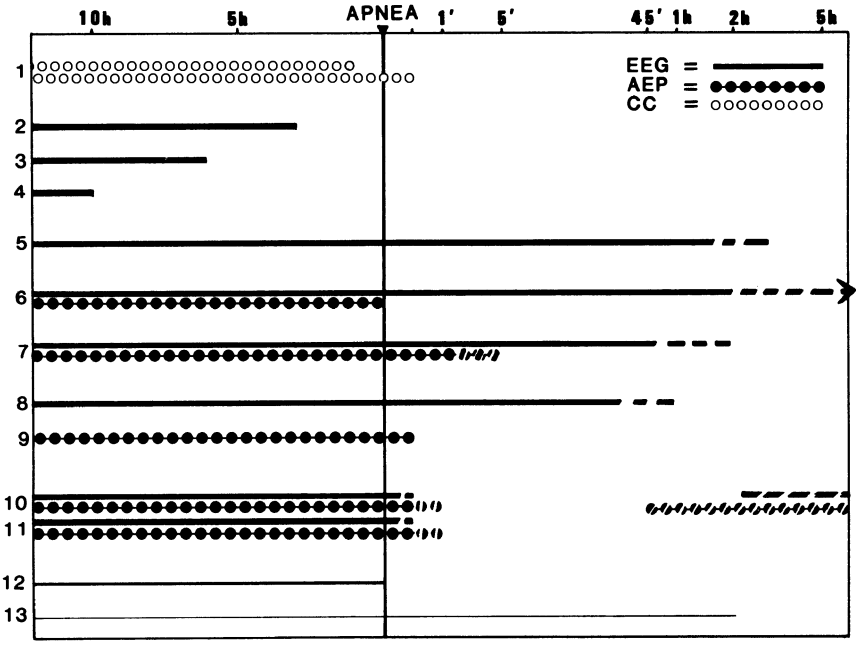


Fig. 3. Time of onset of apnea correlated to other disorders: *1* to *13*, see text. *CC*, cerebral circulation

thrombosis with (6) or without (7) absence of AEP (HAUPT 1985, FERBERT 1984, HACKE, personal communication, 1985).

(9) In some cases of primary supratentorial lesions in an early phase of brain stem areflexia, a persistence of AEP was observed (ULLRICH 1984, HACKE, personal communication, 1985).

(10) HIRSCH (1985) has demonstrated in dogs with experimental complete ischemia of the brain that EEG activity ceased several minutes earlier than the more sensitive AEP. After reopening circulation, AEP reappeared earlier than EEG, provided that complete ischemia had not exceeded 45 min. If ischemia exceeded this limit, no recovery was ever observed (11).

(12) The blink reflex, mediated via the brain stem, does not function in brain death syndrome.

(13) In brain stem areflexia and apnea, myoelectrical activity can be registered in extracranial facial muscles.

## Intracranial Pressure

The latest Swiss criteria (CHIOLERO et al. 1983) are the first to include an increased ICP to diagnose brain death, if it exceeds the systolic blood pressure for more than 30 min. The way to determine ICP, however, has not been specified, implying that epidural, subdural, and intraventricular pressure are equally valid. These, however, differ considerably from each other, especially in phases of rising ICP (RICHARD): A 9-year-old girl (646/81) presented with coma grade IV after head injury. Epidural pressure (Gaeltec equipment) temporarily exceeded simultaneously registered intraventricular pressure (right frontal horn – Statham membrane, Philipps recorder) by 85 mmHg. At one point over a 30-min stretch epidural pressure stayed higher than 170 mmHg, while at the same time blood pressure was only 150 mmHg, i.e., 20 mmHg less than epidural pressure. Although severely disabled, the girl survived. We concluded that epidural pressure alone is not a valid criterion.

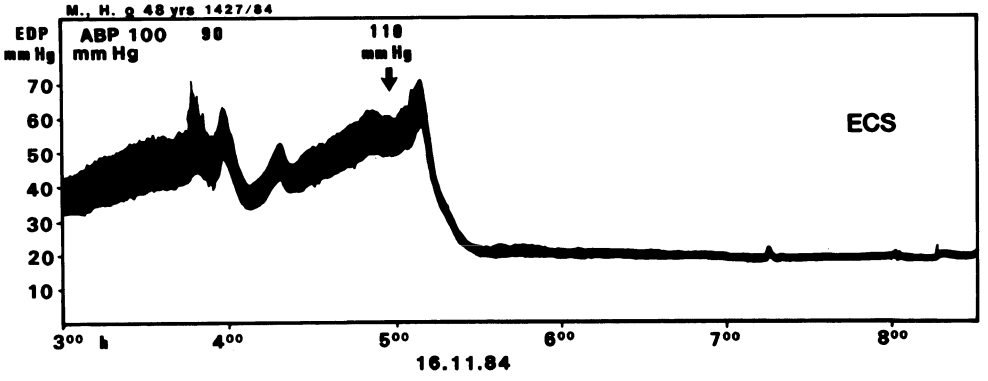


Fig. 4. Intracranial pressure during development of brain death. *ABP*, arterial blood pressure; *EDP*, epidural pressure; *ECS*, electrocortical silence

Another interesting phenomenon has to be reported: In some cases a rising ICP with increased amplitudes has been followed by a sudden drop, indicating the arrest of cerebral circulation coinciding with ECS (Fig. 4). This phenomenon, however, is not always found in severe brain swelling, but if present, it can be helpful in the diagnosis of brain death.

If intracranial pressure were to be used as a part of brain death criteria, an accurate definition of the technical procedures would be necessary.

Summary

The first observation of apneic brain stem areflexia is only a momentary registration of lost brain functions. A sufficiently long duration of apnea and brain stem areflexia, confirmed by means of repeated investigation and the consideration of the kind and location of the original brain lesion, finally leads to the absolutely certain diagnosis of brain death.

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# Limitations of Intensive Care Medicine - as Viewed by a Neurosurgeon

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"I beg you, conduct your business on the method of mechanics. Heal if you are able, kill otherwise. Demand your fees when you have killed." These words are extracted from a letter written by Petrarca, the founder of European humanism, to an unknown doctor of the court in Avignon. Petrarca's motive for these polemics was a warning to the ailing Pope Clemens VI that he should be wary of the incompetent doctors in his district. It is not difficult to relate this to our present day.

From the "gossipy doctors" to the "method of mechanics": During Petrarca's days, around the middle of the 14th century, medicine belonged to the "artes mechanicae" and hence it was classed much lower than the seven "artes liberales". This classification of medicine as a handicraft rejected its claim to be a philosophically based science. Another controversial remark by Petrarca was: "However, can I believe you to be a philosopher, with the knowledge that you are a paid mechanic? I reiterate well this name again, because I have noted that no other insult can hurt you more deeply." A comparison to our present age is also quite easily conceivable in this statement, particularly if we consider the controversy surrounding apparatus medicine, above all in the field of intensive care.

Attitudes toward physicians during the Renaissance period induced reflections upon the period of antiquity. The humanistically educated doctors acquired knowledge of the scientific traditions of medicine, as practised at the Medical School of Salerno, because there philosophy was studied in conjunction with medicine. Legislation governing doctors introduced by the Stauffer Emperor Friedrich II established 3 years' studies on logic and 5 years' reading of the works of Hippocrates and Galen as minimum requirements. The principle of "nil nocere" was therefore never forgotten and was evident even among some doctors during the Middle Ages. The influence of humane philosophers, such as Erasmus, again led to conscious consideration of human beings by doctors. One merely has to consider today what it actually must have meant to a doctor during the great plagues of the Middle Ages to go from house to house at least to offer consolation, being fully aware of the enormous risk of infection and the impossibility of curing it. Notwithstanding the differences, perhaps reflection on the situation in those days may benefit our discussions today.

Even into the New Age the doctor's image, as well as his self-evident status, oscillates between the extremes of philosophy and mechanics. In the modern Prussian Army we had the so-called regiment physician, and the common current English word "physician" is not derived from philosophy, but from physics.

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With this brief excursion into medical history I merely wish to point out amazing parallels to our present situation.

Modern intensive medicine is significantly marked by three problem areas:
1. Physiological limitations
2. Economic limitations
3. Ethical limitations

*Physiological limitations* are determined by the age of a patient. Although differences may exist between the chronological and biological ages of human life, there are absolute limitations on the physiological aging process of the human body that lie slightly above the age of 70 years. The morphology of nerve cells and their lack of regenerative capability will continue, even in the future, to render the replacement of central nerve tissue impossible. Furthermore, the extreme sensitivity of living nerve cells to lack of oxygen is an insurmountable obstacle. We heard today from Prof. Hirsch that the level of tolerance is higher than hitherto assumed and the discussion on barbiturates has shown that with the use of so-called brain-protective drugs a reduction in the metabolic process can possibly prolong the period of interruption of blood circulation to the brain, or spinal cord, which would otherwise lead to the death of nerve cells. Therefore, the specific structure of nerve cells will continue to stipulate its own limits; these limits may perhaps be extended very slightly, but on the whole they will remain impossible to overcome.

The topography of the brain and the specific pathomorphology of brain tumors present us with further biological barriers. Both benign and malignant tumors can, depending on their location, be impossible to operate on. Typical examples are tumors located in the brain stem. They can only be removed by surgery damaging the cerebral tissue, which is irreplaceable for the function of the brain.

Vascular surgery on the brain is restricted greatly by the atherosclerotic alterations arising with increasing age. Even the most subtle microneurosurgery technical aids fail to change this situation.

*Economical restrictions* are the second limitation on intensive neurosurgical medicine; although a certain taboo in our prosperous community, they cannot be completely ignored in the long term. The enormous costs accrued nowadays in intensive care medicine, in transplantation surgery, in cardiosurgery, or in the treatment of blood diseases, rapidly approaches the absolute limits of the domestic economic resources of our society. The treatment of patients in a vegetative state who are kept alive by intensive care medicine will in the foreseeable future become almost unbearable because this huge expenditure is met by the joint community of persons covered by health insurance and the state. In order to overcome particular crisis situations, as are apparent in the field of intensive therapy, such as increased personnel and improved appliances, it will be necessary to make certain savings in other fields of medicine, if we assume that the revenue required for maintaining standards of medical welfare cannot be raised infinitely. Setting priorities will be unavoidable, and will lead finally to decisions exercised on an ethical basis.

The *problems of ethics* – and I have now reached the third area limiting intensive medicine – are extraordinarily manifold and I wish at this juncture to discuss just two: (a) replacement of humanity in hospital by medical apparatus, and (b) termination of intensive treatment and aiding death.

When people today postulate that a right to good health exists, this makes it almost impossible to meet the demands of patients and above all of their relatives. A right to good health would only be feasible if solely exogenous factors were the cause of illness and the latter was therefore merely a sociological problem. A right to receive optimal medical care cannot, of course, be denied and this includes the complete technical treatment available in intensive care medicine. We read almost daily that the dignity of mankind suffers as a result of people being subjugated to technical apparatus, and according to the press an intensive care unit is considered to be like hell for patients. However, one seldom reads of the stress on nursing staff and doctors involved in intensive medicine. Is the technical intensive medicine really inhumane and does it indeed collide with the dignity of a human being? There is no shadow of doubt that the lives of many thousands of patients have been saved by modern intensive care. Nevertheless, whenever intensive medical treatment fails to cure, then – and only then – do we hear of the lack of respect for the dignity of mankind and failing humanity in modern hospitals. The deeply rooted reason lies in the fact that an illness is no longer regarded as fate, and moreover one tends to regard negative treatment as an "avoidable accident", or failure, caused by the doctor conducting treatment. Technique alone can be neither humane nor inhumane, it can only be implemented in a humane or inhumane manner. Hence humanity can only be communicated to, or rejected by, human beings. The humane aspect, particularly in intensive therapy, is an extremely important part of treatment. Whenever the wishes of patients are not met in this respect, then it is certainly not the fault of unwillingness of nursing staff and doctors, but rather of stress situations in full and overfilled intensive care units, which even nowadays are obliged for economic reasons to function without sufficient staff; thus we return again to the economic limitations.

Several years ago I conducted an inquiry among patients who had been treated in intensive care units. A majority of these patients stated after regaining health that they had never experienced such good nursing treatment and human kindliness than during the period of intensive medical care. On the basis of my own experiences with intensive medicine I am able to confirm that nursing staff are to a very high degree fully aware of their tasks, among which, in conjunction with the use of modern equipment, is humanely accompanying the patient throughout the danger period. This is also the reason why we no longer exclude relatives from visiting intensive care units; despite the problems of hygiene, we endeavor to involve them in the care of patients, providing the organizational programme is not disturbed.

The question of *termination of treatment* is closely related to when treatment begins. Intensive medical treatment for brain injuries usually commences nowadays at the scene of the accident, being administered by the emergency doctor. In many cases the emergency doctor is unable to determine the exact extent of injury and assess the likely effect of therapy on the subsequent course. Even the neurosurgeon is frequently only able to determine exactly after weeks, or even months, whether an irreparable vegetative state exists or whether rehabilitative measures might prove successful. When treating a formerly perfectly healthy patient injured in an accident, it is necessary to consider the reaction of close relatives. Should the neurosurgeon be of the opinion that a patient, previously accompanied to the hospital by and receiving constant attention from the emergency doctor, has to be regarded as a lost cause after all the clinical findings, then he must at least give the impression to close relatives that everything possible is being undertaken to save the life. This does not mean that in a clinically dead patient reanimation should be continued ad infinitum.

In the field of neurosurgery the termination of treatment by fatal illness, when intensive medicine can perhaps prolong life but cannot change the fatal outcome, is not quite as dramatic as the word "termination" would see to imply. On the contrary, it is a slow fading out which should not be prolonged by intensive therapy. The moment when a glioblastoma patient, or a hypertensive patient with mass hemorrhage in the stem ganglia, should no longer be given antibiotics, catecholamine, or corticosteroids can only be assessed in individual cases. The pain-killing treatment must be directed at the subjective ailments of a patient when negative side effects, such as are caused by high doses of morphine, are unavoidable. We are obliged to "allow a patient to die" with renunciation of all aggressive methods of treatment.

When we give foremost consideration to the individual patient in our practical dealings, e.g., acting pragmatically, then the question of course arises as to general acceptable standards of ethics which would warrant such conduct. In this respect, we are obliged to accept such terms as "significant" and "reasonable" playing a large role, whereby we should be fully conscious that the significance of another person's life cannot solely rest within our medical and human competence. The question as to whether a patient, through our therapy, can be *restored to life in a humanly dignified manner* can only be answered subjectively and imprecisely when the patient is unconscious. Continuation of treatment is certainly not justified when the patient has declined the treatment in a clear statement of will. A seriously ill patient is undoubtedly under pressure from suffering, which can influence a free and stable decision. Therefore our decision should give due consideration to the presumable will of the patient. When a patient is unconscious, a consultation with close relatives is frequently helpful in taking a decision. However, quite naturally, the reverse situation may arise, when the egoistic interests of close relatives make a clear decision difficult. The problem of so-called patient testaments is rarely discussed without delving into polemics. However, these testaments are often made years previously by a younger healthy person and the doctor is unable to determine whether the patient would in fact still adhere to that testament, particularly bearing in mind his current critical condition. In other words, would the patient really wish to forego possibly successful intensive medical therapy, or even request that treatment already adopted be discontinued? A majority of us have experienced patients happy that an extremely doubtful form of therapy, or one difficult to adhere to, was indeed administered, after it had led to success in the end. This also applies, in my own experience, to many suicide cases. In an individual case I became acquainted with, an elderly patient with whom I discussed the dangers of an operation at length, stated quite clearly: "If it should prove to be a glioblastoma, please do not give me intensive treatment, but allow me to die." I gave him my promise and I would have certainly respected his will. Fortunately it turned out to be a meningioma and the patient is still alive today.

It is my opinion that we can only resolve these briefly related problems of termination of intensive treatment when we have sufficient courage to accept responsibility in each individual case. We should not, however, adhere to general opinion, as was recently demanded by a renowned journalist. The question of whether to continue or abandon treatment cannot be solved by general resolutions made at a round table. The task with which we are confronted almost daily is to intensify our own conscience, which can neither be delegated nor by any means replaced. If we become fully aware that the termination of intensive care in many instances involves a *passive aid* to death, then I myself strictly reject providing an *active aid* for death. Of course,

the difference between passive omission of treatment and actual action is undefined. The principle of "nil nocere" is, however, the basis for all confidential relationships between doctor and patient and should therefore never be violated. We all make compromises daily, which may be a "moral evil". The responsibility for such compromises must be accepted by each individual. The willingness to accept responsibility can only be based on the sound foundations of medical knowledge and experience. It can never be overruled by legislation or regulations. I read 2 weeks ago in a magazine that the "hazy zones" in intensive medical care must be clarified by legislation. Unspoken and hidden behind this demand is again fear of the hubris of the "demigods in white". We can only counter the mistrust directed at us, following the general topical discussions on active aid to die, when we remain continually conscious of our hippocratic responsibility, in order that from the "hazy zones", which are often "havens of humanity", no bureaucratic regulations on aiding death are enforced by law. Pragmatic action undoubtedly involves the danger of unbounded "situation ethics", which we can only diminish by carefully weighing up the risks and benefits in every individual case, in respect of "salus" and also "voluntas aegroti", as comprehended on the grounds of free self-determination of individuals. Whenever we are unable to "heal", we should still have "aid" as our last resort in the sense of accompanying the dying with all the means available to us today, but definitely not by actively aiding death, which attracts so much publicity.

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