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Regulation of Cerebral Blood Flow and Metabolism

Neurosurgical Treatment of Epilepsy

Rehabilitation in Neurosurgery

Edited by
R. Wüllenweber M. Klinger M. Brock

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Preface

The annual meeting of the Deutsche Gesellschaft für Neurochirurgie was held in Bonn on the 4-7 May 1986. It was the first time the society has met there since it was founded in that city in 1950. This 15th volume of the *Advances in Neurosurgery* contains the papers read there on the chief topics.

The first main topic covered is one of the basic aspects of our neurosurgical activity - the regulation of cerebral circulation and brain metabolism - and was the object of lively discussions between neurophysiologists, neurologists, and neurosurgeons. The second main topic, the neurosurgical treatment of epilepsy, has gained new importance because of the new visualizing procedures. The future will show whether the treatment results of the past can be improved by employing these new procedures. The third topic, rehabilitation following neurosurgical diseases, served to demonstrate the organizational and therapeutic problems which make it difficult for patients thus injured to rejoin society. Last but not least, young neurosurgeons were given the opportunity to present their research in short papers and posters.

The publication of all these presentations would exceed the boundaries of the *Advances*. However, it is to be hoped that at least some of these good to excellent reports will find publication elsewhere.

As in earlier years, the annual meeting of the German Association of Neurosurgical Nursing was held at the same time as that of the German Society for neurosurgery. Again, the cooperation between the two societies is very good.

Finally I want to thank all those whose help made the organization of this meeting possible. In addition to the organization committee, consisting of Priv.-Doz. Dr. Klinger, Profs. Drs. Bock, Dietz, Frowein and Lausberg, I am very grateful to the many members of the staff of my department, especially, the head nurse Mrs. Gudrun Braick-Benien, and my chief Oberarzt, Prof. Dr. Wassmann for their outstanding help. Prof. Wassmann was burdened with the major portion of the organizational work for this congress, in addition to his clinical work as Oberarzt. My special thanks also go to Oberarzt Dr. Neumann, who attended to the congress office himself during the meeting.

The publication of this 15th volume of the *Advances* would not be possible without the tireless editorial work of Priv.-Doz. Klinger and Prof. Brock, whose excellent teamwork with Springer-Verlag is greatly appreciated.

Rolf Wüllenweber

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Rede zur Eröffnung der 37. Jahrestagung der Deutschen Gesellschaft für Neurochirurgie

President's Opening Remarks

R. Wüllenweber

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In meiner Rede zur Eröffnung der 27. Jahrestagung vor 10 Jahren in Berlin habe ich versucht die Zwänge zu skizzieren, die unsere tägliche Arbeit einschnürten, ja teilweise unmöglich machten. Das Fazit meiner damaligen Ausführungen war alles andere als erfreulich. Es bestand darin, sich entweder dem defensiven Trend anzuschließen oder trotz aller Schwierigkeiten nicht zu kapitulieren und auf bessere Einsichten der Verursacher zu hoffen. Diese Hoffnung war vergeblich, das ist das Résumée der letzten 10 Jahre. Auch heute regieren staatliche Stellen mehr oder weniger stark in die Universitäten hinein, nach schlechten Erfahrungen zum Teil zwar subtiler, dafür bemüht sich aber beispielsweise Nordrhein-Westfalen, seinen Nachholbedarf an schlechten Erfahrungen schleunigst zu befriedigen. So kommt es, daß wissenschaftliche Leistungen wie die Habilitation in zahlreichen Fällen mit der Entlassung aus der Universität belohnt werden, sobald das 46. Lebensjahr erreicht ist.

In der Novelle zur Approbationsordnung kommt das Fach Neurochirurgie nicht mehr vor. Anstatt Kenntnisse über Behandlungsindikationen bei intrakranieller Raumforderung zu erwerben, sollen die Studenten ein Praktikum der Sportmedizin absolvieren. Stellungnahmen unserer Gesellschaft zur Novellierung blieben von dem zuständigen Bundesministerium unbeantwortet.

Die Forschung läuft heute praktisch nur noch über Drittmittel, deren Kontrolle sich die Bürokratie allerdings bei allem Desinteresse an der Forschung nicht entgehen läßt. Das Anschwellen des bürokratischen Wasserkopfes unserer Verwaltungen hat zwangsläufig zur Folge, daß ein Großteil der Angestellten und Beamten mit der Produktion von beschriebenem oder bedrucktem Papier mit Vorliebe in Form von Rundschreiben beschäftigt wird. Leider werden dabei nicht nur Stilblüten produziert, sondern ich erlebe nicht selten Fehlleistungen der Bürokratie, die mich in einem Ausmaß belasten, das bedrückend und in der täglichen Arbeit lähmend ist. Hinter vielen bürokratischen Auflagen steckt die Angst vor dem Begriff des "Organisationsverschuldens". Dieser Angst versucht man dadurch zu entgehen, daß man Verantwortung von der Bürokratie auf die Ärzte verlagert. Das Bedrückende auch an den lächerlichsten Vorgängen ist, daß offensichtlich niemand mehr bereit ist, im Rahmen einer bürokratischen Tätigkeit persönlich Verantwortung zu übernehmen.

Wer meine Ausführungen zu Problemen der ärztlichen Ethik aus den letzten Jahren kennt, weiß, welche zentrale Stellung der Begriff "Verantwortung" in meiner persönlichen Beurteilung ethischer Fragen einnimmt. Damit stehe ich sicher nicht allein, wie die große Resonanz zeigt, die das Buch von Hans Jonas "Das Prinzip Verantwortung" gefun-

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den hat (Insel-Verlag Frankfurt/Main, 1985). Um einige Punkte herauszugreifen, so hat Jonas sehr klar dargestellt, daß die Freiheit der medizinischen Forschung in Frage gestellt ist, wenn man die möglichen Konsequenzen der Anwendung der verfügbaren Technik, etwa in der Gen-Technik, nicht ins Auge faßt. Die Freiheit der Therapie wird fragwürdig, wenn man das Machbare unreflektiert für indiziert hält und sich der Praxis des Prinzips Verantwortung entzieht. Nun hat Jonas in seinem Buch vehement Ernst Blochs "Das Prinzip Hoffnung" (Suhrkamp, Frankfurt, 3. Bde., 1967) widersprochen. Ich möchte mit einigen Worten auf den Begriff der "Utopie" eingehen, d.h. der Frage, ob wir ohne Utopien in unserem Beruf arbeiten können, ob das Heilen, das wir als unsere vornehmste Aufgabe betrachten, eine Utopie ist. Der Begriff der Utopie ist natürlich in seiner Anwendung außerordentlich vielfältig. Platons "Staat" ist ohne Zweifel eine politische Utopie, die Utopia des Thomas Morus sollte ihm als Grundlage einer natürlichen Religion dienen und des marxistischen Philosophen Bloch "Prinzip Hoffnung" ist eine Sozialutopie: die klassenlose Gesellschaft, die ohne Zwang zur Arbeit ihre Muße pflegt, in einem Paradies lebt, in dem die Steckenpferde zum Beruf werden. Hans Jonas hat nachzuweisen versucht, daß dieses Paradies das Ende der Kreativität, der Menschenwürde und der persönlichen Freiheit ist. Das Prinzip Hoffnung kann in der Medizin bedeuten, daß die heute noch unheilbare Krankheit in der Zukunft heilbar wird, daß diese Utopie damit ein Stachel im Fleisch des Forschers bleibt, und daß vielleicht irgendwann die Utopie zur Realität wird. Bleiben wir bei der Hoffnung: Ich habe damals in Berlin formuliert, daß ich mich nicht befugt fühle, dem Patienten oder seinen Angehörigen den letzten Strohhalm der Hoffnung zu entreißen, auch wenn ich selbst von der Hoffnungslosigkeit einer Situation überzeugt bin. Das bedeutet, daß man in klarer Beurteilung der Realität der Humanitas oder auch der Barmherzigkeit die Priorität einräumt. Der Patient muß - und das ist die Grundlage jedes Vertrauensverhältnisses zwischen dem Patienten und seinem Arzt - in jeder Situation das Gefühl haben, daß sich der Arzt für ihn persönlich verantwortlich fühlt. Mein Fakultätskollege Herr Prof. Stelzner hat seine Eröffnungsrede zum Chirurgenkongreß 1985 mit den Worten beschlossen: "Der Kranke, der zum Chirurgen kommt, hat immer noch eine Verabredung mit dem Schicksal. Das wissen die Chirurgen!". Wir wissen es, aber denken wir immer daran? Ich kann mich häufig des Eindrucks nicht erwehren, daß wegen der derzeit üblichen Bedrohung durch Prozesse wegen mangelnder Aufklärung die Humanitas in vielen Fällen zu kurz kommt und man sich in einer erbarmungslosen Aufklärungspraxis eines Teils der Verantwortung entzieht und sie auf den Patienten abwälzt, wobei ich mich selbst keineswegs ausschließen kann.

Das Problem der Freiheit der medizinischen Forschung wurde schon kurz angesprochen. In den letzten Jahren sind allerorts Ethik-Kommissionen entstanden, die den Forscher beraten sollen und Stellung nehmen, ob ein Forschungsprojekt ethisch tragbar bzw. unbedenklich ist. Diese sicher begrüßenswerten Einrichtungen sollten nicht zu der völlig falschen Annahme verleiten, daß ethische Fragen durch sog. demokratische Mehrheitsbeschlüsse beantwortet werden können. Ich sehe die große Gefahr, daß die Praxis dieser Ethik-Kommissionen darauf hinausläuft, den Eindruck zu erwecken, daß die Meinungen der Ethik-Kommissionen mehr sind als individuelle Ratschläge, und daß sie den Forscher selbst von seiner persönlichen Verantwortung entbinden könnten. Eine Ethik-Kommission kann allenfalls Fehlverhalten verhindern oder zu korrigieren versuchen, nicht aber das Gewissen des einzelnen Forschers ersetzen. Der unleugbare Vorteil dieser Ethik-Kommissionen besteht darin, einen Konsens in der prospektiven Forschung zu erzielen, wie beispielsweise bei der schon erwähnten Gentechnologie. Die Frage aber, ob es ein in die Zukunft gerichtetes kollektives Gewissen gibt, kann ich nicht beantworten.

Zum Schluß kann ich nicht umhin, noch einige Worte zu aktuellen Problemen zu sagen,die ebenfalls Fragen der Verantwortung betreffen, Verantwortung gegenüber unseren Mitarbeitern, unserem Fach und unserer Gesellschaft. Das schließt so aktuelle Themen ein wie arbeitslose Ärzte, Einstellung ausländischer Ärzte, Gründung von neurochirurgischen Abteilungen über die bestehenden Kliniken und Abteilungen hinaus, Qualitätskontrolle, Berufsfragen und neurochirurgische Forschung. Es ist für mich bedrückend, wenn ich sehe, daß die Zahl der ordentlichen Mitglieder unserer Gesellschaft von Mitgliederverzeichnis zu Mitgliederverzeichnis erheblich zugenommen hat. Und ich frage mich als Klinikchef bei jeder neuen Bewerbung, was aus der großen Zahl der Neurochirurgen werden soll, die in wenigen Jahren ausgebildet sein werden. Bei jedem Bewerbungsgespräch schildere ich den Aspiranten in düsteren Farben die Aussichten, die sie in der Neurochirurgie haben und bekomme dann nicht selten zur Antwort, daß bei der Situation auf dem heutigen Arbeitsmarkt jede Chance ergriffen werden müsse, um zumindest vorübergehend einen Ausbildungsplatz zu erhalten, gleichgültig, was nach Erlangung der Facharztanerkennung aus dem Betroffenen wird. Ich muß mich dann daran erinnern, wie es uns, der Nachkriegsgeneration, ergangen ist, die Ende der 40er, Anfang der 50er Jahre nach dem Staatsexamen auf Stellensuche ging. Ich selbst habe auch jede Chance ergriffen, und genauso wird es den meisten ergangen sein, die in meinem Alter sind. Wenn ich heute in einem Vorstellungsgespräch mit meinen pessimistischen Schilderungen der Zukunftsaussichten zu Ende bin, dann höre ich nicht selten von den Bewerbern, "aber ich will unbedingt Neurochirurg werden, und Sie haben es doch damals auch geschafft". In der Tat haben wir es damals geschafft, aber mit äußerst bescheidenen Ansprüchen! Schließlich muß sich dann jeder noch von mir den Spruch anhören: "Bilden Sie sich bitte nicht ein, mit einer 40-Stunden-Woche in der Neurochirurgie Karriere machen zu können!" Diese 40-Stunden-Woche betrifft nicht so sehr die Krankenversorgung wie die Forschung. Nach Einführung des Freizeitausgleiches von Bereitschaftsdiensten hatte ich gehofft, daß die Forschungsaktivitäten in meiner Klinik sprunghaft in die Höhe schnellen würden, weil in jedem Monat 30 Tage für die Forschung zusätzlich zur Verfügung stehen mit Ausnahme der wenigen Tage, wo der Dienstarzt wirklich ein Recht hat auszuschlafen, weil er sich die ganze Nacht um die Ohren schlagen mußte. Das ist nicht der Fall gewesen und zwar nicht nur bei uns, sondern auch in anderen Kliniken, denn ich übersehe nunmehr seit 7 Jahren die Anträge, die von neurochirurgischer Seite an die Deutsche Forschungsgemeinschaft gestellt werden. Es sind nur eine Handvoll im Jahr. Es hat sich die Tendenz breitgemacht, daß es für das Image des einzelnen viel effektiver ist, wenn man ein Symposion oder eine andere Tagung organisiert und zwar zugegebenermaßen in den meisten Fällen hervorragend organisiert. Ich möchte aber trotzdem keinen Zweifel an meiner Einstellung aufkommen lassen, daß eine saubere klinische oder experimentelle Originalarbeit ganz erheblich höheren Wert besitzt als die beste Organisation.

Was die Einstellung ausländischer Kollegen anbelangt, so ist die Haltung der Regierungspräsidenten, die für die Erteilung der Arbeitserlaubnis zuständig sind, außerordentlich restriktiv geworden, und es ist nicht mehr möglich, ausländische Kollegen einzustellen, es sei denn mit Hilfe eines DAAD- oder Humboldt-Stipendiums. Damit ist uns eine große Möglichkeit genommen worden, über die Grenzen hinaus zu wirken und das Image der deutschen Neurochirurgie in anderen europäischen und vor allem außereuropäischen Ländern zu pflegen. Die ausländischen Kollegen, die ihre Ausbildung an unseren Kliniken genossen haben, sind nach ihrer Rückkehr in ihre Heimatländer in den meisten Fällen als kompetente Fachleute anerkannt. Viele halten die Verbindung zu ihren deutschen Ausbildungsstätten aufrecht, und ich bedauere es deshalb außerordentlich, wenn in Zukunft unsere jüngeren Kollegen

nicht mehr die Möglichkeit haben, auf dieser Grundlage internationale Kontakte zu pflegen.

Der Bedarf an neurochirurgischen Krankenhausbetten ist in der Bundesrepublik nahezu erschöpft und die Bildung neuer Abteilungen nur noch an ganz wenigen Orten sinnvoll. Ich kann keinem Kollegen, der - und das habe ich am Anfang schon betont - mit 46 Jahren aus der Universität hinausfliegt, übelnehmen, wenn er zur Versorgung seiner Familie versucht, irgendwo ein paar eigene Betten zu bekommen, um dort Neurochirurgie zu betreiben. Sofern er sich in dieser Mini-Abteilung mit Bandscheiben-Operationen und allenfalls der Versorgung von Schädel-Hirn-Verletzungen zufrieden gibt, bestehen dabei keine Bedenken, denn diese Kollegen sind ja in der Regel gestandene Neurochirurgen, die Opfer unserer Hochschulgesetzgebung sind. Wenn aber derartige Abteilungen mit immer weniger Betten installiert werden und sich nicht auf die erwähnten Operationsindikationen beschränken, dann muß der Standard dieser Abteilungen sinken und zwar aus dem einfachen Grunde, weil nicht genügend Personal, weil nicht genügend Hilfsmittel, keine Intensivstationen zur Versorgung von Tumor-, Aneurysmapatienten usw. zur Verfügung stehen. Ich habe in den letzten 4 Jahren, wo ich als 2. und 1. Vorsitzender unserer Gesellschaft eine Menge Korrespondenz zu erledigen hatte, in keinem einzigen Fall eine Anfrage über die Besetzung einer neurochirurgischen Stelle in einem allgemeinen oder konfessionellen Krankenhaus bekommen. Das heißt, die Neugründung von Abteilungen geht an unserer Gesellschaft vollständig vorbei und wir haben nicht den geringsten Einfluß. Man erfährt dann nur hinterher, daß ein konfessionelles Kuratorium einen Bewerber vorgezogen hat, weil er im Kirchenchor sang. Ich habe immer wieder empörte Briefe bekommen, ob unsere Gesellschaft denn schlafe und sich nicht mehr um diese Dinge kümmern könne. Ich kann darauf nur antworten, die Gesellschaft hat nicht geschlafen, aber ihre Arbeit ist ineffizient, siehe meine früheren Bemerkungen über die Approbationsordnung. Man könnte sich damit trösten, daß wir inzwischen eine Qualitätskontrolle eingeführt haben und daß deshalb der Standard der Mini-Abteilungen zu überwachen ist. Leider ist das nicht der Fall, solange sich diese Mini-Abteilungen nicht an der Qualitätsstudie beteiligen. Bei dem Versuch, den Neurochirurgen selbst, nämlich unserer Gesellschaft, mehr Gehör in der Öffentlichkeit zu verschaffen, haben viele von uns frustriert das Handtuch geworfen. Ich meine aber, wir sollten erneut eine gemeinsame Anstrengung machen, denn in Zukunft werden die Probleme aufgrund der hohen Studenten- und Assistentenzahlen nicht einfacher zu lösen sein. Wir sind bisher ein relativ kleiner Verein gewesen, der sich durch die Solidarität seiner Mitglieder ausgezeichnet hat. Mein herzlicher Wunsch und meine dringende Bitte ist, daß das für die Zukunft so bleiben möge. Nur dann können wir auch den materiellen Schwierigkeiten, die sich aus der Überzahl ausgebildeter Neurochirurgen ergeben, nur dann können wir Neid und Konkurrenzdruck mit Erfolg begegnen.

Otfrid Foerster and "Die Leitungsbahnen des Schmerzgefühls" (1927)

K. J. Zülch

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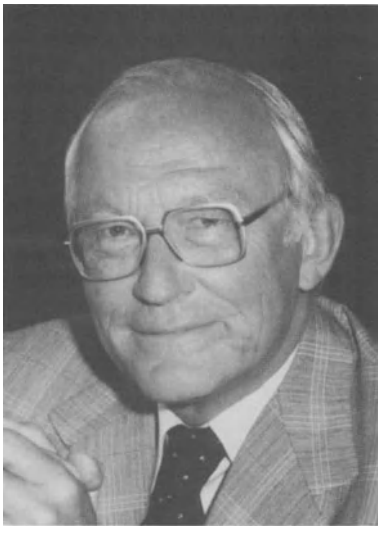

K.J. Zülch

With this lecture the Deutsche Gesellschaft für Neurochirurgie today commemorates the life and work of Otfrid Foerster, the great neurologist and neurosurgeon. Born on the 9th of November, 1873, in Breslau as a son of the professor of "Classical Philology, Archeology, and Eloquence," he died on June 15th, 1941 in Breslau.

As a schoolboy he was one of the best students at the Maria-Magdalena Gymnasium and easily passed his "Abitur-Examination." There had been scientists among his ancestors, but what persuaded him to choose medicine as his life work is not known.

He taught himself to play the flute. He loved the theater, was popular at parties as a student, was said to have been an excellent dancer, and was also a good skater: all in all, one might say that he had a deep interest in social life. At this time in his life, Foerster was a man who was never a stranger to his social environment and who easily made contact with other people. In fact, he seems to have been a pronounced extrovert. Consequently we may wonder what caused his change in personality and decisive turn in lifestyle in later years. Only when we learn of the unexpected death of his first child can we understand: he plunged into scientific work perhaps just to forget. His friends thought that he had become introverted since that event. His old character occasionally shone through afterwards; he could be a

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charming host in his own home or while holding social discussions with interesting visitors or drinking one of his excellent wines with friends. In his later years, nevertheless, when we younger people got to know him, he was cold and reserved, less warm-hearted. Another factor may have been that his international reputation began to grow very early and drove him relentlessly to the hospital and research laboratory.

As a student Foerster had worked in the Mental Hospital in Leubus-Silesia with the great psychiatrist Kraepelin.As an undergraduate student he also came into contact with Wernicke in Breslau; these associations may well explain his interest in neurology.

Upon Wernicke's suggestion Foerster went abroad for 2 years to study with Dejerine in Paris, where he also met Pierre Marie and Babinski. During the summer months he trained in physical therapy with Frenkel-Heiden in Switzerland.

Neurology in Foerster's Time

In order to portray properly Otfrid Foerster's importance for science I shall review the problems with which he, as a neurologist, was concerned at the time. The change in the spectrum of disease between then and our own era has certainly been remarkable. In his time syphilitic infections in their different forms, and particularly the sometimes intolerable lesions in tabetics, were in the foreground of neurological work.

The complicated disturbances of coordination of gait at that time made tabetics almost outcasts from society. In this context Foerster began his first studies in "exercise therapy" (3, 17), which he had learned with Frenkel-Heiden and which remained one of his great topics of interest throughout his scientific life. Furthermore, he had to deal with various forms of pain arising from the tabetic lesions of the posterior nerve roots and from the "crises" in internal organs. Particularly lancinating root pain acquainted him with these problems of intolerable pain.

Posterior Rhizotomy

Foerster started working with the tabetic problems of gait incoordination, yet he was also simultaneously confronted by all kinds of spastic conditions. Stimulated by the observation that hemiplegias in tabetics remained flaccid in the area affected by the syphilitic process, Foerster had the idea that operative transsection of the posterior roots might eliminate the cerebrally conditioned spasticity. Thus in 1908 (4) he suggested posterior nerve root section, an intervention later termed "Foerster's operation." This rapidly made him internationally known.

Moreover, when discussing the pathogenesis of "gastric crises" he pointed to the conduction of pain impulses in the sensory sympathetic fibers of the seventh to ninth thoracic posterior nerve roots. This stimulated him to eliminate these painful syndromes surgically, again by resection of the posterior nerve roots (posterior rhizotomy). He reported on the results at the International Congress for Internal Medicine held in London in 1911 (5). This report increased further his reputation in the medical world, a reputation perhaps enhanced by his command of rhetoric in foreign languages (do not forget that his father was a Professor of Eloquence!).

There remained one further problem to tackle: the sometimes intolerable pain syndromes of tabetic disease, i.e., lancinating root pains. That posterior nerve root section generally could relieve pain was well-known, although there was a high risk of recurrence. The first to employ this technique was Sir William Bennet (1), though perhaps in an unsuitable case, namely sciatic pain. Many other attempts ended with the same disappointing result as was reported by Bennet.

At that time Foerster began to think over the philosophy of pain, which was an originally genuine and - biologically seen - necessary and useful phenomenon: a signal warning of the threatening action of inner and outer nociferous factors, and a means of protection for the inner well-being of the body. However, in disease it could become independent and provoke severe torturous and even intolerable sensations, as in tabetics. It is understandable that pain remained one of his central concerns, and its relief the main obligation of each neurologist.

Resection of the posterior nerve roots turned out to be a very effective and successful operation, but not for lancinating root pain. At first Foerster still believed that because of the overlapping of the dermatomes an enlargement with cutting of more upper and lower nerve roots would be sufficient to control the pain. However, the results did not confirm this assumption. Later, he found the existence of afferent fibers in the anterior spinal roots (19), where pain fibers could then travel upward. However, a simultaneous section of the anterior motor roots and the posterior roots seemed impossible except perhaps in conditions of pain in amputees. Therefore the problem of controlling lancinating pain remained open.

The Dermatomes

In the many posterior nerve root sections he had performed he used to delimit the upper and lower borders of the sensory defect with the utmost diligence. The result was his very exact schematic demonstration of the dermatomes in man, which had previously been illustrated by Sherrington (33), though in the monkey. Foerster's depiction of dermatomes in man has turned out to be the most reliable. The patterns of Keegan and Garnett (26) may look more elegant, but they correspond less exactly to reality when carefully assessed by neurological examination.

Foerster demonstrated the dermatomes in the famous Schorstein lecture (11) in London, and the report was received with great applause. This new scientific insight was, however, only gained as a side-effect of successful surgical therapy.

Anterolateral Cordotomy in the Spinal Cord

We have noted that operative pain control was one of the central research subjects in Foerster's life (8, 13), and that the problem of relief of lancinating root pain in tabetics had remained unsolved. Relief of such pain was finally achieved by an anterolateral cordotomy, first performed by Spiller and Martin (35) in the United States. In fact, Foerster and Tietze (22) also sectioned this tract while quite unaware of Spiller and Martin's operation. Yet it is scarcely known that Schüller of Vienna (32) had already successfully sectioned it in the monkey after investigations by anatomists into the functional significance of this column. Schüller also named the operation *"Chordotomie."*

It is also scarcely known that Foerster himself had to perform cordotomy as a sort of emergency operation. A patient had undergone successful posterior rhizotomy because of gastric crises; however, later a recurrence was noted and a second operation seemed indicated to enlarge the number of root sections. At this operation a putrid infection was apparent at the lower edge of the operative field. In an attempt at disinfection Foerster used iodine at the dura and this in fact led to unbearable pain in the leg, which could not be totally controlled even by large doses of morphine. Thereafter, Foerster decided to section the anterolateral tract and this operation led to a permanent disappearance of pain.

Foerster and Gagel (18) later made a pertinent study of the course of the anterolateral fibers and demonstrated that their course swings anteriorly and posterolaterally and finally even into the posterior columns. Furthermore, Foerster reported extensively on his own clinical experience with the control of pain by cordotomy; finally he recommended "high" sectioning in C2 (even bilateral) and performed such operations himself.

In their excellent functional analysis of the spinal column one structural problem has remained unsolved, namely whether the lamination of the dermatomes in an "onion" (concentric) pattern was really correct, as depicted in the semischematic Fig. 40 of Foerster (23), or whether the different patterns of Kahn and Peet (25), where the three great divisions of the body surface lay one above the other, or of E.A. Walker (38), where they partially overlapped each other, correspond to reality. I have had the opportunity to examine carefully some patients after anterolateral cordotomy and on the basis of my results would favor Walker's concept. Foerster himself used to demonstrate while performing cordotomy how the first superficial cut would induce analgesia up to the inguinal fold, the second somewhat deeper cut, analgesia to the umbilicus, and the third, deepest cut, analgesia to the mamillary segment. I am not, however, convinced that this procedure really proved the concentric arrangement of the segments.

Developments in neurosurgery have in the meantime led to transcutaneous section of the column or even a sectioning "high up" in the posterior fossa. I have seen some patients where such tractotomy has been performed for trigeminal neuralgia according to Sjöqvist (34). If the sectioning was inadequately placed, analgesia was noted in the first and second root of the trigeminal nerve, but simultaneously (in the case of a lesion of the tractus spinothalamicus) in the contralateral side of the body. I even had one case where a bilateral section had been performed with the same results (48, Figs. 3b, 4a, 4e). This allows the design of an arrangement of the pain fibers as seen in Fig. 1 in Zülch (42).

Elimination of Meningocerebral Scars: The "Brain Chart"

The operative relief of focal epilepsy by excision of the scars after brain wounds incurred during the First World War, performed in more than 100 cases under local anesthesia (7), led to further very interesting and important new results for the neurological sciences. The definition of the borders of the responsible brain tissue, which had to be surgically removed, made necessary an exact functional analysis of the cortex before the excision. Thousands of exact stimulations of the cortex had to be performed, the results of which filled the chart of the brain with highly important information about localization of function in the brain. It was at this time that Wilder Penfield

spent more than 6 months in Breslau. Penfield was so impressed by this problem of localization of function that it dominated all his future scientific work (21).

Attempts at an analysis of the cortex had already been begun by Fritsch and Hitzig (23) and continued, for instance, by Fedor Krause, who produced excellent and very precise results (27). This brain chart was now considerably enlarged and controlled, and it is still to be found in textbooks according to the design of Foerster because of its reliability. His brain chart as a basis of *"Lokalisationslehre"* (principles of localization) in the light of Hughlings Jackson's work was presented upon invitation with great success at the International Congress of Neurology on the occasion of Jackson's 100th birthday (14). This memorial lecture gave a synopsis of his life work on the principle of localization. It was concisely reported, particularly in respect of the motor cortex. Foerster was honored and pleased to assume this task because he considered himself an intellectual disciple of Jackson, whose doctrine of "levels" in the organization of the nervous system - in parallel to Herbert Spencer's philosophy - he had been trying to document neurophysiologically all his life.

I would like to report here a little story which showed Foerster in close contact with Oskar Vogt, who wanted to gain him for the Berlin-Buch Kaiser-Wilhelm-Institut with its 60 bed ward for scientific research. O. Vogt had at that time begun to make corresponding experimental stimulations of the cortex, though in monkeys. It is said that both discussed the similarities and dissimilarities of their results very thoroughly. However, in order not to be influenced in their analytic studies they apparently had agreed to mail the results on Friday afternoon, so that the letters would arrive simultaneously on Monday morning. This prevented any imprecise influence in the subsequent discussion about the "data".

Operation on Peripheral Nerve Lesions in World War I

The enormous frequency of peripheral gun shot wounds to the nerves in the First World War (2% of war wounds) raised the problem of surgical interventions, which according to Foerster were not being adequately and successfully performed by the general surgeons. Therefore he began to undertake surgery himself. According to his figures of 1934 he saw 4748 gun shot nerve wounds out of which he operated in 775 cases. In the first *Handbuch der Neurologie* he provided 935 pages of anatomy of the peripheral nerves with superb pictures, including anomalies, anastomoses etc. Furthermore he described the functions of the muscles, his recommendations on the type of operation to be employed, and the results of the various operations. Because of the absence of antibiotics he was a strict partisan of secondary suture. In the second *Handbuch der Neurologie* he wrote another 637 pages on the details of innervation of the musculature (15).

It would be appropriate here to summarize his concepts about pain conditions of the peripheral nerves, but space forbids it. I shall only reproduce here a catalogue of the types of pain which I have formed according to his concepts (8, 9) (Table 1). In particular, I would like to draw attention to his definition of hyperpathia, which seems so important and is so often neglected or misunderstood (Table 2). Both the exact description of the type of pain and the consideration of hyperpathia are basic tools in the interpretation of pain conditions.

Table 1. Characterization of types of pain

1) Painful prickling
2) Stabbing, biting, cutting
3) Squeezing/crushing
4) Tieing up/contracting
5) Burning

Table 2. Features characterizing hyperpathia

1) Increased level of perception and inadequate reaction to stimulus
2) Summation
3) Prolonged duration
4) Latency in appearance, yet
5) Explosive manifestation of perception
6) Abnormally disagreeable character of pain
7) Diffuse and insufficient localization
8) Irradiation

The Significance of the Autonomic Nervous System in Pain

It is apparent that Otfrid Foerster was probably the first to carry out supradiaphragmatic resection of the splanchnic nerves. In 1935 (13) and 1939 (16) he reported comprehensively observations during operations on the autonomic nervous system, which he had already begun performing during World War I in his attempts to radically control pain in recurrences by means of periarterial sympathectomy.

Causalgia

I find it surprising, nevertheless, that Foerster paid so little attention to causalgia, which is the most dramatic pain syndrome after gunshot wounds of the nerves. It is understandable, therefore, that beyond the time of wars knowledge of this syndrome is so scarce and it is commonly neglected. Here I shall repeat only a few statements about this important feature: Causalgia is characterized by extremely torturous "burning pain" and its explosive onset at varying intervals in the majority of cases, as well as by the release by outer irritating factors of mechanical, acoustic, visual, and sensory action or even the mental imagination of such an event. Causalgia is almost restricted to lesions of n. medianus/tibialis/ischiadicus and never occurs after transection of a nerve. As regards its pathogenesis, I conceived the following concept, partly as an observer, partly as personal sufferer (40). I believe that there is a certain stimulation in the territory of the nerve lesion by the production of "transmitters," particularly ot the histamine type, by the efferent sympathetic nerves. These substances stimulate the nerve fibers remaining intact in the contused nerve, where there is a predominance of C fibers, which actually have the highest resistance. By irritation of these fibers the unpleasant burning type of pain arises. Similar pain can be experimentally felt when one applies the Clark tourniquet maneuver and sets a stimulus in the 35th-40th minute (40, p. 213).

My personal observations were as follows: Stimulated by the experiments of Sir Thomas Lewis (28, 29), I injected histamine subcutaneously into the territory of my bruised nerves, which produced a local, intensive, very disagreeable burning pain during regeneration. Only after the war did I get to know the report of Störring and Schorre (36), who were able to produce a recurrence of a typical causalgia syndrome by injecting histamine, even after the pain had already been completely removed by cervical ganglionectomy. I repeated this experiment directly after the war and was able to confirm their observations, though only for the first 2-3 weeks, i.e., so long as the efferent sympathetic fibers after ganglionectomy had not yet undergone Wallerian degeneration. Yet there was a highly interesting result when I repeated the same procedure in cases of truncotomy of the sympathetic chain between T1 and T2. Then recurrence of the causalgic syndrome could be produced until the majority of the somatosensory part of the nerve - namely the A fibers - had recovered, and the spectrum was not restricted mainly to the C fibers. To me, the idea of an "artificial synapsis" has been never convincing and sufficiently provable. To summarize, my concept of pathogenesis is as follows: When median (etc.) nerves are contused and stay in the state of "hyperpathia" (by virtue of the prevalence of C fibers) and so long as still acting efferent sympathetic fibers are present, they can be centrally stimulated to produce transmitters (for instance, of the histamine type). These will release an explosive burning pain travelling along the C fibers. Ganglionectomy will make the action of sympathetic fibers ineffective after Wallerian degeneration. Truncotomy, on the other hand, will interrupt transmission of impulses from the hypothalamus to the sympathetic periphery. If by iatrogenic action transmitters are brought into the general circulation, they can produce burning pain as long as C fibers prevail in the nerve and their action is not suppressed by the regenerated A (etc.) fibers.

The Significance of the Posterior Columns of the Spinal Cord in the Perception of Pain

Foerster had already reported in 1927 (8) that isolated lesions of the posterior columns often produce severe hyperpathia, even when anterolateral and other columns are intact. This led him to the assumption that a suppressing influence from the posterior columns was exerted on the pain system of the anterolateral column. On the other hand, he was able to provoke pain by stimulation of the intact posterior columns at operation (13, p. 57).

Altenburger, the physiologist working at the Breslau Institute, then proved that the intensity of the pain perception points of the skin increased upon stimulation of the posterior columns. William Sweet mentioned in his Otfrid Foerster lecture (37) how Foerster's experiences stimulated his own interest. Foerster apparently believed that a wave of moderating impulses could travel upward together with those of the anterolateral cord.

Similarly Foerster had - as he told us - advised his patients decades before (in the time of the lancinating root pains) to use a small device for the production of faradic currents and to have the faradic wave travelling over the painful dermatome. This actually turned out to be very helpful, since probably as early as 1890 J.B. Mattison had proved that "galvanism" relieves neuralgic pain. These experiences of Foerster to some extent later stimulated the gate control theory of pain of Melzack and Wall (30) and Wall and Sweet (39). The afferent waves arriving in both systems interacted insofar as the anterolateral

system was depressed, preventing pain which would ordinarily have arisen (14).

This reminds me of a similar procedure used in my student days when we had to be sutured after receiving cuts in duels. This was not done by doctors but by medical student colleagues and was often very painful when the lips were involved. Then one of our friends used to stand behind us exerting deep pressure on our mastoid processes, whereby the dull deep pain suppressed the sharp pain of the penetrating needle.

Since William Sweet has broadly discussed this significance of the posterior columns of the spinal cord and the surgical methods adopted for electrical stimulation, here I shall only mention the importance of the model of acupuncture for pain relief, which is based on the same principle.

The Use of Acupuncture to Relieve Pain

During two sojourns to China I had the opportunity of seeing not only many surgical interventions performed under acupuncture hypalgesia (46) but also many attempts at acupuncture therapy in chronic pain conditions. Furthermore, scientific experiments with modern methods were demonstrated to us in the Shanghai Physiological Institute of the Chinese Academy of Science. Finally, I had discussions with the head of a research team on acupuncture in one of the great thoracic hospitals. The modern method was to have the effect of application of the faradic current as near to the operative field as possible. For operations under acupuncture hypalgesia, thyroid surgery was most suitable but surgery on the breast and brain was also possible. Excluded were surgery of trauma and orthopedic surgery. Children were never good candidates. The preparation of the patient and the examination of his autonomic nervous system lasted 1 week, and if there was not good compliance or confidence the day before, the patient was excluded from this sort of anesthesia. In the Physiology Institute every kind of modern research was used to study, for instance, endorphin and other transmitters and to make exact examinations of the action of acupuncture on electric brain stimuli. Pressure on tendons or other pain stimuli were used and the recordings made from single cell leads, where the frequency and amplitude decreased or even began to fade. I shall not repeat more details here (46).

The description of Foerster's experiences and concepts showed that Foerster's interest circled around the most modern conceptions of pain, which are discussed nowadays, half a century later (37, 46a).

The Problem of a Homolateral Pain Pathway - Hemispherectomy

All his life Foerster tried to tackle the problem of restitution of function, which was important for physical exercise on the one side but was also very troublesome and annoying when recurrence of pain ensued. He tried out resection of all possible pathways but not infrequently had to resign himself to failure. At the end of his life he therefore discussed the possibility of an entirely homolateral pathway for pain. He assumed a "bihemispheric representation of parts of the body" (though mainly for "proximal" parts) with a very slow restitution (14, p. 445). In one of his last papers he even mentioned the restitution of sensory functions after "extirpation of a total hemisphere." He explained the restitution of contralateral sensibility after this intervention by the fact "that the afferent fibers not

only ended in the crossed but also in the homolateral hemisphere" (13, p. 22). Yet, at present one finds hardly any reference to these experiment-like models of hemispherectomy in man, be it in clinical or in physiological textbooks.

I want to end the scientific part of this lecture with some personal contributions to the study of the sensory pathways after hemispherectomy. This operation was performed in the 1950s and 1960s as a therapeutic measure at a time when special cases of focal epilepsy did not respond to medication. However, it turned out to be an "experimentum crucis" for our interpretation of the sensory and motor pathways in man (45, 47). My discussions of the structures performing the compensatory motor functions have been published extensively. I shall refrain from any repetition. However, in this context I have to enlarge on sensory performances in order to prove the homolateral pathways (41).

I have examined 27 patients, both before and after operation, and I have been able to reexamine six of them after some eight years. Furthermore, I have carefully restudied our first patient after 25 years (47).

I will describe here the findings in those patients with the best performances after preservation (or restitution?) of sensory functions because there was a great variability in the degree of functional capacity which, however, depended on the primary pathological lesion before operation. Results of sensory examinations (in summary): Light stimuli by cotton wool or nylon threads were perceived at most distant periphery (finger tips, toes). Deep pressure was perceived with "after duration"; topical perception (deep pressure pain) was best perceived at index with an error of 0.5-1 cm only. All pain stimuli of sufficient strength and duration were well localized and perceived as pain with hyperpathia. When deep pain was applied (pressing achilles tendon), pain was very hyperpathic and with a delay of 1 s (due to conduction in C fibers). Warm and cold perception, graphesthesia, position sense, movement perception, and vibration sense at proximal joints was normal (8/8) but only distally slightly decreased. Two points discrimination was good; however, stereognosis was already absent before operation (because of after duration of sensory perception?). "Extinction phenomena" were normal, for instance, at leg, extinction never occurred. (For a detailed description of the data, see Zülch (45, 47).)

Pain perception was also present in two cases of simultaneous thalamectomy (see 41, 45, Fig. 6).

Plasticity, as in the cases of E. Schneider (31) and Hubel and Wiesel (24), could not have played a role because of the age of some patients.

Physiological tests have been performed on the sense organs at the periphery under the auspices of the Physiology Institute of the University of Cologne (Doctor Thesis, Boehm). Evoked potentials (see 47, Fig. 8) applied to the supply area of the median nerve of both sides were registered almost identically in the normal hemisphere.

In defining our concept of the sensory system, at this stage of the discussion we must accordingly conclude that in a given case the sensory modalities, including pain, can be perceived entirely on the basis of an ipsilateral conducting pathway. Basically, it is difficult for me to accept this concept of an ipsilateral system able to perform the same modalities of perception on both sides, and this at

only a slightly lower quantitative level on the ipsilateral side than on the contralateral side. This seems particularly hard to accept because both systems have to work simultaneously and yet at the same time separately for both sides (cf. the discrimination of two simultaneous and topographically identical stimuli in the "extinction" test).

It would be a very complicated system if the stimuli had to cross over on various levels between the two sides, back and forth, and thereafter ascend again. Furthermore, we must not forget that in two of our cases the thalamus was removed at operation.

In Summary

If we accept these findings in the hemispherectomized patients it seems to me that we have to discuss and think over the consequences for surgery of pain. Why did these systems not take up their auxiliary functions immediately after diaschisis had disappeared? The recurrences after anterolateral cordotomy, for instance, are most frequent only after 6-12 months.

I wanted to present these results in order to show that important problems of the neurological sciences will be found - and may be solved - today as in Otfrid Foerster's time. Progress here does not necessarily depend on sophisticated new apparatus.

Foerster's Significance for the Science of His Time

What was the significance of Otfrid Foerster for the neurological sciences in the century in which he lived? Three facets can be emphasized:
1. Scientific enrichment through singular neurological experiences
2. A new style of work
3. New conceptions concerning the organization of the nervous system

Foerster's Scientific Contributions

I shall now try to recapitulate Foerster's most important scientific contributions and to catalogue them. He actively investigated the structure and function of the pain system. We owe to him numerous operations for the modification of intractable pain. He described accurately the topographical and segmental configurations of the peripheral nervous system. He carefully determined which muscles depend on what nerve supply. He was only the second in medical history to remove a quadrigeminal tumor.

He introduced improvements in the techniques of surgery for spinal cord tumors and showed the importance of excision of the meningocerebral cicatrix in the treatment of posttraumatic seizures. A neurophysiologically oriented clinician, he developed our present ideas on basal ganglia and transverse spinal cord syndromes by means of basic analysis. He found that a latent convulsive tendency can be activated by hyperventilation. The term "psychomotor epilepsy" was coined by Foerster. The first direct corticography was carried out in his clinic. We owe to him our knowledge of the dermatome borders. He was the first to point out the importance of physical therapy in neurological illnesses. We owe to his work an accurate analysis of spinal cord, brain stem, and midbrain function and the most reliable "brain chart" (43, 44).

The "Breslau Style" of Research

In this lecture I shall also enlarge on the second point mentioned above; I have discussed the third in length in my monograph on Otfrid Foerster (43, 44).

A striking characteristic of his neurological work was his style. Foerster began to build up a type of neurological institute within whose confines problems were analyzed in greater detail through the collaboration of morphological and physiological teams, basic science workers, and clinicians. A separate department of neurochemistry was planned.

The starting point of any scientific project was always an observation at the beside. A provisional working hypothesis was then formed to be tested clinically during surgery or, if possible beforehand, during an experiment. The hypothesis was then tested neurophysiologically and finally came the morphological control of the organ itself. The result would then be applied at the bedside for diagnostic and therapeutic purposes.

This was the typical "Breslau style" of work in the second to fourth decades of this century. One thinks, of course, of Hughlings Jackson, the brilliant English neurologist whom Foerster adored. His work was firmly oriented philosophically but was practically outside the control of basic science; it represented a kind of anthropological neurophysiology. One thinks also of Sherrington, but his neurophysiology was based solely on animals and had to withstand the clinical tests. It was through Foerster's influence that neurophysiology became clinically oriented. His influence was most evident in the change of direction of American neurophysiology, particularly as seen in its chief representative, John F. Fulton, a frequent visitor of Foerster.

Foerster's Publications

Foerster was one of those happy scientists who were allowed to publish practically every thought they had in the neurological sciences. One may ask today whether Foerster's work reached full fruition. Only rudiments of a major work on brain tumors remained unpublished, but in retrospect one may say with critical judgment that with his particular approach he would not have been able to do further pioneer work of the quality that characterizes all his scientific publications. In the decade between 1927 and 1937 he had been able to preserve for posterity all his knowledge, experience, and achievements in his handbook contributions. As though possessed by a demon, he worked during these years to make use of the time which was left to him. He published around 1767 pages for the *Handbuch der Neurologie*, apart from the earlier 1151 pages for the *Ergänzungsband* of the first *Handbuch* and some 80 pages in *Bethe-Bergmann's Handbuch der Physiologie*. What unbelievable energy! What a memory! What a collection of data! What an amount of studies of the literature!

Foerster's Position in German Neurology

Foerster's leadership in German clinical neurology was secure by 1924. Foerster and Nonne were the intellectual leaders. Foerster, after Nonne's retirement, continued for 8 years until 1932 as the president of the Society of German Neurologists. In general surgery, on the other hand, he felt neglected although he had been a pioneer in special

forms of neurological surgery such a posterior rhizotomy, anterolateral cordotomy, operations on the peripheral nerves, the surgical elimination of meningocerebral scars, special forms of orthopedic operations for neurological problems, the first series of successful operations on spinal gliomas, and the successful resection of a quadrigeminal tumor (as mentioned earlier, only the second in world history, the first having been performed by Fedor Krause). Only his personal friend, the professor of surgery in Breslau, K.-H. Bauer, emphasized officially Foerster's significance ("Foerster is a great doctor, surgeon, neurophysiologist, neuroanatomist, neuropathologist and moreover: a great naturalist").

But we should not forget that in the last decades of his life honours were bestowed upon him more frequently. In 1922 on the recommendation of the German ambassador in Moscow, von Brockdorf-Rantzau, he was called to Lenin's bedside, where he remained with occasional interruptions for 2 years. On Foerster's suggestion Bumke, and later some other German neuropsychiatrists and the Swedish scientist Salomon Henschen, were asked for brief consultations. He himself considered it as a personal gain to have known this extraordinary man so thoroughly during his illness.

The close friendship between Foerster and Cushing was reflected in the scientific work of each, and during his sojourn in 1930 to Cushing's clinic he was named "Surgeon-in-Chief pro tempore", a great honour for him. In 1935, on the hundredth anniversary of Jackson's birthday, he was presented with a golden Jackson Memorial Medal, the highest honour to be accorded at that time to any neurological scientist.

The highlight of his life as a neurosurgeon was certainly the visit in 1937 of the British Association of Neurological Surgeons in Breslau. The society, coming from Tönnis in Berlin, listened to his extended presentation on the diagnosis of brain tumors, offered in fluent English without recourse to notes. He subsequently was accorded the highest honour of the society, a nomination as "member emeritus."

Foerster watched the development of German neurosurgery with sympathy. He contributed a foreword to the first neurosurgical journal, the *Zentralblatt für Neurochirurgie*, edited by Wilhelm Tönnis. For the first issue in 1936 he offered a paper entitled "Ependymoma."

At the time of my first sojourn to Breslau in 1935/36 a decline in his mental capacity was not yet noticeable. He still knew the histories of his more than 100 patients by heart, and Sunday ward rounds were customary, though he did not make remarks when on a fine day one did not show up but went to the "Riesengebirge."

Yet at this time he already seemed to be a lonely man who was highly esteemed but not always loved by his co-workers, and who received greater affection from the Anglo-Saxons than his own people. His name had become widely known and he had attracted young American neurologists and neurosurgeons to his clinic for a decade, just as in earlier years young men had made an effort to spend some time in the Sherrington laboratories. But in the late 1930s, after retirement, his bodily decline was remarkable and he suffered from stenosing vascular disease of the legs, probably a sequela of his permanent cigarette smoking (up to four packs a day). For a long time his asthenic but tough constitution struggled against disease but eventually he began to deteriorate. He died, back in Breslau after some time in a sanatorium in Switzerland, from tuberculosis, to which his life's companion also succumbed 2 days later.

He was not to survive to see the total destruction and dissolution of Germany and the loss of his "Heimat" Silesia. It would have affected him profoundly. The Otfrid Foerster Institute no longer exists for neurology. Foerster is a symbol of hard, tough, self-renouncing work. The clock stood still, his hands fell.

Patriae scientiae inserviendo ... These three words were engraved on the entrance of the Institute. His successor, Viktor von Weizsäcker, added a fourth: "*consumptus*" in his obituary. One now understands the addition of this last word: In his work for neurology and neurosurgery Foerster believed in serving his country. "The work of his hands was the consuming work of his spirit." A crown of Laurels belongs on his bier.

Once more I want to express the deepest thanks for the honour bestowed upon me, a person, I have to confess, whose conceptions of the neurosurgical sciences have been fundamentally fashioned by Otfrid Foerster.

Photograph of the original Foerster medal (43)

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Regulation of Cerebral Blood Flow and Metabolism

Local Blood Flow and Local Metabolism in the Brain

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Local blood flow and local metabolism can be quantified in the brain using methods which are based on the same principles in experimental animals and in man. Local blood flow can be measured using either inert gases or nonvolatile tracers. In experimental animals, autoradiographic methods have been established, since they present several advantages, e.g., they allow a high optical resolution and can be applied in awake animals. A good tracer is (^{14}C)iodoantipyrine, which was used for the quantitation of local cerebral blood flow in the present study. Whereas the principle of local blood flow measurements using autoradiographic methods has been well established for several decades (5), it took a long time to establish a comparable method for the measurement of the local cerebral metabolism. The idea of using a quantitative autoradiographic technique to measure local metabolic rates in the brain tissue was difficult to realize. The normal substrates of cerebral energy metabolism are oxygen and glucose. Both these substrates are so rapidly converted to CO_2 in the brain that a quantitative trapping of only one of them for autoradiographic purposes is impossible. Sokoloff has recently introduced a method which uses a labeled analogue of glucose, 2-deoxy-D-(^{14}C)glucose, ((^{14}C)DG) (8). (^{14}C)DG is metabolized through the main pathway of glucose metabolism. The product of phosphorylation, however, (^{14}C)DG-6-phosphate, is trapped in the tissue; this effect is mandatory for the application of the quantitative autoradiographic technique. In order to achieve a state in which the concentration of radioactivity in the tissue could be correlated to the rate of glucose utilization, Sokoloff has developed a model which is based on the biochemical properties of deoxyglucose and glucose (8). The model takes advantage of the fact that deoxyglucose and glucose are competitive substrates for both blood-brain transport and hexokinase catalyzed phosphorylation. The quantity of (^{14}C)DG-6-phosphate accumulated in the tissue at any time after introduction of (^{14}C)DG into the circulation is equal to the integral of the rate of (^{14}C)DG phosphorylation by hexokinase during that interval of time. This integral is related to the amount of glucose that has been phosphorylated over the same interval, and this relationship can be quantified and expressed as glucose utilization of the brain tissue.

The availability of methods which allow the quantitation of the local glucose utilization and the local blood flow in individual brain areas permits definition of the quantitative relationship between these parameters. Due to the wide variability of measured values of both local cerebral blood flow and local cerebral glucose utilization, it was of interest to investigate this relationship in normal and alert rats. In one experimental group of rats, local glucose utilization was measured in 39 areas of gray and white matter, and in the other group local

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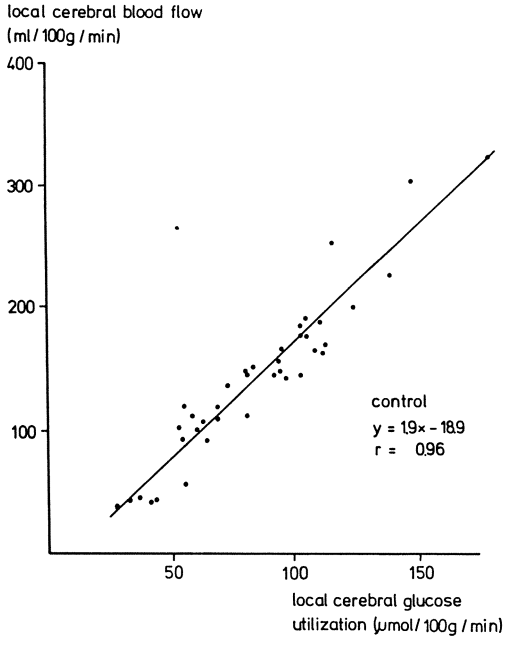

Fig. 1. Correlation between local cerebral glucose utilization and local cerebral blood flow in different brain structures of the normal awake rat

blood flow was determined for the same areas. The results are shown in Fig. 1. The excellent correlation between local cerebral glucose utilization and local cerebral blood flow is apparent. These data can be taken as evidence for a coupling between local metabolism and local blood flow in the brain, which takes place on a long-term basis. The data are in accordance with a study of the relationship between local metabolic rate for oxygen and local blood flow in the brain cortex of man (6). These authors found a correlation between the local metabolic rate of oxygen and local blood flow although the spatial resolution of their method was low. These data reveal a basic mechanism in the rat brain which apparently also exists in man. It can be investigated more thoroughly and with a higher spatial resolution in rats.

It would be of interest to compare the values found for local glucose utilization and local blood flow with the values determined for global metabolism and blood flow in many earlier studies. An additional measurement of global glucose utilization and blood flow became possible with the aid of computer-assisted densitometry (1). The films with the autoradiograms were scanned, and the optical densities of all sections were measured. These values were then converted to either blood flows or glucose utilizations. The average of all these values allows one to compare the results of the autoradiographic studies with the results of studies in which global methods were employed, whereas taking just the average of the 39 measurements could give a different value, since it would only average the values of some selected structures. The averages in this study, obtained by scanning the whole films, were 68.6 µmol/100 g/min for glucose utilization and 106.7 ml/100 g/min for blood flow. These values are within a range to be expected for the awake rat brain from other, global methods (7). The question then arose as to whether this close relationship between local glucose utilization and local blood flow, as shown in Fig. 1, is fixed or variable when the experimental conditions are altered.

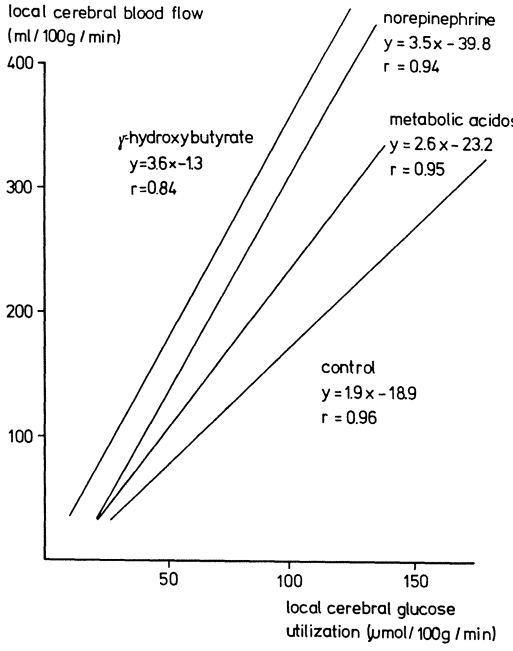

Fig. 2. Correlation between local cerebral glucose utilization and local cerebral blood flow in different brain structures of awake rats under various experimental conditions

Three experimental models were chosen: (a) metabolic acidosis (3), (b) norepinephrine infusion (2), and (c) action of γ-hydroxybutyrate (4). The results of these studies are summarized in Fig. 2. It is evident that the changes induced in these different types of experiments only slightly affected the correlation between local glucose utilization and local blood flow; this is indicated by the nearly unchanged correlation coefficients. On the other hand, there was a difference between the experimental groups: although there was excellent coupling in every condition investigated, the amount of change in blood flow per amount of change in glucose utilization was altered during each condition, when compared to the control condition; this is indicated by the different slopes of the regression lines. All three slopes were significantly ($P< 0.01$) different from the control slope.

The question arose about the cause of the heterogeneity of local blood flow in the brain. We have investigated the question of whether the heterogeneity could be caused by a varying density of perfused capillaries in the brain. The density of perfused capillaries was determined by counting the perfused capillary sections per mm^2 in cryostat sections using fluorescence microscopy according to a method recently developed for the heart (9). Significant differences in the density of perfused capillaries were found between the various brain structures. The densities varied by a factor of 5, with the lowest values found in the corpus callosum and the highest in the inferior colliculus. These local differences in capillary density showed a close correlation to the values of local blood flow (r=0.93) as determined for the same brain structures using the (^{14}C)iodoantipyrine autoradiographic method. Similarly, the values of local capillary density were also closely correlated with the values of local glucose utilization (r=0.97). These data show a close association between the local density of perfused capillaries, the local blood flow, and the local glucose utilization in the brain.

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Determination of Regional Glucose Metabolism in the Brain by Positron Emission Tomography Using ^{18}F-Fluoro-2-deoxy-D-glucose

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Since the energy requirement of the brain is supplied almost exclusively by glucose, the functional state of the tissue can be estimated and quantitatively demonstrated by reference to the glucose metabolism. The investigative method most widely used employs ^{18}F-fluoro-2-deoxy-D-glucose (^{18}FDG) for quantitative imaging of the glucose metabolism by means of PET (16).

Determination of the Regional Cerebral Metabolic Rate for Glucose (rCMRGl)

Glucose metabolism study with ^{18}FDG represents a direct application of the ^{14}C-deoxyglucose autoradiographic model of Sokoloff et al. (17). The model developed by Sokoloff can be applied directly since the fluorodeoxyglucose labeled at point 2 behaves in the same way as deoxyglucose. It is transported into the cell like glucose and, with the aid of hexokinase, is phosphorylated to ^{18}F-deoxyglucose-6-phosphate. Deoxyglucose-6-phosphate, however, cannot be further converted to fructose-6-phosphate and degraded to CO_2 and H_2O, but rather accumulates in the cell. The back reaction (phosphatase) to deoxyglucose occurs with much slower kinetics and the deoxyglucose-6-phosphate can penetrate through the cell membrane only in small amounts. The kinetics of the accumulation of deoxyglucose-6-phosphate can be described with the transport and enzyme constants of a three-compartment model. The corresponding complex formula (16) for calculating the regional cerebral metabolic rate of glucose (rCMRGl) can be presented in the following simplified form (14):

$$rCMRGl = \frac{(Gl) \times C(^{18}F) - C(FDG)}{LC \qquad A_b}$$

Here $C(^{18}F)$ corresponds to the total fluorine activity measured in the tissue, which is determined directly in the PET. C(FDG) corresponds to the concentration of free FDG in the tissue, calculated from the plasma concentration up to time point T with the aid of the constants of the model. The difference between these two values states the local tissue concentration of FDG-6-phosphate. A_b represents the total quantity of FDG which was released into the tissue and is calculated from the plasma FDG concentration curve up to time point T, decreased by the delay in the tissue equilibration using the corresponding model constants. The quotient therefore represents the proportional phosphorylation rate of FDG. Multiplication with the plasma concentration of glucose (Gl) would yield the rate of glucose phosphorylation if it were to behave like FDG. Since the arterial-venous extraction of glu-

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cose is not identical to that of FDG, the value must be corrected with an experimentally determined constant (LC= lumped constant). For the measurement of the regional glucose consumption in the brain, therefore, after intravenous administration of 3-6 mCi ^{18}FDG one must determine the plasma curve of ^{18}FDG from the time of injection to the measurement time point (usually determined in arterialized venous blood), the glucose value in plasma, and the regional ^{18}F activity in the brain.

Metabolic Studies in Healthy Volunteers

In healthy volunteers, a mean glucose consumption of 29-32 µmol/100 g/min was found by means of FDG and PET (8, 9, 12, 16). Under controlled conditions (darkened laboratory and steady noise from fans of equipment cooling systems) the functional anatomy of the brain is reflected in the metabolic activity of the axial section. The metabolic rates can then be compared directly by matching the gray value (or the color) with the reference scale. The highest values are found in the visual cortex (45-50 µmol/100 g/min) and in the striatum (42-46 µmol/100 g/min). Values in other areas of the cerebral cortex and in the basal ganglia (35-42 µmol/100 g/min) and in the gray structures of the posterior cranial fossa (25-30 µmol/100 g/min) are lower. The lowest lCMRGl are found in the white substance (15-22 µmol/100 g/min).

Functional Activation

Because of the coupling of the metabolism to the function, functional activation by specific stimuli or tasks leads to a regional increase in the glucose metabolism in corresponding cerebral structures. Investigations with different stimulus modes and while performing different partial functions have demonstrated a direct relationship between metabolic activation and intensity and the complexity of the stimuli or tasks (15). Planning and execution of motoric performances, e.g., movement of fingers and hand, also cause increases of metabolism in the respective brain regions (11). In four right-handed and four left-handed healthy volunteers, spontaneous speech induced metabolic activation more in the left (14% increase) than in the right hemisphere (12% increase), independent of the handedness. The increases in various brain regions, however, were significantly different: the most pronounced responses were found in the left (44%) and right (32%) sensomotoric cortex, in the right cerebellar hemisphere (27%), in both thalami (23%), in the left Wernicke region (20%), and in Broca's region (19%), while changes in the pons, the parieto-occipital cortex, and the hippocampus were insignificant (2%-8%) (PAWLIK et al., in preparation).

Sleep and Dream

The decrease in cerebral activity during sleep combined with the blockage of sensory impressions from outside leads to a reduction in CMRGl compared to the waking state in all cortical and basal gray structures. No specific increase in one cerebral structure (sleep center?) was observed. In the dreaming state, an increase in CMRGl occurred which was particularly clear in the visual cortex and in parts of the temporal and frontal lobes (5).

Convulsive Disorders

Convulsive disorders are functional disturbances of the brain activity and as such lead to particularly marked changes in brain metabolism (and through coupling also in cerebral blood flow). Frequently, however, no morphologic changes can be detected. The metabolic changes discovered by means of PET can frequently complement the electrophysiologic findings and can contribute to the clarification of foci: in the epileptogenic foci, the metabolism is increased during an attack due to the increased activity, and the spread of the convulsive activity to other brain structures is manifested as an increase in metabolism; in the attack-free interval, the foci are frequently recognizable as hypometabolic areas. PET investigations in convulsive patients can therefore also contribute to therapeutic decisions (indication for surgical removal of an epileptogenic focus)(4, 10). That PET can reveal foci in CT and MRI negative cases was demonstrated in a study on ten patients with complex partial seizures, reported elsewhere in this volume (2).

Acute Cerebrovascular Disease

The most frequent cerebral insults, the ischemic strokes, are caused by focal disturbances in blood flow, the localization, degree of severity, and duration of the regional blood flow deficiency governing the severity of the clinical symptoms - reversible functional deficits or irreversible disturbances of tissue structures. The regional disturbance of blood flow is the cause of the ischemic insult, and the regional metabolic disturbance thereby triggered can exceed the blood flow disturbance in extent and duration and thus exerts a direct influence on the nature of the neurologic syndrome, the severity of the psycho-organic syndrome which exceeds the localizable symptoms, the clinical course, and the restorability of the deficits. Metabolism and blood flow are frequently uncoupled in the ischemic tissue in the first phase after the insult (1, 9, 18). It became apparent particularly in the FDG studies that areas of disturbed metabolism are always greater than the morphologically detectable lesions (CT and MRI). In regions which were definable as infarction on CT scans, the lowest rCMRGl were found. In addition, however, morphologically intact brain structures - homolateral cortical and subcortical areas outside the infarction, contralateral cerebellar hemisphere - also show reduced glucose metabolism. This reduction in the glucose metabolism in areas not primarily affected by the blood flow disturbance is caused by functional deactivation after interruption of the connecting fiber systems. This explains impairments of the brain performance which exceed the local syndrome caused by the infarction, characterize the organic psychosyndrome, and influence the rehabilitative capacity of patients after stroke (7, 9, 13).

In addition to complementing CT and MRI in the way described above, PET permits the demonstration of pathophysiologic mechanisms and potential functional capabilities (6): in 4 of 11 patients with acute infarcts, areas with higher FDG uptake than that of surrounding or contralateral nonischemic tissue were found; in two those areas were within hyperperfused regions, but the two phenomena did not overlap. Thus PET demonstrated uncoupling of flow and metabolism in early stroke, and additionally yielded evidence of increased anaerobic glycolysis in areas with incomplete ischemia. PET studies also permit the examination of functional activation after physiologic stimulation: in patients with ischemic lesions within the territory of the middle cerebral artery of the dominant hemisphere at least partial preservation of the function of the speech centers could be demonstrated during

metabolic activation of the areas in question by spontaneous automatic speech.

Tumors

In cerebral tumors, CMRGl is changed as a function of the malignancy (3): in grade I-II astrocytomas the mean metabolic rate for glucose was 3.8 ± 1.8 mg/100 g/min, in grade III astrocytomas 5.4 ± 2.7 mg/100 g/min, and in grade IV astrocytomas and glioblastomas 7.3 ± 3.6 mg/100 g/min.

Particularly in the more malignant tumors, especially glioblastomas, the metabolism in the tumor itself varies greatly: especially active tumor areas show high glucose uptake, while in necrosis or cysts the metabolism is distinctly reduced. As a restriction in the quantitative assessment of the regionally measured results, the disturbance of the blood-brain barrier in tumors, which may lead to a change in the "lumped constant" and the transport constants, must be taken into account.

Conclusion

These few examples of the application of PET to studies of local cerebral metabolism only give a vague idea of the vast potential of the method. Basically, a large number of organic compounds can be labeled with positron emitters, e.g., ^{11}C, ^{13}N, and ^{18}F, to allow quantitative imaging of such processes as the metabolism of various substrates, protein synthesis, function and distribution of receptors, pH, tumor growth, and the distribution of drugs. With ^{15}O, produced directly in a cyclotron, local oxygen utilization can be measured. With simple compounds containing either ^{15}O or other radionuclides (^{11}C, ^{18}F), regional blood flow and blood volume can be determined quantitatively and three-dimensionally. All these applications of PET as a complex but noninvasive method provide insights into the functional anatomy, physiology, and pathology of the human brain unmatched by any other currently known technology.

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Relationships Between Cerebral Perfusion and Electrical Activity in Man

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Introduction

Flow thresholds for synaptic transmission have been demonstrated in basic studies in baboons (3, 4). In man, we have also found a threshold relationship between (a) prolongation of the central conduction time (CCT), defined as the time interval between the arrival of the impulse at the C_2 level and at the somatosensory cortex, and (b) the hemispheric CBF measured by a simple two-channel system (6): at a flow value below 30 ml/100 g/min, CCT was significantly prolonged in proportion to the reduction in CBF.

A region of "ischemic penumbra" exists in acute circumstances of ischemia (7, 8), and basic studies in baboons indicate that the penumbra is viable but electrically silent at flow levels between 10 and 16 ml/100 g/min (1) and will recover its electrical activity if adequate flow is reestablished promptly (within 30 min in the baboon: 2).

Central conduction has been used as a guideline to the safety of induced acute ischemia in mainly perioperative monitoring of evoked responses in over 100 operations for intracranial aneurysm, including 40 cases in which temporary clips were applied to major arteries of the circle of Willis. Assessment of the safety of temporary vascular occlusion has been by electrophysiological monitoring. Data from the 40 cases of temporal vascular occlusion are presented here.

Clinical Material and Method

Somatosensory evoked responses were recorded perioperatively in 40 patients with 44 aneurysms. In 20 of these patients the operations were performed between 1 day and 3 weeks following a subarachnoid hemorrhage (SAH); in 12 patients the operations were performed several months after an SAH; and in 8 patients the operations were for non-ruptured aneurysms (including giant aneurysms). Preoperative clinical grading according to the Hunt and Hess scale (5) was carried out by one of us (LS).

Somatosensory evoked responses were generated by stimulation of the median nerve at the wrist by square waves of 0.15 ms duration delivered at a rate of 3 Hz to two silver cup electrodes placed with the cathode 3 cm proximal to the anode, and at a stimulation intensity 3 times subjective threshold at preoperative recording and sufficient to elicit a small thumb twitch. Recording electrodes were at C_2 and at the $C_3/_4$ position on the scalp according to the international 10-20 system. Frontal reference (Fpz) was used (9).

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Effects of Internal Carotid Artery Occlusion

Of 16 patients, 12 (75%) showed significant changes in CCT following internal carotid artery (ICA) occlusion. There was no significant relationship between the period of ICA occlusion and the recovery time of CCT, correlating with the discrepancy between time of occlusion and neurological outcome in these cases. Temporary occlusion for up to 12 min was sustained without permanent neurological deficits except in one grade 4 patient. It seems likely that the ICA can be occluded up to 10 min even if the cortical response becomes flat, provided its disappearance takes more than 2 min following occlusion.

Effects of Middle Cerebral Artery Occlusion

Of 13 patients, 7 showed no significant changes in CCT following middle cerebral artery (MCA) occlusion for up to 12 min and 45 s, and in the present series no postoperative morbidity has been seen in any patient without CCT abnormality. It is thus likely that the MCA may be occluded for at least 10 min without neurological deficit if no significant change in CCT is observed after the application of a temporary clip.

Of the 13 patients, 6 showed significant abnormality in CCT within 4 min following temporary occlusion, and where the N_2O potential disappeared the time course of the decline of the N_2O was similar to that following acute MCA occlusion in baboons (2). Three of these patients showed postoperative morbidity, which was completely reversible in two cases.

Experimental study in baboons indicates that 15 min of MCA occlusion can be followed by prompt and almost complete recovery of the somatosensory evoked response (2). The longest time of MCA occlusion without neurological deficit in this series was 15 min and 50 s, but in a further case not in the present study, MCA occlusion for 45 min was tolerated without postoperative deficit.

Relationship Between Changes in CCT and Neurological Outcome

No postoperative morbidity has been seen unless a significant abnormality in CCT followed occlusion of major vessels - the ICA and MCA. Permanent neurological deficit occurred only after abolition of the cortical response. These results indicate a significant correlation between perioperative abnormality in CCT and neurological outcome, and we have demonstrated the functional recovery of cortical tissue which is electrically silent but viable in the acute circumstances of ischemia (1, 2). Complete abolition of the cortical response for up to 45 min could occur without permanent neurological deficit, indicating the reversibility of functional suppression of the cortical tissue lying in the ischemic penumbra. When the cortical response is sustained for over 3-4 min following vascular occlusion, even if it then disappears, permanent irreversible neurological deficit is unlikely. If the cortical response does disappear within 4 min, the clinical outcome can still be expected to be good if the N_2O peak recovers within 20 min after recirculation.

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Oxygen Metabolism and Microcirculation of the Brain in Various Conditions: Experimental Investigations

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Introduction

The regulation of cerebral blood flow (CBF) is mainly attributed to myogenic mechanisms and metabolic influences. The myogenic reaction to intraluminal pressure is considered to provide cerebral autoregulation (8), whereas pCO_2 tension and tissue lactate level are assumed to regulate regional cerebral blood flow (rCBF) according to metabolic requirements (7, 10). The means by which regulation of local cerebral microcirculation (lCBF) occurs, however, remains unknown (10).

After brain lesion, it is generally held that vasogenic edema reduces the CBF and impairs cerebral oxygen supply, and the main objectives of treatment are therefore to increase CBF and oxygenation. However, brain damage is associated with many biochemical derangements, including release of neurotransmitters and local mediators and disturbances of the ion homeostasis in the tissue. Disturbances of cerebral metabolism and vasomotor control after brain damage which are not yet clarified thus acquire significance for therapy and prognosis.

We therefore investigated the relation between local oxygen metabolism and microflow in normal brain cortex, following vasogenic edema, and following calcium antagonistic treatment.

Material and Methods

Measurement of Oxygen Metabolism and lCBF

Local cortical tension (tpO_2), local metabolic rate of oxygen ($lCMRO_2$), and lCBF were measured with a polarographic multiwire surface electrode. In contrast to preliminary experiments (13), tpO_2 was measured with Au electrodes, each 15 µm thick, which give a more stable polarographic plateau than Pt wires (5). In addition, four 100-µm Pt electrodes were encased in the same glass electrode for measuring tissue hydrogen tension (pH_2); these Pt wires were palladinated before each investigation (6). These signal electrodes were surrounded by an Ag/AgCl reference electrode divided into two separate semicircular parts. Using different polarization voltages this integrated electrode allowed a simultaneous record of oxygen and hydrogen tension: the tpO_2 was measured in the stable plateau at -750 mV and remained unaffected by the simultaneous pH_2 record at +100 mV.

The electrode was prepared with Teflon membrane as described in (13) and counterbalanced during recording to avoid any pressure on the cortex.

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tpO_2 was measured continuously; lCBF was measured by H_2 clearance at intervals. At the end of each experiment, $lCMRO_2$ was approximated by the decrease in tpO_2 following sudden and complete CBF arrest. The CBF interruption was achieved by inflating a cervical cuff balloon up to 400 mmHg, after which the EEG proved to be isoelectric within 4-6 s.

Animals, Anesthesia, Injury, Treatment

We used male SPD rats weighing 250-340 g randomized into groups of at least eight animals:

The "normal animals" (control group) were anesthetized with 65 mg/kg sodium pentobarbital or 320 mg/kg ketamine hydrochloride and trepanned between the coronal, sagittal, and lambdoid sutures (breathing spontaneously). pO_2, lCBF and $lCMRO_2$ were measured on the right cortex.

The injured animals were further randomized into three groups. In anesthesia with sodium pentobarbital a standardized cold brain injury was produced as described previously (4). Either 24, 48, or 72 h after trauma, these animals were trephined and oxygen metabolism and lCBF were measured in the perifocal edematous area outside the necrosis as well as over the opposite, "collateral" hemisphere.

The treatment group was trepanned 24 h after injury, and during recording of pO_2 and lCBF, nimodipine (Nimotop) was infused at 20 µg/kg/min via the tail vein.

In all animals, blood gases, systemic arterial pressure (femoral artery), and body temperature were measured in addition.

Evaluation

All measurements were evaluated on-line with computer (Intertechnique IN 110, 16 channel A/D converter):

tpO_2 was plotted as a histogram (Figs. 1-4), and histogram statistics (arithmetic mean, median, mode, skewness, curtosis) calculated.

The lCBF measurement started with the rats breathing a mixture of 8% H_2, 20% O_2, and 72% N_2; after saturation of the tissue with H_2 (stable plateau) the gas mixture was changed to air. The H_2 clearance curve was approximated by the regression function:

$$tpH_2(t) = A \cdot e^{-b \cdot t} \qquad (1)$$

With t in min, b directly equals lCBF in ml/100 g/min (12).

The time constant of the electrode is too high for direct measurement of $lCMRO_2$ from pO_2 clearance after circulatory arrest. The clearance curve was therefore corrected by the computer according to:

$$O = dpO_{2meas} \cdot (a \cdot / AdpO_{2real} /^{-b} / 1) - dpO_{2real} \qquad (2)$$

This formula was derived from step response of the electrode after DIRAC impulse (2, 12).

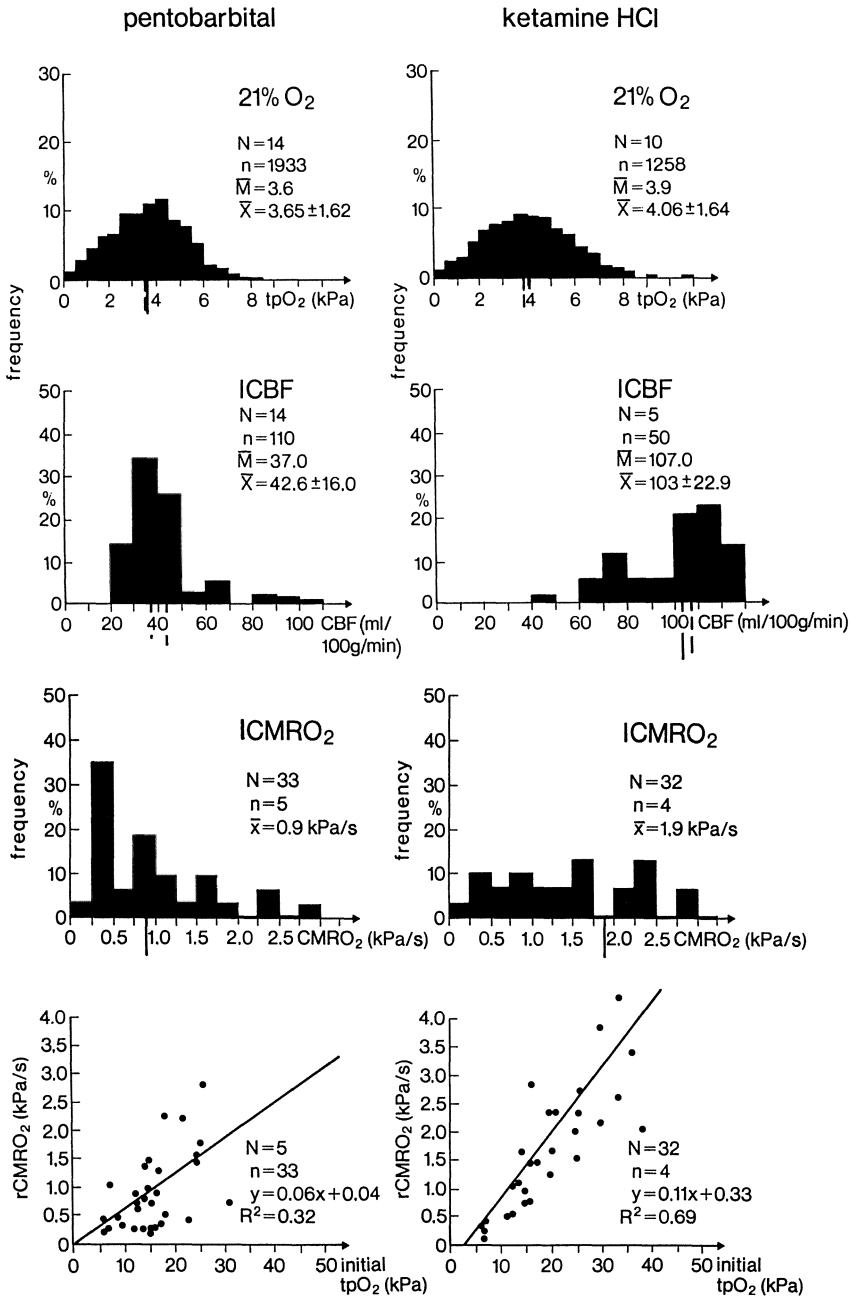

Fig. 1. Oxygen metabolism and lCBF with sodium pentobarbital and ketamine hydrochloride: tpO_2 almost identical, normal histogram; but lCBF and $lCMRO_2$ were twofold higher with ketamine

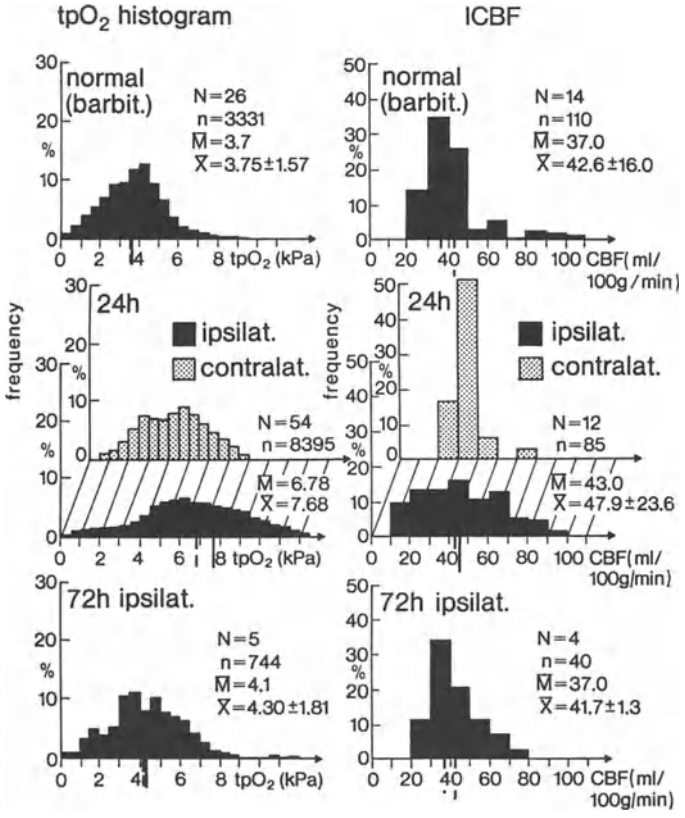

Fig. 2. Oxygen tension and lCBF in vasogenic edema. Twenty-four hours after trauma a broad and flat tpO_2 histogram is seen; recovery after 72 h (*left*). lCBF histogram also broadened after 24 h and recovering after 72 h (*right*). Absolute values of tpO_2 and lCBF not reduced!

For statistical comparison, data were evaluated with the Kolmogoroff-Smirnoff test (unpaired values) or Student's *t*-test (paired values).

Results

Normal Brain

In normal healthy animals the pO_2 histogram, which demonstrates the oxygen tension in tissue, was almost identical with both narcotics. This regularly shaped, "Gaussian" histogram corresponds to the typical normal tpO_2 distribution with an intact autoregulation described by KESSLER, LÜBBERS et al. (5, 6, 9). This same "healthy" tpO_2, however, was reached with different lCBF in barbiturate and ketamine anesthesia (Fig. 1). To gain the same tpO_2, much higher blood flow was needed during ketamine anesthesia (about double the flow) than during barbiturate anesthesia. The main reason for this higher lCBF requirement for sufficient oxygen supply in ketamine anesthesia is the increased oxygen metabolism (Fig. 1): the $lCMRO_2$ is twice as high as under pentobarbital!

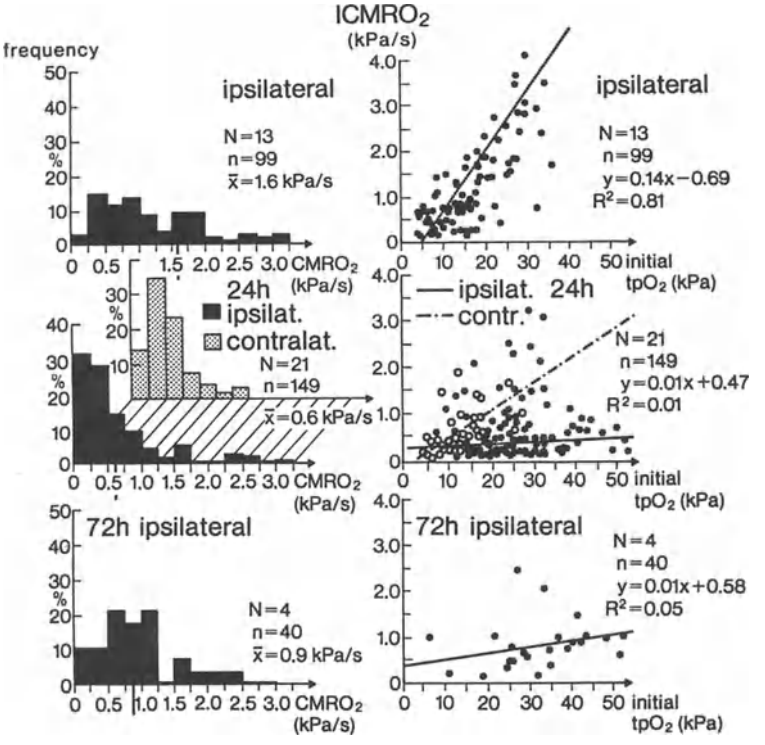

Fig. 3. Oxygen consumption in vasogenic edema. $lCMRO_2$ considerably reduced (shifted to left) 24 h after trauma; improvement after 72 h (*left*). Correlation between tpO_2 and $lCMRO_2$ after 24 h compared to opposite hemisphere (*broken line*); recovery at 72 h (*right*)

With both narcotics, however, the lCBF was adjusted to the oxygen requirement, as can be seen in the correlation analysis between tpO_2 and $lCMRO_2$ (Fig. 1): the cerebral regions with the highest $lCMRO_2$ also have the highest initial tpO_2.

Vasogenic Edema

When measuring tpO_2 in the perifocal edematous area, the pO_2 was not decreased as expected but instead was higher than in the healthy or in the less affected, almost normal contralateral hemisphere. This tpO_2 in edema has a clearly abnormal distribution (Fig. 2): the histogram is broad and flat, sometimes double-peaked, with large differences between arithmetic mean and median. This can be interpreted as a disturbed lCBF regulation which corresponds to local flow values (Fig. 2): the lCBF histogram is also broadened and flattened, but comparing it to normal brains or to the contralateral hemisphere we find an lCBF increase in arithmetic mean and median. The $lCMRO_2$ was clearly decreased in the edematous cerebral areas as compared to the contralateral side or to the normal animal (Fig. 3). Especially spectacular is a comparison between oxygen tissue tension and oxygen requirement: While on the unaffected contralateral hemisphere we find areas with high demand to have high supply of O_2 at a reduced level ("diachisis"),

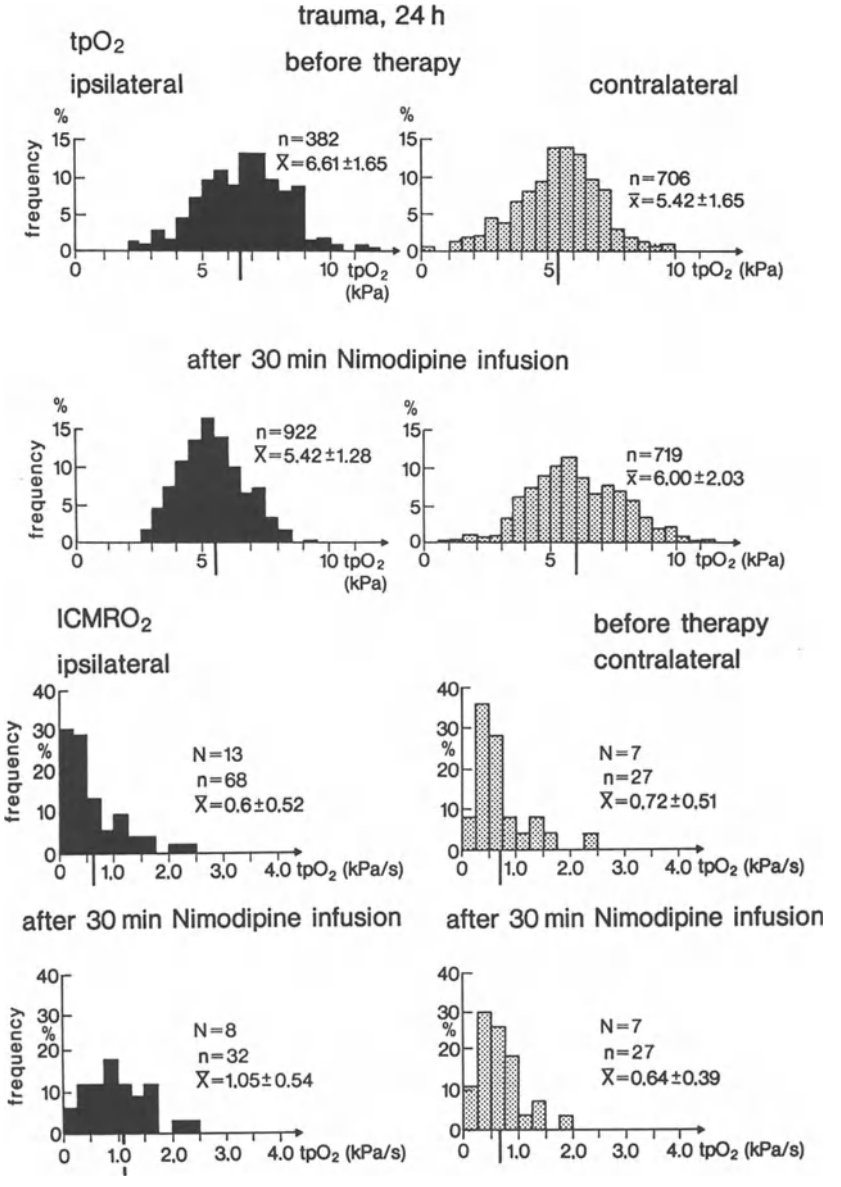

Fig. 4. Effect of nimodipine on oxygen metabolism in edema: tpO_2 normalizes; $lCMRO_2$ increases twofold in traumatized hemisphere during nimodipine infusion 24 h after trauma

the affected hemisphere seems totally deregulated and there is no correlation between tpO_2 and $lCMRO_2$.

This disturbance is potentially reversible, as shown by the comparison of the edema 24 h and 72 h after the trauma (Figs. 2, 3): 72 h after injury the O_2 histogram was nearly back to normal. The lCBF had decreased again and showed a regular, obviously regulated appearance.

The oxygen demand 72 h after trauma had definitely increased again and although it was still slightly decreased in absolute terms, there again appeared to be a correlation between oxygen supply and demand. We interpret this as a regained control over the microflow regulation.

Nimodipine Treatment

A disturbance of oxygen metabolism due to calcium influx into the cell has been discussed (1). This could explain the clear improvement of oxygen metabolism and microcirculation (Fig. 4) following the infusion of the calcium entry blocker nimodipine: the tpO_2 histogram normalized, the absolute pO_2 values decreased, and the $lCMRO_2$ increased significantly.

Discussion

According to our results, the lCBF is regulated to accommodate the regions with the highest oxygen demand with the most oxygen supply in the healthy brain cortex. This local regulation of microflow distribution should not be confounded with "autoregulation"; there is no relationship to blood pressure, to ICP, or to cerebral perfusion pressure. One could assume that the local microflow is controlled by the CO_2 tension. CO_2 in brain tissue, however, usually modifies the CBF in larger areas due to the more rapid diffusion (10). In other organs, data from KESSLER and HÖPER (5) suggest a regulation of the microflow by oxygen demand via "signal oxidases": if the oxygen consumption increases in an area, the signal is transmitted via a "cellular signal chain", from cell to cell, and the blood supply to this area is adjusted accordingly. A coherence with the aerobic metabolism in the mitochondria is suggested (5). In the brain, too, such a local flow regulation at the cellular level may exist (glial cells?).

In vasogenic edema following cold brain injury, we see an increase in tpO_2 with a pathologically broadened histogram. At the same time the lCBF shows a distinct increase and, also, an irregular distribution. Although there is a high CBF and a sufficient tpO_2, the $CMRO_2$ is considerably decreased and the normal correlation between areas with high oxygen demand receiving high supply is lost. We conclude that as long as the ICP dose not compensate, the edematous brain does not suffer from reduced CBF or insufficient oxygen supply, at least not in our cold brain injury model. On the contrary, we find a primary disturbance of oxygen metabolism: the sufficiently supplied oxygen cannot be consumed in aerobic glucose metabolism. Here our results agree with data from PAPPIUS and WOLFE (11), who have shown an increased anaerobic glycolysis in a similar cold brain injury model. In this vasogenic edema, there is a primary disturbance in oxygen and glucose metabolism together with a loss of microflow regulation.

Therapy for this metabolic disturbance should not concentrate on an indiscriminate increase in CBF and O_2 supply of the brain. Instead the secondary brain damage should be prevented on a biochemical level of disturbed oxygen and glucose metabolism. A possible approach in this direction could be the use of calcium antagonists, as suggested by the rapid improvement of oxygen consumption and tpO_2 after nimodipine infusion.

Conclusions

In normal brain cortex, microflow and oxygen supply are closely regulated by the local oxygen demand. Oxygen metabolism and local microflow regulation are primarily disturbed in vasogenic edema after cold injury; CBF and tpO_2 are not reduced in absolute terms. The metabolic disturbance is potentially reversible; calcium antagonists are promising drugs in treating and/or preventing this disturbance in O_2 consumption and lCBF control in vasogenic edema.

Acknowledgment. This work was supported by grants from the Deutsche Forschungsgemeinschaft (Ga 273/2).

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Prostaglandin and Thromboxane Production in Postischemic Gerbil Brain

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Introduction

The search for the pathophysiologically most significant factor in the course of cerebral ischemia has not yet come up with a conclusive answer. However, evidence is increasing that a multitude of parameters contribute to the maturation of the infarct. Recent studies suggest an involvement of prostaglandins (PGs) in the disease process (3). Some PGs, on the other hand, might also be protective by improving the microcirculation, or by modulation of excitatory transmitter action. In a first attempt to characterize the role of eicosanoids in cerebral ischemia, Gaudet and Levine found increased tissue concentrations of PGD_2, PGE_2, PGF_{2a}, TXB_2, and 6-keto-$PGF_{1\alpha}$ during the early recirculation phase in Mongolian gerbils (3). Although these initial observations have been confirmed by others, their pioneering work created many new questions. It is unclear whether there is only an increase of tissue PGs, reflecting the fact that arachidonic acid is released in ischemia, or whether there are also changes in the metabolic pathways favoring the synthesis of other eicosanoid classes than occurs under normal conditions. Other questions concern the sites of PG production, the influence of a functioning microcirculation on PG removal, etc. To investigate some of these questions, the capacity of discrete brain regions to produce PGs was studied by a new ex vivo technique (8). This method utilizes brain slices incubated "ex vivo" under standardized conditions, allowing measurement of PG production over a given period.

The results of this study indicate that differential changes in eicosanoid production - site, time and PG specific - are developing after ischemia and recirculation.

Methods

The experiments were performed on 150 Mongolian gerbils (12 weeks old, 50-70 g body weight, Tumblebrook Farms, NY) under halothane anesthesia (2% in oxygen). Body temperature was controlled at 37°C. After microsurgical exposure of both carotids, a defined tension (15 g) was applied to ligatures around the vessels, thereby occluding them simultaneously. Ischemia was maintained for 15 min, and the animals were killed after varying times of recirculation or recovery from sham operation (0 min, 5 min, 30 min, 4 h, 24 h). Brains were removed on ice for the preparation of brain slices. Small samples of brain tissue (1-2 mm^3) from cortex, hippocampus, and striatum were isolated and incubated in vitro as previously described (8). After washing, the slices were incubated for 1 h in 1 ml of oxygenated (95% O_2, 5% CO_2)

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Krebs-Ringer solution (pH 7.4, 37°C, 0.1% glucose). Supernatants were collected for PG analysis. Tissue protein was measured according to LOWRY (6). PGD_2, PGE_2, and TXB_2 in the incubation media were measured by RIA as previously described (8). Antibodies were obtained from New England Nuclear (Boston, Ma) and from L. LEVINE, Brandeis University, Ma. Unlabeled prostaglandins used as standards were purchased from Sigma Chemical Co. (St. Louis, Mo).

Results

Tissue from cortex, hippocampus, striatum, and hypothalamus released significant amounts of eicosanoids. Between 2 and 5 times more PGs were released into the incubation medium than have been found in the tissue by extraction (data not shown), demonstrating the PG synthesizing capacity of brain tissue in vitro. PGD_2 was predominantly produced and exceeded the other prostaglandins by nearly two orders of magnitude. The most pronounced changes were found for PGD_2 and PGE_2, with increases up to 300%. Data for these two PGs are shown in Fig. 1. In general, changes were region specific. There was a tendency toward increasing PGE_2 production in cortex, hippocampus, and striatum during the first 4 h of recirculation. In hippocampus and striatum this tendency reached the level of significance in the ANOVA ($P<0.025$ and $P<0.001$). PGE_2 production decreased in all brain regions studied after 24 h. In contrast to PGE_2 all other PGs were produced at the highest rates immediately after reperfusion. With increases of nearly 300%, changes in PGD_2 were most dramatic in cortex (Fig. 1). In striatum, PGD_2 rose significantly after 5 min. PGD_2 production was reduced in all areas to less than 50% of the control level after 4 h. Such low levels of PGD_2 were still seen after 24 h. TXB_2 (not shown) increased by far less than PGD_2. Nevertheless, changes were significant in cortex and striatum, with maximal increases after 5 min of reperfusion in all groups. Later on TXB_2 decreased, and it reached a minimum (37% of controls in the striatum, $P<0.001$) at 4 h.

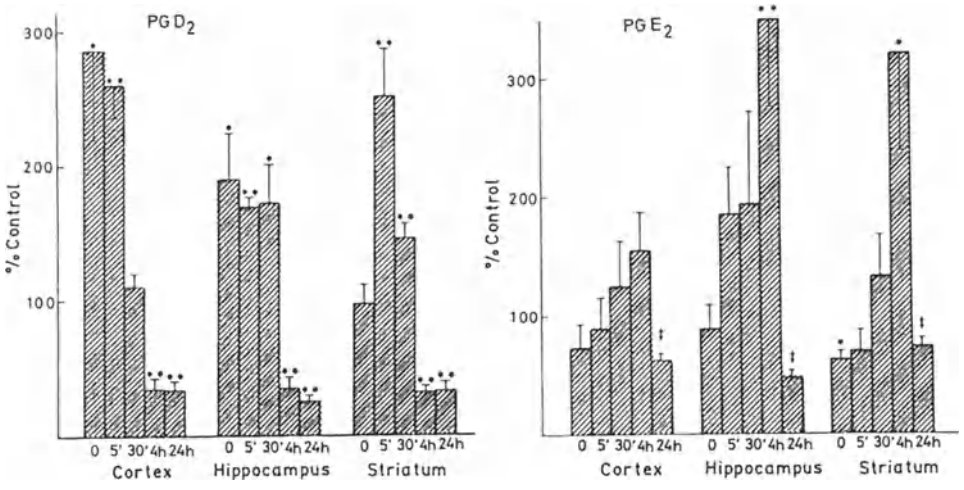

Fig. 1. Ex vivo production of PGD_2 and PGE_2 after varying times of reperfusion after cerebral ischemia. Data are expressed in percent of prostaglandin concentrations found in supernatants from brain slices isolated from sham-operated controls (±SEM). *$P<0.05$, **$P<0.001$ vs controls; ±$P<0.01$ vs 4 h values

Discussion

The ex vivo method used in this study has been introduced recently as an approach to study the turnover of arachidonate to PGs in cerebral tissues. Very small tissue samples can be studied, allowing comparison of discrete brain regions. The influence of blood elements is reduced since samples are free of big vessels and are washed prior to the experiment. The linear increase of PGs in the medium (not shown) reflects PG synthesis and not just a washout of PGs already present in the tissue at the time of explantation (8).

An unbiased analysis of the significance of eicosanoids in cerebral ischemia and recirculation is hampered by the complexity of the prostaglandin cascade. PGs can act on all cell types present in the brain. The blood-brain barrier might be affected as well as brain microcirculation and neuronal function. The crucial, up to now neglected question concerning the role of PGs in cerebral ischemia is whether they are mediators of pathologic damage (BBB breakdown, platelet aggregation, disturbed neural function), or whether their release signals normal function or even a protective effect (e.g., on microcirculation, modulation of neurotransmitter action). PGD_2 has been proposed as a modulator of excitatory and inhibitory transmitter actions, potentiating especially the effects of GABA (5). PGD_2 has sleep-inducing capacities (10), and it has been postulated that reduced production of PGD_2 is responsible for spontaneous convulsions in a strain of gerbils (7). Since enhanced glutamate release is discussed as a possible mediator of ischemic brain damage (1), a modulatory role of PGD_2, potentiating inhibitory inputs, might well be seen as an "inbuilt" protective mechanism. Interestingly, PGD_2 release is lowest in hippocampus, which is also most susceptible to neuronal hyperexcitation and damage after ischemia (9). PGE_2 is a vasoactive prostanoid with mostly vasoconstrictive properties (11). E-type PGs can cause edema and signs of inflammation (2), or potentiate edema and inflammatory reactions produced by other agents (e.g., leukotrienes). Therefore, excessive PGE production might be an unwanted phenomenon after ischemia. On the other hand, PGE - like PGD - is sleep inducing, and has been described as a modulator of neural function (2). The production of PGE_2 as well as of PGD_2 was decreased after 4 h of reperfusion in all brain areas tested. This may signal a malfunction of an inbuilt defense mechanism.

Very little is known about effects of thromboxane on neuronal functions. Thromboxanes are vasoconstrictive and cause platelet aggregation. Studies by HALLENBECK et al. (4) suggest detrimental effects of thromboxane very early after release of compression-induced ischemia. Hence, the early increase of TXB_2 found in the present study may indicate a pathologic trend which could be reached by specific therapy. At later times of reperfusion TXB_2 formation was reduced.

The results of this study underline the significance of changing pathways of prostanoid production during recirculation. Future research should focus on the site-specific action of PGs, identify cell types responsible for their release, and investigate possible beneficial effects of "E" and "D" class prostaglandins during and after cerebral ischemia.

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Prostaglandin Metabolism Following Experimental Subarachnoid Hemorrhage

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Introduction

The occurrence of pre- or postoperative cerebral vasospasm still represents the major threat to patients with subarachnoid hemorrhage (SAH) from aneurysm rupture (10, 20, 24, 25). Despite considerable efforts in experimental and clinical research, the pathogenesis and pathophysiology of this severe complication remain substantially unresolved. It has been derived from recent investigations that pathological changes in prostaglandin metabolism following SAH may play a major role in the development of late cerebral vasospasm (5, 6, 7, 8, 9, 21, 23, 27, 28, 34). Under physiological circumstances a delicate balance is thought to exist between prostacyclin (PGI_2), a potent vasodilating and antithrombotic agent, and thromboxane A_2 (TXA_2), a strong vasoconstrictor with considerable platelet aggregating properties. As a result of several pathological events following SAH the above-mentioned homeostasis is disturbed, leading to a disproportionate relationship between vasodilating and antithrombotic PGI_2 and vasospastic prostaglandins, especially TXA_2 and PGE_2, which may result in cerebral vasospasm.

However, investigations concerning the course of prostaglandin metabolism following experimental SAH in a standardized model of vasospasm are rare. Therefore it was the aim of our experimental study using a reliable and reproducible model of chronic cerebral vasospasm to evaluate the course of the three major arachidonic acid metabolites prostacyclin, TXA_2, and PGE_2, in the CSF in relationship to angiographically demonstrable cerebral vasospasm.

Material and Methods

For our experimental study we have adopted and partially modified the so-called two hemorrhage canine model of chronic cerebral vasospasm (11, 38). Fifteen mongrel dogs of both sexes weighing between 22 and 27 kg were used for the experiments.

On day 1 following induction of general anesthesia the dogs were put on continuous artificial respiration after oral intubation. Blood gases were checked at constant intervals and kept within physiological limits. Following transfemoral catheterization of the vertebral artery a baseline angiogram of the basilar artery was performed using 6 ml iopromid (0.623 g/ml). The cisterna magna was then aseptically punctured and 4 ml of CSF withdrawn for radioimmunosassay (RIA) (16, 29) examination of PGI_2, TXA_2, and PGE_2. As PGI_2 and TXA_2 are unstable metabolites with short half-lives of 3 min and 30 s respectively, their

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concentration in the CSF was measured as a function of stable degradation products 6-keto-$PGF_{1\alpha}$ and TXB_2. Thereafter 5 ml of autologous blood was injected into the cisterna magna within 2 min. Afterwards the dogs were tilted with the head down 15° for 30 min to allow distribution of the blood around the basilar artery. On day 3 under light anesthesia 4 ml of CSF was withdrawn and 5 ml of autologous blood was again injected into the cisterna magna as already described. On day 8 a second angiogram was carried out to demonstrate the occurrence of arterial vasospasm and for assessment of changes in the diameter of the basilar artery. Again CSF was withdrawn for RIA examinations. Red and white blood cell counts were performed daily.

Measurements of the diameter of the basilar artery were made at seven selected points along the course of the vessel, identical in both angiograms. The vessel diameters were measured at a tenfold magnification using a Zeiss stereomicroscope (SV 8) with a micrometer ocular.

The control group consisted of three dogs which underwent sham operation using the same procedure as described above but without injection of autologous blood into the cisterna magna.

Statistical evaluations of changes in vessel diameter were made using paired and nonpaired Student's *t*-test. Statistical evaluations of arachidonic acid metabolite concentrations in the CSF were made using the Wilcoxon matched pairs signed rank test.

Results

A significant decrease in the diameter of the basilar artery on day 8 compared to day 1 could be noticed in all animals with experimental SAH. The mean diameter of the basilar artery in the baseline angiogram on day 1 was 1.23 mm ± 0.06 with a range from 0.94 mm to 1.64 mm. The mean diameter on day 8 was 0.05 mm ± 0.08 with a range from 0.40 mm to 0.74 mm. The mean decrease of the basilar artery diameter between day 1 and day 8 was 0.68 mm ± 0.10 mm which represents a reduction in vessel diameter of 54%. In comparison no change in the diameter of the basilar artery between day 1 and day 8 could be noted in the sham-operated control group (mean diameter day 1: 1.10 mm ± 0.24; day 8: 1.13 mm ± 0.08) (Fig. 1, Table 1).

No significant changes could be found in blood gas parameters (pH, pCO_2, pO_2, HCO_3^-, O_2 sat., base excess) when comparing day 1 to day 8 (Table 2).

In all animals with experimental SAH there was a significant increase in the CSF concentrations of all three prostaglandins tested from day 1 to day 3 and day 8 as well as in comparison to the sham-operated control group ($P<0.001$). No significant changes in prostaglandin CSF concentrations were observed in the sham-operated animals between day 1 and days 3 and 8. In contrast, in the experimental animals 6-keto-$PGF_{1\alpha}$ increased from a baseline level of 134 pg to 1181 pg on day 3 and to 1543 pg on day 8; PGE_2 increased from 361 pg on day 1 to 1006 pg on day 3 and to 4330 pg on day 8; and TXB_2 increased from 35 pg on day 1 to 95 pg on day 3 and to 918 pg on day 8. The change in 6-keto-$PGF_{1\alpha}$ concentration between day 1 and day 8 represents an 11.4-fold increase ($P<0.001$); the rise in PGE_2 concentration between day 1 and day 8 represents a 12-fold increase ($P<0.0001$); and the rise in TXB_2 concentration between day 1 and day 8 represents a 26.1-fold increase ($P<0.001$) (Figs. 2-3).

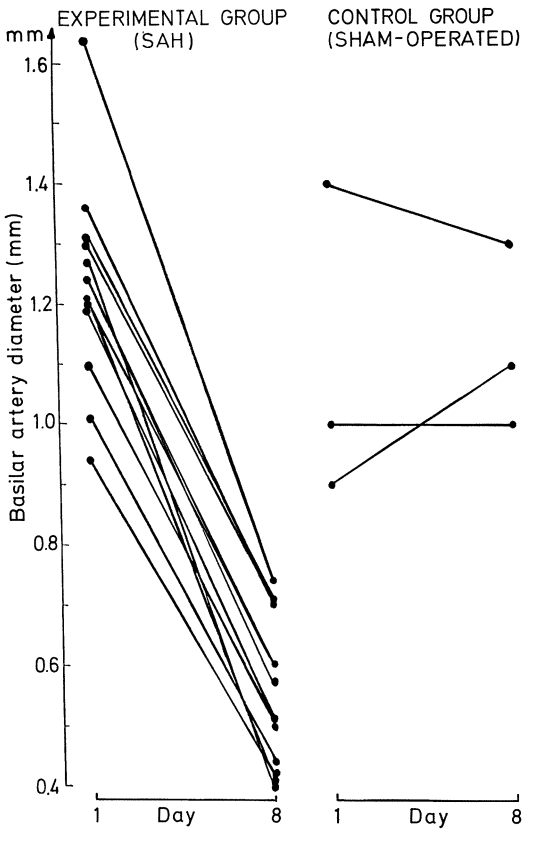

Fig. 1. Arteriographic changes in basilar artery diameter following experimental SAH

Discussion

Since the first pioneering studies on the effects of prostaglandins on the cerebral circulation by DENTON, KATSUKI, WHITE and others (12, 26, 40, 41, 43) in the early 1970s, a considerable number of experimental and clinical investigations have attempted to clarify the role of arachidonic acid metabolites during different states of impaired brain perfusion like cerebral infarction, brain edema, and especially cerebral vasospasm (2, 3, 4, 6, 8, 14, 17, 18, 19, 30, 35, 36, 39, 42). A precise relationship between prostacyclin (PGI_2), with its vasodilating and antithrombotic properties, and potential spasm-provoking and platelet-aggregating prostaglandins like TXA_2 and PGE_2 seems to be essential for the maintenance of cerebral vascular tone. Pathomorphological changes of the cerebral vessels, with endothelial damage regularly detectable after SAH and specific inhibition of prostacyclin synthetase, are thought to be responsible for a diminished synthesis of prostacyclin in the face of increasing concentrations of TXA_2 produced from aggregating platelets which preferably adhere to the damaged endothelium. Additionally PGE_2 is a strong vasoconstricting metabolite. It has been demonstrated that following experimental SAH the vessel adventitia is infiltrated by inflammatory cells, especially macrophages. It has been suggested that these macrophages may be the source of enhanced PGE_2 concentration (15, 33, 39, 44). However, verification of this hypothesis in a reliable experimental model of chronic cerebral vasospasm is still lacking.

Table 1. Changes in basilar artery diameter after experimental SAH

Dog no.	Mean basilar artery diameter (mm) Day 1 (baseline)	Day 8	Decrease (mm) day 8 - day 1	% Decrease in diameter
Experimental group (SAH)				
4	1.24 ± 0.10	0.57 ± 0.12	-0.67 ± 0.20	-54
5	1.27 ± 0.10	0.40 ± 0.06	-0.87 ± 0.11	-69
7	1.01 ± 0.07	0.44 ± 0.05	-0.57 ± 0.05	-56
8	0.94 ± 0.05	0.43 ± 0.05	-0.52 ± 0.07	-55
9	1.21 ± 0.12	0.41 ± 0.04	-0.80 ± 0.10	-66
10	1.31 ± 0.07	0.71 ± 0.10	-0.60 ± 0.12	-46
13	1.36 ± 0.10	0.71 ± 0.08	-0.65 ± 0.10	-48
14	1.19 ± 0.07	0.51 ± 0.07	-0.67 ± 0.10	-57
15	1.10 ± 0.09	0.50 ± 0.08	-0.59 ± 0.12	-55
16	1.20 ± 0.07	0.60 ± 0.08	-0.60 ± 0.09	-50
17	1.64 ± 0.05	0.74 ± 0.05	-0.90 ± 0.08	-55
19	1.30 ± 0.21	0.66 ± 0.07	-0.60 ± 0.22	-46
$\bar{x}$	1.23 ± 0.06	0.50 ± 0.08	-0.68 ± 0.10	54 ± 7.1
Control group (sham-operated)				
20	0.90 ± 0.07	1.10 ± 0.10	+0.16 ± 0.08	+22
21	1.00 ± 0.10	1.00 ± 0.04	±0.10 ± 0.10	± 0
22	1.40 ± 0.04	1.30 ± 0.07	-0.10 ± 0.06	- 7
$\bar{x}$	1.10 ± 0.24	1.13 ± 0.08	+0.00 ± 0.17	+5 (±15)

Table 2. Changes in blood gas parameters, day 8 vs. day 1, after experimental SAH

Dog no.	% Decrease in basilar artery diameter	pH	pCO_2	pO_2	HCO_3^-	O_2 sat.	B.E.
Experimental group (SAH)							
4	-54	+0.04	-4.7	-15.2	+1.1	+0.3	+1.3
5	-69	+0.05	-2.5	-12.1	-0.6	+0.6	+4.0
7	-56	+1.20	-7.0	+11.3	+0.2	+0.5	-0.3
8	-55	-0.60	-6.8	+ 8.5	-5.8	±0	-2.9
9	-66	-0.12	+7.6	+21.7	+1.0	-0.3	+2.7
10	-46	-0.70	-6.1	-20.6	-1.6	-4.0	-0.3
13	-48	+0.70	-7.8	+41.1	-0.9	+1.3	+1.2
14	-57	+0.21	-8.9	+73.2	+5.7	+2.5	+7.2
15	-55	-0.90	-14.1	-60.8	-0.9	-1.7	-1.2
16	-50	-0.90	- 7.7	+ 6.2	-1.3	-1.1	+4.0
17	-55	+1.60	- 6.5	+55.2	-0.6	+0.8	+1.4
19	-46	+0.60	- 3.1	- 1.8	+1.0	±0	+2.4
$\bar{x}$	-54	+0.09	- 5.6	+ 9.8	-0.2	-0.09	+1.6
Control group (sham-operated)							
20	+22	+0.23	+ 2.7	+35.7	+4.1	+0.5	+2.0
21	±0	+0.06	- 6.7	-44.7	-1.5	-0.3	+0.6
22	-7	+0.01	- 7.3	-34.7	-3.6	-0.2	-2.5
$\bar{x}$	+5						

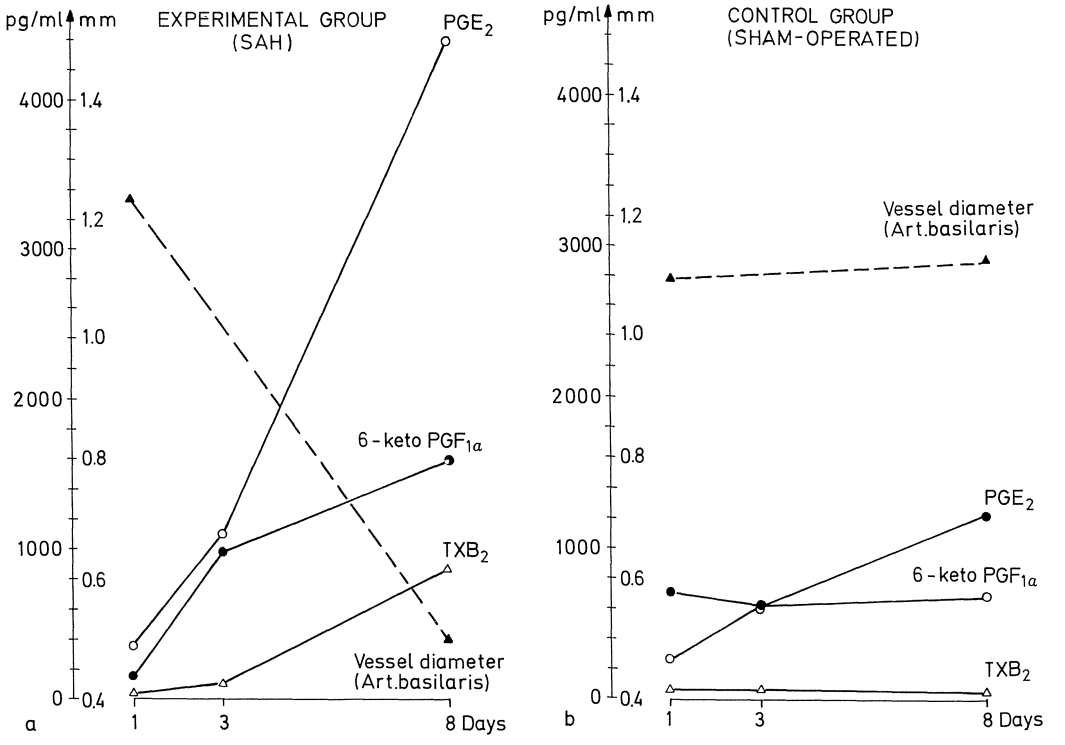

Fig. 2. CSF levels of tested prostaglandins and mean decrease in basilar artery diameter in the experimental group (*a*) and the sham-operated control group (*b*)

In our experimental study using the two hemorrhage model of SAH we were able to induce a severe chronic cerebral vasospasm with a mean reduction of the basilar artery diameter of more than 50% in nearly all experimental animals. The pathological changes in the vessel closely resembled those found in humans after death from cerebral vasospasm, with endothelial damage, thickening of the elastica lamina, increased vacuolation, and myonecrotic changes (1, 13, 22, 31, 44). In summary, this experimental set-up presents a reliable and reproducible model of chronic cerebral vasospasm in the dog.

The angiographically demonstrable arterial narrowing was closely paralleled by the changes in prostaglandin levels in the CSF. All three prostaglandins showed a significant increase from day 1 to day 3 and day 8 in comparison to their basic levels and to the prostaglandin values of the sham-operated group. In contrast to other investigators we were not able to show a decreased synthesis of prostacyclin following experimental SAH (5, 28). However, the experimental set-ups of these investigators were different from ours (most used in vitro studies or a rather simple method of cerebral vasospasm with only slight changes in vessel diameter) so that the different courses of PGI_2 values may be due to methodological reasons. Despite the fact that no decrease in PGI_2 synthesis occurred, the alteration of the PGI_2-TXA_2/PGE_2 relationship is striking. The 11.4-fold increase in PGI_2 concentration stood in contrast to a 12-fold increase in PGE_2 concentration and an excessive 26.1-fold increase in TXA_2 concentration. From our experimental investigation, which is in agreement with a previous cli-

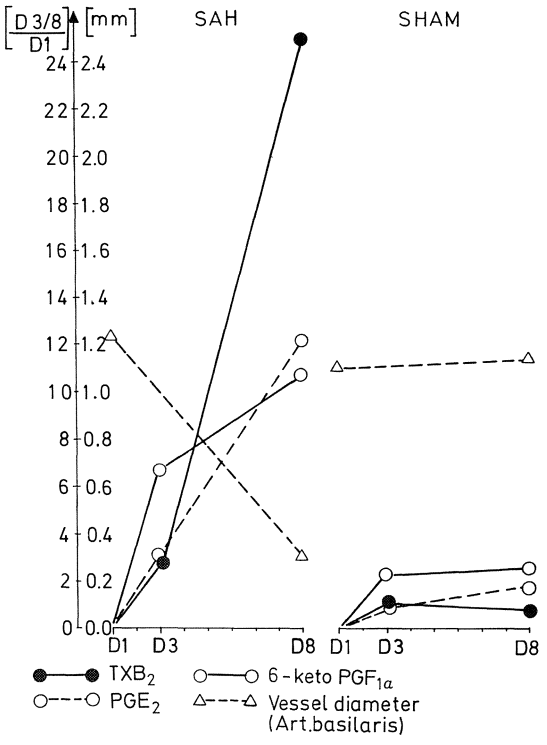

Fig. 3. Comparative increase in tested prostaglandins from day 1 and day 8 in the experimental group and the sham-operated control group

nical study by our department concerning the arachidonic acid metabolism in the CSF of patients following SAH (37), we have drawn the preliminary conclusion that a decrease in PGI_2 concentration is not in fact the major causative factor underlying cerebral vasospasm. The increased PGI_2 concentration after SAH may reflect a protective mechanism against the combined increase of the vasospastic arachidonic acid metabolites TXA_2 and PGE_2, which seemed to be one of the major pathogenic factors in the development of chronic cerebral vasospasm.

More experimental studies are needed to clarify further the complicated relationship of different prostaglandins during the course of chronic cerebral vasospasm following SAH.

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Regulation of Cerebral Blood Flow in the Recirculation Period After Prolonged Ischemia of the Cat Brain

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Introduction

In 1890 ROY and SHERRINGTON (19) examined the regulation of cerebral blood flow (CBF) and came to the conclusion that "chemical products of cerebral metabolism can cause variations of the calibre of cerebral vessels." Since then several chemical factors have been identified that serve as mediators between cerebral metabolism and blood flow: H^+, CO_2, K^+, Ca^{2+}, adenosine, and others (2, 22).

After a period of ischemia this chemical coupling between metabolism and CBF is disturbed as the CBF falls to subnormal values (delayed hypoperfusion) (7) whereas the oxygen uptake of the recovering brain normalizes or even overshoots (8). In this situation of hypoperfusion it can be demonstrated that at least one important chemical mediator, CO_2, is ineffective. Whereas the normal brain responds to induced hypercapnia with a large rise in CBF (18), the postischemic brain circulation is unresponsive to induced hypercapnia and the CBF remains at a low level (7). The loss of one or several coupling mechanisms may be of importance for the recovering brain as a mismatch such as decreased flow and increased metabolic activity may develop (9).

In this study CBF was measured in normocapnia and hypercapnia before and after ischemia of 1 h duration in the cat brain. As the actual site of the postischemic vascular dysregulation remains unidentified, we measured pressure in pial arteries and calculated lumped resistances of an "upstream" segment comprising the aorta and large extracortical vessels and a "downstream" segment including the intracortical vessels, capillaries, and venous system (1, 20).

Materials and Methods

Cats (n=22 animals undergoing ischemia and n=5 controls) were anesthetized with halothane/nitrous oxide and ventilated. Brain ischemia was produced by a combination of induced hypotension, ligation of the mammary arteries, and clamping of the innominate and left subclavian arteries (6). Recirculation was performed by raising the blood pressure above 160 mmHg and treating systemic acidosis and brain edema. Ventilation was continued for 6 h and the electrocorticogram (ECoG) recorded to monitor brain recovery. CBF was measured before ischemia (n=10) and at 15 min (n=9), 2-4 h (n=13), and 5-6 h (n=13) recirculation using an intraarterial ^{133}xenon bolus technique and calculations described by HUTTEN and BROCK (10). Hypercapnia was induced by ventilating with 6% CO_2.

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In a subgroup (n= 5 controls, n= 9 ischemia experiments) pial artery pressure (PAP) was measured using a feedback-controlled measuring system (WPI Instruments, New Haven CT, USA), and in addition systemic arterial pressure (SAP) and central venous pressure (CVP). Two segments were distinguished (20). One segment is "upstream" to the pial arteries and resistance is built up by the large extra- and intracranial arteries up to the recording site; the other segment is "downstream" and comprises the resistance of the pial and intracortical arterioles, capillaries, and the venous system. Upstream resistance (Rup) is calculated as Rup=(SAP-PAP)/CBF and downstream resistance (Rdown) as Rdown=(PAP-CVP)/CBF. All data are given as means (SE).

Results

Control CBF was 44.8 (5.0) ml x 100 g^{-1} x min^{-1} at normocapnia ($apCO_2$ =30 (1) mmHg). During hypercapnia ($apCO_2$=55 (2) mmHg) CBF rose to 81.5 (10.4) ml x 100 g^{-1} x min^{-1} (paired t-test: $P<0.05$) (Fig. 1). A marked hyperemia at 15 min recirculation (CBF=97.2 (11.6) ml x 100 g^{-1} x min^{-1}) was followed by delayed postischemic hypoperfusion at 2-4 h with a CBF of 22.4 (2.2) ml x 100 g^{-1} x min^{-1} (comparison against control with analysis of variance and t-test: $P<0.05$) which persisted at 5-6 h with a CBF of 22.2 (1.9) ml x 100 g^{-1} x min^{-1} ($P<0.05$). During this hypoperfusion phase the cerebrovascular reactivity to CO_2 was abolished (Fig. 1).

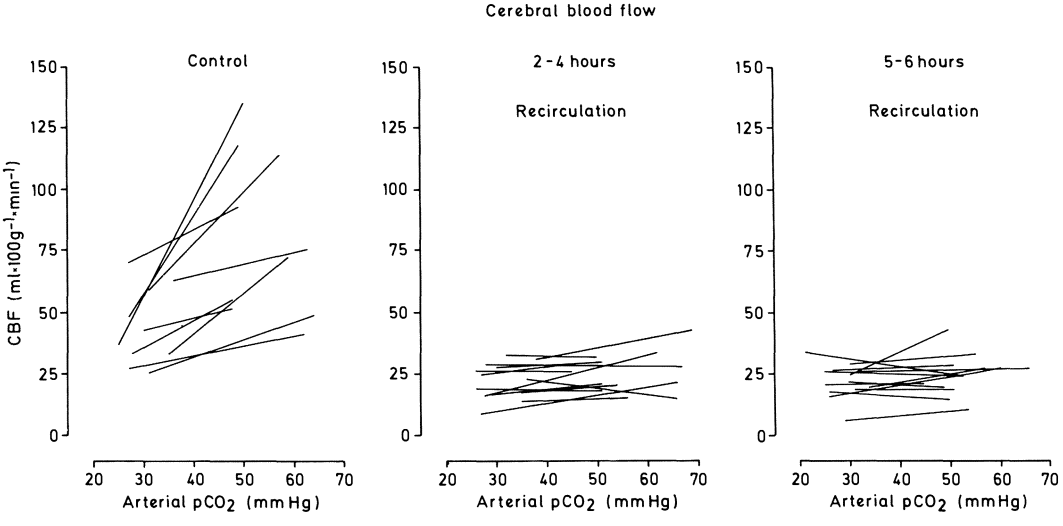
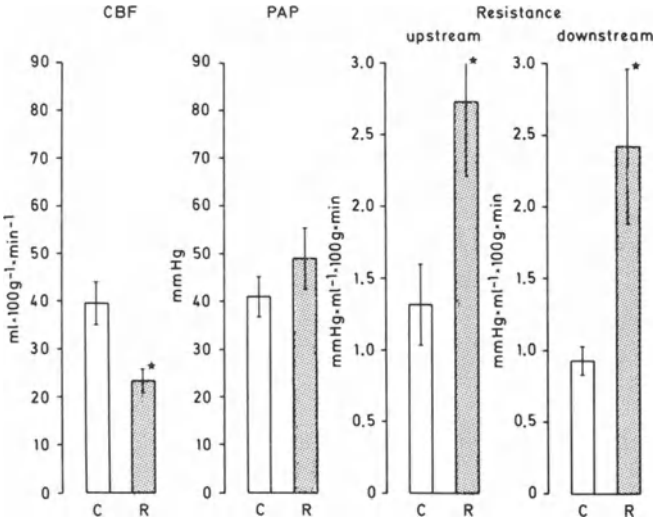


Fig. 1. Paired measurements of cerebral blood flow in normocapnia and hypercapnia in the control phase and at 2-4 and 5-6 h of recirculation after 1 h of global ischemia

The results of PAP measurements and calculated resistances in controls and in experimental animals after 3-6 h of recirculation are shown in Fig. 2. During the control phase PAP was 41(4) mmHg or 47% of control. Calculated segmental resistances were Rup=1.30 (0.28) and Rdown=0.94 (0.10) mmHg x ml^{-1} x 100 g x min. In the hypoperfusion phase PAP amounted to 49 (5) mmHg or 49% of SAP. Both Rup with 2.73 (0.51) and Rdown



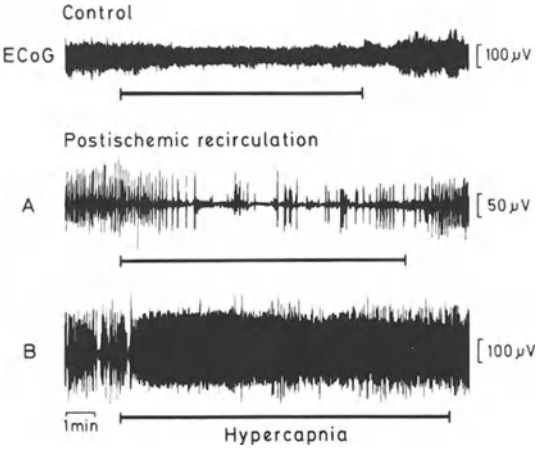


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Fig. 2. Cerebral blood flow (*CBF*), pial artery pressure (*PAP*), and upstream and downstream resistances in controls (*C*) and animals with 3-6 h recirculation (*R*) after 1 h of global ischemia. Statistics were calculated using the Mann-Whitney U-test ($P<0.05$)

◁ Fig. 3. Electrocorticogram (*ECoG*) in a control animal and in two situations 5-6 h postischemic recirculation (*A*, *B*) under the induction of hypercapnia (marked by *bars*). *A* shows an example of ECoG suppression during hypercapnia, and *B* an example of activation

with 2.73 (0.55) mmHg x ml^{-1} x 100 g x min were increased above control (Mann-Whitney U-test: $P<0.05$).

Testing for CO_2-reactivity by recording of PAP gave further information. In controls, hypercapnia resulted in a fall of PAP from 41 (4) to 28 (2) mmHg (paired *t*-test: $P<0.01$) and Rdown markedly fell from 0.94 (0.10) to 0.28 (0.05) mmHg x ml^{-1} x 100 g x min ($P<0.01$), indicating intracortical vasodilation. After ischemia there was no reaction of the PAP in hypercapnia and calculated resistances remained constant.

Induction of hypercapnia depressed the amplitude of the ECoG in the anesthetized control brain (Fig. 3). Interestingly, this neurophysiological response to hypercapnia was also seen after ischemia. When animals undergoing PAP and CBF measurements and showing recovery of continuous ECoG activity ($n=4$) were analyzed the ECoG was found to be depressed in $n=6$ readings (Fig. 3, type A) and activation of rhythmic

discharges was seen in n=2 (Fig. 3, type B). Consequently, the change in CO_2 levels or the related systemic acidosis provoked electrophysiological changes in the absence of a CBF or PAP response.

Discussion

The present study confirms the pronounced disturbance of the CO_2 reactivity of the brain after global ischemia (7, 12, 13, 16). Furthermore, by the measurement of pial artery pressure and calculation of segmental resistances it could be demonstrated that both the extracranial and the intracranial vessels are in a state of constriction. Loss of CO_2 reactivity, therefore, must be due to a pathological regulation of the smooth muscle tone. Interestingly, depression of ECoG activity observed during induced hypercapnia does reflect indirect effects on neuronal activity.

We can compare this loss of CO_2 response after ischemia with that in other brain injuries. In the recovery phase after severe hypoglycemia hypoperfusion is observed and CO_2 reactivity lost (17). In the same situation, the arteriovenous differences for oxygen ($AVDO_2$) are increased, indicating that there is a true hypoperfusion. A similar phenomenon is observed after 1 h of global ischemia in the cat, where the oxygen extraction is increased during the hypoperfusion period (9). Therefore, both ischemia and hypoglycemia as conditions involving a severe disturbance of energy metabolism are characterized by a hypoperfusion period, loss of CO_2 response, and increased $AVDO_2$. This situation is different from anesthesia of the normal brain with barbiturates, where the reduction of flow is paralleled by a reduction in metabolism and the CO_2 response is attenuated (4). A full dilation of the cerebral vessels as occurs in hyperemia (21) or in the autoregulatory response to hypotension (5) can preclude further dilatatory action of CO_2. This is different from the postischemic situation, where a vasoconstriction could be demonstrated. Other severe brain injuries are accompanied by loss of CO_2 reactivity: experimental head trauma (14) and subarachnoid hemorrhage (11, 15). At present no common denominator for all these pathophysiological conditions can be identified, and therefore loss of CO_2 reactivity may constitute a nonspecific response of the vascular bed.

As CO_2/H^+ is only one factor in the regulation of blood flow, further conclusions can only be drawn when the entire coupling process is understood. Interestingly, conditions exist even in the normal activated brain where the increase in flow is uncoupled from related oxidative metabolism (3).

In conclusion, after brain ischemia the vascular resistance is increased and the CO_2 reactivity lost. The exact mechanism underlying this disturbance remains unidentified but the relevance of this true hypoperfusion becomes evident when the oxygen extraction of the recovering brain increases at the same time.

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A New Experimental Model of Sinus Thrombosis in Rats

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Introduction

Primary cerebral venous thrombosis is a rare disease with polymorphic clinical manifestations; its pathophysiology is poorly understood and controversy exists as to the appropriate therapy. By contrast with research into arterial cerebrovascular disorders, only a few studies have focused on the venous manifestations (1, 4-9). Several experimental approaches (often failures) have been made in larger animals (2, 3; cf. Table 1), whereas to the best of our knowledge no experimental model exists in small laboratory animals to study pertinent functional and structural aspects. The current report describes a novel experimental method for inducing sinus thrombosis in rats which can be survived on a long-term basis. Thus, acute and chronic sequelae can be investigated.

Table 1. Experimental studies on sinus thrombosis

Model	Experimental animals	Results	References
Injection or insertion of thrombogenic material: gauze, fatty acids, α-cyanoacrylate, wool, paraffin, etc.	Dog, cat	Ø	BIZE (1931)
		Ø	BECK and RUSSELL (1946)
		CV	HEINZ et al. (1972)
		SSS, ST, CV	FUJITA et al. (1983)
Coagulation of sinus sagittalis	Dog	SSS	SATO et al. (1982)
Ligation of sinus sagittalis plus injection of thrombogenic material	Cat	?	WOOLF (1954)

CV, cortical vein; SSS, sinus sagittalis superior; ST, sinus transversus

Material and Methods

The calvaria of Sprague-Dawley or Wistar rats of 250-350 g b.w. was removed under chloral hydrate anesthesia using an operating microscope and a dental drill. The sinus sagittalis superior was exposed and ligated rostrally and close to the confluens sinuum. 100 µl of PTT reagent (Boehringer Mannheim, Inc.) was then slowly injected into the sinus within 10 min. Fluorescence angiography was carried out in 20 animals before and after injection of the thrombogenic material to visualize the remaining venous circulation. The animals (n= 3 per group) were killed for histological studies after 30 min, 24 h, or 4 days by bleeding and then subjected to perfusion fixation with 5% formalin. Frontal sections of the brain were made and stained by conventional histological methods. In further experiments, two small cranial windows were made over the sinus sagittalis for introduction of a catheter. Twenty-four hours later, continuous EEG recordings for power spectrographic analysis were carried out before and after ligation and injection of the thrombogenic material into awake animals. In ten further animals, spontaneous running was measured in activity cages during a control phase of 21 days prior to thrombosis. After induction of thrombosis (n= 5) or sham operation (n= 5), spontaneous wheel running was followed up for 28 days.

Results

Fluorescence Angiography

Multiple ligations of the sinus sagittalis led to its dilatation and to a reversal of blood flow in the draining cerebral veins. Thrombosis was found only in those animals in which ligation of the sinus was combined with injection of the PTT reagent. Thrombosis of the sinus developed in all 20 animals studied, while it extended into the draining cortical veins in 11 animals in this group.

Histology

Thirty minutes after induction of thrombosis leading to complete occlusion of the sinus sagittalis, only minor histological changes were found. However, 24 h later a wedge-shaped, demarcated parenchymatous area of necrosis developed around the sinus, reaching to the corpus callosum, the hippocampus, and the lateral ventricle. On the other hand, the parenchyma at the depth of the intrahemispheric cleft appeared intact. Extensive advanced hemorrhagic necrosis involving both hemispheres was found in animals with 4 days' survival.

EEG

Immediately after thrombosis formation, the spontaneous electrical activity of the brain was almost completely depressed. Forty-five minutes later, the electrical function recovered, with a marked shift of the EEG frequencies to the delta and theta ranges. Then, slow wave activity with high amplitudes (200-300 µV) persisted for hours.

Spontaneous Activity

Immediately after recovery from the surgical procedure, spontaneous wheel running was depressed in both experimental and control animals

with sham operation. However, while a normal level of activity was reached within a few days in the sham-operated group, wheel running in animals with sinus thrombosis remained decreased to 60% of the control level. The depression of the spontaneous motor behavior persisted during the whole observation period of 4-5 weeks, although evidence of limb paresis was not obtained.

Summary

A novel experimental model of sinus thrombosis in small animals is presented. Induction of thrombosis was accomplished by combination of sinus ligation and subsequent injection of thrombogenic material into the sinus. Fluorescence angiography and histology demonstrated thrombosis formation in the sinus sagittalis superior in all animals studied. Additional spread of thrombosis into the draining cortical veins was observed in approximately 50%. Acutely, induction of thrombosis led to a marked depression of the spontaneous motor activity and electrical function of the brain. Recovery was characterized by a shift of the EEG frequency domains into a lower range. The model appears suitable for the investigation of the pathogenic mechanisms of venous infarction at a structural and functional level, as a basis for developing better forms of treatment.

Acknowledgments. The secretarial assistance of Ruth Demmer is gratefully acknowledged. Activity cages for long-term studies were kindly made available by Prof. J. Aschoff, Max-Planck-Institute of Behavioral Physiology, Erling-Andechs.

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Stable Xenon Effects on Regional Cerebral Blood Flow and Electroencephalography in Normal Baboons and Volunteers

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Introduction

Measurement of local cerebral blood flow (lCBF) with CT and inhalation of stable xenon (Xe^S) has received widespread attention. It makes possible three-dimensional measurement of lCBF with high spatial resolution and needs little equipment apart from a CT scanner.

Most centers which work with Xe^S prefer concentrations of 35% xenon in oxygen. This concentration has a sufficient effect as a contrast medium without having too pronounced anesthetic side-effects. However, an influence of Xe^S on CBF has been reported (1, 3, 4). Therefore the effect of 35% Xe^S on CBF and EEG was evaluated in two studies.

Method

Animal Experiment

Six adult baboons of either sex and weighing between 12 and 15 kg were used for this experiment. After intraperitoneal injection of pentobarbital (25 mg/kg) and intravenous injection of 0.2 mg/kg pancuronium, the animals were ventilated by nitrous oxide in oxygen (3:1). One femoral artery and one femoral vein were cannulated to record continuously blood pressure and central venous pressure and to measure blood gases. The left lingual artery was exposed by a cervical cut. A thin polyethylene catheter was introduced into the lingual artery to position its tip at the orifice of the internal carotid artery.

The external carotid artery was ligated. All xenon 133 injected through the catheter entered only the internal carotid artery. Eight NaJ detectors with a collimation of 14 mm and a crystal diameter of 8 mm were positioned over the left hemisphere. For measurement of rCBF 1.0-1.4 mCi xenon 133 in 1 ml normal saline was injected through the lingual catheter. Saturation and desaturation were recorded by a multichannel analyzer (Wenzel, Munich). Desaturation was recorded for 8.5 min. Clearance curves were calculated according to the stochastic method to express flow in ml/min/100 g. EEG was recorded with six electrodes over both hemispheres and conveyed to an analog digital converter. The events per second were analyzed according to their frequency. Incidence and amplitude of the frequenceies were multiplied, expressed as EPE (electrical power equivalent). Autoregulation was tested by reducing blood pressure by about 25 mmHg using a nitroprusside natrium perfusion. CO_2 reactivity was tested by additional inhalation of 30 ml CO_2, which raised $PaCO_2$ by 10-15 mmHg.

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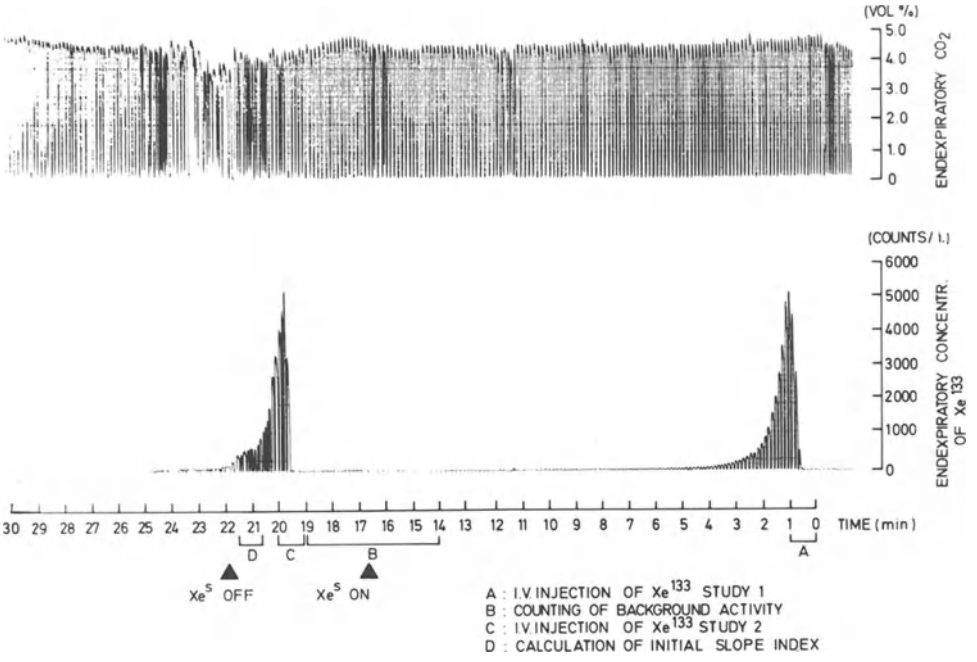

Fig. 1. Protocol of Xe^S inhalation study with measurement of rCBF by the intravenous xenon 133 method. The chart reads from right to left. Stepts of the protocol are indicated by capital letters (*A-D*). During inhalation of Xe^S involuntary hyperventilation decreased end-expiratory pCO_2

Study with Volunteers

The study was performed in seven volunteers (one female, six males) aged from 27 to 42 years. One volunteer had to be excluded because of excessive movement during inhalation of Xe^S. CBF was measured with the intravenous injection of xenon 133 and recording of the clearance curves was performed with a cerebrograph (Novo). Thirty-two NaJ detectors with a crystal size of 3/4 in. and a collimation of 20 mm were arranged in a helmet shape over the skull. Clearance curves were recorded for 10 min and stored on a PDP computer. EEG was recorded and analyzed in the same manner as described above. EPE, the product of amplitude and frequency, was used. Inhalation of Xe^S was performed for 5 min. Calculation of rCBF took place between the 4th and 5th minute of inhalation of Xe^S.

Results

Animal Experiment (Fig. 1)

Steady state mrCBF was 40.5±5.3 (ml/min/100 g). During autoregulation CBF remained unchanged (40.5±10.2 ml/min/100 g). During inhalation of Xe^S and decreased blood pressure CBF increased from 40.5 to 55.3±18.5 ml/min/100 g (36.5%). By additional inhalation of CO_2 and increasing $PaCO_2$ by 10 to 15 mmHg, a CO_2 reactivity factor of 1.04% was calculated. During Xe^S inhalation CO_2 reactivity increased significantly to

Table 1. CBF in normal baboons. All values with the exception of line 2 have been corrected for the $PaCO_2$ by a reactivity factor of 0.43 ml/min/100 g/mmHg without Xe^S and by a reactivity factor of 1.04 ml/min/100 g/mmHg with Xe^S. Values of line 9 were measured only in two baboons. Values marked with a * differ significantly from the steady state ($P<0.05$)

	CBF (ml/100 g/min)
1. Steady state	40.5 ± 5.3
2. CO_2 reactivity without Xe^S	44.9 ± 4.7*
3. Autoregulation without Xe^S	40.5 ± 10.2
4. CO_2 reactivity with Xe^S	42.1 ± 11.4
5. Autoregulation with Xe^S	55.3 ± 18.4*
6. Beginning of Xe^S inhalation	48.9 ± 12.5*
7. Between 10th and 18.5th minute of Xe^S inhalation	43.7 ± 20.0
8. Between 20th and 28.5th minute	37.8 ± 14.6
9. Between 30th and 28.5th minute	22.5 ± 8.3
10. Right after end of inhalation	42.6 ± 12.0

2.61%. During prolonged inhalation of Xe^S CBF rose during the first 10 min from 40 to 48.9±12.5 ml/min/100 g (22.25%). Afterwards CBF dropped continuously to normal and subnormal values. At 30 and 40 min of Xe^S inhalation (two baboons) rCBF was 22.5±8.5 ml/min/100 g. After the end of inhalation CBF returned to the initial steady state value (42.6±12.1).

Study with Volunteers

EEG: During the first few minutes of Xe^S inhalation there was a significant drop in alpha and beta activity and a small increase in theta and delta wave activity. After the end of inhalation EEG recovered within 2 min (Fig. 2).

CBF (Fig. 3): In one volunteer CBF remained constant during excessive hyperventilation. In two volunteers there was a slight increase in CBF. In one person there was a significant increase in CBF only over one hemisphere. In two volunteers a significant increase of about 25% to 30% was observed. The mean increase in ISI was 12.8% ± 9.9%, not corrected for the decreased $PaCO_2$.

Discussion

GUR (1985) described a 17% increase in CBF after 2-4.5 min of inhalation of 35% Xe^S in oxygen, measured with microspheres in baboons. JUNCK (1985) described an overall increase in CBF after 2 min of inhalation of 40% xenon in oxygen, measured with iodine 123-antipyrine in rats. OBRIST and JAGGI (1985) described a 28% increase in ISI and a 17% increase in CBF during 6 min of inhalation of 30%-35% xenon in young volunteers without correction for the $PaCO_2$.

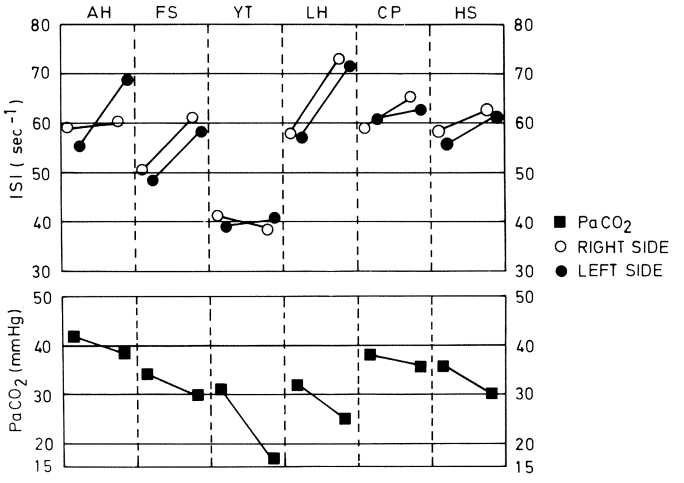

Fig. 2. Mean rCBF expressed as initial slope index (ISI) and pCO_2 before (*left*) and during (*right*) inhalation of Xe^S by six normal volunteers. *Open circles*, right hemisphere; *closed circles* left hemisphere. Despite decrease of pCO_2 due to involuntary hyperventilation, CBF increased in the majority of hemispheres

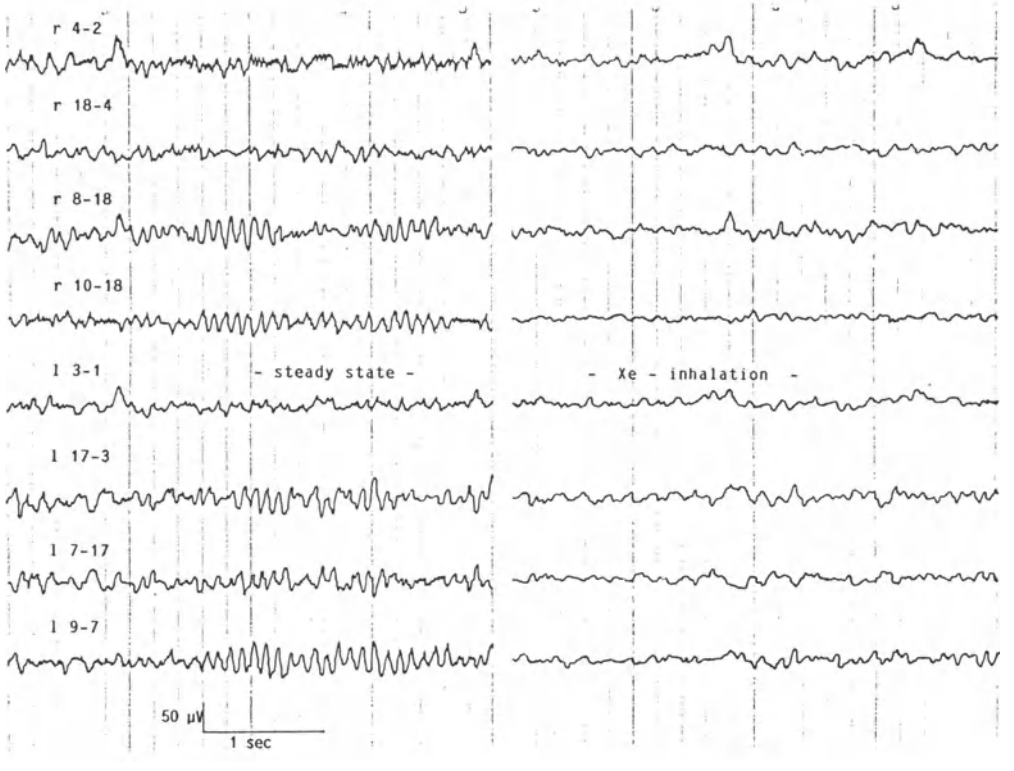

Fig. 3. Typical EEG tracing in volunteer before (steady state) and during Xe^S inhalation. EEG needles were positioned according to the Jasper technique. During inhalation of Xe^S EEG amplitude and frequency decreased significantly

It is not clear how to explain the initial increase in CBF during Xe^S inhalation. There might be some direct influence of Xe^S on the vessels or the nervous system providing the vessels: there might be some excitation due to the anesthetic character of Xe^S. However, there was no hint of this in EEG. During prolonged inhalation CBF decreased in correlation with EEG slowing. The effect on CBF and autoregulation make further investigations necessary, to evaluate whether ICP might rise under pathological conditions or whether there is a steal phenomenon. With respect to CBF increase, it might be of some advantage to measure lCBF with Xe^S and CT during desaturation rather than during saturation.

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Pathophysiology of Experimental Brain Infarction

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Introduction

Normal supply of oxygen and glucose to the brain requires continuous blood perfusion, which in gray matter structures amounts to about 50 ml/100 g/min. Because of the low energy reserves of the brain, interruption of blood flow rapidly induces metabolic disturbances which may cause considerable functional deficits or even tissue necrosis. In the following, the pathophysiology of these disturbances is described in experimental brain infarcts, produced in cats by transorbital middle cerebral artery occlusion. A detailed account of the original material used for this discussion is given elsewhere (4, 6, 7, 12, 15).

Material and Methods

In adult cats under light barbiturate or halothane/nitrous oxide anesthesia the left middle cerebral artery was exposed by a transorbital approach. The vessel was either occluded with a small aneurysm clip, or gradually compressed with an electronically controlled micro-occluder. Cerebral blood flow was measured continuously with a heated thermoelement placed on the surface of the suprasylvian gyrus (1), intermittently with labeled microspheres (14), or at the end of the experiment by ^{131}I-iodo-amphetamine autoradiography (9). For measurement of regional blood perfusion pressure, a small pial artery on the surface of the suprasylvian gyrus was punctured with a micropipette connected to a servo-nulling feedback-controlled micropressure recording system (5).

Functional deficits during ischemia were monitored by recording the electrocorticogram, the cortical DC potential, and cortical impedance (for calculation of relative extracellular volume). Changes of water and electrolyte content were determined in tissue samples harvested at the end of the experiment.

Regional biochemical alterations were studied in cryostat sections of brains frozen in situ: glucose utilization was determined by ^{14}C-deoxyglucose autoradiography (16), regional glucose (11) and ATP (8) content by induced tissue bioluminescence, regional tissue pH with the fluorescent pH indicator umbelliferone (3), and regional potassium content with a histochemical technique (10).

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Results and Discussion

Vascular Stenosis and Focal Blood Perfusion Pressure

The diameter of the middle cerebral artery in cats is about 0.7-0.8 mm. During gradual compression of the artery, hemodynamic changes are noticed as soon as vessel diameter is reduced to about 200 µm, corresponding to reduction of luminal cross-section by more than 90%. Initially, pial arterial pressure - as a measure of focal blood perfusion pressure - begins to decrease, followed by a decrease in cerebral blood flow and a reduction in the amplitude of the electrocorticogram as soon as the diameter of the middle cerebral artery is further reduced to less than 100 µm, corresponding to a decrease in vessel aperture to less than 5% of control. This indicates that a considerable degree of local cerebral artery stenosis can be tolerated without any major hemodynamic changes.

The relationship between pial arterial pressure and cerebral blood flow was studied by stepwise compression of the middle cerebral artery (Fig. 1). Under physiological conditions, pial arterial pressure of the cat is about 60 mmHg or 50% of systemic arterial pressure. The threshold for maintenance of normal blood flow is about 40 mmHg (Fig. 2). A decrease in local perfusion pressure to below this value causes a mild, and at values below 20 mmHg a steep decline of cerebral blood flow. Pial arterial pressure after complete occlusion of blood flow is about 8 mmHg, and the remaining flow rate below 30% of control.

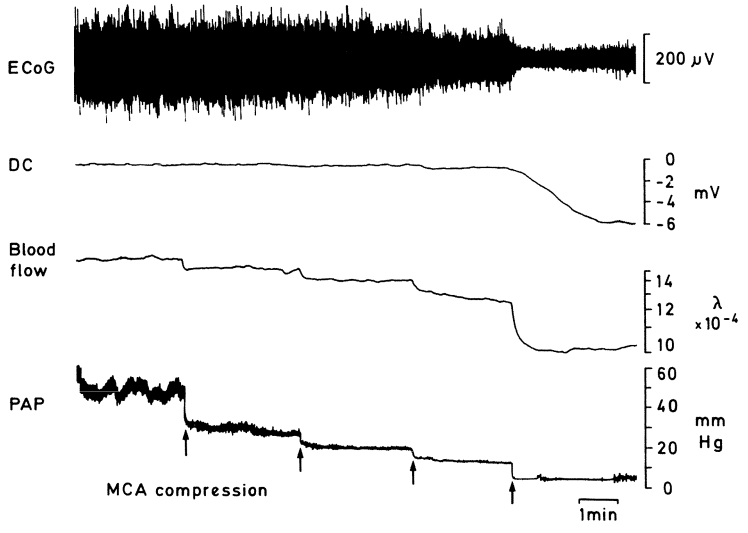

Fig. 1. Recording of the electrocorticogram (*ECoG*), cortical steady potential (*DC*), blood flow, and pial artery pressure (*PAP*) during stepwise compression (*arrows*) of the left middle cerebral artery (*MCA*). Note the different thresholds of PAP and blood flow for inducing changes of ECoG and steady potential. λ, thermal conductivity (4)

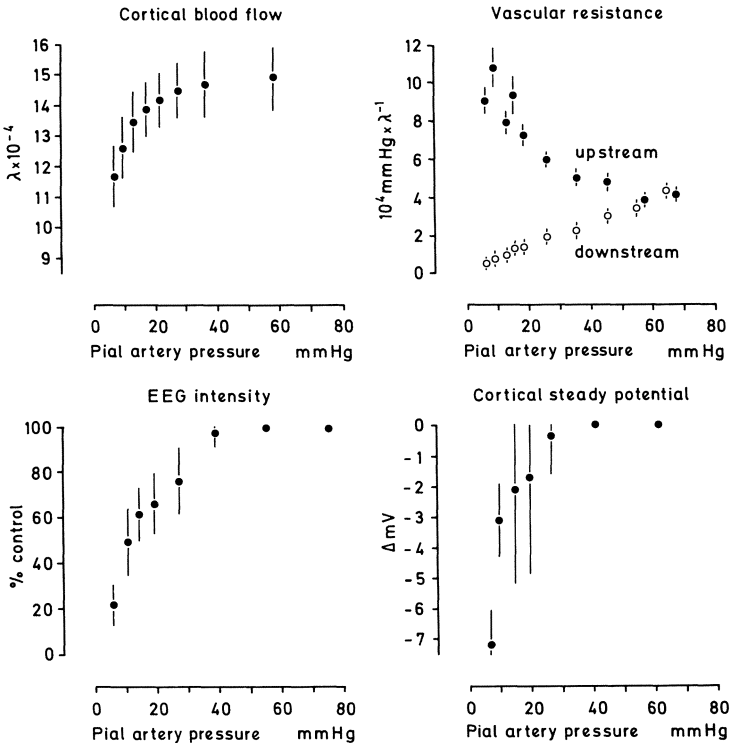

Fig. 2. Relationship between pial artery pressure, cortical blood flow, vascular resistance, EEG intensity, and cortical steady potential during compression of the left middle cerebral artery. Upstream vascular resistance refers to the extracerebral vascular bed from the aorta to the pial arteries, and downstream resistance from the pial arteries to the cerebral veins (means ± SD). λ, thermal conductivity (4)

The intensity of electrocortical activity (measured by Fourier frequency analysis) begins to decline as soon as pial arterial pressure decreases to between 30 and 40 mmHg. Changes of cortical steady potential appear as soon as pial arterial pressure is reduced to 20-30 mmHg. Maximum changes in both EEG and cortical steady potential appear no sooner than the middle cerebral artery is completely occluded, i.e., at a pial arterial pressure below 10 mmHg.

Determination of fractional pressure drops between systemic arterial and pial arterial, and pial arterial and central venous pressure allows the calculation of segmental resistances of the peripheral and intracerebral vascular bed, respectively. As shown in Fig. 2, intracerebral resistance gradually declines over the whole range of pial arterial pressures observed, indicating that maximum dilation of parenchymal vessels does not occur before the middle cerebral artery is completely occluded. This demonstrates that blood flow begins to decrease before the lower limit of the autoregulatory capacity of the vascular bed is reached.

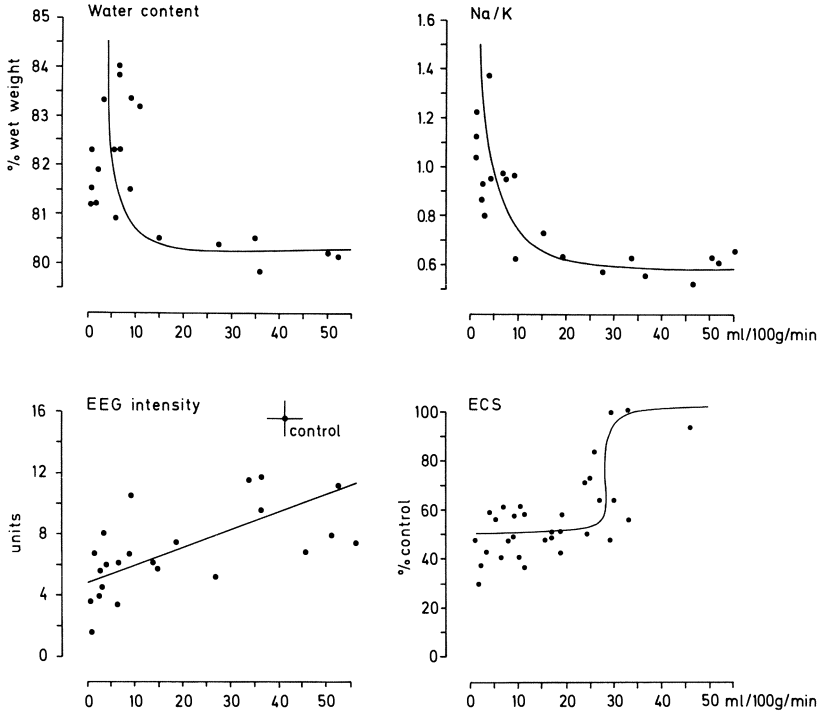

Fig. 3. Relationship between blood flow (*abscissa*) and brain water, the ratio of sodium/potassium content (Na/K), the relative volume of extracellular space (*ECS*), and EEG intensity (*ordinates*) 1-4 h following middle cerebral artery occlusion. Measurements were performed in the cortex of the middle cerebral artery territory. Preischemic control values of EEG intensity are indicated by the *bars* (mean ± SE) (6)

Evolution of Brain Infarction

Thresholds of cerebral blood flow for maintenance of water and electrolyte homeostasis were determined in animals in which blood flow was measured by the intracardial microsphere injection technique. This allowed the measurement of blood flow in the same tissue sample which was used for the analytical assay. The threshold for maintenance of water and electrolyte homeostasis was 10-12 ml/100 g/min (Fig. 3); this value closely corresponds to the threshold determined by BRANSTON et al. (2) with ion-sensitive electrodes. The threshold for the beginning narrowing of extracellular space was substantially higher and amounted to 25-30 ml/100 g/min. Disturbances of cellular volume regulation, in consequence, occur at a higher threshold than those of total water or electrolyte content of tissue.

Metabolic disturbances after middle cerebral artery occlusion also occur at flow levels which are substantially higher than those for maintenance of ion homeostasis. Using multiparametric imaging techniques for simultaneous measurement of regional blood flow, regional pH, and the regional tissue content of ATP, glucose, and potassium, evidence could be provided that tissue acidosis and disturbances of energy state occur at flow values between 20 and 30 ml/100 g/min, whereas decrease in tissue content was restricted to those areas in which blood flow de-

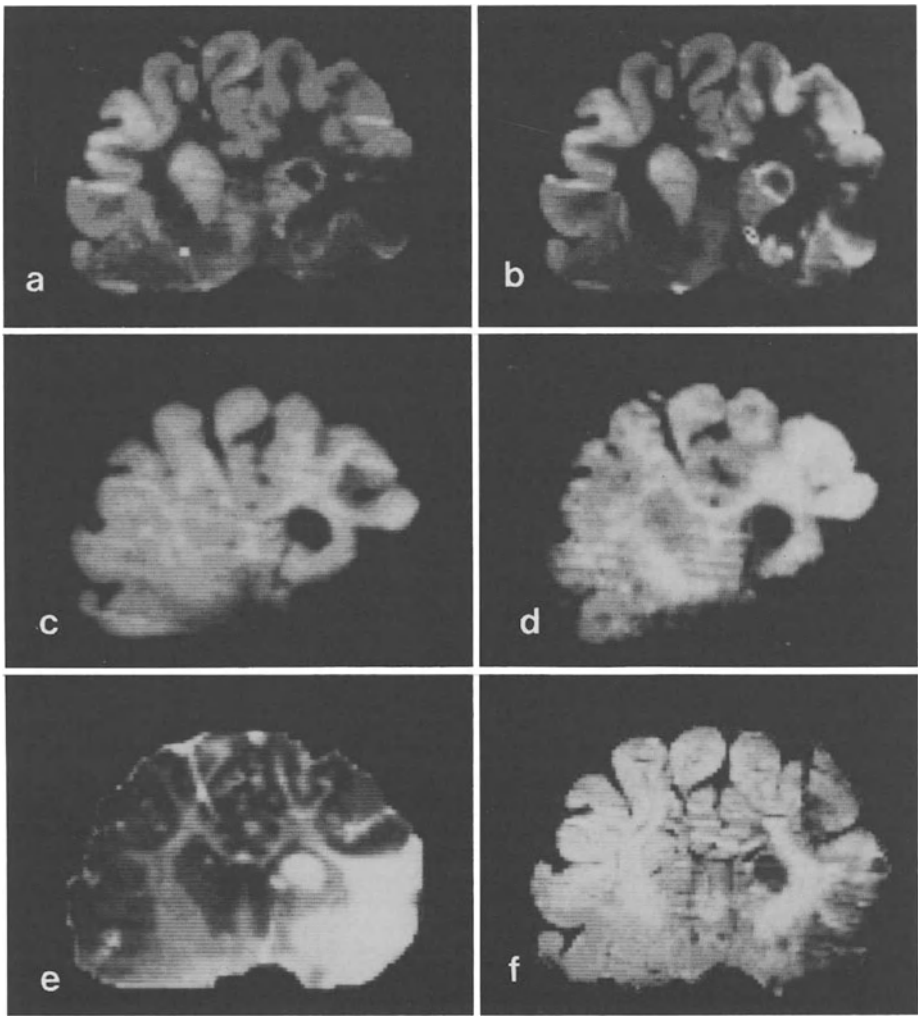

Fig. 4. Multiparametric imaging of cerebral blood flow (a), glucose utilization (b), ATP (c), glucose (d), tissue pH (e), and potassium content (f) 2 h after occlusion of the left middle cerebral artery in cat. Note the different regional extent of hemodynamic and metabolic alterations. Density coded reconstructed images; high brightness corresponds to high values with the exception of tissue pH, which decreases with increasing brightness (7)

creased to below 10 ml/100 g/min. Owing to the gradually decreasing perfusion pressure from the periphery toward the central parts of the middle cerebral artery territory, flow values are usually higher in the periphery than in the center of the affected territory. Accordingly, the extent of areas with manifested metabolic disturbances or tissue acidosis is usually much larger than the regions in which ion homeostasis is disturbed (Fig. 4). The decrease in intracellular pH causes a stimulation of the Na^+/H^+-antiporter, resulting in a shift

of sodium and water from the extracellular into the intracellular compartment. This explains why the threshold of blood flow for disturbances of cell volume regulation is in the same range as that for maintenance of normal metabolic activity.

The *relationship between blood flow and glucose utilization* is complex because decreasing blood flow initially activates glycolysis before glucose utilization begins to decrease. Moreover, glucose use does not correlate with ATP production because the energy yield of anaerobic glycolysis is only 5% of oxidative phosphorylation. Even the simultaneous measurement of oxygen consumption does not allow the calculation of energy yield because ischemia may cause various degrees of uncoupling of oxidative phosphorylation (13). It is, therefore, not surprising that during the early phase of infarct evolution glucose utilization does not correlate with either blood flow, energy state, or electrolyte homeostasis (Fig. 4). Such a correlation develops only after demarcation of infarct, i.e., after all metabolic activity has ceased due to tissue necrosis.

Conclusions

Experimental studies on the evolution of brain infarction in cat have revealed that correlations exist between regional perfusion pressure, blood flow, and disturbances of functional and metabolic activity of brain tissue. However, owing to inhomogeneities of perfusion pressure within the ischemic territory, metabolic and functional disturbances are also inhomogeneous. The regional extent of metabolic disturbances correlates best with the development of tissue acidosis, whereas cell membrane depolarization as an indicator of critical functional impairment correlates with the beginning decrease in tissue potassium content. During the early stage of infarct evolution the relationship between regional glucose utilization and either hemodynamic or metabolic disturbances is complex and, therefore, of little relevance for the evaluation of the density and severity of the ischemic impact. Measurements of blood flow, on the other hand, are meaningful only if the various thresholds of ischemic injury are considered. The effects of therapeutic interventions in ameliorating evolving stroke, therefore, cannot be evaluated by measuring blood flow and metabolic rate alone but should be assessed by determining the energy state and ion homeostasis of the brain.

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Experimental Basis for Secondary Prophylaxis in Atherosclerosis of Brain-Supplying Arteries

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Bypass operations in patients with stenosis or occlusion of arteries supplying the brain are confronted by the problem of having to avoid recurrences or occlusions of other arteries. The therapist attempts to eliminate evident risk factors as far as possible, for example by recommending a suitable diet to avoid or reduce hyperlipidemia. Whether secondary prophylaxis of atherogenesis by additional treatment with drugs is justifiable depends on the availability of suitable drugs. There are substances which decrease blood lipids or serum cholesterol in certain forms of hyperlipidemia, e.g., *cholestyramine* is a typical representative of a group of drugs which decrease serum cholesterol. Various drugs which contain derivatives of *clofibrate* can decrease the level of low density lipoproteins in blood and, in combination with anticoagulants or inhibitors of platelet aggregation, the formation of thrombi at the surface of a vessel wall denuded of its endothelium.

However, despite the possibility of secondary prophylaxis of arterial occlusions, reinfarctions due to atherosclerotic lesions are frequent. This may be attributable to the multifactorial nature of atherogenesis and to the fact that very often it is not sufficient merely to decrease the cholesterol level in blood. Hence it is imperative to control the development of atherogenesis.

In patients it is difficult to check the inhibitory effect of an antiatherogenic drug within a reasonable period of time. This is obviously due to the lack of methods which are sensitive enough to follow the development of intimal proliferation with a precision that allows the controlling of its thickness. The present state of development in the therapeutic sector calls for other possibilities for controlling atherogenesis. The investigation of antiatherogenic drugs in recent years has led to the development of experimental techniques which permit precise control of drug effects on ahterogenesis. Although results obtained from animal experiments and cell cultures still require verification and controls in patients, they have become an indispensable instrument in this field of research. Experiments in animals where atheromas in a carotid artery wall can be produced are suitable for the study of atherogenesis in arteries that supply the brain.

By means of a technique which primarily does not crudely destroy the endothelial lining, a proliferate can be produced at a selected site of a carotid artery. The wall of the artery is transmurally stimulated with locally applied weak electrical stimuli (for details of the procedure, see BETZ and HÄMMERLE 1984). Daily repeated transmural stimulation for 30 min in the morning and 15 min in the afternoon with 0.1 mA, 12 Hz, 10 ms/impulses causes within a short time a proliferate beneath the anode. After a 10-day period of stimulation the proliferate consists

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mainly of smooth muscle cells (SMCS) which migrate through the elastic internal lamina into the subendothelial space and proliferate within the intima. The plaque also contains small amounts of granulocytes and mononuclear cells from the blood. In rabbits which received 1% cholesterol in the chow the stimulation caused within the same period of time a typical atheroma. The atheroma contained not only SMCS but also a higher amount of lipid-loaded macrophages. After a stimulation period of 28 days with the same type of stimuli as in the 10-day experiments, proliferations of considerable thickness developed. Standardization of time, intensity, and duration of stimulation permits the measurement of the development of a proliferate. After a stimulation period of 28 days with standardized stimuli the maximal number of cell layers which developed at the stimulated site was counted and amounted to 13.3 ± 7 cell layers. The vessels were stimulated as described above. With this simple technique a standardized procedures is available by means of which one can ascertain whether a drug added to the food of animals or administered by injections is antiatherogenic.

Table 1. Effect of various drugs administered either orally with food pellets (O) or by subcutaneous injection (s.c.). The measure of the thickness of the proliferation was obtained by counting the maximal number of cell layers which had grown beneath the stimulating electrodes. The table gives the % reduction of plaque growth in drug-treated animals with 1% cholesterol in their food in comparison with animals which received a chow containing 1% cholesterol but no drugs. The changes in serum cholesterol and serum triglycerides are also compared with animals not treated with drugs

Substance	Daily doses (mg/kg body weight)		% change of plaque growth in comparison with controls (number of cell layers)	% change of serum cholesterol in treated animals	%change of serum triglycerides in treated animals
Etofibrate	200	(O)	-25	-15	+80
SP 54	25	(s.c.)	-55	-25	+280
Flunarizine	30	(O)	-68	-35	-30
Verapamil	21.5	(O+s.c.)	-48	- 5	+50
Oktimibate	30	(O)	- 5	-25	+15

It was observed that different drugs were capable of inhibiting the proliferation of SMCS in vivo (Table 1). Investigation of the uptake of oil red stainable lipids into the artery wall revealed that no strict coupling exists between the extent of proliferation beneath the stimulating electrodes and the degree of lipid content of the plaque. There is also no clear correlation between serum cholesterol or serum triglycerides and the development of plaques under the influence of drugs. The proliferate did not grow in fixed proportions to the serum cholesterol or serum triglycerides. Furthermore, the initial stimulations caused significant increases in the permeability of macromolecules up to a molecular weight of 40 000 mass units beneath the anode, the site where proliferations appear. Oral or subcutaneous administration of *flunarizine*, *verapamil* or *nimodipine* to the animal inhibited the permeation of peroxidase through the endothelial lining, thus indicating that one component of the antiatherogenic action of these calcium antagonists is the inhibition of endothelial permeability to macromolecules.

The question of whether the inhibitory effect of a drug on the development of a plaque can be attributed to its toxicity to the proliferating cells cannot be resolved with sufficient precision in animal experiments alone. Furthermore, in vivo experiments cannot reveal whether the drugs inhibit specifically the growth of the SMCS or whether proliferation and growth of other cells are also influenced. In order to address this question, cultures of SMCS and fibroblasts and in some cases endothelial cells were used. It could be seen that some of the antiatherogenic drugs, e.g., *calcium antagonists* or *etofibrate* inhibit, unspecifically, myocytes as well as fibroblasts. Some calcium antagonists inhibit massively endothelial cells. Other drugs are also available which specifically inhibit the proliferation of SMCS without influencing the growth of fibroblasts. Polyanions of the heparin type are drugs which act in this way. Thus, one can see that the individual drugs affect different processes of atherogenesis. Of the substances mentioned, heparin derivatives seem to be most closely related to the inhibitory substances produced by the body to prevent excessive proliferation of cells. However, drugs of this type have the disadvantage that the doses have to be relatively high before sufficient blood concentrations can be obtained. In heparins, apart from the molecular weight, the degree of sulfation also plays a role in the inhibitory effect and further experience is necessary before suitable *sulfated polyanions* can be produced to inhibit effectively SMC proliferation in vivo.

The other substances mentioned are already in use as drugs but they do not inhibit specifically a single cell type. In the experiments the drugs were not applied in combination so as to avoid obscuring the individual drug action. Although the combination of various drugs is possible for secondary prophylaxis of atheromatosis, one has to realize that atherogenesis is multifactorial prior to justifying a particular therapeutic system for the fight against this widespread disease.

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Improvement of Cerebral Blood Flow in Acute Ischemia of the Brain

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The most appropriate therapy for acute cerebral ischemia is still a matter of debate. Attempts at vasodilation by hypercapnia (14a), pharmacological vasodilatation (16), and barbiturate protection (17) have not gained general acceptance:
Hypercapnia and administration of *cerebral vasodilators* may cause steal effects, so decreasing flow in the tissue of concern. *Hyperventilation* with consecutive vasoconstriction may cause an increase of flow in the ischemic tissue if vasoparalysis has taken place. However, in the neighborhood with reacting vessels, blood flow may be at a critical level which during hypocapnia leads to further flow depression and provocation of true ischemia.

Barbiturate protection, which has proven to be of benefit in some but not all experimental studies with global and focal ischemia (14, 19), has been investigated in one clinical study of acute ischemic stroke (1). However, the mortality was unacceptably high in the control group, which was treated with dextran. Therefore the design of the study could not prove that barbiturate therapy is superior to the natural course or to other therapeutic protocols which have shown some beneficial effects (8, 9, 13, 21). An important disadvantage of barbiturate therapy is the need for it to be introduced very early, at a stage where the clinician - even if using all the technical tools available - cannot decide on the likely clinical fate of the patient. Moreover barbiturate therapy would require a general anesthetic for *all* patients, including those with initial mild deficit. This seems highly impractical and excludes this therapy from the routine management.

Improvement of *perfusion pressure* may be of advantage to the tissue if autoregulation has failed. In cases with elevated intracranial pressure (ICP), administration of hyperosmolar solutions is able to reduce ICP, this increasing perfusion pressure transiently. However, substances with slow excretion such as mannitol may cross the damaged blood-brain barrier and then reverse the osmotic gradient. This provokes an increase in tissue water content in the second phase, with reduction of flow and increase in ICP (rebound phenomenon). Therefore hyperosmolar solutions should be administered only if brain edema with a space-occupying effect has been proven by computerized tomography or by clinical signs. Direct measurements of ICP would be desirable but are not undertaken at present in most patients with ischemic stroke.

An increase in perfusion pressure may be further achieved by elevation of blood pressure. This procedure may be used during surgical intervention to overcome the ischemic effects of existing vasospasms. In cases with thromboembolism and subsequent cerebral insult an increase

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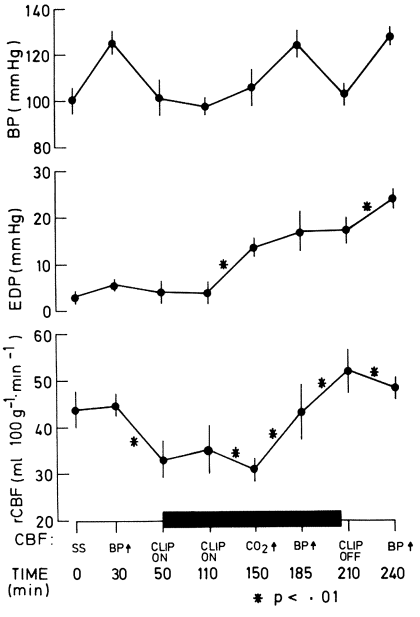

Fig. 1. Effect of high blood pressure on cerebral blood flow in focal cerebral ischemia (n=3). Focal cerebral ischemia was provoked by ligation of the middle cerebral artery *(black bar in the horizontal axis)*. rCBF was measured over the territory of the middle cerebral artery using the intraarterial xenon 133 device and externally arranged sodium iodine crystals. *BP*, blood pressure; *EDP*, epidural pressure; *rCBF*, regional blood flow. The figure indicates that during postischemic hyperperfusion (at 210 min) rCBF increased and that increase in blood pressure (at 240 min) increases EDP and decreases flow (inverse autoregulation).

in blood pressure can result in hemorrhagic infarction (though this has been described only rarely). In addition, an increase in blood pressure is capable of decreasing cerebral blood flow (CBF) by the following mechanisms: Figure 1 indicates the results of an experiment in three baboons. During steady state, an increase in blood pressure did not have any effect on epidural pressure (EDP) and regional CBF (rCBF) in the territory of the middle cerebral artery. After complete clipping of the middle cerebral artery, hypercapnia (CO_2) resulted in an increase in EDP and a decrease in rCBF but not in a significant change in blood pressure. The decrease in rCBF was probably due to steal effects. During the increase in blood pressure (at 185 min after the start of the protocol), EDP did not change significantly but rCBF increased since perfusion pressure was improved. After the clip was taken off (at 210 min) rCBF rose significantly to luxury perfusion although EDP was increased. At this stage blood pressure was kept normal. If blood pressure was now increased again, EDP rose by induced hypervolemia and led to a reduction in flow. This observation indicates that during luxury perfusion with consequent hypervolemia ICP might increase and that any additional procedure which increases total intracranial volume may cause a reduction in rCBF (inverse autoregulation). It cannot be excluded that the increase in blood pressure after 200 min of provoked ischemia with release of the clip and luxury perfusion might support the development of brain edema (vasogenic type). This again underlines that improvement of perfusion pressure by increasing blood pressure should be undertaken with great care and direct measurement of ICP and CBF.

Rheology

Besides vascular diameter and perfusion pressure, blood flow to the brain is further influenced by metabolic control mechanisms of the brain and by characteristics of blood itself. There are almost no

studies which prove significant improvement of brain function during acute ischemia by metabolic therapeutic regimens (in contrast to experimental cardiac ischemia (23). In respect to blood characteristics it must be noted that during the normal state of tissue perfusion rheologic parameters have little influence on CBF. However, if metabolic control and control by autoregulation and CO_2 responsiveness are lost, rheologic parameters may play a decisive role in cerebral flow. This effect has been used to increase CBF by reducing hematocrit following hemodilution (10, 11). Studies in patients with cerebrovascular disease have revealed that infusion of low molecular dextran might increase flow by between about 2% (11) and more than 50% (10). However, these studies have not been performed in patients with acute cerebral ischemia and therefore do not prove that hemodilution in acute ischemia might normalize flow. Our own studies with hydroxyethylstarch (500 ml 200/0.5) or low molecular weight dextran (500 ml dextran 40) have indicated that rCBF might be increased, if hemodilution is performed for at least 7 days. This protocol, however, does not prove that hemodilution really normalizes tissue *function* and *clinical* condition in acute strokes. Clinical studies are contradictory (9, 13) and at present there is no incontrovertible proof that hypervolemic or isovolemic hemodilution is of benefit to patients with acute cerebral ischemia.

From the experimental point of view there are some arguments against the beneficial effect of reducing hematocrit:

1. If the cardiopulmonary reserve is reduced, hemodilution to a hematocrit of 35% might reduce oxygen transport capacity in dogs (20).
2. During isovolemic hemodilution and ligation of the middle cerebral artery in cats, cortical PO_2 might not rise above the pathologic decreased value (5). CBF was not measured.
3. Therapeutic plasmapheresis in patients with elevated plasma viscosity might reduce viscosity and keep hematocrit constant. Brown and Marshall have reported that in this protocol CBF did not change, thus indicating that hemodilution leads to an increase in CBF only to compensate for the reduction of flowing red cells per volume blood and time (4). From this study it seems that *plasma* viscosity has only a slight influence on blood flow in the brain. It should be noted that these patients did not suffer from strokes.

Since cardiopulmonary reserve is not always restricted and since patients with stroke lack the physiologic control of cerebral circulation by vascular diameter, autoregulation, blood gas reactivity, and metabolic demand, there are some indications for the importance of hemodilution in these patients. However, several requirements must be fulfilled:

1. It must be possible to increase cardiac output (direct measurement of cardiac output).
2. CBF above normal values (luxury perfusion) must be excluded to avoid further hypervolemia by hemodilution. CBF should be measured.
3. Blood-brain barrier lesions must be excluded by computerized tomography (contrast medium injection). If the blood-brain barrier is damaged, oncotic solutions can cross it and cause vasogenic edema.
4. ICP must not be increased (if possible it should be controlled by direct measurements) to avoid further hypervolemia by hemodilution with provocation of critical ICP values.

Calcium Antagonists

Calcium antagonists have received considerable interest in recent years in respect of cerebral function. Under physiologic circumstances the extracellular concentration of calcium (10^{-3} µ/liter) is 10 000-fold higher than that inside the cell. The gradient is attributed to the limited permeability of the cell membrane and to a sensitive mechanism of calcium exchange between calmodulin, mitochondrium, calcium-binding protein, sarcoplasmic reticulum, calcium binding to the cell membrane, and the outward transport via a Na^+-Ca^+ antiport system and an ATPase-dependent calcium pump. Following extracellular stimulation, Ca^+ may enter the intracellular space via a receptor-operated or a voltage-operated channel. It then exerts its effects as a second messenger.

Following complete ischemia the dysfunction of the Na^+/K^+-ATPase leads to massive extrusion of K^+ from the cell and simultaneous Na^+ influx (18). Extracellular accumulation of K^+ provokes vasoconstriction, which is further promoted by influx of Ca^+ and binding to contractile proteins within the vascular smooth muscle.

Attempts have been made to counteract the influx of Ca^+ using so-called calcium antagonists, of which a few have received attention in regard to cerebral ischemia.

Nimodipine, a derivative of nifedipine (which is used in the treatment of cardiac insufficiency and high blood pressure) acts primarily on the cerebral vascular wall and is able to cross the blood-brain barrier. In the light of experimental observations nimodipine is believed to neutralize pathologic vasoconstriction and has been used in two important clinical studies: ALLEN et al. (2) evaluated the clinical effect of oral nimodipine in a double-blind controlled multicenter study in patients suffering from subarachnoid hemorrhage (SAH) and found that in the treated group fatal courses occurred significantly less often. This beneficial effect was believed to be due to the antispastic action of nimodipine. While the study was not designed to answer the question of whether nimodipine is able to dilate *existing* vasospasm, it seems obvious that the development of vasoconstriction following SAH may be impaired. In addition to this, BRÖKER et al. (3) have reported that injection of nimodipine into the internal carotid artery of the involved side may resolve or at least reduce existing vasospasms. This last report did not state whether the clinical picture due to existing vasospasm may be mitigated.

The effect of nimodipine on CBF in patients with SAH has not been evaluated sufficiently. Gaab et al. (1985) have stated that nimodipine does not cause intracerebral steal phenomena. However, this study was not based on patients with *acute* ischemia (vasoparalysis with the possibility of steal effects occurs predominantly during the acute stage of ischemia). Our own limited experience in patients receiving nimodipine indicates that there may be shifting of blood between differing territories of vascular supply, resulting in steal or counter-steal phenomena (Fig. 2).

The only study which has evaluated the effect of nimodipine in patients with acute cerebral ischemia due to thromboembolism on a controlled basis has been that by GELMERS (8). The control group, which was treated with hemodiluting maneuvers only, had a slower and less complete recovery than the group treated with nimodipine in addition. The improvement concerned primarily the level of consciousness. Our interpretation of the literature available to date is that the calcium

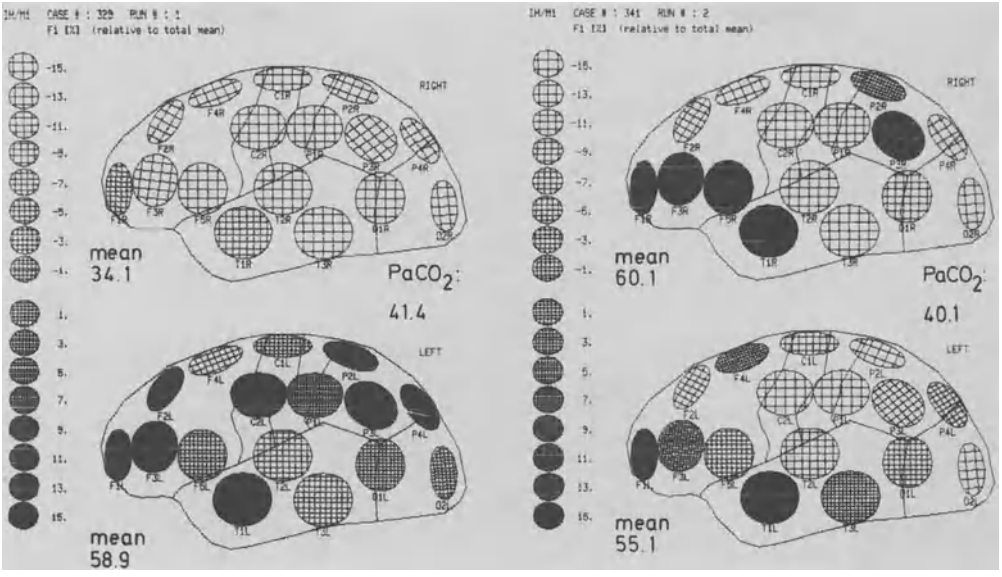

Fig. 2. Regional cerebral blood flow in subarachnoid hemorrhage. Hemispheres on the *left* of the figure indicate relative distribution of flow on day 5 after hemorrhage; hemispheres on the *right* indicate flow distribution 6 days later, after therapy with nimodipine. Vasospasm was demonstrated by angiography and controlled by transcranial Doppler sonography. From day 5 to day 11 blood flow in the right hemisphere increased from 34.1 to 60.1 (ml/100 g/min) *(upper hemispheres, left* and *right* of figure). Mean flow in the left sides of the brain (*lower hemispheres* in the figure) did not change significantly but the territory of the middle cerebral artery presented with flow reduction after nimodipine therapy. A rebleeding had not occurred.

antagonists have not been investigated sufficiently to replace other therapeutic regiments for cerebral ischemia due to thromboembolism. However, if increased ICP (which should be directly measured), vasoparalysis (controlled by blood flow measurements), and communicating hydrocephalus are excluded, we do use nimodipine as a preventive agent in patients with SAH who are not operated on immediately.

Flunarizine seems attractive since it is said to cross the blood-brain barrier as well and has primarily cell-protecting effects (22). It was shown that flunarizine prevents the pathologic overload of Ca^+ in the intracellular space and does not block the normal transfer via the Ca^+ channels. Several studies have indicated a beneficial effect on classic migraine (15).

As yet no study has proven that flunarizine has beneficial effects on clinical action in cerebral ischemia following SAH or thromboembolism. Our own experiences in baboons with focal ischemia, however, indicate that after clipping of the middle cerebral artery, early administration of doses of 0.5-1.0 mg/kg body weight may partially impair the ischemic cascade, resulting in progressive flow reduction. It is too early to draw any clinical conclusions from these observations.

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The Effect of Nimodipine on Cerebral Blood Flow Autoregulation

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Introduction

Experimental and clinical investigations show that the cerebrovascular calcium antagonist, nimodipine, a dihydropyridine derivative, increases the cerebral blood flow (CBF) (5, 8, 11, 13). The effect is attributed to a loss of contractibility of the major vessels of the brain (16) and to a dilatation of the pial vessel (1). Cerebral autoregulation is an adaptive reaction which maintains the blood flow to the brain nearly constant in spite of variations in cerebral perfusion pressure (15). Autoregulation depends on the responsiveness of the cerebral arteries and the cerebral microvasculature to changes in the arterial blood pressure (9). With mean arterial blood pressures above the lower limit of autoregulation, the CBF is maintained by constriction of cerebral arteries and microvessels (9). Conceivably, an agent which inhibits smooth muscle contraction of the vessels by blocking the calcium influx might impair the cerebral autoregulation. Although important for clinical decisions, the effects of nimodipine on cerebral autoregulation have not been clarified up to now.

Material and Methods

Animals, Anesthesia, Operation

Twenty Wistar rats weighing 250-280 g were randomized into two groups of ten rats each. Anesthesia was induced with ketamine (Ketanest) (100 mg/kg b.wt.) and xylazine (Rompun) (20 mg/kg b.wt.) and then maintained by ketamine 60 mg/kg every 30 min. The left femoral artery and both femoral veins were catheterized and the animals were tracheotomized. The skulls were affixed in a sterotactic frame, the scalp was incised, and on each side a small craniotomy was performed 1 mm shy of the sagittal, coronal, and lambdoid sutures, reaching laterally 1 mm below the superior temporal line. The dura was opened under the microscope. A laser Doppler flow probe (Periflux) was installed on one craniotomy and a superficial hydrogen electrode (Eschweiler Company, Kiel, FRG) on the other for assessment of local cortical blood flow (lCBF). All animals received 1 ml of a 6% solution of hydroxy ethyl starch of molecular weight 60 000 to compensate for potential losses of volume during surgery. The arterial blood pressure was monitored and the lCBF determined as described below at various blood pressure levels. Variations were induced by infusion of norfenefrine (Novodral) (pressure increase) and by hemorrhage (pressure decrease).

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Treatment

In the treatment group the animals received a continuous infusion of nimodipine at a dosage of 12-24 µg/kg b.wt./h for at least 15 min before commencing the measurements at different blood pressure levels. The dosage was adjusted within this range so that only a slight decrease in blood pressure was observed.

Determination of CBF

The CBF was determined by a laser Doppler flow probe, which gives relative values of lCBF, and by the hydrogen clearance method (2, 7, 14, 17), which allows a quantitative approach. The ion selective multiwire electrode (Eschweiler Company, Kiel, FRG) consists of platinum wires in an insulating medium inside a ring-shaped Ag/AgCl reference electrode with a diameter of 4 mm. It is placed directly on the brain surface with a counterbalance allowing only gentle contact and no pressure to the tissue. It measures the local tissue hydrogen concentration. The animal inhales a gas mixture containing 10% H_2 until a steady state is reached. After finishing inhalation the clearance curve is plotted. The slope of the curve yields the lCBF in ml/g tissue/min. The slope was computed from the clearance curve over a time interval of 50 s, excluding the first half-time from evaluation.

Results

The *control* animals showed a typical autoregulation curve, with a lower limit of 70 mmHg and an upper limit of 120 mmHg. Within this range the lCBF was maintained nearly constant at a level of about 120 ml/100 g tissue/min (Figs. 1, 2). In the *nimodipine-treated* animals the curve showed only a slight diminution of the slope but *no constant plateau* of the blood flow in the range at which autoregulation would be expected (Figs. 3, 4). The lCBF was increased markedly by nimodipine at all blood pressure levels. Interestingly, in three animals of the nimodipine group a massive subarachnoid hemorrhage was observed at blood pressure of 150 mmHg. In the control group only one bleeding occurred, this at a blood pressure of 200 mmHg.

The Doppler values were evaluated only intraindividually, which seems logical because they are only *relative* data not readily comparable with data from the other animals. The interpretation is still equivocal but in the majority of animals without nimodipine an increase in blood pressure resulted in a rise of the Periflux signal, and vice versa, over the whole range without showing a tendency toward maintenance. Precise evaluation was difficult because of the shift of the signal level during the experiment, so that changes could only be judged from one step to the other. In the nimodipine-treated rats the relation was similar but there was a tendency to maintain the Doppler signals within a more limited range.

Discussion

The autoregulation curve of the control animals agrees quite well with data from the literature, especially with regard to the lower limit (3, 9, 10, 12, 18). The upper limit is lower than the reported values of about 160 mmHg. This may be explained by the use of ketamine, as autoregulation depends on various influences, including anesthesia (15). The same holds true for the absolute flow values,

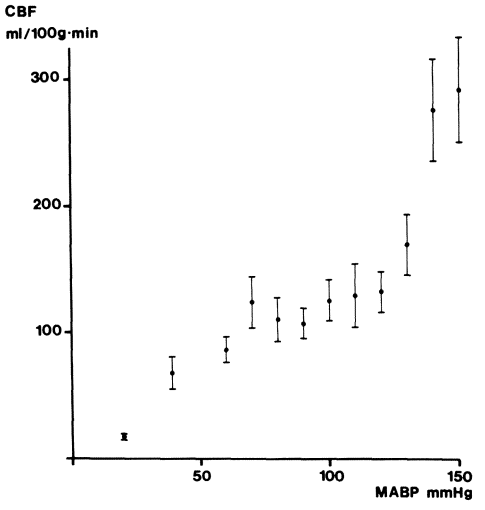

Fig. 1. Values of CBF at various mean arterial blood pressures *(MABP)* of the control animals (means ± SE)

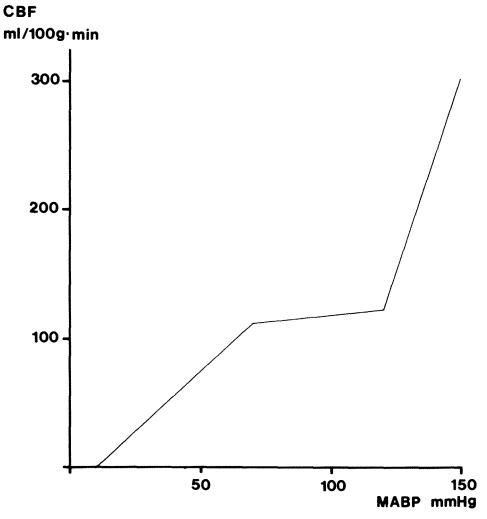

Fig. 2. Correlation curve of MABP and CBF of the control animals obtained by calculating least squares regression lines

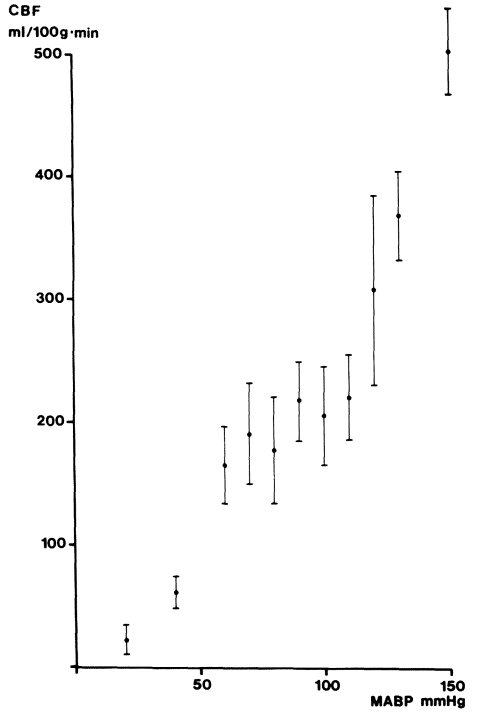

Fig. 3. Values of CBF at various mean arterial blood pressures *(MABP)* of the nimodipine-treated animals (means ± SE)

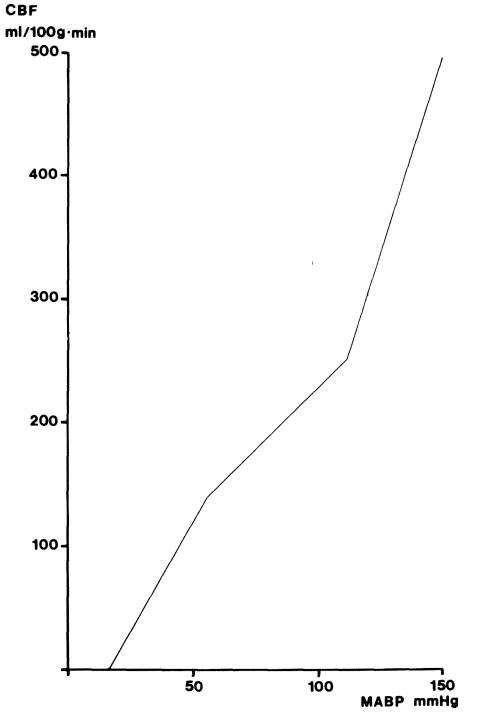

Fig. 4. Correlation curve of MABP and CBF of the nimodipine-treated animals obtained by calculating least squares regression lines

which are rather high in our study, probably due to elevated cerebral metabolism with ketamine (6). Nevertheless, the values from the control group and from nimodipine-treated animals can be compared because they were obtained in identical conditions except for the infusion of nimodipine. It could be shown that the CBF increase induced by nimodipine is at least partly due to impairment of autoregulation. With regard to the clinical situation it has to be noted that this may be beneficial in cases of partial impairment of autoregulation combined with low CBF, e.g., vasospasm following subarachnoid hemorrhage, because an increase in the total CBF can be achieved. On the other hand, it has to be kept in mind that particularly at higher blood pressures the protective effect of autoregulation is abolished, resulting in the possibility of breakthrough bleedings. This is probably more likely in the presence of lesional damage to the vasculature.

The laser Doppler does not seem to be a suitable device for the evaluation of CBF. This appears conceivable because the laser Doppler probe measures the blood velocity. Maintaining the CBF constant by constriction of the pial vessels at increasing blood pressure values should necessarily lead to an acceleration in the blood cell velocity, and this has indeed been proved recently (4). Our observations support these findings. The less marked response of the Doppler signal to variations in blood pressure under nimodipine agrees with this theory.

Conclusions

The increase in CBF during nimodipine infusion is combined with an impairment of cerebral autoregulation. This is probably caused by the vascular smooth muscles being rendered less responsive to changes in blood pressure.

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The Influence of Barbiturates on Cerebral Metabolism in Patients with Borderline Cerebrovascular Reserve in Carotid Surgery

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Introduction

When reconstructive operations on cerebral arteries are performed with temporary interruption of the blood supply to dependent perfusion beds, sufficient collateral circulation is of great importance. Without a sufficient collateral circulation, lack of oxygen and glucose will rapidly lead to profound changes in cerebral energy production. Concentration of lactate in the brain can be considered an important parameter of disturbance of cerebral metabolism.

EEG monitoring will soon detect an insufficient cerebrovascular reserve when cerebral blood flow is stopped during a test interruption pre- or intraoperatively (1). If there are symptoms of cerebral ischemia while performing the carotid compression test and if the operation is absolutely necessary, we propose that it be performed using so-called brain-protective measures. Experimental studies of such methods provide every reason to believe that barbiturates such as methohexital can diminish the disturbances of metabolism which occur during temporary cerebral ischemia or anoxia. The question we addressed was whether and to what extent methohexital-induced reduction of the cerebral metabolic rate as expressed by the burst suppression time in the EEG can influence the accumulation of lactate during transient cerebral ischemia.

Method

We examined 20 patients showing clinical symptoms as well as EEG signs of cerebral ischemia during a pre- and intraoperative test clamping of the internal carotid artery. Assessment of neurologic status was carried out pre- and postoperatively. Induction of anesthesia was performed with thiobarbiturate/fentanyl, while continuously and directly monitoring the blood pressure and the ECG. Anesthesia was continued by inhalation of enflurane in oxygen-nitrous oxide 50:50. During surgery under temporary interruption of the blood flow in the carotid artery for about 30 min, EEG was continuously monitored analyzed. Besides arterial blood samples according to the side operated on cerebral venous blood samples were taken before, 30 min after clamping of the carotid artery, and 10 min after reperfusion. Having collected the first sample, methohexital was administered until the induction of burst suppression on the EEG. Only then was cross-clamping of the carotid artery performed.

Among other parameters lactate concentrations were measured enzymatically and the arteriovenous difference (AVD) calculated. According to

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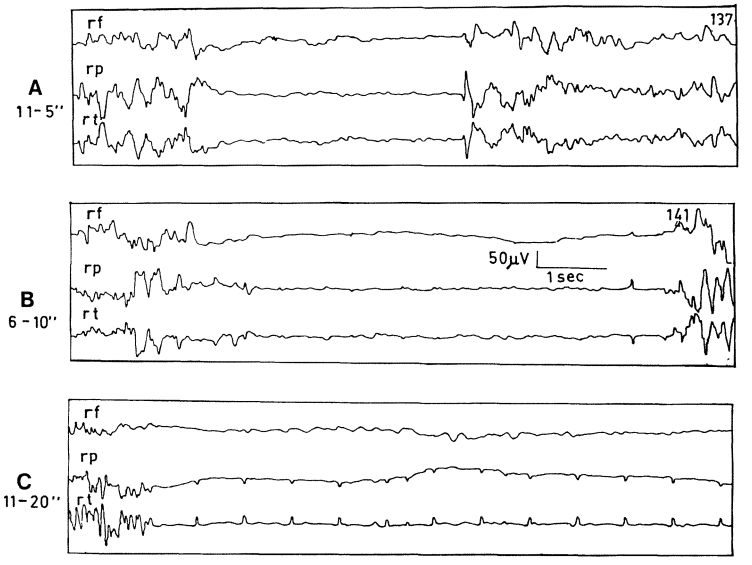

Fig. 1. Typical EEG pattern of patients in groups A, B, and C. *rf*, right frontal; *rp*, right parietal; *rt*, right temporal

the duration of burst suppression, patients could be divided into three groups (Fig. 1):
Group A: 6 patients with burst suppression time 1-5 s
Group B: 7 patients with burst suppression time 6-10 s
Group c: 7 patients with burst suppression time 11-20 s
In each of these groups the lactate concentrations were measured.

Results

The neurologic follow-up examination of all 20 patients showed that none had developed a neurologic deficit which could be related to the temporary cross-clamping of the internal carotid artery. Only one patient in group A (case 5) developed a speech disorder, probably caused by embolism 24 h after operation.

A synopsis of the lactate concentrations 30 min after cross-clamping of the internal carotid artery shows an increase to the upper limit in three patients in each of groups A and B (Fig. 2). In group C, with the most prolonged burst suppression time, all lactate concentrations remained in the normal range. The AVD lactate values in groups A and B appeared to be higher than in group C: The average for AVD lactate (Fig. 3) was 4.3 in group A, 1.5 in group B, and 0.87 mg/100 ml in group C.

The mean value for cerebral venous lactate concentrations was 18.1 mg/100 ml in group A, 15.5. in group B, and 10.5 in group C. The concentrations for blood glucose were in the normal range and did not show a correlation with the lactate concentrations.

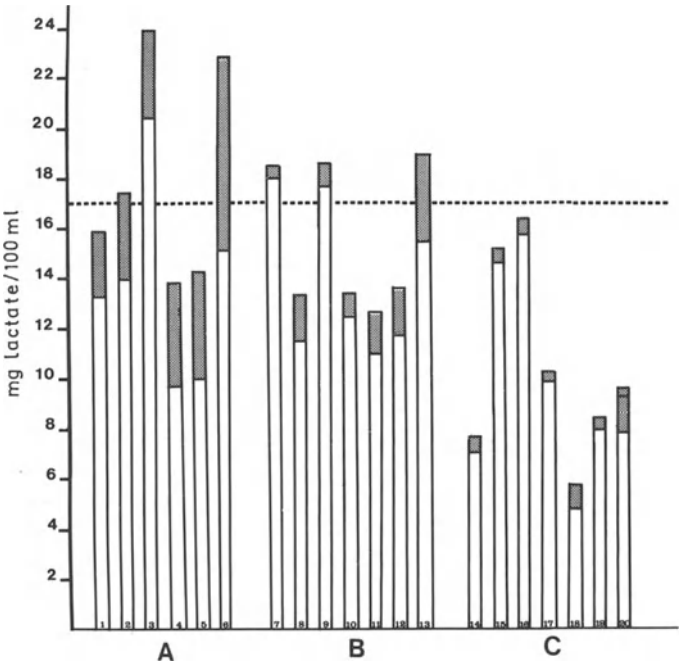

Fig. 2. Lactate concentrations 30 min after cross-clamping of the internal carotid artery. Patients are divided into groups A, B, and C corresponding to their burst suppression time. *Open bars* represent arterial and *hatched bars* cerebral venous lactate concentrations

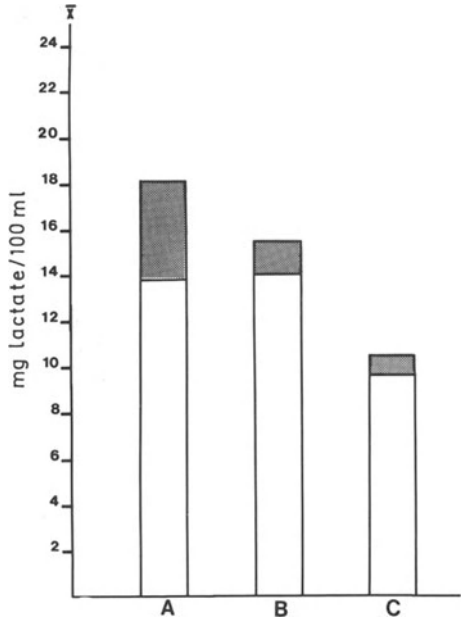

Fig. 3. Average lactate concentrations in groups A, B, and C 30 min after cross-clamping of the internal carotid artery. *Matched bars* represent AVD lactate values

Discussion and Conclusion

MICHENFELDER et al. (2) and SELMAN et al. (3) have described how barbiturates given before experimental occlusion of the middle cerebral artery of primates could lead to a significant reduction in the size of brain infarction and during general ischemia could ameliorate the cerebral energy production. HANKE and KRIEGELSTEIN (1) showed in their studies on isolated perfused brains of rats that as the basic mechanism of "brain protection," inhibition of the accelerated glycolysis due to the ischemia has to be considered. In their experiments SIESJÖ and WIELOCH (4, 5) described an immediate rapid increase in lactate concentration in cerebral ischemia, with a critical borderline of 15-25 $\mu mol \cdot g^{-1}$.

Our 20 patients with multilocular obstructive lesions of the cerebral arteries showing signs of borderline or even insufficient cerebrovascular reserve during the preoperative carotid compression test and having received methohexital during cross-clamping of the carotid artery did not show neurologic deficits due to ischemia during the postoperative neurologic follow-up, although six patients did show slightly elevated lactate concentrations during the phase of temporary ischemia.

The correlation of AVD lactate with the methohexital-induced burst suppression time could be an indicator that accumulation of lactate can be diminished by prolonged burst suppression time. In this connection it is noteworthy that none of the patients in group C (with a burst suppression time of 11-20 s) showed increased lactate concentrations and that AVD lactate values in this group were the lowest registered.

The question of "ideal" burst suppression time as an index for reduction of cerebral metabolism rate without impairment of cerebral perfusion pressure should be further investigated.

Acknowledgment. The authors wish to acknowledge the technical assistance provided by Mrs. M. Melchers and H. Jüngling.

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The Effect of Pentoxifylline on Cortical pO_2 in Cat and Human Brain

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The effect of pentoxifylline (Trental) on cortical pO_2 of normal cats was studied experimentally. Analogous measurements were performed in patients who underwent surgery for cerebrovascular disease.

The cats were anesthetized by intravenous injection of sodium hexobarbital and artificial respiration was performed. Arterial blood pressure, hematocrit, and hemoglobin as well as blood gases were monitored continuously. A parietal craniotomy was performed and a multiwire surface electrode (6) was placed on the brain cortex, using a specially balanced support. Thus, pressure effects of the electrode could be avoided and brain pulsations followed by the electrode.

After a steady state of all monitored functions had been achieved, baseline tissue pO_2 values were determined. With continuous registration of the pO_2 values, pentoxifylline was administered intravenously in a dosage of 10 mg/kg body weight over 2 min.

In all ten animals an increase in the pO_2 values could be observed following the infusion. In 77 documented recording sites, the initial values of 42.8 ± 21.2 mmHg increased to 50.8 ± 20.4 mmHg 1 min after the end of the injection and reached a maximum of 53.6 ± 21.1 mmHg 2 min after injection (Table 1). During the next 2 h, cortical pO_2 decreased slowly yet did not reach the initial value.

Table 1. Cortical tissue pO_2 and arterial pH, pO_2, and pCO_2 in dependence on the time after injection of pentoxifylline 10 mg/kg body weight in ten cats

Time after injection	Cortical pO_2 (mmHg)	pH	pCO_2 art (mmHg)	pO_2 art (mmHg)
Control	42.8 ± 21.2	7.39	29.4	115.2
1 min	50.8 ± 20.4			
2 min	53.6 ± 21.1			
15 min	50.0 ± 19.4	7.4	29.3	109.4
30 min	49.0 ± 18.1	7.39	29.3	116.6
60 min	47.0 ± 19.4	7.42	28.4	111.5
120 min	45.6 ± 20.4	7.42	28.5	118.7

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The t-test for paired samples was applied to prove statistical significance. During the first 30 min, the increase in pO_2 was significant at a level of 1% error probability. Arterial pH, pO_2, and pCO_2 did not show any significant changes (Table 1).

In order to test the clinical applicability of these observations, similar examinations were performed in six patients during extra-intracranial bypass operations. All of them underwent surgery because of cerebrovascular disease that had led to transient ischemic attacks corresponding to the brain area where the anastomosis was performed, i.e., the territory of the middle cerebral artery. All operations were performed before publication of the results of the international EC/IC bypass study.

The patients were kept in neuroleptanalgesia, arterial blood pressure was recorded continuously, and blood gases and chemistry were checked during the measurements. A small craniotomy was performed and the brain surface was exposed. The electrode was placed by using the same support, including a micromanipulator for exact movement across definite areas of the cortex. A pO_2 histogram was taken over 154 recording points (7), this technique being applicable only because of the use of the computerized equipment described by HAUSS (4). Sterilization of our electrode was also performed in the same manner as described in this publication. After the baseline histogram had been taken, 300 mg pentoxifylline in 5% was injected intravenously over 10 min. Five minutes after the end of infusion a second pO_2 histogram was taken in a similar manner and in the same area as before.

In all patients, pO_2 histograms shifted to the right after the administration of the drug, indicating an increase in mean pO_2 values. Figures 1 and 2 give an example of a pair of corresponding histograms with a right shift from a mean value of 52.5 mmHg to 66.3 mmHg. The right shift is stressed by a change in the distribution pattern of the histogram, with an asymmetric distribution of the value.

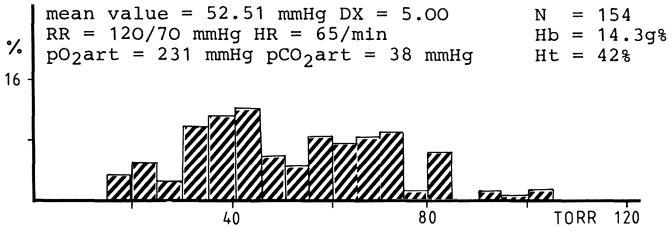

Fig. 1. Tissue pO_2 histogram of human brain cortex taken before administration of 300 mg pentoxifylline

The mean values of all 154 recordings per histogram are given in Table 2 for all patients. Their mean of 51.5 ± 27.1 mmHg before administration of pentoxifylline increased to 67.7 ± 32.9 mmHg afterward. The mean value for the individual differences of the histogram pairs is 16.25 ± 7.7 mmHg.

Application of the t-test again proves a significant difference between pO_2 values taken before and after the injection, with a probability of error of 1%.

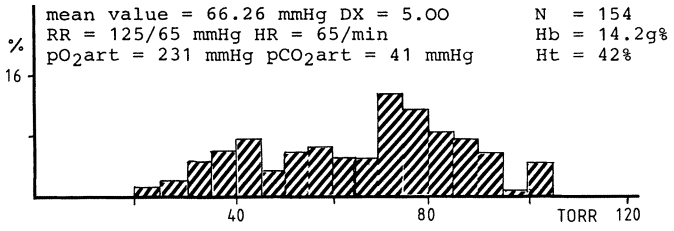

Fig. 2. Tissue pO_2 histogram of human brain cortex taken 5 min after the injection of 300 mg pentoxifylline. Note the right shift to higher pO_2 values in comparison to Fig. 1; the mean value for the histogram in Fig. 1 increases from 52.51 mmHg to 66.26 mmHg after the injection

Table 2. Cortical tissue pO_2 and arterial pH, pO_2 and pCO_2 before and after the injection of 300 mg pentoxifylline. Cortical tissue pO_2 is represented by the mean of all values contributing to a pO_2 histogram

Patient Nr.	Cortical pO_2 (mmHg)		pH		pO_2art (mmHg)		pCO_2 (mmHg)	
	Before	After	Before	After	Before	After	Before	After
1	22.22	34.48	7.43	7.41	159.6	177.5	34.2	39.4
2	52.51	66.26	7.46	7.44	231.0	231.0	38.3	41.3
3	44.70	66.81	7.43	7.42	225.0	222.0	35.7	37.6
4	102.61	130.44	7.39	7.38	225.9	214.9	31.5	31.8
5	39.59	55.1	7.46	7.43	183.6	167.4	31.0	34.5
6	47.19	53.25	7.46	7.56	193.0	209.5	28.1	19.0

Blood pressure, body temperature, hemoglobin concentration, and hematocrit remained stable during examination, while arterial pO_2 values and pCO_2 values did not show a significant difference (Table 2) - in some cases even a decrease in arterial pO_2 was followed by an increase in cortical pO_2. The mean values for all patients were pO_2art = 203 ± 28.8 mmHg before and 203.7 ± 25.5 mmHg after injection and pCO_2art = 33.3 ± 3.7 mmHg before and 33.9 ± 8 mmHg after.

Thus, the observed increase in cortical tissue pO_2 is due only to the administered drug, as all physiological parameters influencing the pO_2 values show changes only to an extent that could not explain the significant difference between the groups. The constancy of all these parameters also suggests that the effect is due to an improvement of microcirculation, as has been described for skeletal muscle (5). Pentoxifylline affects the deformability of erythrocytes, thus lowering blood viscosity (2).

Our investigation proves for the first time that pentoxifylline is a drug which effectively improves oxygenation of the brain cortex not only in healthy laboratory animals but also in patients suffering from cerebrovascular disease. The observation is paralleled by HARTMANN's observation that rCBF increases after administration of pentoxifylline in patients with acute cerebrovascular disease (3). The increase in local cortical tissue pO_2 is of a range that suggests it is the basis for the good clinical effect observed by BEYREDER (1) in acute cerebrovascular insufficiency.

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Regional Cerebral Blood Flow Evaluations with Iodine 123 Amphetamine (IMP) SPECT and Xenon 133 Inhalation in Cerebrovascular Disorders

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Introduction

The Xe-133 inhalation method with recording and processing of cranial desaturation curves enables one to estimate regional cerebral blood flow (rCBF). Cerebral uptake and local distribution of I-123-*N*-isoprophylamphetamine (IMP) have been stated to reflect local cerebral tissue perfusion (8). In accordance with this assumption, quantitative rCBF measurements by IMP using single-photon emission computed tomography (SPECT) with rather invasive arterial input sampling have been reported (3, 4). However, uncertainty about high-capacity low-specifity adrenergic receptor binding sites (8) may limit the reliability of the IMP technique in respect of quantitative rCBF evaluations. On the other hand, its nearly complete cerebral extraction fraction immediately following administration of the tracer and the rather stable subsequent distribution for a certain period caused by the slow washout from the brain, like "chemical microembolus" (8) still suggest this substance to be desirable for quantitative rCBF evaluations.

In this study, we have evaluated semiquantitatively assessed cerebral IMP uptake with a three-dimensional SPECT device for its clinical usefulness in cerebrovascular disorders as compared with the two-dimensional Xe-133 inhalation method.

Patients and Methods

Both the two-dimensional Xe-133 technique and three-dimensional IMP SPECT were performed in 15 patients (age: 49.3 ± 14.1 years) suffering from ischemic cerebrovascular disorders represented as completed stroke. Electroencephalography (EEG) and computed tomography (CT) were also performed in each patient on the day of admission. In most cases, measurements of Xe-133 rCBF were performed on days 1-3 after admission, while measurements with IMP SPECT were performed on days 3-4 after admission.

The rCBF was measured by the noninvasive Xe-133 inhalation technique with a NOVO 32 c Cerebrograph; 20-25 mCi of Xe-133 was inhaled over 60 s from an 8-liter airbag, followed by recording of 32 cranial raw curves for 10 min with detectors of 20-mm collimations over both hemispheres in a helmet-like arrangement. The rCBF was calculated with the initial slope index (ISI), a flow index defined as 100 times the monoexponential slope between 0.5 and 1.5 min after desaturation, reflecting primarily clearance from the fast-perfused compartment (5). End-expiratory CO_2 was continuously monitored by a capnograph. The raw

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ISI values were mildly corrected for CO_2 to the standard $PaCO_2$ value of 40 mmHg in each patient, with a correction of 2.0%/mmHg.

The cerebral IMP uptake was estimated by means of SPECT devices with a single-head rotating gamma camera (Gammatone T 9000/CGR) after i.v. injection of 6 mCi IMP (Amersham). Data acquisition was performed 30 min p.i. over 20 min with 64 images of 4K matrix by a 360° rotation of the gamma camera with a high-resolution low-energy collimator (FWHM = 11-13 mm). The IMP was produced by (P, 2n) reaction and the contamination of I-124 was less than 2%. For the correlation with Xe-133 rCBF, the IMP SPECT images in four slices were subdivided into cylindrical areas extending from the superficial (=outer) to the deeper (=inner) part of the horizontal brain cut; these areas were correlated with 32 regions of detectors by Xe-133 cerebrograph.

Results

The correlations among the EEG findings, the CT findings, and the regional ratios for maximal ischemic areas in each case with Xe-133 rCBF and cerebral IMP uptake are shown in Table 1. The regional ratios of Xe-133 rCBF and cerebral IMP uptake are expressed as percent deviations of regional ISI values and outer regional IMP counts/pixel from hemispheric mean values. In 9 out of 15 patients EEG showed a focus corresponding to the clinical symptoms, and in seven cases the CT findings showed hypodense areas. In four cases, the EEG and CT findings did not correspond. The regional ratios for ischemic areas were more homogeneous with two-dimensional Xe-133 rCBF than with three-dimensional IMP SPECT. Even in cases with a focus in the EEG and normal CT findings, the regional ratios of Xe-133 rCBF and IMP count/pixel for ischemic areas indicated differences. In every case, the regional ratio of ischemic area by Xe-133 rCBF was within 1.0, while the regional ratio by IMP SPECT exceeded 1.0 in one patient with normal EEG findings and a hypodense area on the CT scan.

The following correlations were evaluated between the ISI values with the two-dimensional Xe-133 inhalation method and the IMP counts/pixel with three-dimensional IMP SPECT: (1) ratio between affected and nonaffected hemispheres (=interhemispheric evaluations), (2) absolute mean values in the affected and/or nonaffected hemispheres (=absolute value evaluations), (3) percent deviations from hemispheric means for maximal ischemic and hyperemic regions in each case (=regional ischemic and hyperemic evaluations).

Interhemispheric Evaluations (Fig. 1)

Ratios between the affected and nonaffected hemispheres of cerebral IMP uptake showed significant correlations ($P<0.05$) with those of mean ISI values by the Xe-133 inhalation method. The hemispheric mean IMP counts/pixel of affected/nonaffected hemisphere showed a more stable correlation with ISI values than did either the outer hemispheric mean counts or the inner hemispheric mean counts; however, the correlation was still poor in some patients with higher ISI ratios (more than 0.95) between affected and nonaffected hemispheres, as shown in Fig. 1.

Absolute Value Evaluations (Fig. 2)

Mean IMP counts/pixel showed correlations with mean ISI values in the affected and nonaffected hemispheres ($r = 0.3764$, $P<0.05$) and in the

Table 1. Correlations among the findings of EEG, CT, Xe-133 rCBF, and IMP SPECT in cerebrovascular disorders

Case	Sex	Age (ys)	Side	Focus in EEG	Hypodensity in CT	Regional ratio for ischemia	
						Xe-133	IMP SPECT
1.	F	36	L	+	+	0.82	0.72
2.	M	41	R	+	-	0.85	0.84
3.	F	52	L	+	+	0.84	0.72
4.	M	44	L	-	-	0.84	0.63
5.	F	35	R	+	-	0.88	0.40
6.	M	65	L	-	-	0.92	0.48
7.	M	35	L	+	+	0.88	0.47
8.	M	45	L	+	+	0.90	0.74
9.	F	73	L	-	-	0.87	0.87
10.	M	60	L	-	-	0.75	0.81
11.	F	26	R	+	+	0.92	0.65
12.	M	49	L	-	-	0.75	0.62
13.	M	53	L	-	+	0.88	1.05
14.	M	74	L	+	-	0.87	0.66
15.	M	51	L	+	+	0.69	0.67

affected hemisphere alone (r = 0.4919, 0.05 < P < 0.1), but not in the nonaffected hemisphere alone (r = 0.1299, NS), with corrections of ISI values for $PaCO_2$ to the standard value of 40 mmHg. Without corrections for $PaCO_2$, absolute values of IMP and ISI showed no correlations in the two hemispheres. In one patient (shown as closed circles in parentheses in Fig. 2) hemispheric mean IMP counts/pixel in the affected hemisphere showed a far lower value than in other cases, probably due to an inappropriate ROI setting (regions of interest), and this patient was therefore excluded from statistical evaluations.

Regional Ischemic and Hyperemic Evaluations (Fig. 3)

In regional CBF evaluations, expressed as percent deviations from hemispheric mean values, the regional ratios of outer IMP showed a better correlation (r = 0.6222, P<0.001) with ISI values than did the ratios of inner IMP (r = 0.3692, P<0.05). Moreover, the regression line between ISI and outer IMP was located beneath the 1:1 correlation; this was more marked for hyperemic regions, as shown in Fig. 3.

Discussion

The EEG and CT findings generally showed good correlations with regional ratios for ischemic areas with Xe-133 rCBF and cerebral IMP uptake. The three cases with a focus in the EEG and normal CT findings showed differences in the regional ratios of IMP SPECT as well as of Xe-133 rCBF, although the regional ratios of Xe-133 rCBF were more homogeneous than those of IMP. As an example of such inhomogeneity in regional

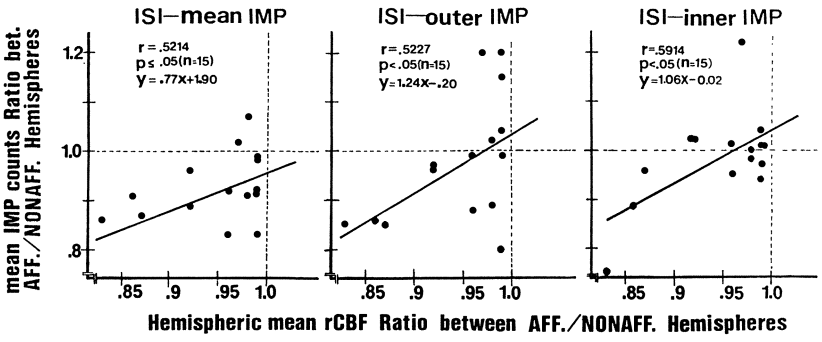

Fig. 1. Correlations between hemispheric mean rCBF ratio of ISI and ratio of hemispheric mean IMP counts/pixel of affected/nonaffected hemisphere. The IMP counts/pixel were calculated as hemispheric mean *(left)*, outer hemispheric mean *(center)*, and inner hemispheric mean (*right*) IMP counts/pixel. The *vertical* and *horizontal dotted lines* represent the ratios of 1.0 for ISI and IMP, respectively

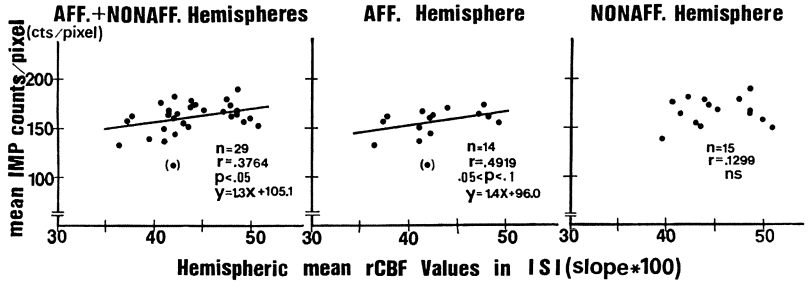

Fig. 2. Correlations between mean rCBF values in ISI and mean IMP counts/pixel in the affected and nonaffected hemispheres (*left*), in the affected hemisphere (*center*), and in the nonaffected hemisphere (*right*). The *closed circles in parentheses* represent a case in which mean IMP counts/pixel in the affected hemisphere showed a far lower value than in other cases

ratios of IMP uptake, one patient showed a regional ratio exceeding 1.0, which was probably due to variable IMP counts/pixel with manually fixed ROIs in the ischemic brain, as reported previously (7).

The ratios between affected and nonaffected hemispheres seemed to be less useful in cases with milder ischemia in whom the ratios evaluated by the Xe-133 method were higher than 0.95. The ratios evaluated by hemispheric mean IMP counts/pixel showed a more stable correlation with ISI values than did the ratios evaluated by other IMP values.

The observation that absolute values of hemispheric mean IMP counts/pixel showed no correlations with ISI values in the nonaffected hemisphere but correlated with ISI values in the affected hemisphere might be a reflection of the characteristics of cerebral IMP uptake being variable in relatively normal circulation but sensitive for ischemic conditions after cerebrovascular disorders.

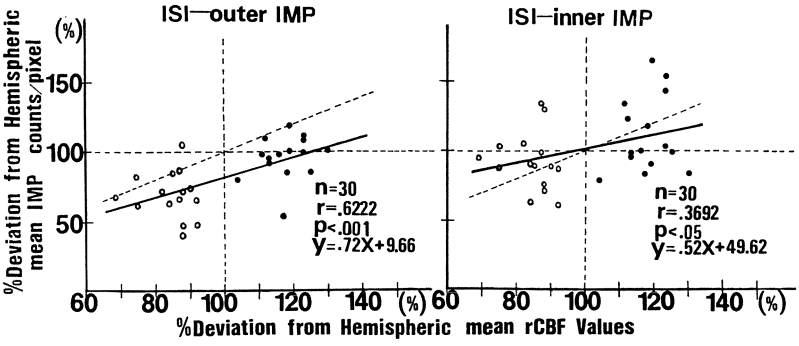

Fig. 3. Correlations of the percent deviations from hemispheric mean values between regional ISI values and regional IMP counts/pixel for maximal ischemic (o) and hyperemic (●) regions in each case. The percent deviations of regional IMP counts/pixel were expressed as percent of outer (*left*) or inner (*right*) IMP counts/pixel divided by the hemispheric mean IMP counts/pixel. The *vertical* and *horizontal dotted lines* represent 100% for ISI and IMP, respectively. The *dotted linear regression lines* represent 1:1 correlations between ISI and IMP.

In regional ischemic and hyperemic evaluations, the regional ratios of outer IMP showed a better correlation with ISI than did the ratios of inner IMP, which suggested that the outer part of the cylindrical areas in SPECT images might correlate better with two-dimensional Xe-133 rCBF values, due to the low energy and limited capacity of Xe-133 to reflect flows of deeper structures.

The regression line between the regional ischemic and hyperemic ratios of ISI and of outer IMP was located beneath the 1:1 correlation; this was more marked for hyperemic regions in our study. That is comparing low flow and high flow areas, IMP SPECT correlated better with the Xe-133 rCBF method in tissues with reduced perfusion. For ischemic areas, the sensitivity of IMP SPECT was very good (possibly better than the Xe-133 rCBF method), while it was not so good for hyperemic areas, tending to underestimate them, as in the "luxury perfusion syndrome." Such characteristics of IMP, i.e., decreased uptake in the state of luxury perfusion, have been suggested previously (1) and were recently observed in one case (6).

It was reported by KUHL et al. (3) that the relationship between local CBF values based on IMP deposition and those based on microspheres deteriorated at high flow values in five dogs. A decreased IMP extraction fraction in the brain accompanied by a decreased arterial pH with an increase in CBF was also observed experimentally, which suggested that the partition coefficient varied with pH (4). Similarly, it has been suggested (7) that lack of IMP uptake even in vascular tumors is a clear demonstration that cerebral IMP uptake is not only a function of perfusion but also of IMP tissue extraction. It was asserted (4) that local CBF estimated by IMP trapping due to local disease was most likely to be in the direction of reduced IMP deposition, producing an exaggerated defect in the scan pattern. Such observations are almost in accordance with our findings of semiquantitatively assessed cerebral IMP uptake.

Noninvasive semiquantitative rCBF assessment with IMP SPECT might be useful for evaluating cerebrovascular disorders despite the above-

mentioned tendencies of IMP, because of its sensitive detection of ischemia and good correlations with absolute mean ISI values by the Xe-133 inhalation method in the ischemic brain, without the need for arterial sampling. Further improvements of this noninvasive semiquantitative rCBF evaluation with IMP SPECT might be possible in the near future as SPECT devices are further refined.

Acknowledgment. This study was partially supported by the Alexander von Humboldt-Stiftung, Federal Republic of Germany.

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Single Photon Emission CT (SPECT) with ^{99m}Tc-HMPAO for Measurement of Regional Cerebral Blood Flow in Patients with Ischemic Stroke

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Introduction

Hexamethylpropyleneamine oxime (HMPAO) is a new tracer for the measurement and imaging of regional cerebral blood flow (rCBF). It is labeled with ^{99m}Tc and therefore easily available. HMPAO is lipid soluble and thus crosses the blood-brain barrier mainly during its first passage. Within the cerebral tissue the molecule is split up and becomes water soluble; rediffusion of the blood-brain barrier is not then possible (3). Single photon emission computerized tomography (SPECT) is suitable for transforming the information in slices comparable to transmission CT (TCT). We have used ^{99m}Tc HMPAO in 28 patients with ischemic strokes and below report our first results with this method.

Patients and Methods

We have investigated 28 patients with ischemic strokes. Clinical, TCT findings, and angiological information (angiography or Doppler sonography) were available in all patients. Fourteen patients had TIA or PRIND, including minimal persistent neurological deficit, and 14 patients had completed stroke. The investigation was performed 5 days to 14 years after the stroke. Twenty-four patients had low density areas visible on TCT.

Fifteen mCi ^{99m}Tc-HMPAO was injected intravenously. Ten minutes thereafter rotation was started with a duration of 20 min. We used a rotating double head gamma camera. The defects were visually compared by size with the infarct in TCT. HMPAO slices were quantified by 14 regions of interest (six outer and one inner area on each side) and diseased-to-undiseased ratios of corresponding interhemispheric regions of interest were calculated. Differences of more than 10% were interpreted as pathological.

Results

In 28 patients we found 29 regions of decreased or, less often, increased rCBF. In 40% of the areas of altered rCBF the defect shown by SPECT was larger than that shown by TCT (Fig. 1) (this group included four patients with normal TCT). However, in most cases there was only a small difference in spatial extension of the defects. In 48%, findings in both methods were similar in size and 12% SPECT findings were smaller the infarction in TCT.

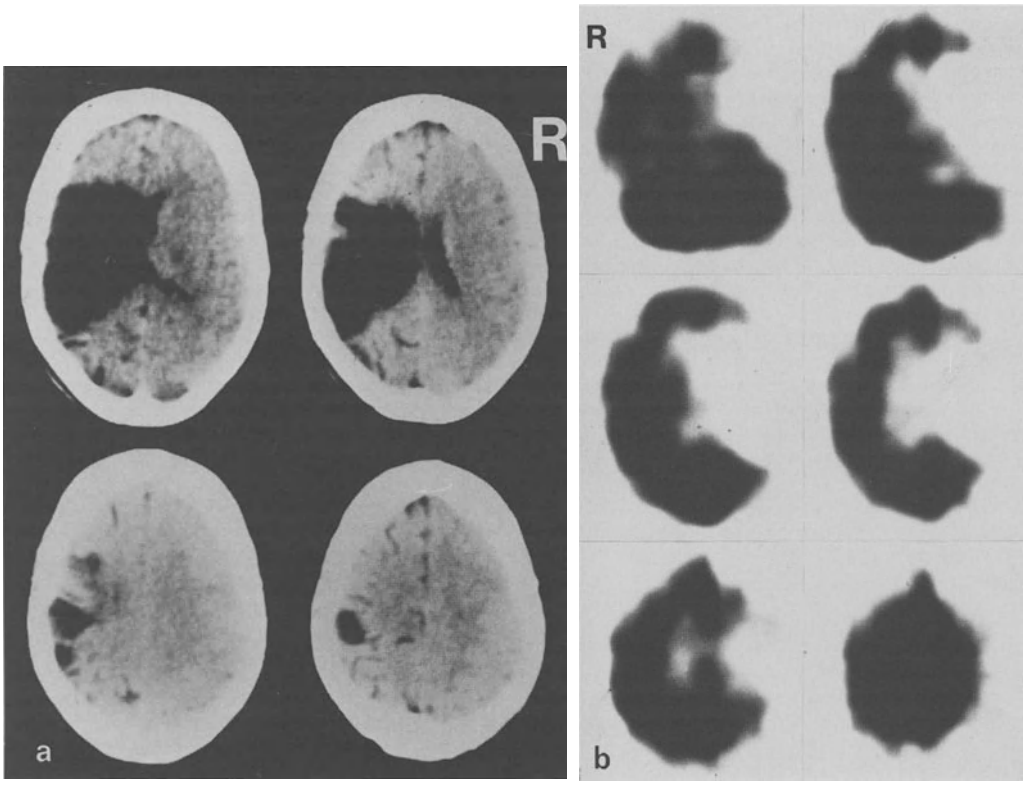

Fig. 1a,b. 30-year-old female with an embolic stroke 8 years prior to examination. a TCT shows an infarction in the territory of the left middle cerebral artery. b In HMPAO-SPECT the rCBF defect exceeds the defect in TCT, especially in the frontal lobe

In four patients with cerebral infarctions who underwent SPECT 7-11 days after the stroke, a large area of increased rCBF was found (Fig. 2).

Our results in respect of quantification are part of a four-center study. We observed a 22%-32% deficit in the affected hemisphere compared to the nonaffected hemisphere in patients with completed stroke, whereas in patients with reversible syndromes, the deficits were 12%-25% in the affected hemisphere.

Discussion

^{133}Xe- and ^{123}I-amphetamine have been used for SPECT in patients with cerebrovascular disease (1, 2). With both methods a relatively low spatial resolution is achieved. Our first results with ^{99m}Tc-HMPAO demonstrate a better spatial resolution. Moreover, ^{99m}Tc is available daily, in contrast to ^{133}Xe and ^{123}I. However, as yet absolute values for rCBF cannot be measured using ^{99m}Tc-HMPAO. Therefore, we use a programme for calculating diseased-to-undiseased ratios from regions of interest. This procedure seems suitable for quantifying areas of

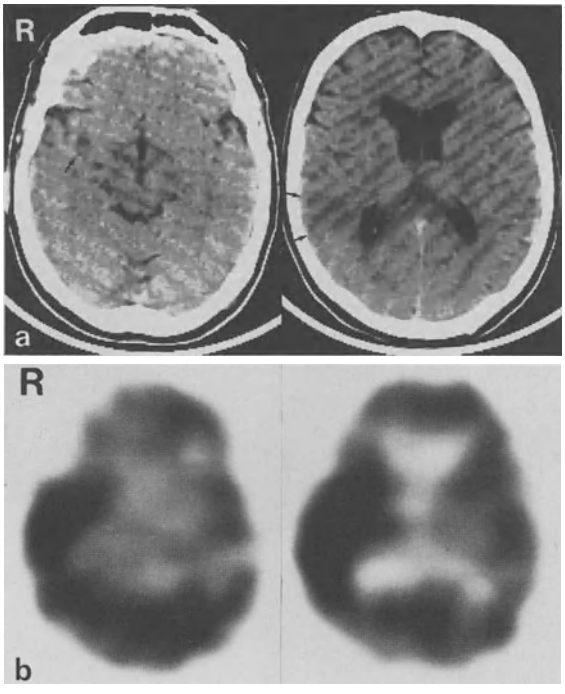

Fig. 2a,b. 46-year-old male with an embolic stroke 5 days prior to examination. a TCT shows a small cortical and an additional small subcortical infarction in the territory of the right middle cerebral artery. b HMPAO-SPECT demonstrates increased rCBF in the right temporal region

focal low or high flow and thus may help to classify subgroups of patients with cerebrovascular disease.

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Transcranial Doppler Sonographic Study of Flow Velocities Before and After AVM Removal - Normal Recordings and CO_2 Reactivity

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Introduction

Ever since the first transcranial Doppler sonographic study, performed in 1982 by Aaslid, we have been able to record the flow velocities in intracranial basal cerebral arteries. One can identify the vessels according to the depth of measurement, the direction of flow, and the results of compression tests on the cervical common carotid artery (1-4). The flow velocity values are usually indicated in kHz or cm/s, where 1 kHz of Doppler shift is equivalent to 39 cm/s.

Material and Methods

Using a 2-MHz Doppler system with pulsed performance (EME, D-7770 Überlingen, commercially available as TC2-62 transcranial Doppler), we investigated flow velocities of angioma feeders as well as brain-supplying arteries before and after angioma removal in 51 patients. In 24 of these, we studied the reaction to pCO_2 changes. As is known, the diameter of large basal cerebral vessels does not change under hypercapnia or hypocapnia (7). Therefore, one can gain a good impression of the distal vasomotoricity when changes are seen in the flow velocities of basal arteries.

Results

Transcranial Doppler Findings in Arteriovenous Malformations

Angioma feeders have high flow velocities within particular elevated diastolic values. One can distinguish whether the vessel supplies an angioma fully or partially. The ratio of systolic to diastolic flow velocities gives an impression of the peripheral stream resistance. Using the formula of Pourcelot, one can calculate the resistance index, which is 0.5-0.6 in normal brain arteries and can decrease to 0.2 in angioma feeders (Fig. 1).

If the angiographic diameter and flow velocity of cerebral arteries are known, the blood flow rate of these vessels can be estimated. Such calculations have been shown to correspond very well with electromagnetic flow measurements (10). Correlations exist between the flow velocities and angiographic patterns:

- There is a significant correlation between size and flow rate of angiomas: the flow rate is higher in larger arteriovenous malformations (AVMs).

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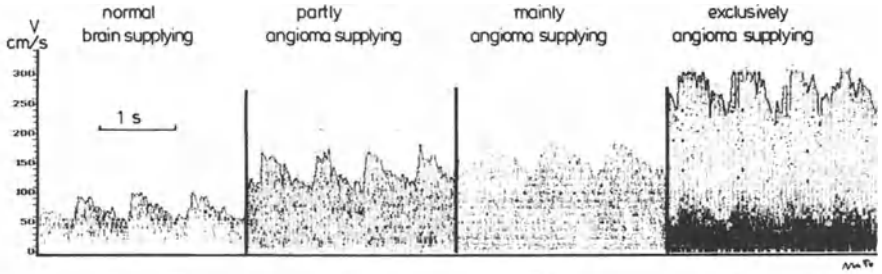

systolic flow velocities	100	170	180	310	cm/s
diastolic flow velocities	50	110	130	235	cm/s
mean flow velocities	64	132	156	278	cm/s
index of resistance	0,5	0,35	0,27	0,24	
diastolic amplitude / systolic amplitude	50%	65%	72%	76%	

Fig. 1. Flow characteristics of angioma feeders

- There is a significant correlation between diameter and flow velocity of the feeding arteries: the larger the feeder, the higher its flow velocity.
- There is a significant correlation between length of a feeder on one side and its stream resistance and flow velocity on the other: longer feeders show increasing resistance and decreasing velocities.

Transcranial Doppler Findings After AVM Removal

Following AVM removal, the flow velocities in former feeders drop considerably and their resistance indices rise (Fig. 2). The duration of overshooting flow deceleration and raised vascular resistance depends on the volume and hemodynamic impact of the former AVM. In small angiomas, this phenomenon lasts for 1 or 2 days, while in larger AVMs it can continue for up to 3 weeks (Fig. 3). These findings correspond to the so-called stagnating arteries shown by immediate postoperative angiography (6). These have very slow flow velocities, high intravascular pressure (10), and high stream resistance. They may persist for up to 3 weeks (5, 9).

CO_2 Reactivity in AVMs

Hypocapnia down to pCO_2 levels of 20 mmHg was induced by hyperventilation; hypercapnia up to pCO_2 levels of 60 mmHg was achieved by CO_2 application. Changes of blood flow velocities in vessels supplying brain and angioma were studied. Normal brain-supplying vessels show increasing velocities in hypercapnia, whereas in hypocapnia velocities decrease. These changes reflect the vasomotor response of peripheral resistance vessels. They occur in systolic as well as diastolic velocities. End-diastolic values in brain-supplying arteries drop to 0.5 kHz (19 cm/s) in hypocapnia. Angioma-supplying vessels lack such vasomotoric capabilities. Depending on their degree of AVM supply, flow velocities in basal cerebral arteries show a poor or no response to pCO_2 changes (Fig. 4). Exclusively AVM feeding arteries show no response; partial AVM feeders react slightly, with changes in systolic velocities being more pronounced than those in diastolic values. Only in very large angiomas did the velocity in neighboring brain-supplying arteries show diminished response to pCO_2 changes as well. Such vessels

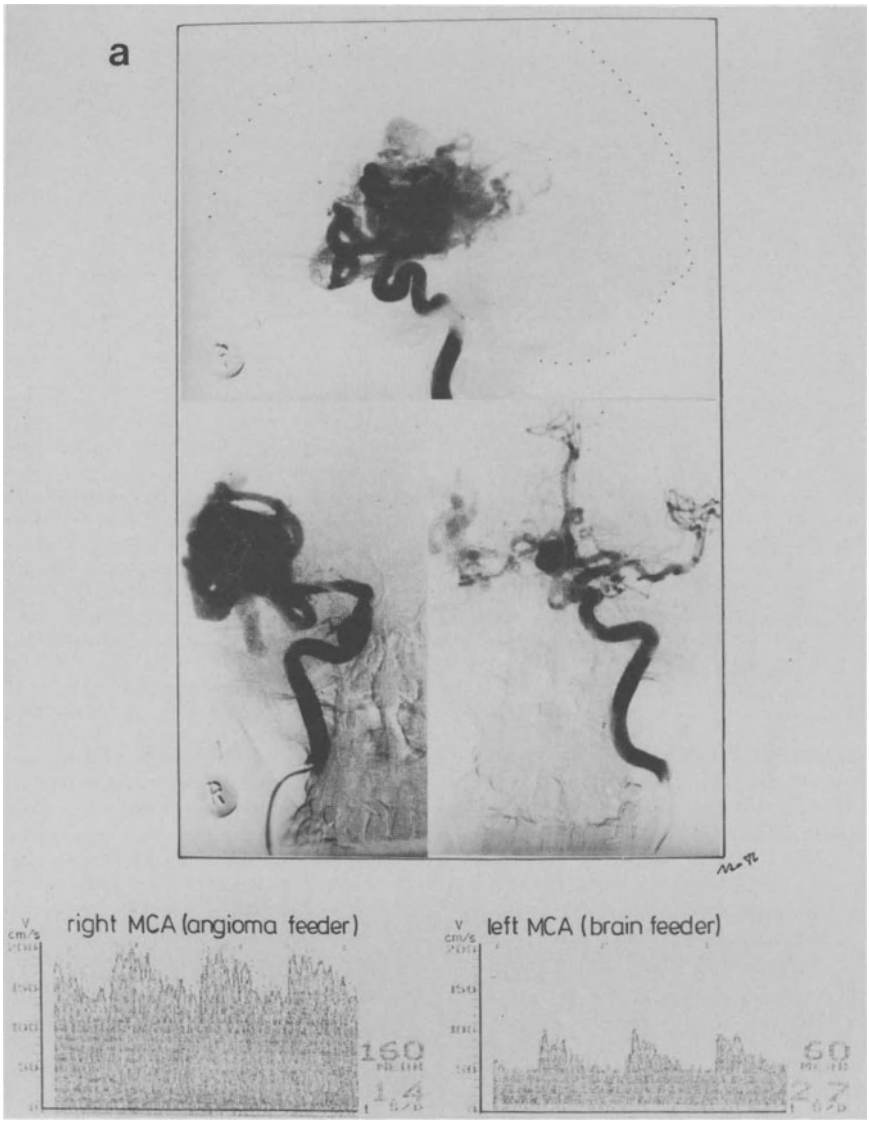

Fig. 2a,b. Large angioma of right sylvian fissure, ACommA aneurysm. a Transcranial Doppler patterns showing high flow velocities in feeding right MCA compared to normal findings in left MCA (Fig. 2b see p. 114)

are dilated due to low intravascular pressure and this autoregulative force obviously prevails over the effect of pCO_2 changes.

CO_2 Reactivity After AVM Removal

Immediately following the removal of angiomas, CO_2 responses in neighboring brain arteries are normal. Former feeders of small AVM also immediately develop normal reactivity. Former feeders of large AVMs, how-

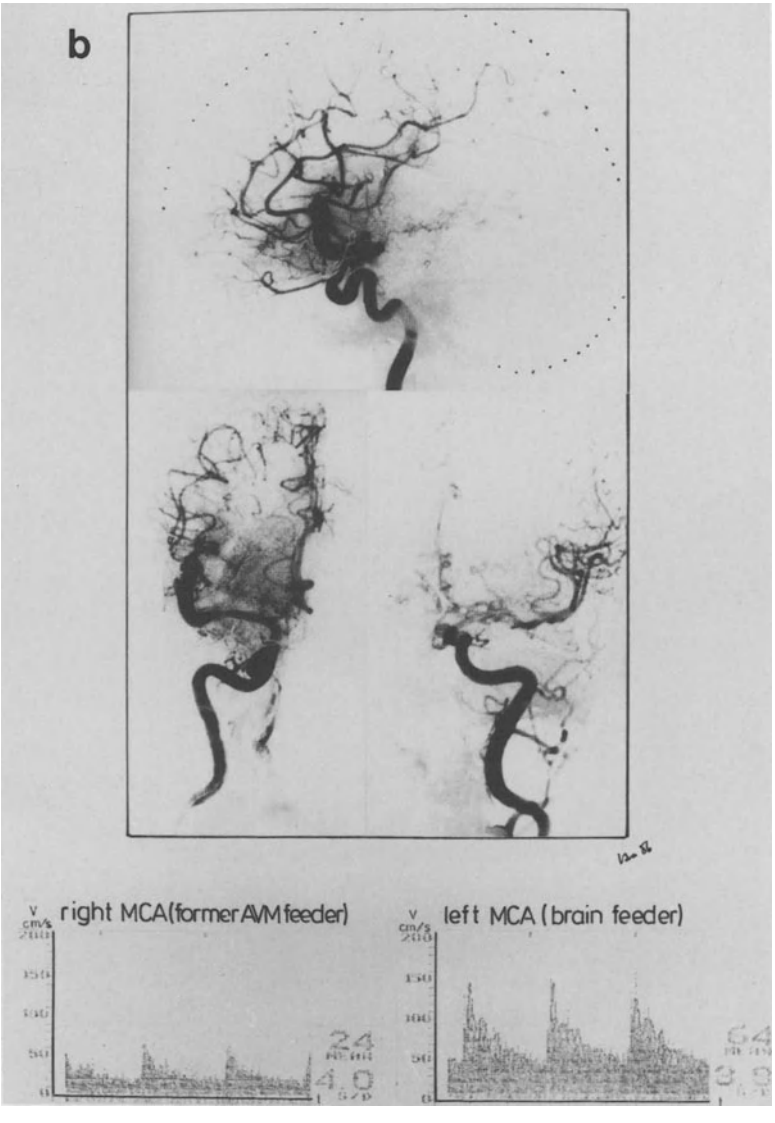

Fig. 2b. Doppler findings 7 days after removal of AVM and clipping of aneurysm that had not ruptured; the former feeder shows flow deceleration whereas in the contralateral MCA only slight changes have occurred

ever, show special phenomena. Postoperative flow velocities being excessively low in these vessels, hypocapnia did not lead to further decrease. Hypercapnia-induced increases in flow velocities were also diminished after the operation. Subsequent normalization of flow velocities was accompanied by normalization of CO_2 reactivity.

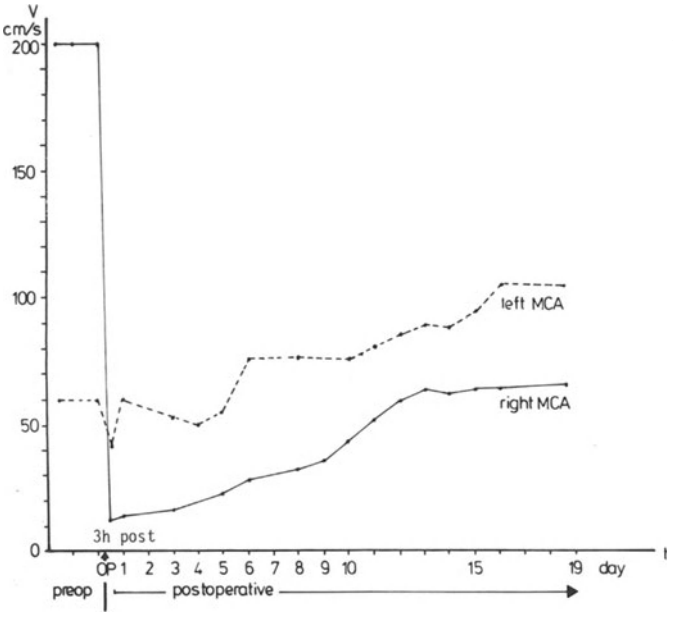

Fig. 3. Time course of mean flow velocities in right and left MCA after removal of right sylvian AVM

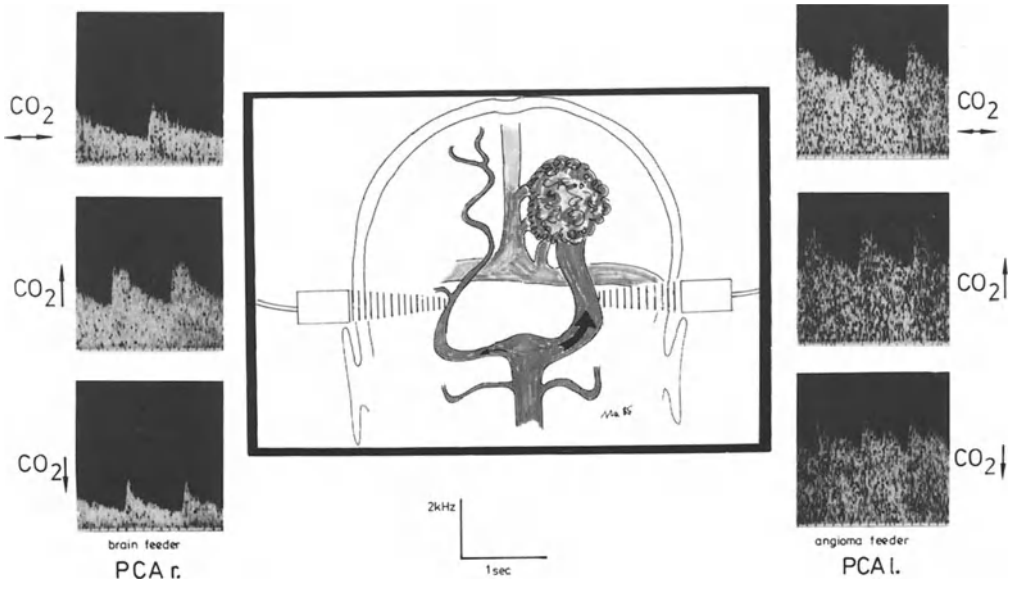

Fig. 4. pCO_2 responses in normal and AVM feeding cerebral arteries: normal right PCA shows increasing velocity in hypercapnia and decreasing values in hypocapnia; AVM feeding left PCA shows no change in response to varying pCO_2

Conclusion

Transcranial Doppler sonography allows identification of fully or partially AVM feeding arteries. These show typical Doppler flow patterns as well as reduced response to pCO_2 changes.

Following AVM removal, the former feeders show extremely low flow velocities and very high resistance indices. These changes subside in the subsequent period. In contrast to general opinion (8, 10, 12), they suggest intact postoperative vasomotoricity of peripheral resistance vessels in the vicinity of the former AVM.

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Amino Acid Metabolism in Brain Tumors

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Introduction

Positron emission tomography (PET) has become the most sophisticated method for studying regional metabolic functions of the brain (PHELPS 1986; REIVICH and ALAVI 1986). While blood flow, glucose consumption, and receptor densities are all highly structured, with active centers in normal and in pathological conditions, other functions, like oxygen extraction and protein synthesis, show a more uniform distribution in normal physiological situations (FRACKOWIAK and LAMMERTSMA 1985). However, oxygen extraction is a high level process in brain tissue, whereas protein synthesis is low in normal brain. Therefore increased protein synthesis in pathological states may be an ideal indicator, with high contrast for abnormally growing tissue in the brain.

Attempts to set up quantitative kinetic models for the determination of protein synthesis rates in brain tissue have been made by SMITH et al. (1980), PHELPS et al. (1984), BUSTANY and COMAR (1985), and BARRIO (1986). However, because of the complexity of the physiological basis of the model, metabolic turnover rates for brain protein synthesis have not been determined quantitatively up to now. Furthermore, the models rely on an intact blood-brain barrier (BBB) and are therefore not directly applicable to protein synthesis rates in tumors. The limitations which are imposed on the quantification of protein synthesis rates may be overcome, however, if the degree of BBB damage becomes measurable.

First attempts to investigate protein synthesis in brain tumors by PET were reported by HÜBNER et al. (1982), who used ^{11}C-labeled D,L-valine, D,L-tryptophan, and D,L-aminocyclohexane-carboxylic acid (D,L-ACHC) to image brain tumors. The uptake contribution by BBB damage in these studies was not evaluated, however. BERGSTRÖM et al. (1983) demonstrated discrepancies in the extent of a brain tumor as determined by CT and PET using ^{68}Ga-EDTA, ^{11}C-glucose, and ^{11}C-L-methionine. Subsequent investigations showed a limited influence of BBB damage on the amino acid accumulation (ERICSON et al. 1985).

^{11}C-L-methionine was chosen as the amino acid because it is known from in vitro studies (KUBOTA et al. 1984) and from nutritional support (GADISSEUX et al. 1984) that methionine exhibits high tumor to non-tumor ratios in gliomas and metastatic brain tumors. In normal brain the uptake of single pass extraction measurements is quite high too (OLDENDORF 1981). When compared with other amino acids, the amount of free methionine in brain tissue is small. This indicates a high utilization rate which should make it a suitable tracer for protein syn-

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thesis. Finally, the routine production of optically pure ^{11}C-labeled stereoisomeres of methionine posed no problems (MEYER et al. 1982).

Despite the difficulties associated with the quantification of protein synthesis rates in tumors, simple uptake ratios of amino acids in tumor to nontumor tissue may prove useful for both the semiquantitative understanding of the biochemical process in vivo and the clinical need for differential diagnosis (MEYER et al. 1985).

Patients and Methods

The preparation and quality control of ^{11}C-L-methionine is described elsewhere (MEYER et al. 1983). The optical purity of the isomer was controlled by analysis of the product by circular dichroism and polarimetry. Both methods confirmed that the L-form is obtained in >90% purity. The racemization under physiological solvent conditions is negligible.

Tomographic imaging was performed on 28 patients with brain tumors prior to surgery and in 6 patients with stroke. None of the individuals had undergone prior chemical or radiation therapy. Final verification of the diagnosis and the grading of the tumors were obtained from histological data subsequent to surgery. All patients gave informed consent to the following protocol. About 20 mCi of ^{11}C-L-methionine was injected intravenously. Ten minutes after the injection the patient was positioned under the positron camera (Model 4200 Cyc. Corp.) in the supine positron, and a 20-min recording of the head was performed (SCHOBER et al. 1985a). Absorption correction was carried out with ellipse phantom calculations. Up to ten slices with a thickness of about 15-18 mm were reconstructed. All data presented here are treated for relative uptake of tumor to nontumor regions in the brain (SCHOBER et al. 1985b).

Results

All methionine uptake data in slices containing tumor tissue are summarized in Fig. 1.

The uptake of methionine increased with the malignancy of the tumor, with the highest ratios of up to 3.2 being found in astrocytomas IV and glioblastomas IV. In meningiomas a high methionine uptake was observed in the tumor, but not in the surrounding edema. In six stroke patients we found a diminished methionine uptake.

In ten patients conventional ^{99m}Tc-DTPA scans were performed in order to investigate damage to the BBB. Four patients with a positive ^{99m}Tc scan accumulated no or only very small amounts of ^{11}C-methionine, while the patients with the astrocytoma II, who showed no ^{99m}Tc-DTPA uptake, had a positive ^{11}C-methionine accumulation. Four of the stroke patients showed a positive ^{99m}Tc-DTPA scan.

In reconstructed slices which contained no tumor tissue according to the final diagnosis, the left over right hemisphere ratio was 1.0 ± 0.09 (n=50). Although some brain structure could be seen in these cases, a rather homogeneous activity distribution predominated except for the mucosa of the nasal cavity and the salivary glands, which accumulated the amino acid.

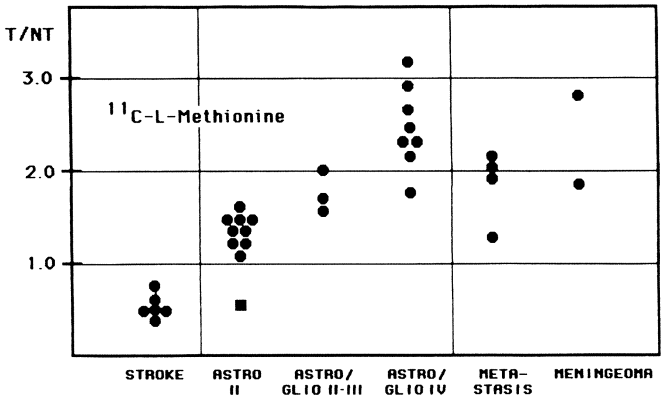

Fig. 1. Tumor over nontumor accumulation ratio of ^{11}C-L-methionine in patients with various lesions of the brain

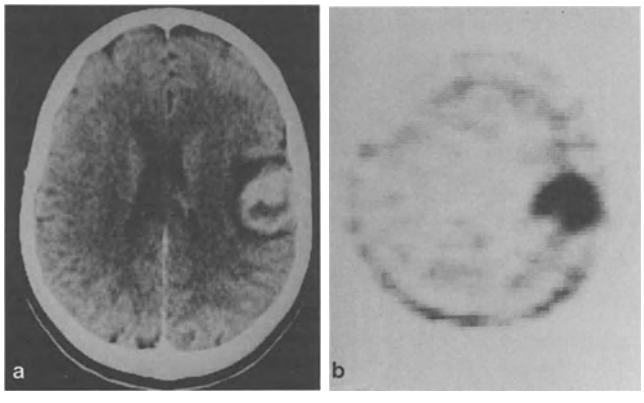

Fig. 2. Corresponding CT (*left*) and PET (*right*) slices of a metastasis of a highly malignant mesenchymal tumor with an accumulation ratio of 2.6

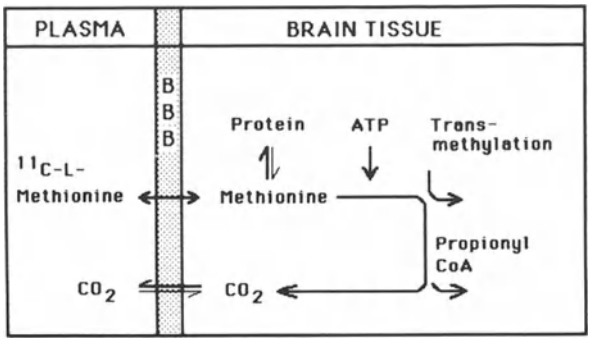

Fig. 3. Simplified scheme of the metabolic pathways of L-methionine in brain tissue

Figure 2 represents an example of a PET slice as compared with the contrast-enhanced CT scan at the corresponding level. As verified postoperatively, the patient had a highly malignant metastasis of a mesenchymal tumor, which gave rise to a tumor over nontumor accumulation ratio of 2.6.

Discussion

When compared with other amino acids, the amount of free methionine in brain tissue is small. However, the uptake of methionine in single pass extraction measurements is relatively high and is surpassed only by phenylalanine, leucine, and tyrosine (OLDENDORF 1981). This indicates a high utilization rate of methionine, which should make it a suitable tracer for protein synthesis. A recent comparison of ten amino acids for tumor uptake confirmed the high uptake of methionine (KUBOTA et al. 1984).

Amino acids may enter the brain by different uptake mechanisms. With an intact BBB, the main transport of amino acids into brain tissue is carrier facilitated (LAJITHA and TOTH 1963; NEAME 1968). Any increased uptake due to this mechanism could be related to enhanced metabolic activity of the tissue.

Slight to moderate damage of the BBB can result in an inhibition of the transport system and a diminished uptake of the tracer, while a higher degree of damage may lead to a free diffusible uptake (STEINWALL 1968). The carrier-mediated uptake also can be suppressed by overloading of the carrier system with competing substrates. The remaining diffusible uptake is flow limited, as can be expected, according to the model by RENKIN (1959) and CRONE (1963) ($E=\exp(-PxS/F)$; E: extraction; PxS: permeability surface-area product; F: flow). Nevertheless, decreased perfusion does not necessarily lead to increased uptake due to enhanced extraction, because the uptake is a product of vascularization and extraction, and remains unpredictable in most pathological cases.

As outlined in Fig. 3, methionine may follow two different reaction pathways after it leaves the plasma. It may be activated for protein synthesis by aminoacyl-tRNA-synthetase and ATP or may be activated by ATP, yielding *S*-adenosyl-methionine which undergoes subsequent degradation. With ^{11}C-labeled methionine labeled in the S-methyl position, difficulties may arise from transmethylation reactions. Because these reactions occur not only in brain tissue but also in the rest of the body, and especially in the liver, the plasma pool becomes contaminated with metabolites. For the quantitative measurement of protein synthesis rates, it is therefore necessary to control the plasma constituents or to label methionine in the 1-carboxyl position, and to include the $^{11}CO_2$ pool in the compartment model (PHELPS et al. 1984; BARRIO 1986). However, as long as no absolute quantitative data are derived from the measurements, the transmethylated reaction products which account for only a small fraction in brain tissue and may be neglected (BUSTANY and COMAR 1985).

Because usually the diffusive uptake is a relatively slow process and typically BBB breakdown can be visualized in ^{99m}Tc-DTPA scans in late images only, the present findings, which were obtained within 30 min after injection, seem to refer to an active metabolic process. The strongest support for this interpretation stems from the observation that in two cases the positive ^{99m}Tc-scan was accompanied by no or only slight ^{11}C-L-methionine uptake, while astrocytomas II with no

BBB damage showed a distinct methionine uptake. In infarctions with BBB breakdown the methionine uptake was insignificant.

A similar finding was reported by the NIH group in ^{18}FDG uptake studies for CNS tumors (DICHIRO et al. 1982, 1985; PATRONAS et al. 1984). In these studies a correlation was found for uptake and tumor grade also with mismatch of CT contrast enhancement - due to BBB disrupture - and ^{18}FDG uptake. Further evidence that active metabolic processes govern the amino acid uptake rather than diffusive processes stems from the observation that soft tissue tumors exhibit both enhanced perfusion and a concomitant glutamate uptake (Knapp et al. 1984), while most cerebral tumors have only slightly changed perfusion when compared with the unaffected tissue on the contralateral side (LAMMERTSMA et al. 1983a,b; cf. also WALKER 1984).

For the quantification of metabolic processes in tumor tissue and other disorders by PET measurements, a major difficulty stems from the uncertainty of uptake contribution due to BBB damage. Measurements with ^{68}Ga-EDTA (KESSLER et al. 1984) and ^{82}Rb (BROOKS et al. 1984) have clearly shown the possible use of these tracers for the localization of tumors with BBB disruption. While these findings are very similar to the results obtainable by contrast-enhanced CT imaging, a quantitative analysis of the BBB leak rate, which varies significantly in different types of tumors and with their grade of malignancy, is highly desirable. The use of different tracers, which are not metabolized but enter the brain by defined transport mechanisms, e.g., 3-^{18}F-2'-deoxyglucose, ^{11}C-methylglucose, or synthetic amino acids, may allow a more detailed analysis of various degrees of BBB damage.

Conclusion

Although a contribution to the uptake of ^{11}C-L-methionine in brain tumors by BBB damage cannot be ruled out from the current data, the missing uptake in proven BBB damage cases indicates that the extent of the contribution by diffusive processes is relatively small. Our clinical data support the suggestion that there is a correlation of methionine uptake with the tumor grade in astrocytomas.

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Selective Effect of Adenosine on Tumor Blood Flow

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Introduction

Brain tumor chemotherapy is limited by insufficient drug delivery to the tumor (1, 5). Delivery of water-soluble drugs is impaired by the partially intact blood-brain barrier (BBB), while delivery of drugs which easily cross the BBB (e.g., nitrosoureas) is impaired by the relatively low blood flow found in brain tumours (6). Therefore one way to increase drug delivery is to increase blood flow in tumors.

From a previous study (8) we know that adenosine, a potent vasodilator (4), increases selectively blood flow in virally induced canine brain tumors and has no significant effect on blood flow in normal brain as it poorly crosses the BBB. In this study we tested whether this effect could also be achieved in xenotransplanted human gliomas. We chose the D-54 MG human glioma because of its relatively high permeability for water-soluble compounds, which should permit adenosine to enter the tumor whereas it is restricted from the brain by the BBB.

Material and Methods

Sixteen nude rats were injected intracerebrally with 5 µl of a D-54 MG tumor cell suspension. The animals were checked for neurological symptoms on a daily basis. When the first rat developed neurological signs the group was randomly split into a control group and a group treated with adenosine. Each animal received an arterial and venous femoral catheter. The animals were allowed to recover from general anesthesia for 2 h before the experiment was performed. Body temperature, blood pressure, and blood gases were monitored during the preparation of the animals.

Initially a dose-response curve for the effect of increasing adenosine infusions (from 1 µM/kg/min to 40 µM/kg/min) was obtained in Fischer-344 rats. In the actual blood flow experiments 10 µM/kg/min adenosine or saline for controls was infused intravenously. Four minutes after the start of the infusion 80 µC of ^{14}C-iodoantipyrine (IAP) was infused into the femoral vein and simultaneously arterial plasma samples were obtained. Thirty seconds after the start of the ^{14}C-IAP infusion the animal was decapitated and the brain processed for quantitative autoradiography (QAR) as described previously (2). Blood flow calculations were performed using QAR and the Kety-Schmidt equations as modified by SAKURADA et al. (9). A video camera was used to digitize the brain sections with a resolution of 50 x 50 µm (2).

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Results

We observed a statistically significant decrease in blood pressure during the adenosine infusion but the pressure remained within the physiological range. There were no significant changes in blood gases or temperature.

Table 1 summarizes our blood flow measurements in different tumor regions and in surrounding brain of treated and control animals. First of all there was a significant increase in blood flow to whole tumor (124.9 ± 64.3 ml/100 g/min) compared to the nontreated animals (62.8 ± 19.1 ml/100 g/min). Regional analysis of tumor blood flow revealed that adenosine led to a significant increase in blood flow only in tumor periphery, not in tumor center. In the adenosine-treated animals there was also a significantly higher blood flow in brain adjacent to tumor. No significant change in blood flow could be observed in normal brain.

Table 1. Blood flow values measured in D-54 MG gliomas with and without intravenous adenosine. A significant increase in blood flow (*$p < 0.05$, Student's t-test) could be observed only in the tumor itself and in brain adjacent to tumor (BAT) which covers an area of 250 µm outside the tumor margin. In brain surrounding the tumor (BST) outside the BAT margin no significant change could be observed

	Blood flow (ml/100 g/min)		
	Whole tumor	BAT	BST
Adenosine	124.9 ± 64.3*	143.4 ± 54.5*	151.5 ± 63.2
Controls	62.8 ± 19.1	98.0 ± 14.6	75.8 ± 30.8

Discussion

Our results suggest that adenosine is able to selectively increase blood flow to experimental gliomas. The selective effect presumably depends on the different vasculature of brain tumors (10), which allows adenosine to cross the BBB, whereas it is excluded from normal brain. The tumor delivery of chemotherapeutic drugs like BCNU, CCNU, and ACNU, which are lipid soluble, depends directly on blood flow to the tumor (3, 7). Therefore intravenous adenosine may provide an approach for increasing drug delivery to brain tumors.

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Evaluation of Improvement in Microcirculation Using Visual Evoked Potentials

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Introduction

Evoked potentials (EPs) have been introduced into clinical practice as a very good method of monitoring brain activity (2, 5). The most important advantage of this method is its noninvasiveness and the resulting possibility of applying the tests as many times as is necessary. In our investigations the visual evoked potentials (VEPs) have been applied to study the effect of hemodilution on brain activity in the intracranial expanding mass model. In our previous studies on brain edema an improvement in cerebral blood flow after hemodilution was found. The aim of the present study was to ascertain to what extent hemodilution can improve brain function.

Material and Methods

The study was carried out on eight cats divided into two groups containing four animals each. The epidural balloon model was used. In group A the balloon was inflated 1 ml per hour up to a total volume of 1.9-2.1 ml, when pupil dilatation was observed. In group B the balloon was inflated at the same rate but to a total volume of 1 ml. The VEPs were studied using ANOPS, an averaging computer manufactured in the laboratories at the Warsaw Technogical University. In group A the VEP tests were performed before balloon inflation, at the 0.5-ml balloon stage, at the 1-ml balloon stage, and when pupil dilatation was observed. Then 20 ml of blood was withdrawn and replaced with 20 ml of low-molecular-weight dextran. After 10 min the VEPs were recorded again. In group B the VEPs were studied before balloon inflation, after balloon inflation was completed (1-ml balloon), and after 6 h of balloon compression. At that time brain edema already occurs (1). After the VEP study, hemodilution was performed using the above-described procedure. Fifteen minutes later the VEPs were studied again. Analyzing the VEP curve, the latency and amplitude changes were evaluated.

Results and Discussion

In group A, when signs of brain herniation were observed the VEP response disappeared. The hemodilution did not improve the brain function and no VEP response was found.

There was a moderate effect of hemodilution in group B animals. Figure 1 presents the normal VEP curve. After 6 h of brain compression with a 1-ml balloon the average latency of the wave n60 approached

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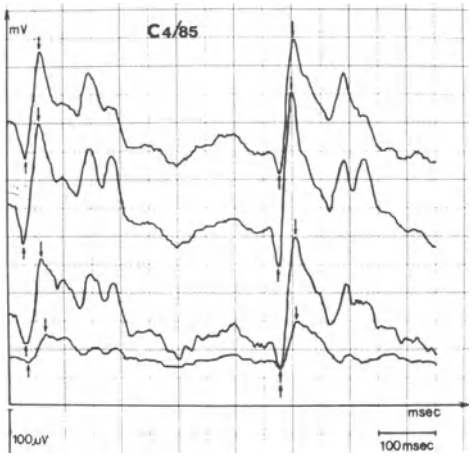

Fig. 1. Visual evoked potentials recorded in cat 4/85 before balloon inflation

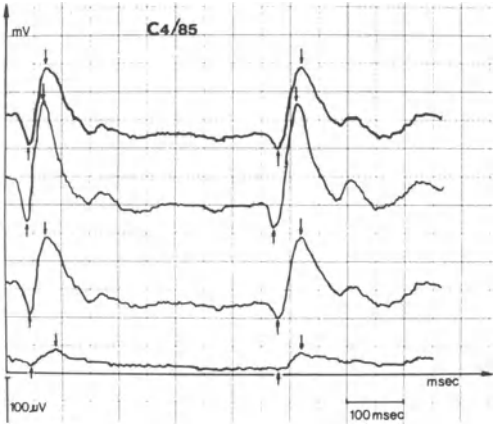

Fig. 2. Visual evoked potentials recorded in cat 4/85 after 6 h of brain compression

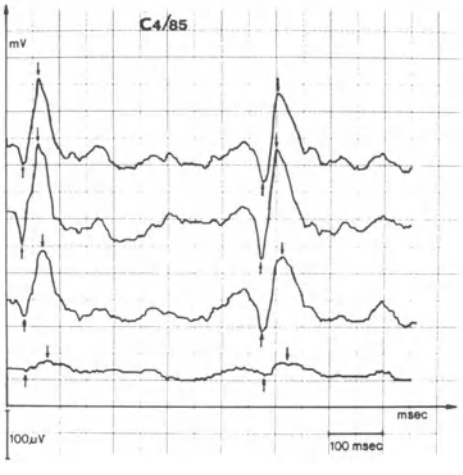

Fig. 3. Visual evoked potentials recorded in cat 4/85 15 min after hemodilution

about 30 ms (Fig. 2). After hemodilution was performed, the latency time was diminished and almost normal values were obtained (Fig. 3).

The amplitude changes were found to be much more difficult to evaluate owing to their marked variability. This parameter will be studied in future experiments. The positive effect of hemodilution was limited in our study only to the slight, reversible changes. According to our previous report (4), hemodilution in cats with epidural brain compression prevents or slows down the development of brain edema. Thus the results presented here correspond very well with our previously obtained data. Our studies, as well as others (3, 6), show the VEP method to be very useful in the evaluation of the intracranial situation in cases of intracranial hypertension. Especially suitable for this purpose are the latency data, as also found by York and co-workers (7).

Summary

Visual evoked potentials were used to study the effect of hemodilution on brain function in animals undergoing epidural balloon compression. In cats with signs of brain herniation no positive effect of hemodilution was observed. In another group of animals with developing brain edema, hemodilution improved the already changed VEP pattern.

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Spontaneous Recanalization of an Occlusion of the Internal Carotid Artery

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As has been repeatedly described in the literature, vascular diseases of the extracranial arteries are dynamic processes and not static events. Since angiography is a diagnostic procedure involving a certain amount of risk and since any pathologic findings are almost always treated by surgery, follow-up angiographic examinations are rare. As early as 1959 LUESSENHOP (5) reported that occlusions of the internal carotid artery are found more frequently on angiograms made directly after an attack than on late angiograms. The recanalizations observed most frequently by angiography are those of the middle cerebral artery. The few available follow-ups tend to indicate that embolization of thrombotic material, and subsequently deterioration of neurologic status, is an indicator of recanalization. The new neurologic symptoms are produced by the embolization of thrombotic material during recanalization. Most cases of "reversible angiopathy" can be attributed to spontaneous dissection, vasculitis, or "idiopathic regressive angiopathy" (1). In the cervical vessels, this phenomenon is most frequently associated with dissecting aneurysms; it is not, however, a true recanalization. In particular, these observations have been described in stenoses of the distal carotid artery, where direct surgery and, therefore, histologic evaluation, was impossible.

In such cases, an increase in the cross-sectional area of the vessel, and hence angiographic improvement, is so characteristic that repeat angiography is mandatory before surgery to avoid unnecessary interventions (3). The diagnosis should be supported by Doppler evaluation. Transcranial Doppler sonography, the most recent development, is particularly useful, since it is capable of examining the segments of intracranial vessels as well as the cervical vessels. The examiner, of course, should be aware of the indication and limitations. The main advantage of this method is that it is noninvasive and that follow-up studies can therefore be made without subjecting the patient to undue stress.

Recanalizations are infrequent occurrences. In many cases, the angiographically demonstrated "occlusion" was not really an occlusion. Such "reversible angiopathy" is particularly questionable with "tandem stenosis" (4). In rare cases, the phenomenon is, in fact, an angiographic artifact, that is, a "flow effect." Dissecting aneurysms can be caused by direct puncture, or occasionally by catheter angiography: a transient occlusion can even be caused by subintimal or paravascular injection or hemorrhage. Diagnosis of an occlusion by angiography is not as reliable as we initially assumed (6). Our finding that massive vascular changes with marked calcium deposition were limited to the common carotid bifurcation corresponds with observations reported in the literature. More distally localized stenoses and occlusions are general-

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ly only apposition thrombi. This also explains why recanalizations have been observed most frequently in distal stenoses and occlusions. Since direct operative treatment and, therefore, histologic evaluation, was possible only in the carotid bifurcation, carotid recanalizations have seldom been investigated histologically in vivo.

We would like to report a case in which a recanalization was observed and histologically investigated. To the best of our knowledge, no publications to date have demonstrated this phenomenon in a living subject, since open angioplasty was not performed. All previous observations reported histologic findings obtained in autopsy specimens.

Our 48-year-old patient complained of severe headaches on 31 March 1985. Five days later, he developed disorders of speech with central paresis of the facial nerve. Horner's syndrome was not demonstrable. The patient was admitted to a neurologic hospital because of progressive neurologic symptoms. The CT scan was unremarkable; Doppler evaluation showed signs of intracranial stenosis of the carotids. A small fresh infarct in the region of the semioval center consistent with internal carotid artery constriction or occlusion was visible on a CT scan made 16 days after admission. Subsequent angiography showed high-grade localized stenosis of the left internal carotid artery close to the base of the skull (Fig. 1). A less pronounced stenosis was detected at almost the same localization on the right side. The patient was treated conservatively and presented at our outpatient clinic. Routine preoperative EEG evaluation with digital compression of the left internal carotid artery revealed a mild decline of electric background activity; no new neurologic symptoms could be provoked. We opted for disobliteration and open angioplasty. On 10 June 1985, the common carotid

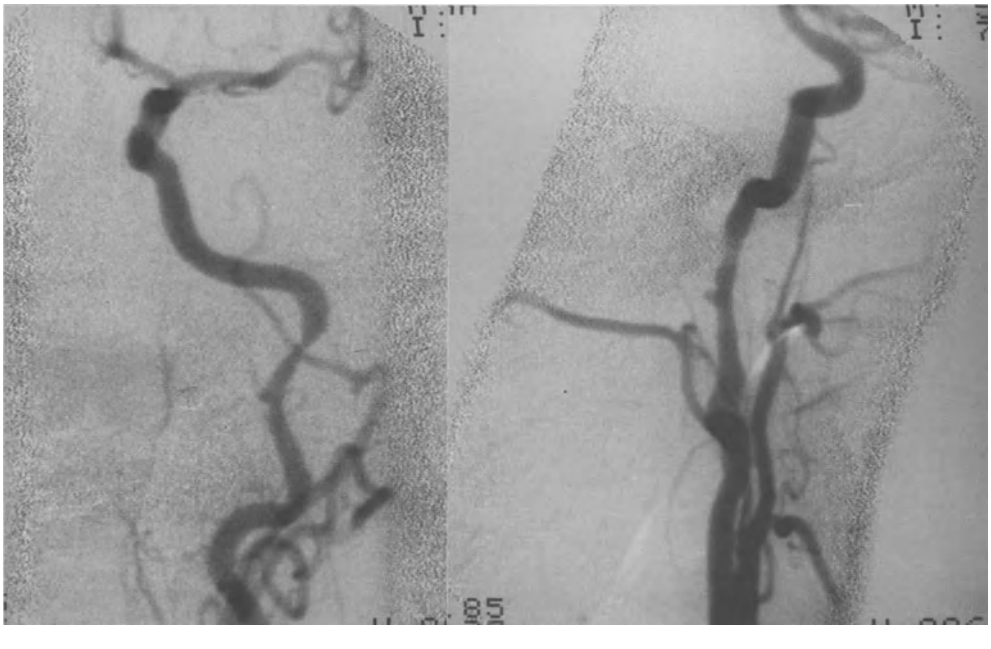

Fig. 1. Preoperative angiogram. Long segment narrowing of the left internal carotid artery under the skull base

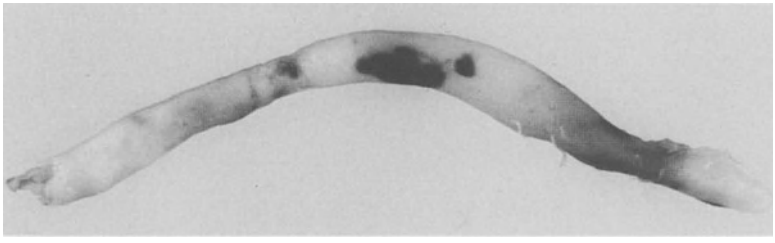

Fig. 2. The extracted 5 cm long thrombus

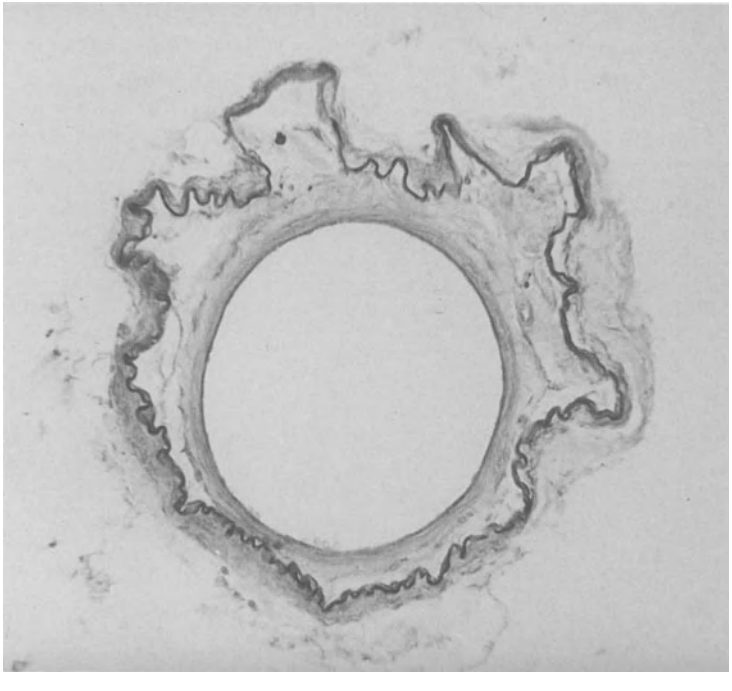

Fig. 3. Photomicrograph showing the thrombus with an arterial vessel-like lumen and wall

bifurcation was opened under barbiturate protection. Considerable arteriosclerotic material was found on the vessel walls; the cross-sectional area of the vessel was not significantly narrowed. The material was removed by routine methods, and a balloon catheter inserted to dilate the angiographically demonstrated distal stenosis. An approximately 5 cm long, organized, tubular thrombus was withdrawn with the catheter after dilatation (Fig. 2). Histologic evaluation of the thrombus showed it to be a recanalization vessel (Fig. 3) that had developed within the thrombotically occluded internal carotid artery. Repeat angiography 10 days after surgery showed marked distention of the left internal carotid artery at the site of the former stenosis (Fig. 4). One very interesting question is the association between neurologic symptoms and occlusion and/or recanalization. BODOSI et al. (2), however, reported that, with distal stenoses, the risk of vascular occlu-

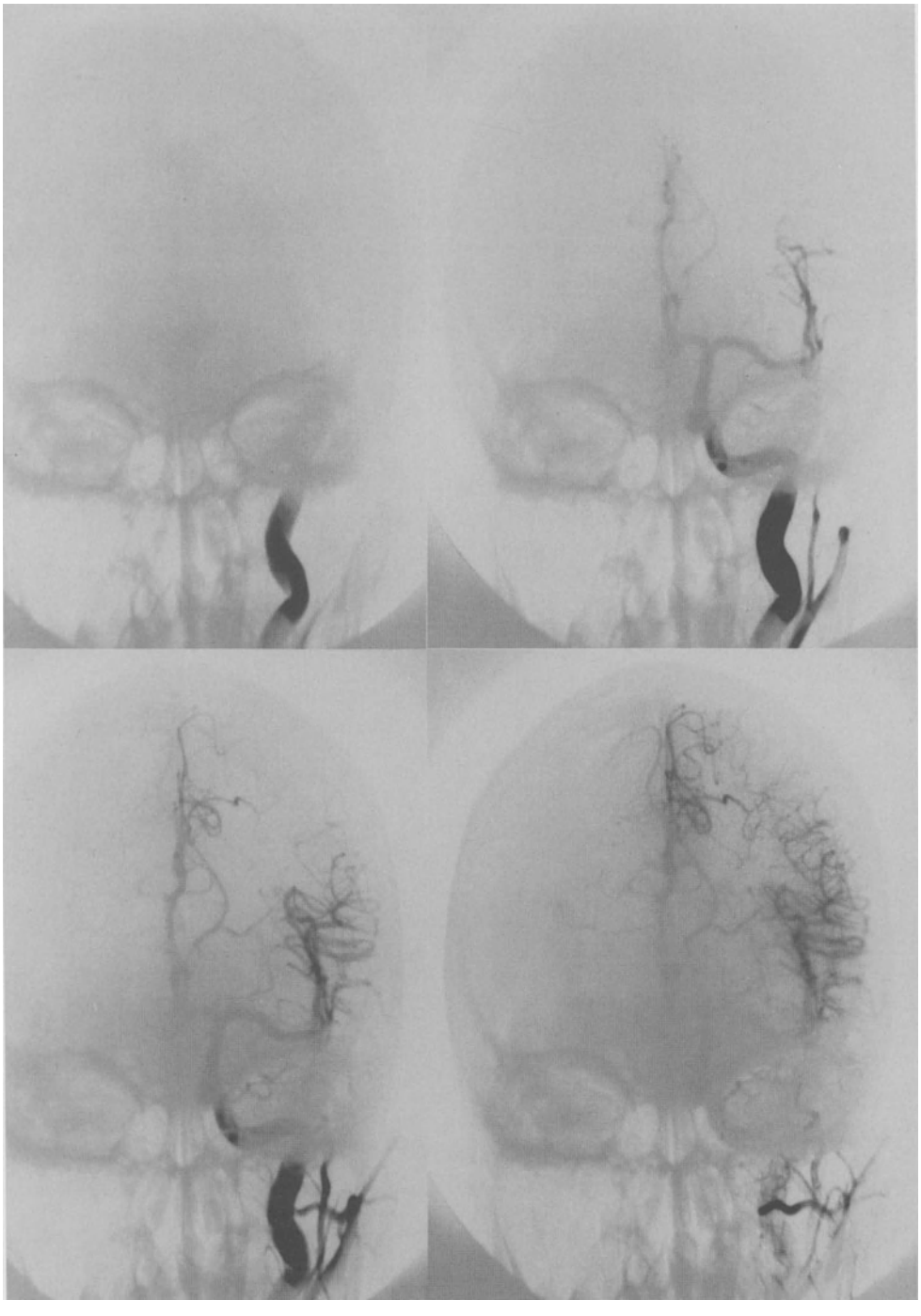

Fig. 4. Postoperative angiogram showing an internal carotid artery without any narrowing

sion and corresponding neurologic symptoms is higher than the risk of embolism. We are of the opinion that, in our case, the neurologic symptoms appeared at the time of recanalization and not at the time of occlusion. Thrombotic material very probably embolized into the cerebral circulation during recanalization. The indication for surgery should be a subject of further discussion, since the untreated right internal carotid artery also improved considerably. In such cases, Doppler evaluation could be useful at the follow-up examination to establish the indication for surgery on the basis of the progression of the stenosis or demonstrated turbulences, both sources of emboli.

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Neurosurgical Treatment of Epilepsy

The Role of the Anterior Choroidal Artery in Supplying the Amygdalo-unco-hippocampal Region

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Introduction

Selective amygdalo-hippocampectomy as a surgical method for the treatment of psychomotoric seizures unresponsive to medical therapy was introduced in 1975 and reported in detail in 1985 by YASARGIL et al. (16).

The pattern of vascularization of the amygdalo-unco-hippocampal region varies frequently; YASARGIL et al. intraoperatively verified multiple variations (16). Other authors (2-5, 10, 11, 13), by contrast, have not been able to quantify the vascular supply to this area.

In the study reported here we tried to demonstrate the origin, course, and role of the anterior choroidal artery.

Material and Methods

The anterior choroidal artery was cannulated via the internal carotid artery selectively in 42 cerebral hemispheres from 21 adult human cadavers after being perfused with Ringer's solution and injected with Hypoxid (Biodar, Heidelberg). The brains were fixed in formalin. The neurovascular relations were studied during microanatomical preparation with regard to selective microsurgical procedures.

Results and Discussion

The anterior choroidal artery was present in all of the 42 hemispheres. Its absence was reported by CARPENTER et al. (6) in one of 60 hemispheres.

Origin

All of the 42 examined arteries originated from the internal carotid artery (Fig. 1). The middle cerebral and the posterior communicating arteries are reported to be the most frequent extracarotid sites of origin (6, 10, 13, 14). Forty-one of the 42 arteries arose as a single trunk (Fig. 1). Double anterior choroidal arteries were found in one case. Although a double trunk is rare, some authors have reported a double origin of the artery in 0.5%-4% of cases (7, 12, 15).

The diameter of the anterior choroidal artery at its origin ranged from 0.4 to 3.4 mm (average 1.24 mm). This is comparable to a range of 0.7-2.3 mm reported in previous studies (6, 12, 13, 14).

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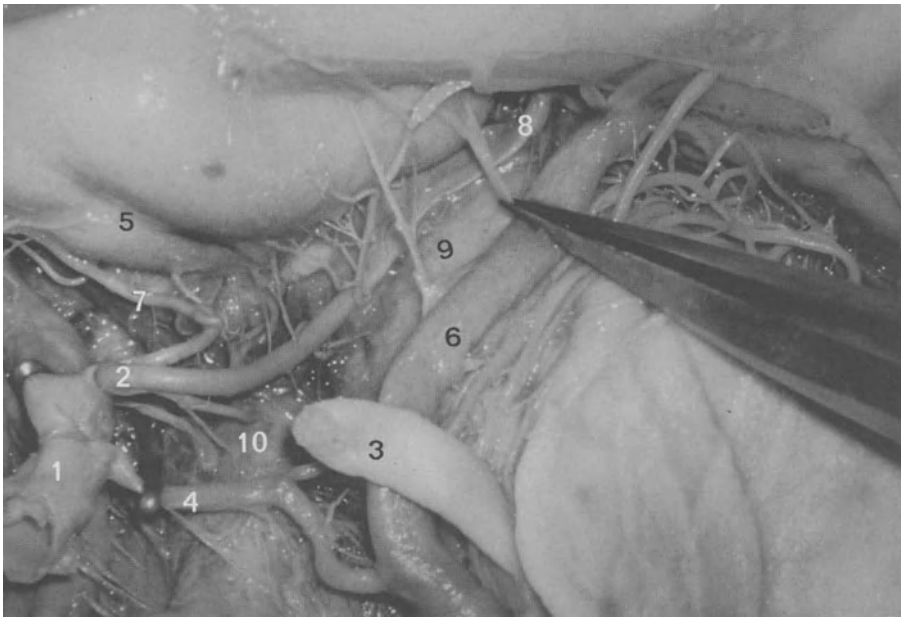

Fig. 1. Origin and course of the anterior choroidal artery. *1*, internal carotid artery with clipped middle cerebral artery; *2*, anterior choroidal artery (a.ch.a.) selectively injected; *3*, oculomotor nerve; *4*, clipped posterior communicating artery; *5*, uncus; *6*, posterior cerebral artery (P_2) with hippocampal branches; *7*, small uncal artery; *8*, choroidal fissure; the a.ch.a. enters the choroid plexus; *9*, cerebral peduncle with perforating branches from the a.ch.a.; *10*, optic tract with perforating branch

The anterior choroidal artery was the first branch of the internal carotid artery distal to the posterior communicating artery in all 42 hemispheres. The anterior choroidal artery arose 1.1-5.9 mm (average 3.2 mm) distal to the origin of the posterior communicating artery. RHOTON et al. (14) have reported the artery to arise from 1.1 to 9.0 mm (average 2.9 mm) distal to the posterior communicating artery.

Course

The course of the anterior choroidal artery was posteromedial behind the internal carotid artery (Fig. 1). The origin of the artery was lateral to the optic tract in all cases. The initial posteromedial course reached the lateral margin of the optic tract in all cases (of RHOTON et al.(14) - 98% of hemispheres; CARPENTER et al. (6) - 97% of hemispheres).

The medial part of the artery crossed from the lateral to the medial side of the optic tract in most cases (75%) (RHOTON et al. (14) - 54%). In 25% the artery passed along the optic tract to reach the lateral part of the cerebral peduncle. The artery again crossed the optic tract from medial to lateral at the anterior margin of the lateral geniculate body to the crural cistern. It then ran through the choroidal fissure to join the choroid plexus of the temporal horn (Figs. 2, 3). In

38 cases the artery terminated in the choroid plexus. The artery was traced posteriorly in some cases along the collateral sulcus to the medullary stria. In one hemisphere the anterior choroidal artery was large and provided branches to the medial and lateral temporo-occipital gyrus and to the hippocampal gyrus. This variation was reported also by BLACKBURN (5) and GOLDBERG (9).

In its course we divided the anterior choroidal artery into five main supplying segments:
Segment I was represented in about 80%, arising from the anterior choroidal artery in the first third of its course. In the second third of its course (segment II) a large lateral branch arose from the anterior choroidal artery in 87% of cases and ran from dorsal to rostral and disappeared in the hippocampal sulcus. In this area it anastomosed in 51% of cases with hippocampal branches of the posterior cerebral artery. Only in a few cases could this branch be followed to the collateral sulcus.

In 97% we found a branch of variable size to the uncus immediately after the origin of the anterior choroidal artery (uncal artery of 12 and 16). In two cases this branch arose separately from the internal carotid artery.

Branches of segment III penetrating through the optic tract and the medial brain substance supplied the anterior two-thirds of the pallidal corpus in all cases, the optic tract in 80%, and the amygdala in 88%.

In segment IV small branches supplied the anterior third of the cerebral peduncle in 97.5% and the lateral geniculate body in 61% (Figs. 1, 2). Perforating branches at the level of the lateral geniculate body supplied the posterior limb of the internal capsule in 61% (Table 1).

In most cases the anterior choroidal artery ran with one trunk through the choroidal fissure and supplied the choroidal plexus of the temporal horn of the lateral ventricle (segment V). In this area we frequently found rich anastomoses with the posterior choroidal arteries.

The hippocampal branch which is demonstrated in Fig. 2 was variable in its size and enlargement; these variations are based on the size of the hippocampal branches from the posterior cerebral artery. The branches of the IIIrd to Vth segment (Figs. 2, 3), which are also partly supplied by the posterior cerebral artery, may be greatly enlarged and associated with hypoplasia of the branches from the posterior cerebral artery. These facts were reported in a radiological study by GOLDBERG (9) and in other studies (3-5, 9, 11, 12, 14, 16).

Branches of the anterior choroidal artery anastomose in 51% of cases with branches of the posterior cerebral and in 14% with branches of the posterior communicating arteries. The richest anastomotic connections are found with the lateral posterior choroidal artery (Fig. 3) from the posterior cerebral artery. Other connections were found at the hippocampal sulcus and partially at the surface of the lateral geniculate body. These many zones of the anastomoses provide a route for collateral circulation to the posterior cerebral artery (8, 9, 14).

The results of this study might be very useful in interpreting preoperative angiograms while planning surgical procedures in the medial part of the temporal lobe.

Table 1. Structures supplied by the anterior choroidal artery in the segments I-V

Diameter of the anterior choroidal artery	1.24 mm	(0.4-3.4 mm)	(n=42)
Diameter of the posterior communicating artery	1.15 mm	(0.4-3.3 mm)	(n=42)
Distance of the anterior choroidal artery to posterior communicating artery	3.2 mm	(1.1-5.9 mm)	(n=42)
Anterior part of the hippocampal gyrus (semilunar gyrus/ambient gyrus/temporal pole)	20% 25% 12% 20%	1x +++ / 2.5% 2x +++ 1x ++ / 2.5% 2x ++ 1x + / 25% 2x + / 7% 2x + Ø	
Inferior part of the hippocampal gyrus (uncus / hippocampal sulcus)	41% 32% 34% 2.5%	1x +++ / 2.5% 2x +++ 1x ++ / 10% 2x ++ 1x + / 22% 2x + Ø	
Optic tract medial and lateral branches / perforating branches to pallidal corpus / amygdala	25% 27% 46% 12%	1x +++ / 7% 2x +++ 1x ++ / 25% 2x ++/15% 2x ++ 1x + / 25% 2x + Ø	
Optic tract	2.5% 12% 50% 20%	1x ++ / 2.5% 2x ++ 1x + / 10% = 2x / 1-10x (+) Ø	
Cerebral peduncle	2.5% 31% 68% 2.5%	1x +++ 1-3x ++ 1-7x / 10% (+) Ø	
Lateral geniculate body	2.5% 32% 22%	+++ ++ + / 5% (+)	
Perforating branches to deep structures (internal capsule, optic radiation)	17% 34% 10% 39%	1x +++ / 10% 1x +++ 1-3x ++ 1-2x + Ø	
Enter to the choroidal plexus	92.5% 5% 2.5%	1 branch 2 branches 3 branches	
Anastomoses to the segments I-IV	a.ch.a. a.ch.a. a.ch.a. a.ch.a.	with p.c.a. 51% with m.c.a. 12% with p.co.a. 14% with i.c.a. 5%	

+++ = very large branches; ++ = large branches; + = moderate branch; (+) = thin branch

Fig.3. The plexal segment of the anterior choroidal artery. *1*, anterior choroidal artery; *2*, choroid plexus; *3*, lateral posterior choroidal artery, a large anastomosis with the a.ch.a.; right below: part P_3 of the posterior cerebral artery (*4*)

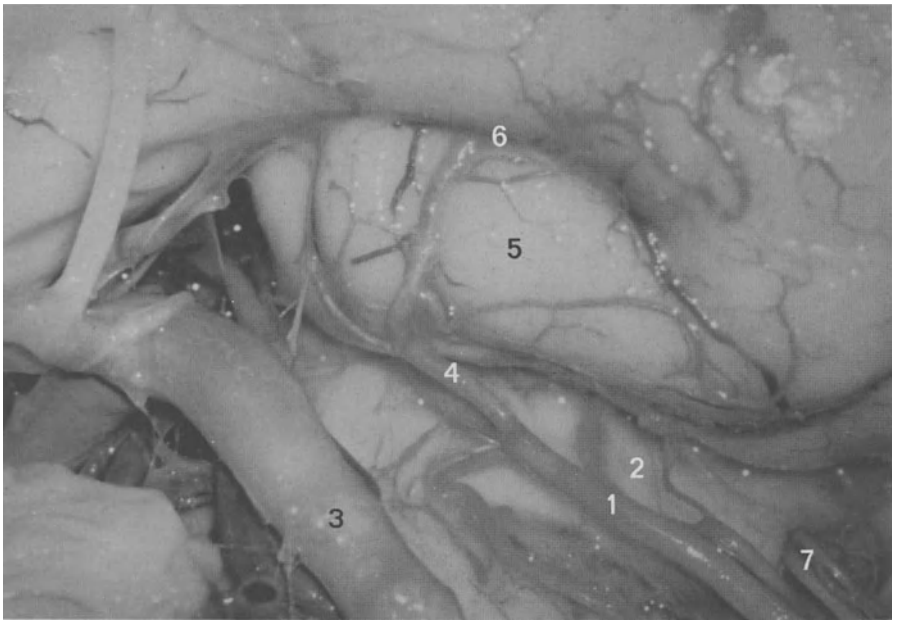

Fig. 2. The hippocampal branch from the anterior choroidal artery (a. ch.a.). *1*, a.ch.a.; *2*, optic tract; *3*, posterior cerebral artery (P_2); *4*, large hippocampal branch with anastomosis with branches from the posterior cerebral artery; *5*, hippocampus anteromedial part; *6*, hippocampal sulcus; *7*, perforating branches through the optic tract

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Presurgical Level I Intensive Evaluation of Patients with Drug-Resistant Epilepsy

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The aim of surgical treatment of patients with drug-resistant focal epilepsies is to eliminate the epileptogenic area responsible for the habitual seizures. In order to determine the epileptogenic area, intensive presurgical evaluation by means of different investigative techniques is necessary. This complex presurgical procedure is indicated if absolute drug resistance exists and clinical data provide hints that the seizures are due to a localization-related epilepsy.

In order to prove genuine drug resistance, epileptic seizures have to be documented by means of video-EEG and antiepileptic drugs of first choice (carbamazepine, diphenylhydantoin) have to be administered as a monotherapy in sufficient dosage. If the seizure frequency does not decrease, the dose can be increased while controlling serum concentrations simultaneously until side-effects appear. If monotherapy is not successful, polytherapy (e.g., barbiturates or valproate) has to be administered. The procedure proving genuine drug resistance usually takes 2-4 years. Additional criteria for intensive presurgical evaluation are seizure frequency (several per month) and sufficient intellectual function and motivation. Patients with severe cardiac and pulmonary diseases (risk with regard to narcosis), diabetes mellitus, and Jakob-Creutzfeldt disease are excluded. Intensive presurgical evaluation is not to be recommended in patients with intellectual deficit (IQ < 60) or psychosis.

The presurgical evaluation serves to answer the following questions: Where and how precisely can the epileptogenic process be located? Does a morphological and/or functional lesion exist in addition? Do the findings provide hints that surgery may lead to intolerable neurological or psychological effects? Is surgery indicated? In order to answer these questions, different investigative neuroradiological techniques are employed. Synchronized video-EEG documentation of behavior and epileptic biosignals is a very important part of intensive monitoring. Selective data reduction of long-term video-EEG recordings can be performed by either a human observer, who marks the time of occurrence of a seizure at the time by pressing a button, or by means of an automatic EEG analysis for seizure detection (5). Applying these methods interictal and ictal epileptic activity can be localized and nonepileptic pseudoseizures recognized. The differentiation of seizure types can be of great importance with respect to surgery, as shown, for instance, by DELGADO-ESCUETA et al. (3), who differentiated complex partial seizures into types 1-3.

Intensive monitoring can be divided into a first and a second level. The first level includes noninvasive long-term video-EEG monitoring with extradural and basal (scalp and sphenoidal) electrodes. Level II

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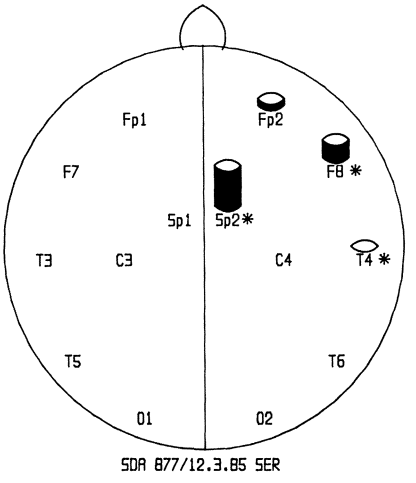

Fig. 1. Amplitude mapping of interictal spike activity (maximum at Sp2)

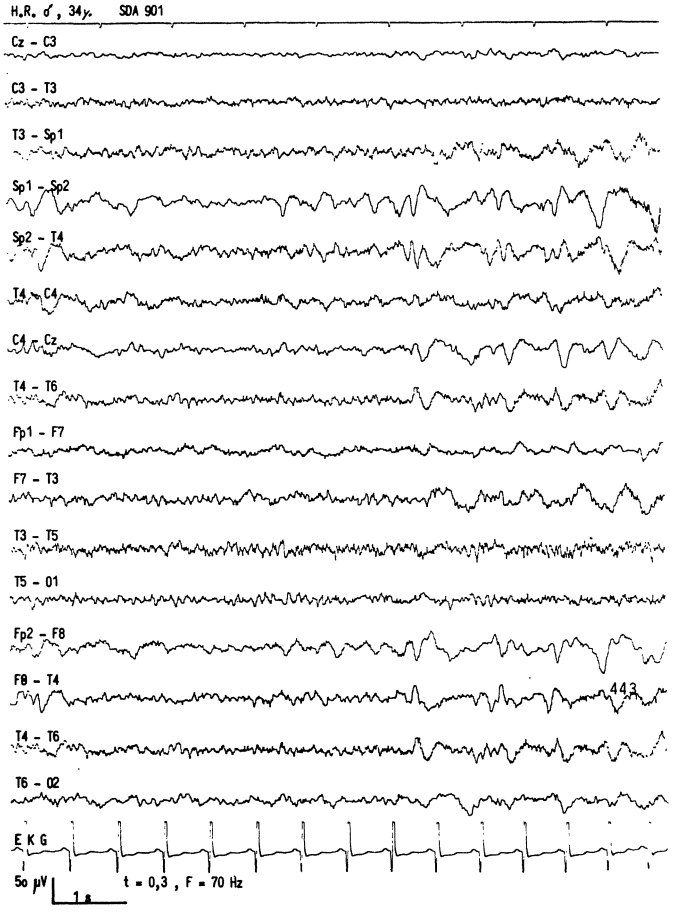

Fig. 2. Ictal regional onset, right temporal (from 7)

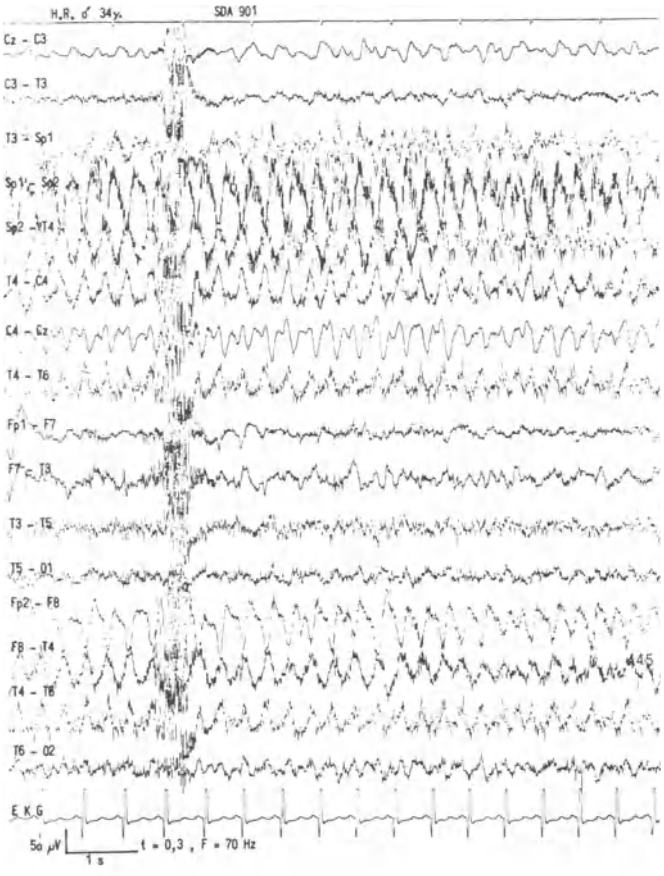

Fig. 3. Unilateral rhythmic activity in the right hemisphere in a later epoch of the seizure (from 7)

comprises invasive intracranial electrodes (8). During level I long-term monitoring, interictal focal epileptic activity can be defined by using amplitude mapping (6) (Fig. 1) which can be compared with the onset of ictal activity. In patients with focal disturbances in the temporal region, lateralization of epileptic activity to one hemisphere (using 16-channel scalp and sphenoidal long-term recording) is possible in 60%-80%. In level I evaluation CT and MRI serve as indicators for morphological lesions and single emission computed tomography (SPECT) or positron emission tomography (PET) for the detection of a functional deficit (1, 2, 4). The success of surgery depends on an extremely exact determination of the relevant epileptogenic region. It is very important that a reasonable hypothesis concerning the seizure origin is established and already tested in level I with great accuracy. If a constant unilateral interictal focus (Figs. 2, 3) correlates with the region of seizure onset and coincides with a functional deficit or morphological lesion, the patient can be recommended for surgery. If there is discordance of interictal and ictal localization, bilateral epileptic activity, or, for example, suspicion of extratemporal activity in addition to epileptic activity in the temporal region, further noninvasive EEG explorations using closely spaced electrodes (6) are necessary, or even only invasive level II investigations using subdural or depth electrodes may allow recognition of the relevant epileptogenic area.

When the noninvasive EEG findings do not correspond to the neuroimaging results (CT, MRT, SPECT or PET), patients should be submitted to additional extensive investigations before surgery is further considered.

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Presurgical Level II Evaluation of Epileptics

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Introduction

The rationale of surgical treatment of epilepsy depends on the concept of the "epileptic focus." Excision of the focus containing a mass of "highly explosive cells" (1) might be expected to be therapeutically beneficial, and this in a rather causal sense. Besides control of otherwise intractable seizures, two other goals are aimed at: (a) functional and behavioral improvement, and (b) possible prevention of kindling-like mechanisms, i.e., interruption of an otherwise ongoing epileptic process.

It should be emphasized that the concept of the epileptic focus is a functional and dynamic one, in the sense that the pathological, hyperactive, and more or less autonomic "epileptic pacemaker neurons" (5) are intermixed with other neurons whose firing patterns may fluctuate between various degrees of epileptic burst firing and normal firing rates, depending on the degree of recruitment. When the extent of the "focus" is widened, a critical mass is reached, at which point clinical manifestations and/or propagation of the pathological cellular activity is apparent. The circuits of spread obviously depend on the cells of seizure origin and on the prewired hodology and connectivity of the brain.

From this, it follows that the most important information in terms of surgical treatment of epilepsy consists in knowing the exact site of the seizure origin. This can be inferred from appropriately localizing the initial seizure discharge and careful analysis of the accompanying clinical signs and symptoms. It is of further importance to know the extent of the pathological brain volume which has to be removed in order to obtain sufficient seizure control. At present this question cannot always be answered with certainty. Empirically, sometimes spikes may persist postoperatively without further clinical seizures. Experimentally it has been shown that a logarithmic relation exists between seizure frequency and the number of group 1 epileptic neurons (11).

Monitoring the spread of seizure discharges is important because (a) it helps to explain the clinical accompaniments of the seizure, and (b) it may give additional confirmatory evidence for seizure origin locus. Furthermore, in certain instances, where resection of the focus is not possible, the preferential pathways themselves may be attacked in terms of "palliative" therapeutic interventions.

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The Presurgical Evaluation Protocol

If the generally accepted criteria for judging a drug-resistant seizure patient as a potential candidate for surgical treatment are fulfilled (4, 6), the patient should be referred to a specialized surgical epilepsy center. There a careful presurgical evaluation has to be done with the aim of answering the above-mentioned questions with the certainty and precision necessary for a surgical intervention. The diagnostic armamentarium consists of examinations which can be described as (a) tests of functional deficits, (b) tests of morphological lesions, (c) tests of epileptic excitability, and (d) localization of seizure origin (7-9). Some of these are noninvasive procedures, but others are invasive. It has become customary to speak of level I and level II diagnostics. This division, however, is somewhat misleading, as in reality the presurgical evaluation is a highly interactive, multidirectional, and goal-directed decision process which makes use of several feedback loops (8). Only with these restrictions in mind may one tolerate the naming of the more special and increasingly invasive examinations as "level II" examinations.

Localization on the basis of functional deficits alone should never be considered sufficient to recommend resective surgical treatment. It is mandatory to demonstrate the relevant epileptogenicity of such a functional lesion using electrophysiological techniques. The documentation of a structural lesion is very important. It is, however, crucial to remember that it need not correspond to the site of the actual seizure onset. In fact the morphological lesion, if present, can be located at a considerable distance from the actual seizure onset area and might thus be misleading (8).

As the information which can be obtained from scalp-EEG with regard to the definition of the seizure onset area is severely restricted, a number of other EEG recording techniques have been developed, such as sphenoidal electrode recordings and intracranial recording techniques. Stereo-electroencephalography (stereo-EEG, SEEG), i.e., simultaneous surface and depth EEG recording from stereotactically implanted multipolar depth probes (see Fig. 1), is probably the most widely used method (6-9). It is especially suited to solving problems encountered with temporal lobe surgery. The epicortical "foramen ovale" electrode recording technique (10) can be very helpful for localizing epileptic foci in the mesial aspect of the temporal lobes (see Fig. 2). Subdural strips (12) and epidural grids (2) might be asked for to delineate epileptic foci, especially if located extratemporally. All these techniques have in common that they circumvent the restrictions of electrocorticography, insofar as they allow the electroclinical recording of several spontaneous and habitual seizures, which provide the most valuable information. Today, integrated telemetry-computer-videosystems (3, 9) are able to accomplish considerable data reduction and have the additional advantage that they allow the EEG of interest to be subjected to further computer analysis (9).

As the invasive electrophysiological recording techniques are not without risks, rigorous criteria for their use are required. Furthermore, because of the sampling problems inherent to them, their use should be restricted to those patients in whom these methods alone can provide essential information towards solution of their pending diagnostic problems. In our understanding, invasive level II procedures are only indicated if (a) level I diagnostic data are inconclusive or insufficient and must be improved in order to allow sound judgments with regard to the possibility of surgical treatment, or (b) if it is necessary to resolve discrepancies in the information hitherto

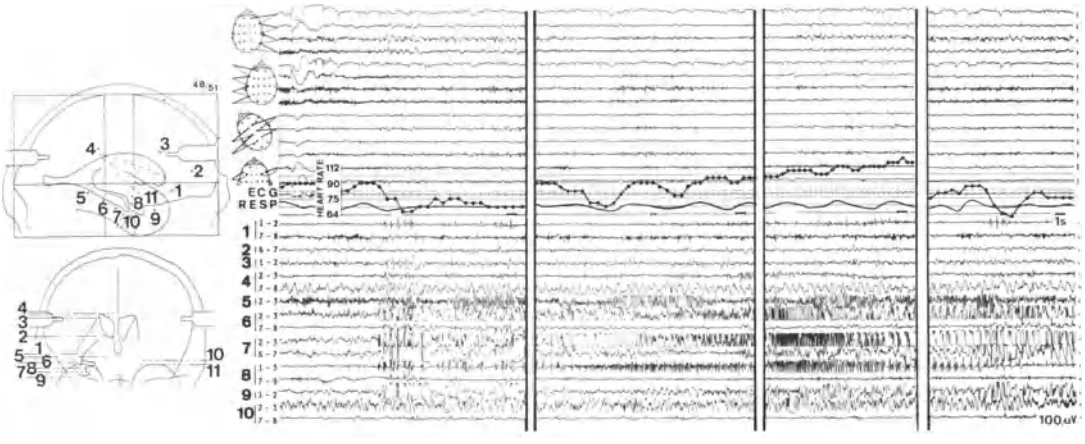

Fig. 1. Example of a combined surface and depth EEG recorded seizure. Following a "semi-ictal" relatively widespread regional spike-wave activity right temporal (section 1), the high-frequency low-amplitude seizure discharge starts in the right amygdala (8/1-3) (section 2), involving progressively the homolateral anterior (7/2-3) and posterior (6/2-3) hippocampus (section 3). Note the marked ictal changes in the heart rate and the initial respiratory arrest (ECG electrocardiogram; RESP, respiration). The position of the depth electrodes (*large numbers*) is as indicated in the brain map. *Small numbers* refer to the contacts of one electrode and are numbered from inside out

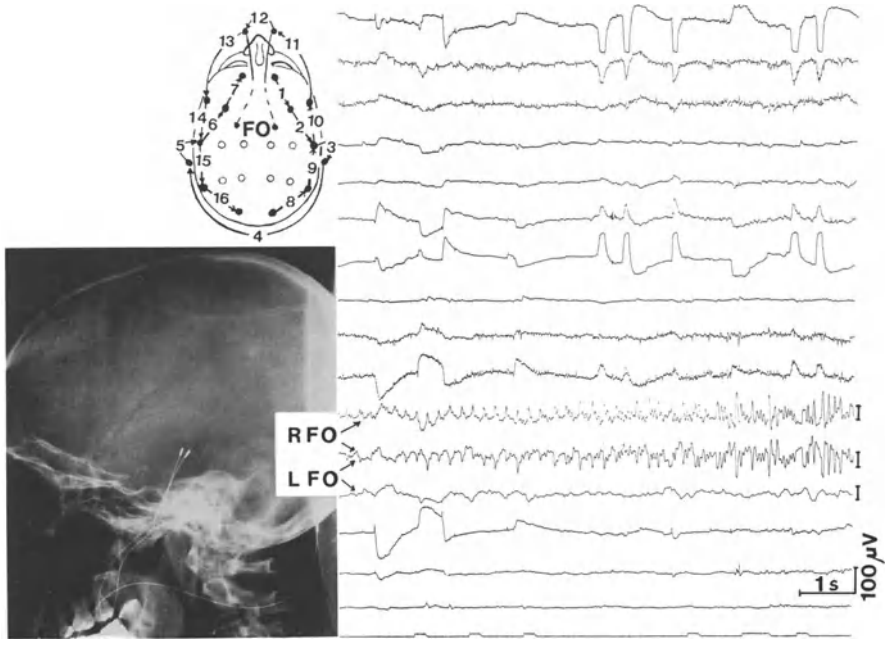

Fig. 2. Example of foramen ovale electrode and scalp EEG recordings during a right mesiobasal limbic seizure. The x-ray visualizes the position of the foramen ovale electrodes, with their tips at the level of the uncus hippocampi

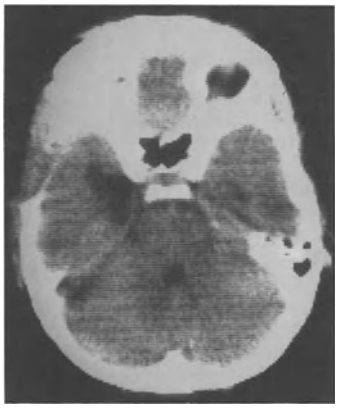

Fig. 3. CT scan after left selective amygdalohippocampectomy

obtained from the level I procedures which themselves would preclude a therapeutic operation. It is obvious that the types of therapeutic operation which can be offered by a surgical center will also determine to a certain extent whether invasive examinations will be necessary or not. This is because highly tailored resections, such as the selective amygdalohippocampectomy for the treatment of unilateral mesiobasal limbic epilepsy (7, 13), demand a much higher degree of diagnostic precision than a temporal lobectomy (see Fig. 3).

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Preoperative Neuropsychological Evaluation of Patients with Temporolimbic Epilepsy

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In the clinical work-up of patients with temporolimbic epilepsy and particularly of those who are candidates for surgical treatment, neuropsychological investigation and testing has become an increasingly important tool for clinical diagnosis, localization, indications for and prognosis of surgery, as well as evaluation of outcome. This article will primarily focus on the preoperative neuropsychological procedures.

In certain cases, the history and clinical manifestations of temporolimbic seizure disorders may be entirely typical. However, there are patients who will present predominantly with behavioral alterations or symptoms that usually are not associated with seizure disorders.

Over the last two decades a wider range of behavioral changes or abnormalities have been identified as being paralleled by epileptogenic discharges in the temporolimbic network. These behavioral alterations can be broadly categorized as sensory, motor, autonomic, hallucinatory, experiential, and emotional. They range from stuttering, slurred speech and speech arrest (2, 6, 9, 17, 20), epigastric distress (14, 18, 22), metamorphosia, sudden crying (7, 24), and explosive laughter (27) to altered sexual behavior (5, 21, 23, 25) and are listed in more detail in Table 1 (12).

Whether the patient experiences only selected symptoms or a combination of these will depend on the origin and spread of the seizure within the temporolimbic network. The symptomatology as described in Table 1 is more likely to be associated with temporolimbic discharges if it shows an abrupt and transient profile and occurs outside of the context of the environmental situation. Furthermore, there are well-established correlations between the behavioral alterations and the functional disturbances of particular cerebral regions. Simple visual or vertiginous experiences are likely to be associated with a discharge in the posterior temporal or parietal-occipital regions. Complex auditory hallucinations have been shown to be correlated to ictal discharges in or near Heschl's gyrus (27). Experiential, emotional, and autonomic manifestations seem to be associated with a seizure focus lateralized to the right hemisphere (8). Experiential and emotional manifestations of limbic epilepsy are most likely to be related to seizure activity in the limbic regions of the temporal lobe, whereas the temporal neocortex is apparently not a crucial substrate (7, 27). A careful evaluation of the patient's medical and neurobehavioral history may therefore alert the clinician to patients with a potential limbic seizure disorder and help to support the electroencephalographer's investigative steps.

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Table 1. Behavioral aspects of ictal phenomena in patients with temporolimbic epilepsy

a) Sensory:	Headache, tingling, numbness, dizziness, vertiginous sensations
b) Motor:	Complex automatisms, staring, twitching, head turning, furtive scanning, unusual facial expression or body posture, stuttering, slurred speech, complete speech arrest
c) Autonomic:	Flushing or "hot sensations," shortness of breath, frank apneic attacks, chest pain, pounding or racing heart, nausea or epigastric distress
d) Hallucinatory:	
- Visual:	White or colored lights, complex images, metamorphosia, micropsia, macropsia
- Auditory:	Ringing or buzzing sounds, voices
- Gustatory:	Metallic or foul taste
- Olfactory:	Odors like ammonia or burning rubber, decaying or fecal odor
e) Experiential:	Memory flashback, déjà or jamais vu/vécu, illusion of being possessed, altered feeling of chronological order
f) Emotional:	Embarrassment, sadness, depression, sudden crying, explosive laughter, "oneness with the universe," fear, anger, explosive but undirected aggression, spontaneous orgasm, pleasurable genital sensations, exhibitionism, forced obsessive or compulsive thoughts, tendency toward self-mutilation.

The general neuropsychological evaluation should be a basic routine in the work-up of every patient with temporal lobe epilepsy, because some of these patients have evidence of cognitive impairment. The cognitive deficits may correspond to areas of structural damage. In some cases the patients may have succeeded in managing their daily life by using alternative strategies; in other cases the function of the damaged epileptogenic area may have been taken over by adjacent or contralateral cerebral regions. Among other factors the compensatory capacities of the brain are associated with age, sex, and handedness (4, 10, 11).

Furthermore, ongoing epileptic activity may interfere with the functional integrity of the brain, not only at the focus, but also in other distant areas. Therefore excision of the epileptogenic focus in these patients often improves their cognitive performance (1). The improvement of cognitive functions may, indeed, be related to the homologous region contralateral to the seizure focus (15). One possible mechanism for this finding may be that the relevant regions are released from disturbing interferences of the primary seizure focus. The preoperative neuropsychological assessment, therefore, necessarily serves as a baseline for the evaluation of the cognitive outcome in patients who have undergone surgical treatment of temporolimbic epilepsy.

In our clinic we screen the patients according to our bedside mental status examination. Routinely vigilance, verbal and nonverbal memory, verbal and nonverbal information processing, reasoning and abstraction,

Table 2. Neuropsychological tests for different cognitive tasks

1)	General screening:	Bedside mental status examination
2)	Standardized tests:	
	a) Vigilance:	Digit span Corsi block test
	b) Language:	Aachen diagnostic aphasia examination Token test
	c) Memory:	Wechsler Adult Memory Scale Rey test for auditory verbal learning Rey-Osterrieht test for complex figures
	d) Calculation:	HAWIE - arithmetic subtest
	e) Complex perception:	Benton line orientation test Poppelreuter figures Seashore test of musical talent
	f) Construction:	HAWIE - block design test
	g) Abstraction and reasoning:	HAWIE - comprehension and simularities subtests Raven progressive matrices Wisconsin card sort test
	h) Planning and sequencing:	Porteus maze test Alternating motor sequences

right-left orientation, and calculation abilities are tested. For further evaluation standardized tests will be used as shown by Table 2.

The neuropsychological work-up of epileptogenic patients who are potential candidates for surgical treatment should also include the investigation of cerebral dominance patterns, especially for memory and language processing. The formal testing procedures are thought to guard against significant deficits of speech and memory functions. For this purpose we use the Edinburgh Inventory for Handedness by R.C. Oldfield (16), tachistoscopic hemifield stimulation with verbal material and finally the Wada technique (26).

Handedness questionnaires are very common and well established. They give a good idea of motor preference, which is correlated with cerebral dominance for language as shown by Table 3 (13, 19). Besides this indirect approach to cerebral dominance for language we also try a more direct determination by hemifield tachistoscopy with verbal stimuli. The left hemisphere (right visual field) is usually superior for verbal information processing (3), but there may be a nonsignificant right visual field superiority for left-handers (28). The lack of a significant difference between right and left visual fields for verbal information processing may question a clear-cut pattern of cerebral dominance for language.

The most reliable information on cerebral dominance patterns is provided by the Wada technique, which is carried out in most centers. It is only justified, however, if the patient is definitely considered a candidate for surgical treatment. The Wada test can be characterized as intracarotid injection of amobarbital to each hemisphere. During a period of a few minutes after the amobarbital injection, the ipsilateral hemisphere's function is markedly depressed. Testing of speech and

Table 3. Correlation of handedness (R, right-handers; L, left-handers; A, ambidexters) and hemispheral dominance patterns for language (RH, right hemisphere; LH, left hemisphere; BH, bihemispheral)

A) Patients without early brain damage

Cerebral dominance for language	Handedness		
	R	L	A
LH	96%	70%	70%
RH		15%	15%
BH		15%	15%

B) Patients with early brain damage to the left hemisphere

Cerebral dominance for language	Handedness		
	R	L	A
LH	80%	30%	30%
RH		51%	51%
BH		19%	19%

memory during this interval reveals the hemispheric dominance pattern for these functions.

There are two major uses of the Wada test. First, if the side to be operated on is dominant for language, then special intraoperative precautions are necessary in order to avoid postsurgical aphasia. Second, if barbiturization of one side results in a profound amnesia, then the traditional temporal lobectomy on that side is contraindicated (12).

We may summarize the function of neuropsychology in the preoperative work-up of patients with temporolimbic epilepsy as follows: Neuropsychological investigative techniques are useful to focus on cerebral regions possibly involved in epileptogenic activity, to provide an idea of the patient's intellectual integrity, and to avoid major deficits of memory and language function by determination of cerebral dominance patterns.

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New Diagnostic Tools for Localizing the Epileptic Focus: Positron Emission Tomography of Cerebral Glucose Metabolism and Magnetic Resonance Imaging in Patients with Complex Partial Seizures

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Introduction

The need for presurgical localization of the epileptic focus is obvious. In patients with drug-resistant complex partial seizures, positron emission tomography (PET) and magnetic resonance imaging (MRI) are likely to increase the diagnostic accuracy achieved by the more conventional noninvasive technical methods, such as CT and surface and sphenoidal EEG recordings (6), and by analysis of ictal symptoms. However, previous studies only compared PET and EEG (3, 15, 18), or MRI and EEG (7, 10). Therefore, this study was designed to demonstrate the diagnostic value of all these methods combined.

Patients

The study was performed in five male and five female patients with focal epilepsy, aged 19 to 51 with a median age of 29 years. All had a unilateral focus in conventional surface EEG and in seven cases MRI was abnormal. Five had complex partial seizures evolving to generalized tonic-clonic seizures in another group of five. The time since first manifestation of symptoms ranged from 5 to 23 years (median interval 17.5 years). All patients were on antiepileptic medication.

Methods

EEG procedures (surface and sphenoidal electrodes) and closed-circuit video-recording have been described in detail elsewhere (14). PET studies with ^{18}F-deoxyglucose were carried out using a Scanditronix PC 384 positron camera. Fourteen slices with an in-plane resolution of 7.8 mm FWHM, a mean slice thickness of 11 mm, and a center-to center distance of 13.7 mm were obtained and analyzed as previously described in detail (4, 5, 11, 17).

MRI studies were performed on a Picker 2000 system with a superconducting magnet operating at 0.5 Tesla. T_1-weighted images were recorded in the inversion recovery technique (TR: 1860 ms, TI: 500 ms); the spin-echo technique (T_2) was applied with repetition times of 2320 ms and echo times of 80 ms. In two cases, a repetition time of 1500 ms and echo time of 120 ms were used additionally. When required for better demonstration of the lesion, MRI scans were also obtained in the coronal or sagittal plane. CT studies were carried out either on a Phillips 2000 or a Tomoscan 350 scanner.

Complex partial seizures were classified as type I or type II by clinical symptoms according to DELGADO-ESCUETA and WALSH (1, 2, 16).

Results

Pertinent clinical data as well as the results of the different methods are summarized in Table 1.

Constant, unspecific, unilateral EEG foci were detected in seven patients. Specific unilateral electrical activities were found on interictal recordings of six patients. Four patients showed bilateral specific activities. During seizures, initial regional (inferior temporomesial) discharges were recorded in four cases; in four patients some lateralization and, in one case, a changeover was observed. In one subject, no side of origin could be determined. Nine patients had type I and one patient type II seizures.

CT scans were "false"-negative in seven patients. Morphological alterations of the left and right temporal pole, respectively, were found in two cases. In another patient, a cystic abnormality was detected in the posterior sylvian fissure in coincidence with the side of the EEG focus. All pathological CT findings correlated with MRI. T_2-weighted MR images showed a focal increase in the signal intensity of Ammon's horn in four cases. In three patients with extrahippocampal pathology, MRI findings were localized in the temporal pole, in one case in the center of the temporal lobe, appearing larger than the corresponding cyst on CT. No bi- or extratemporal foci were noticed. In two cases, MRI was negative.

In eight patients, unilateral hypometabolism was detected by PET, representing the characteristic interictal appearance of epileptogenic foci (8). Bilateral hypometabolic areas were found in two cases. Hypometabolism affected the temporal pole and Ammon's horn in nine patients, while in two cases (No. 1 and 4) the inferior frontal lobe also showed diffuse metabolic depression. Case No. 7 exhibited a well-defined region of hypometabolism in the inferior insular cortex in addition to ipsilateral temporal hypometabolism. Within the widespread hypometabolic area, the localization of a center was usually possible. In general, it corresponded with the lesion seen on MRI or CT (Fig. 1, lower row; Fig. 2). A second hypometabolic focus not shown on MRI was detected in the contralateral temporal pole in two patients (No. 9 and 10) and in the temporo-parieto-occipital cortex in another patient (No. 5). Although MRI was negative in patients 3 (Fig. 3) and 7, a focus was found by PET (No. 3, anterior mesial temporal pole including frontal part of hippocampus; No. 7, anterior temporal lobe and inferior insular cortex). In patient 6, both the hippocampus and the temporal pole were markedly involved. In case 8, a hypermetabolic focus next to the hypometabolic lesion was taken as evidence of epileptic activity: The patient had suffered an ictus just before scanning, and she reported an aura during the dynamic recordings. In an interictal control PET, hypermetabolism was no longer found (Fig. 1, lower row). In all cases, the hypometabolic foci on PET corresponded with the origin of ictal discharges in EEG, if the latter was positive at all. In eight patients, the sides of hypometabolism corresponded completely with the sides of interictal epileptic activity. Cases No. 7 and 8 also showed contralateral specific interictal activity in EEG without corresponding hypometabolic foci on PET. No specific EEG focus could be related to the temporo-parieto-occipital hypometabolic area in case 5.

Table 1. Patients and diagnostic findings

Pat. no.	Age (yrs)	Diagnosis	Seizure type	Duration (yrs)	Epileptic EEG activity: Interictal Ictal
1	42	CPS[a], TCS[b]	I	23	Inf. mes. right Reg. inf. mes. right
2	51	CPS	I	20	Inf. mes. > ant. temp. left Reg. inf. mes. left
3	35	CPS, TCS	I	17	Inf. mes. > ant. temp. right Reg. inf. mes. right
4	25	CPS, TCS	I	6	Inf. mes.-ant. temp. right Lat. frontotemp. right
5	19	CPS	I	5	A. Inf. mes. right B. Midtemp. right Reg. inf. mes. right
6	30	CPS, TCS	I	18	Inf. mes.-ant. temp. right Lat. right
7	31	CPS, TCS	II	26	A. Inf. mes.-ant. temp. right (95%) B. Inf. mes. left (5%) Lat. right
8	22	CPS	I	18	A. Inf. mes.-midtemp. right B. Inf. mes. left Lat. inf. mes. or midtemp. right
9	28	CPS	I	7	A. Inf. mes.-ant. temp. left and right B. Mid.-ant. temp. right Alternation left and right frontotemp.
10	28	CPS	I	14	A. Inf. mes.-midtemp. left B. Inf. mes.-midtemp. right

[a]Complex partial seizures; [b]Tonic-clonic seizures

Localized abnormalities		
PET	MRI	CT
Inf. mes. > temp. pole > inf. fron. right	Ant. hippoc. right	-
Inf. mes. > temp. pole > left	Uncus hippoc. left	-
Temp. pole and inf. mes. right	-	-
Inf. mes., temp. pole > temp. lat. > inf. fron. right	Ant. hippoc. right	-
A. Inf. mes. > temp. pole right B. Temp.-par.-occ. right	Ant. hippoc. right	-
A. Post-inf. lat. temp. lobe right B. Temp. pole and inf. mes. right	Midtemp. right	Insular right (cyst)
A. Inf. mes. and temp. pole right B. Insular right	-	-
A. Mes. temp. pole right B. Hypermetabolism lat. temp. pole right	Temp. pole right	Temp. pole right
A. Temp. pole and inf. mes. left B. Temp. pole and inf. mes. right	Temp. pole lat. right	-
A. Temp. pole and inf. mes. left B. Temp. pole and inf. mes. right	Temp. pole left	Temp. pole left

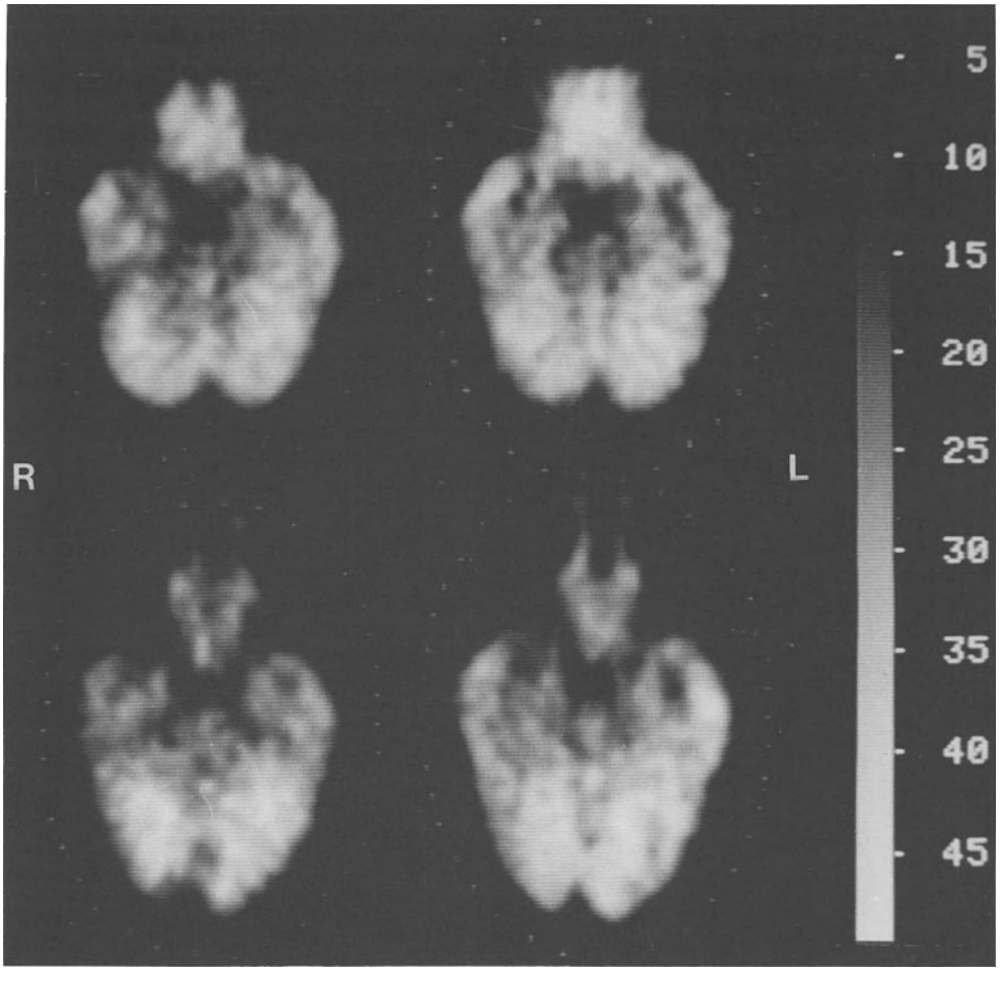

Fig. 1. Metabolic maps in units of μmol/100 g/brain tissue/min (bottom view) of a 22-year-old female with complex partial seizures since age 4, during ictus (*upper row*) and in the interictal state (*lower row*). The hypometabolic focus in the right mesial temporal pole is clearly visualized. Ictal scans show a hypermetabolic focus lateral to the hypometabolism

Discussion

In agreement with the results of others (9, 12, 13), regional or lateralized specific EEG activity could be demonstrated in 80% of patients. Perhaps on account of the mode of patient selection, the number of focally increased T_2 relaxation times (8x) was larger than has been reported from other studies. Corresponding lesions on CT were detected in three cases. JANZ et al. (7) reported a sensitivity of 15 out of 40 patients for increased focal T_2 times in MRI and 10 out of 40 for pathological CT findings; McLACHLAN (10) gave corresponding figures of 8 and 0 for a series of 10 patients. These discrepancies

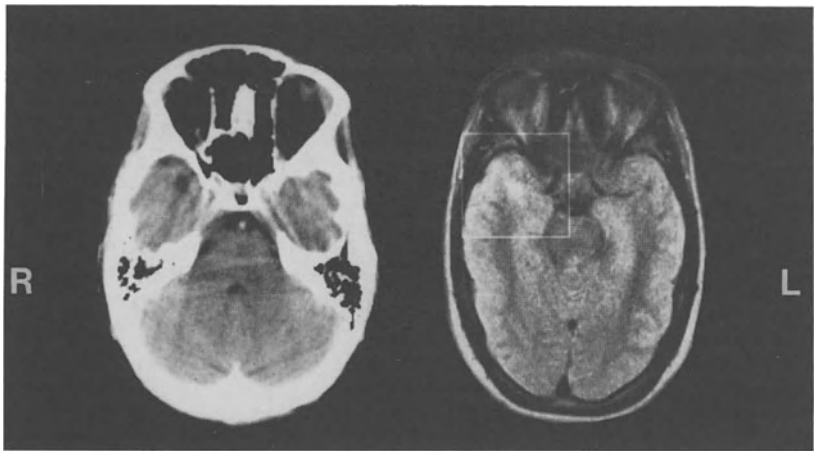

Fig. 2. CT (*left*) and T_2-weighted MR image (*right;* TR: 1500 ms, TE: 120 ms) of the same patient as in Fig. 1, showing a morphological lesion in the right mesial temporal pole

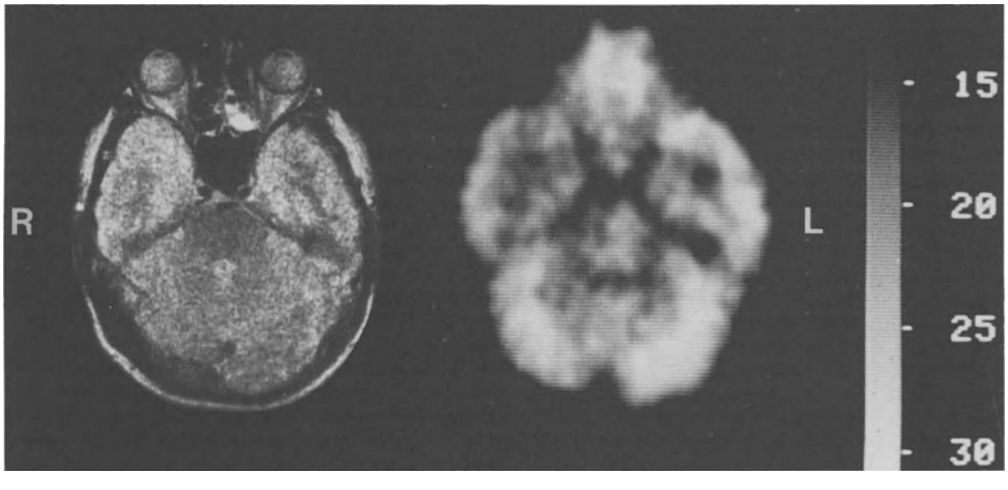

Fig. 3. Characteristic MR (*left*) and PET images (*right*) of a 35-year-old male with complex partial seizures (evolving to generalized tonic-clonic seizures) since age 18. Metabolic maps show a hypometabolic focus in the right anterior-mesial temporal pole, with the anterior part of hippocampus included. No lesion could be detected on T_2-weighted MR images performed with TR = 1500 ms and TE = 120 ms

probably are due to the different diagnostic criteria applied by different examiners.

In the present study, all focal findings (increased T_2 signal) in MRI had corresponding EEG foci. This observation is in agreement with the results of JANZ et al. (7). McLACHLAN et al. (10) reported one posi-

tive MRI finding without a corresponding EEG focus in a series of 8 patients.

The number of hypometabolic foci in PET with corresponding specific foci in EEG was larger than described in other studies (3, 15, 18). Again, selection of patients (with positive MRI findings) must be taken into account. In one case, there was a hypometabolic focus in PET without an epileptic correlate in EEG. Because of the high specificity of EEG, this PET finding must be judged with caution (3).

The comparison of PET and MRI revealed greater sensitivity of PET. Of course, pathology shows better on MRI owing to its higher spatial resolution. Unlike MRI, however, PET demonstrates the involvement of other brain areas corresponding with unspecific abnormalities in EEG.

Comparison of PET results and seizure symptoms revealed that only the patient with type II symptoms had a circumscribed extratemporal hypometabolic focus. This is in agreement with the theory of an extratemporal participation in this type of seizure (2).

Summary

Ten patients with complex partial seizures (five evolving to generalized tonic-clonic seizures) were studied by CT, MRI, PET (with ^{18}F-deoxyglucose), and EEG (surface and sphenoidal electrodes). In all patients, PET revealed unilateral (8x) or bilateral (2x) temporal hypometabolic areas with corresponding specific EEG findings. In addition to ipsilateral temporal hypometabolism, one patient each showed a well-delineated hypometabolic focus in the inferior insular cortex and in the temporo-parieto-occipital cortex, the latter remaining without corresponding EEG findings. MRI appeared somewhat less sensitive than PET: only in eight cases was a unilateral abnormality detected. Three patients had positive findings on CT.

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Single Photon Emission Computerized Tomography (SPECT) with Xenon 133 in the Diagnosis of Temporal Lobe Epilepsy

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Introduction

Focus determination in focal epilepsies is not always without problems. The traditional methods, EEG and cranial computerized tomography (CCT), often provide inconclusive results. Magnetic resonance imaging (MRI) has proved an important improvement (2), and further information may be expected from advanced metabolic studies of brain function (2).

We have been using single photon emission computerized tomography (SPECT) in the diagnosis of epilepsy for 4 years. Following our previous report (3), the results of SPECT with xenon 133 in 67 patients with temporal lobe epilepsy are reported.

Method and Material

The tracer kinetic method requires the administration of xenon 133 for 1 min, followed by continuous SPECT scanning during a 3-min washout period. The entire investigation thus takes 4 min. The regional cerebral blood flow was evaluated quantitatively in our study.

The subjects were 67 adult patients with complex focal seizures with or without secondary generalized tonic-clonic seizures. They were all studied in the interictal state. In about one-third of the patients, SPECT was repeated up to four times. All had a CCT and several EEGs. Eighteen had an EEG registration with a mobile 8-channel Medilog system during the scanning. MRI was available in 47 cases.

Results and Discussion

In 51 of the 67 patients, SPECT revealed decreased regional perfusion of various degrees. Table 1 presents a synopsis of focal findings with the four methods being compared. EEG, MRI, and SPECT have similar high rates of positive findings, whereas CCT provided much less information on the site of the focus. Positive findings of other investigations were confirmed in about 80%-90% of cases by SPECT (Table 2).

The combination of various methods should enhance the information provided regarding the focus. If one examines those cases in which the four methods of investigation failed to reveal information, and the information gained by the introduction of a second method (Table 3), CCT again had relatively little to contribute whereas the other three methods provided additional information in a significant proportion of cases. The gain of information by SPECT is considerable, and seems

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Table 1. Focal abnormal findings

	No.	Positive findings	%
EEG	67	52	78
SPECT	67	51	76
CCT	67	18	27
MRI	47	34	72

Table 2. Agreement in abnormal findings

Abnormal (*n*)		SPECT abnormal (%)	
CCT	(18)	16	(89%)
MRI	(34)	27	(79%)
EEG	(52)	42	(81%)

Table 3. Gain of information

Normal (*n*)		Abnormal (%)			
		CCT	MRI	EEG	SPECT
CCT	(49)	-	64	73	71
MRI	(13)	0	-	69	69
EEG	(15)	13	50	-	60
SPECT	(16)	13	64	63	-

most prominent in addition to the morphological methods, CCT and MRI. However, the combination with EEG as another functional method also proved quite valuable. More precisely, unilateral abnormalities were detected by SPECT in 17 of 28 patients whose EEG was either normal or demonstrated bilateral findings (Table 4).

In contrast, in only two patients with a unilateral EEG focus were bilateral abnormalities found with SPECT, and in only one patient were the EEG and SPECT foci not on the same side. If the EEG was unrevealing, equally useful information was gained by SPECT or MRI, but of six patients with both negative EEG and MRI, localization by SPECT was still possible in four (Table 4).

Positive results of the four methods were not identical in nine patients. In six of these, there was agreement of EEG and SPECT against MRI, but in two, EEG and MRI disagreed with SPECT.

Looking at the intraindividual consistency of SPECT findings, fluctuation of the severity of decreased cerebral perfusion was found in 58% of the investigated cases. One patient showed a normal finding in the control SPECT in contrast to a former abnormal result. Another patient had a shift of the abnormal finding from the temporal lobe to the

Table 4. Information about laterality

Lateralization	(*n*)	Unilaterally abnormal		
		SPECT	MRI	SPECT and/or MRI
EEG unclear	(28)	17 (61%)	18 (65%)	20 (71%)
EEG unclear MRI unclear	(6)	4 (67%)	-	-

parietal lobe. The side of abnormal findings, however, never shifted from one hemisphere to the other.

In the 18 simultaneous EEGs during SPECT, no epileptic activities were registered in 14, probably because of the short duration of the scanning. In the other four, no significant correlation between spike frequency and severity of abnormal perfusion was detected. This suggests that SPECT, just like PET (1), and EEG represent different aspects of the dysfunction in epilepsy.

Conclusion

In our study of 67 adult patients with temporal lobe epilepsy, SPECT proved to be a useful method for determining the site of the focus. It was equally as useful as EEG and MRI, whereas CCT was less informative. In over 60% of the cases with inconclusive EEG, MRI, or EEG plus MRI findings, SPECT provided information about the laterality of the focus. The SPECT findings seem to be consistent intraindividually concerning laterality. They are, however, not sufficiently circumscribed for exact localization of the epileptic focus.

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Initial Experience with ^{99m}Tc-Hexamethylpropyleneamine Oxime (HMPAO) SPECT in Patients with Focal Epilepsy

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In addition to EEG, CT, MRI, and SPECT have gained importance as diagnostic tools for the localization of structural and functional disturbances in focal epilepsies. In the following study ^{99m}Tc-HMPAO SPECT was used for the first time for investigation in patients with focal epilepsies, in relation to EEG-proven foci. The results are compared with those of CT and MRI.

Sixteen patients with focal epilepsy (nine male and seven female between 18 and 50 years old) with mainly complex partial and/or simple partial epileptic seizures were examined by means of a 16-channel surface EEG with montage according to the 10/20 system. In all patients an EEG focus was registered. After proving focal EEG activity, these patients were also investigated with ^{99m}Tc-HMPAO SPECT.

Results were defined as pathologic if the acitivity uptake in one region of the brain differed by about 30% from that of the contralateral hemisphere. In 12 cases we saw a pathologic SPECT result (75%). A pathologic CT result was revealed in 25%, and a pathologic MRI result in 77% (n=13). The pathologic CT results (n=4) correlated in all cases with the SPECT results, while 61.5% of the MRI findings correlated with the SPECT results concerning the side of the hemisphere and the localization of the pathologic area. In 11 cases (69%) the pathologic SPECT results and the focal EEG activity were localized in the same hemisphere. Five patients (30%) had bilateral epileptic EEG activity. In three of these patients a pathologic SPECT result was present only on one side.

The results of these investigations with ^{99m}Tc-HMPAO SPECT show that this method is suitable for revealing circumscribed disturbance of brain function. In addition to the morphological information provided by MRI, functional diagnosis by ^{99m}Tc-HMPAO SPECT may represent a method for establishing laterality in patients with bilateral EEG foci. The results presented in this study give additional information concerning functional disturbances in patients under consideration for epilepsy surgery.

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Single Cell Recordings of the Nucleus Amygdalae in Conscious Cats. A Contribution to Research into Focal Epilepsy

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Introduction

Complex partial seizures originating from the mesial parts of the temporal lobe are characterized by autonomic, psychic, and motor symptoms like changes in heart frequency and blood pressure, gastrointestinal sensations, fear, anger, and automatisms, accompanied by impairment or even loss of consciousness in the case of secondary generalization (1). Often the focus is localized in the amygdaloid complex (AC) (9), a part of the limbic system receiving afferents from the brain stem, subcortical, and cortical structures and projecting to the neocortex, the hippocampus, the hypothalamus, and the brain stem. The AC is critically involved in the selection and elaboration of contextually appropriate patterns of behavior (4). Complex partial seizures are often medically refractory. In these cases surgical removal of the focus must be considered (10, 13). In part the epileptogenic activity is triggered by scars or small dysontogenetic tumors (6); in most cases no morphological substrate can be found (1). To narrow down the precise focus, electrophysiological investigations (standard, sphenoidal, and stereo-electroencephalography) are necessary. In 20% of such patients depth electrode recordings reveal bilateral epileptic activity (2, 17). For clinical purposes the primary or leading focus has to be unequivocally determined and the question arises as to whether the secondary focus can trigger seizures by itself.

Two different types of experiments were done in cats to contribute to the solution of these questions. (1) In the kindling model of epilepsy (5) we studied the effect of kindling on blood pressure, heart rate, cortical and subcortical electrical activity, and behavior in unrestrained cats. (2) The influence of spontaneous single neuron discharges recorded in the AC on contralateral amygdala and cortical activity was tested.

Materials and Methods

For the kindling experiments cats were chronically implanted with bipolar electrodes in both amygdalae, the hippocampus, and the left frontal cortex using the stereotaxic coordinates from the atlas of REINOSO-SUAREZ (14). Blood pressure and heart rate were recorded with a Statham transducer via a catheter implanted in the abdominal aorta. Recordings of the experiments were documented on an EEG polygraph. Electrical stimuli were applied daily in the right AC. Stimulus parameters were 50-300 µA, 40 cps, and 0.5 ms pulse duration (square waves) delivered for 5 s. Kindling was carried out at intensities 100 µA below the threshold to induce afterdischarges as tested in pilot stud-

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ies. For the recording experiments in a second group of cats, a socket was chronically implanted for mounting a microdrive to lower tungsten microelectrodes (tip diameter 10 µm) into the AC to record single cell discharges. EMG activity of neck muscles was picked up by stainless steel wires. EEGs and blood pressure were recorded in the same way as described for the kindling experiments.

Results

Kindling Experiments

By daily stimulations the animals developed tonic-clonic seizures within 14-24 days, going through different stages. A representative example is shown in Fig. 1 ending at day 23, 1 day before tonic-clonic seizures appeared. Even on the first day of stimulation a moderate increase in heart rate and blood pressure was observed. On day 6 a hypersynchronization developed in the kindled side, accompanied by a shorter lasting hypersynchronization of the contralateral AC indicative of the spread of kindling. The cortical EEG became desynchronized, outlasting the stimulation. The animal showed a behavioral arousal reaction. On day 18 afterdischarges in the kindled side and hypersynchronizations of the same duration appeared in the left amygdala, hippocampal, and cortical EEG. Blood pressure and heart rate were elevated and a poststimulatory hyperventilation appeared. On the same day the cat developed salivation, bilateral facial twitches, and head movements. On day 23 massive afterdischarges in both ACs and the hippocampus appeared together with a poststimulatory cortical hypersynchronization. It was a constant observation that in the course of the kindling procedure autonomic effects preceded changes in the electrical activity of the contralateral AC, hippocampus, and cortex. These findings are in accordance with the clinical observation in patients that the so-called aura of seizures is characterized by autonomic phenomena preceding the development of abnormal EEG activity.

Recording Experiments

In these experiments 20 neurons in the central and 19 in the basal part of the amygdala were recorded for up to 3 h. In most recordings the mean discharge frequency was below 10 impulses/s. The neurons often discharged in bursts of two to three spikes within 10 ms interrupted by silent periods. During quiet wakefulness natural stimuli (e.g., acoustic) were presented to the animals. A typical example is given in Fig. 2. In response to barking of dogs the discharge frequency of the neuron in the central part of the AC increased. The desynchronization in the electrical activity of the contralateral AC was observed 150 ms later. The autonomic response shown by the short increase, decrease, and reincrease of blood pressure starts nearly 1 s after the activation of the amygdala neuron together with the desynchroniztion of the cortical EEG. Beginning of somatomotor activity was indicated by EMG activity of neck muscles. The cat lifted the head as a component of the arousal reaction after 3 s. Very often after the initiation of such responses the neurons reduced their mean discharge frequencies to below the prevalues for up to 20 s.

The relations between the discharge times of the single neurons and EEG activities of the contralateral cortex and AC were determined by computing cross-correlation histograms. In these histograms the plot to the right of the ordinate gives the course of the electrical activity of the cortex or the amygdala in dependence on the discharges of

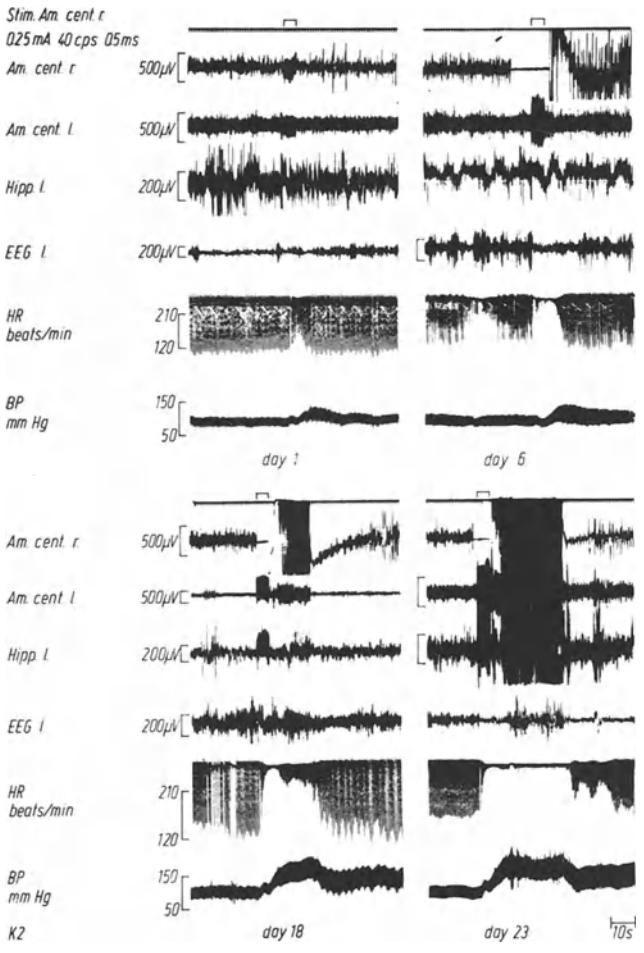

Fig. 1. Development of cardiovascular and EEG changes in response to daily electrical stimulation of the central amygdala of the right hemisphere (*Am. cent. r.*) in a cat. EEGs of left hemispheric central amygdala (*Am. cent. l.*), hippocampus (*Hipp. l.*), frontal cortex (*EEG l.*), heart rate (*HR*), and arterial blood pressure (*BP*) are shown. EEGs were recorded with bipolar electrodes (interpolar distance 1 mm). Duration of electrical stimulation (5s) is indicated at the top of the *individual panels*. Stimulus parameters were: 0.25 mA, 40 cps, 0.5 ms impulse duration

the neuron (Neuron >ECoG or EAmG) whereas the plot to the left of the ordinate indicates the dependence of the neuronal discharge times on cortical or subcortical activity (Neuron <ECoG or EAmG). In the event of independence of the signals, the histograms are flat and fluctuate around the mean value represented by the abscissa. An effect on contralateral amygdala activity was proven for 11 of 20 cells in the central and 8 of 16 cells in the basal part. Timing of cortical EEG waves depended on the discharges of 12 of 20 cells in the central and 9 of 16 in the basal part. Several neurons in both subnuclei had an influence on the cortex as well as on the contralateral AC at the same time. In Fig. 3 two examples of positive correlations are shown. All histo-

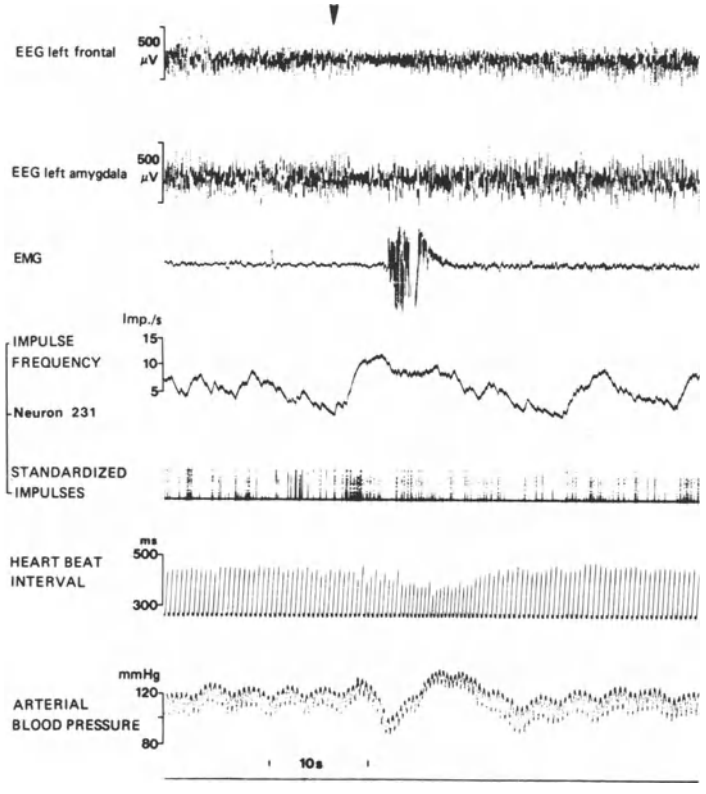

Fig. 2. Response to barking of dogs (*arrow*) in the EEGs of left frontal cortex and left amygdala, EMG, single neuron activity of the right amygdala shown as an integrated impulse frequency curve and standardized impulses, heart beat interval, and arterial blood pressure. For further explanation, see text

grams display a maximum right to the ordinate, indicating that the EEG wave of the cortex and the AC have a relatively fixed latency and phase relation to the discharge sequences of the two neurons. The maxima are not repeated in the further course of the histograms except in the correlation of neuron 72 EAmG, which shows two repetitions with an interval of 600 ms. The histograms suggest that the neuronal discharges determine the timing of events in the dependent neuronal structures, thereby coordinating their performance. The latencies of the maxima were between 60 and 300 ms (mainly 100-160 ms), which indicates that the propagation uses oligo- or polysynaptic pathways. In long-lasting recordings of single cells the positive correlation to the cortex and/or the AC could disappear and reappear, indicating a clear dependence on the functional situation. Furthermore, in cases of a positive correlation with the contralateral AC it was observed that at one time the maximum was on the right of the ordinate and at another time on the left. This underlines the reciprocal connectivity of the amygdala nuclei.

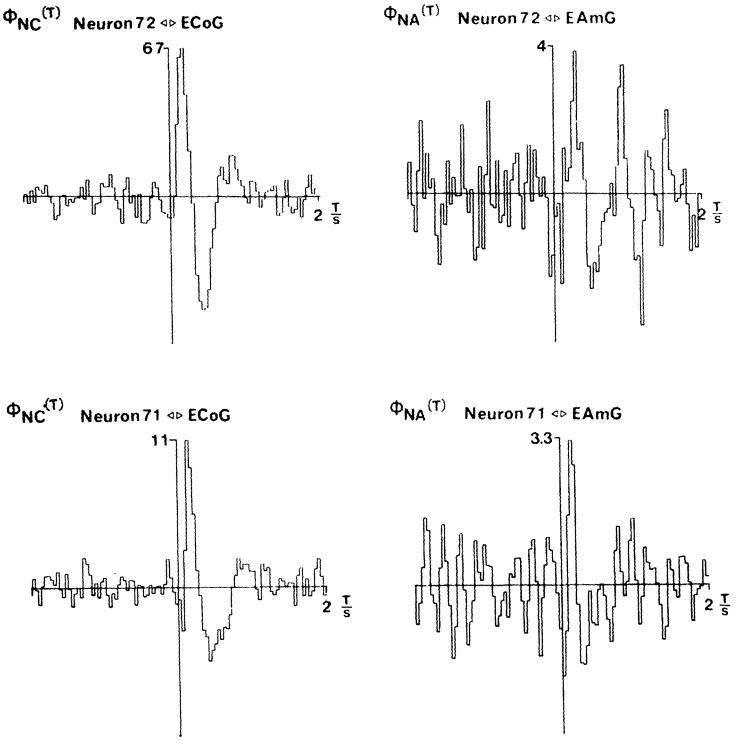

Fig. 3. Cross-covariance histograms between the discharge sequences of two different single neurons (71, 72) recorded in the central part of the amygdala and contralaterally recorded EEGs of cortex and amygdala for demonstration of temporal dependencies. Computations were done with the event times of neuronal discharges and EEGs filtered 1-15 Hz and sampled 50 times per second. Correlation times were 20.48 s according to a bin width of 40 ms and 512 bins. Histograms were plotted for $\tau = \pm$ 2s, ordinate scaled in relative figures. Cross-covariances were obtained from cross-correlations by subtraction of the average value. The maxima *right of the ordinate* indicate that the electrical activity in the cortex and the amygdala depends on contralateral neuronal discharges

Discussion

The close temporal interdependencies of the activities of both ACs and cortex, blood pressure, and somatomotor performance are indicative of the role of the AC in complex patterns of behavior (4, 15). In cases of epilepsy the use of physiological connections facilitates the distribution of seizure activity to the contralateral AC, leading to a secondary focus as found in stereo-EEG recordings (2, 17). Concerning the pathophysiological mechanisms leading to an epileptogenic focus, a long-term potentiation in excitatory pathway and a defect (probably at the neurotransmitter level) of an inhibitory mechanism have been discussed (7, 12). The observation that the neurons reduced their discharge rates below prevalues after the induction of a behavioral reaction would support this assumption. The inhibitory mechanism would limit an activation of AC neurons. Furthermore, it must be

discussed that the timing effect seen for single neurons on AC and cortical EEG activities requires the synchronous activity of a larger group of neurons. This is supported by the observation that neighboring neurons recorded simultaneously displayed the same positive correlations with the EEGs. Such a synchronous activity needs a self-limiting mechanism to prevent hypersynchronization. The kindling experiments as well as the single cell recordings show that a transfer of activity to the contralateral AC occurs within 100 ms. Long-lasting periods of psychomotor seizures arising from one temporal lobe were followed by the development of seizures triggered from the contralateral, originally uninvolved temporal lobe (8). In kindling experiments the focus could also be transferred to the other side (5). These secondary foci were able to induce seizures themselves (16). Even after destruction of the primary focus, seizure activity persisted in kindled animals (11). Therefore in cases of medically refractory complex partial seizures a surgical intervention with a highly selective removal of tissue involved should be considered at an early stage.

Summary

The results presented suggest that the propagation of seizure activity of an epileptogenic focus in the AC follows the physiological pathways. A transfer of the activity to the contralateral AC and thereby the temporal lobe occurs within 100 ms. This explains the bilateral seizure activity in stereo-EEG recordings. In view of the discussion and the experimental results that the secondary focus can become a focus by itself, in cases of medically refractory complex partial seizures surgical intervention should be considered at an early stage.

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Morphological Causes of Focal Epilepsy that is Difficult to Regulate, and How It Can Be Influenced Operatively

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Introduction

The number of people who suffer from epileptic fits is substantial, the proportion of the population being approximately 0.5% (2). In some patients epilepsy is difficult to regulate or cannot be regulated at all with the use of antiepileptics. The stereotactic operations for interrupting important paths that spread and "unload" fits, and also for switching off control systems, have been well-known for a long time and have been performed in particular by Hassler and Riechert and their schools (4). An increasing number of patients suffering from focal fits profit from an open surgical operation. The quality of the preoperative diagnosis is decisive for the success of the operation. The introduction of computed tomography has meant a great deal of progress, for by means of this technique it has become possible to prove that small neoplasms or malformations are the cause of focal fits. These foci are for the most part not space occupying and, for this reason, were not representable using the former neuroradiological methods, such as angiography or air encephalography. The tumors, of course, are frequently to be found in the temporal lobes, but they do not have to be localized there; they can occur in all regions of the brain. If at all possible, the foci should be removed completely since any residue can continue to act as the focus of fits.

The aim of this paper is to point out the nature of these neoformations and also to delimit them from temporal lobe epilepsy of different origin.

Material and Method

The case histories of all patients operated on since 1983 for brain tumors or vascular malformations were evaluated, and the patients who, in anamnesis, had produced epilepsy that was either difficult to regulate or could not be regulated at all were put together in one group. Particular value was placed on a satisfactory pre- and postoperative neuroradiological diagnosis. The pre- and postoperative electroencephalograms were compared, and so were the clinical findings before and after the operations.

Results

Six patients suffering from epilepsy that was difficult or impossible to regulate medicinally had small tumors or malformations. All six patients (four girls, two boys) were children or young persons between

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20 months and 18 years of age. All of them had suffered from epileptic fits for years and, in two cases, the fits had already occurred for the first time when the patients were infants or small children (cases 4 and 6). The changes in the electroencephalograms pointed to a focus - except for cases 4 and 6 - but they did not indicate any comparable pathological findings. With all of the patients the nature and frequency of the fits also varied (Table 1). The neoplasms, or malformations, could all be detected on the computed tomograms and the average size was 2 cm. The localizations varied: 1 x temporo-occipital r., 1 x hippocampus r., 1 x temporal l., 1 x parietal r., 1 x parietal l., 1 x frontal l. (Table 2). In the case of No. 2, an 18-year-old girl, a poorly defined hypodense area could be detected on the computed tomogram temporally on the left and there was only moderate contrast enhancement (Fig. 1). The positron emission tomography carried out with ^{68}Ga-EDTA showed a pathological accumulation of activity in this area (Fig. 2). In this case the morphological examination revealed a gliovascular hamartoma. The other diagnoses were: 2 x ganglioglioma; 2 x glioma: grade II, the oligodendroglial portion predominating in both cases with calcifications; 1 x arteriovenous angioma (Table 2). In the postoperative phase only one of the patients (case 6) receiving anticonvulsive therapy suffered from fits. The first operation had been carried out on this child when it was 20 months old. During this operation only the peripheral area of the tumor was removed. The fits continued to occur. The child was operated on again when it was 2 3/4 years old and the tumor was removed. Since then the fits have ceased even in this patient. In all of the cases the dosage of antiepileptics could be reduced. The postoperative encephalograms showed an increasing tendency to return to normal.

Discussion

Surgical treatment of focal epilepsy is increasingly gaining in importance. By using noninvasive methods, such as EEG long-term leads, video recordings of the fits, and computed, nuclear spin, and positron emission tomography, as well as invasive procedures such as EEG by means of stereotactically implanted deep action electrodes, we can prove the focal nature of the fits and localize the focus precisely. What forms the basis of a fit is a pathological synchronization of nerve cell activity, which - as a result of an inhibition functioning physically - cannot be kept in check. This kind of excessive synchronization comes about when a milieu that supports synchronization is built up in an area of the cortex. The initial situation is different from that when there is a general increase in the readiness to synchronize, and - as an extremely local phenomenon - it would call for an enormous medicinal influence approaching total suppression of nerve cell activity if one wished to eliminate it (3).

Cutting out the focus clears up a local finding. With these foci it may be a question of isolated metabolic disorders, that is to say metabolic epilepsy. In these cases one wonders whether the focus can be resected without causing any intolerable neurological failures. As a rule one only operates if 3-4 years of medicinal anticonvulsive therapy have been carried out by experts without success. By performing a selective amygdalo-hippocampectomy satisfactory results have been achieved in Zurich with regard to the so-called mediobasal form of limbic epilepsy, the most important subsidiary form of temporal lobe epilepsy (5).

The situation is different in the case of focal epilepsy, in which the focus corresponds to a small tumor or vascular malformation. These foci

Table 1. Analysis of the type and frequency of the epileptic fits and of the EEG findings in the six patients with epilepsy resistant to therapy

Case No.	Age in years	Duration of epilepsy in years	Fit		EEG findings
			Type	Frequency	
1	18	Several	Grand mal	Daily	Epileptogenic focus, temporal, right-hand side
2	18	7	Psychomotor grand mal	1 per day	Dysrhythmic groups, left-hand side temporal, without any absolute proof of convulsive activity
3	14	4	Psychomotor	2-6 x per day	Epileptogenic focus, left, temporoparietal, nonspecific deceleration focus, right, temporal, slight general changes
4	12	11	Psychomotor	1-2 x per month up to 2 x per week	No definite pathological finding
5	13	2	Grand mal psychomotor	2-3 x daily	Moderately active sharp-wave focus, left-hand side, pre-central
6	2 3/4	2 1/2	Grand mal focal fits	Several times daily	Without any definite pathological finding

Table 2. Analysis of the neuroradiological and morphological findings with regard to the six patients with epilepsy resistant to therapy

Case No.	Age in years	Sex	CT finding	Localization	Morphological diagnosis
1	18	Female	Small hypodense area with calcification	Temporo-occipital, right-hand side	Ganglioglioma
2	18	Female	Unclearly defined hypodense area, moderate enhancement	Temporal, left-hand side	Gliovascular hamartoma
3	14	Female	Hypodense area with contrast medium enhancement	Parietal, left-hand side	Arteriovenous angioma
4	12	Female	Hypodense area with calcification	Hippocampus, right-hand side	Glioma, grade II (predominantly oligodendroglioma)
5	13	Male	Hypodense focus, indicating subarachnoid cyst	Frontal, left-hand side	Glioma, grade II
6	2 3/4	Male	Hyperdense focus, no change after adding contrast medium	Frontoparietal, right-hand side	Ganglioglioma

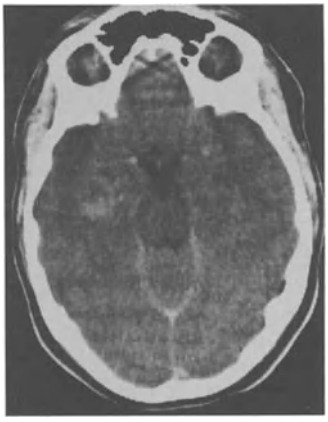

Fig. 1. *Case No. 2.* Hypodense focus, left-hand side, temporal, with moderate enhancement after contrast medium was added

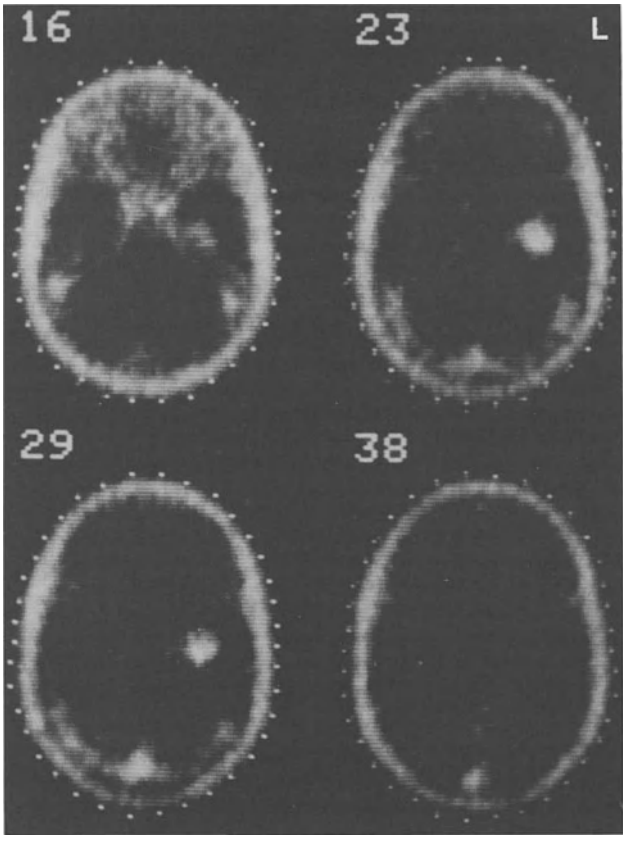

Fig. 2. *Case No. 2.* Positron-emission tomogram with ^{68}Ga-EDTA: Pathological accumulation of activity, left-hand side, temporomedial

are too small to be represented on the angiogram, since they are not of a space-occupying nature and do not have any pathological vascular structures. The tumors or hamartomas we examined were all revealed on the computed tomograms. The nuclear spin and positron emission tomograms confirmed the findings.

If tumors have been proven to be the cause of the fits, the operation should be performed immediately. It is by no means always a question of malformation tumors such as gangliocytomas, which in our experience grow only slowly, if at all. In the case of gangliogliomas, as with gliomas, there is a tendency for them to become larger and malignant, even if the neoplastic glia in gangliogliomas is less aggressive than in gliomas without any ganglion cell component (1). In the case of angiomatous malformations - as with all angiomas - there is a risk of hemorrhage. If microhemorrhages occur in angiomatous malformations they are organized by connective tissues. It is above all tumors or angiomas with a high degree of connective tissue that are ictogenic, because in these cases regulation of the microcirculation - which is sufficient for the connective tissue - is achieved instead of the blood supply that is optimum for brain tissue. By resecting these foci the normal condition is reproduced to an approximate degree (3). As a rule, the scars that develop in the brain after optimum neurosurgical operations do not go up and down with a neoformation of collagenic fibers, but the astrocytes form a fine glial fiber scar.

Summary

In the case of six patients between the ages of 20 months and 18 years, small tumors or hamartomas were found to be the cause of focal epilepsy that was difficult or impossible to regulate. These neoformations were too small to be proven using conventional neuroradiological methods of examination. By contrast, with an appropriate layer thickness all of them could be proven on computed tomograms. Nuclear spin and positron emission tomograms confirmed the findings. After the operations all of the patients stopped suffering from fits, and the anticonvulsive medication could be reduced or, after some time, discontinued altogether. The scars that develop after optimum neurosurgical intervention are of a glial nature and, for this reason, do not act as ictogenic foci.

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Histopathological Study and Neurosurgical Findings in 17 Patients with Hamartomas Presenting Epileptic Seizures

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Introduction

Hamartomas are lesions falling between tumors and malformations that are seldom seen in the central nervous system (9, 10, 11, 15). Such lesions are mainly localized in the mesial part of the temporal lobe in children and adults with a prolonged history of epilepsy (1). They are considered to be an embryological malformation with the inherent potential to progress and proliferate (3, 12). In the following, the neurosurgical and histopathological findings in 17 patients with focal epilepsy and tumor-like lesions in or near the temporal lobe are presented.

Material and Methods

A total of 17 patients have been studied over the last 8 years. In all cases the pathological substrate for the seizures was localized in or near the temporal lobe. In every case the material was prepared for histological evaluation and stained with the following techniques: hematoxylin and eosin, cresyl-violet, a trichromic stain, PAS and silver impregnations of Rio Ortega and Cajal. The presence or absence of 50 histological characteristics was analyzed with the help of a personal computer (7, 8). In the last 11 cases the following immunohistological reactions were tested: GFAP (glial fibrillary acidic protein), S-100, neurofilaments, and MBP (myelin basic protein). In nine cases part of the material was fixed in glutaraldehyde and studied by electron microscopy.

Results

Table 1 depicts the most important clinical and surgical findings in the 17 patients. All patients except one (case 11) suffered from medically refractory complex partial and/or generalized seizures. Three patients had additional psychic disturbances and only two had neurological deficits. The histological and immunohistological studies revealed different areas in which typical and atypical neurons are intermingled with embryonal and adult glial cells. Ectopic neuronal foci in the meninges and subcortical white matter were seen as well as small cortical dysplasias. The vascular net was often prominent and the structure of the vascular wall aberrant. These pathological findings were classified as hamartomas or gangliogliomas. Two cases were classified as having a hamartoma-like image because they resembled a fibrillary astrocytoma with atypical vascularized areas and foci of neuronal groupings. Tables 2-4 show the most outstanding histological findings which

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Table 1. Most important clinical and surgical findings in the 17 patients studied

Case	Sex	Age (years)	Duration of the symptoms	Clinical symptoms	Localization
1	M	35	8 yr	F. epilepsy Psych disturb.	Le. temporal
2	F	36	16 yr	F. epilepsy Psych. disturb.	Ri. temporal
3	F	43	23 yr	F. epilepsy	Ri. temporal
4	F	17	7 yr	F. epilepsy	Le. frontal
5	F	29	12 yr	F. epilepsy	Ri. temporal
6	M	28	11 yr	F. epilepsy	Le. temporal
7	M	10	6 yr	F. epilepsy	Le. temporal
8	F	20	8 yr	F. epilepsy Psych. disturb.	Ri. temporal
9	F	28	11 yr	F. epilepsy	Le. temporal
10	M	33	21 yr	F. epilepsy Aphasia	Le. temporal
11	M	34	3 mo	F. epilepsy	Ri. temporal
12	F	24	11 yr	F. epilepsy	Ri. parietal
13	M	23	15 yr	F. epilepsy	Le. temporal
14	F	8	7 yr	F. epilepsy	Le. temporal
15	F	24	8 yr	F. epilepsy	Ri. temporal
16	F	26	3 yr	F. epilepsy Hemianopsia	Le. temporo-occipital
17	M	29	1 yr	F. epilepsy	Le. temporal

Abbreviations: Tl, temporal lobe; F, focal; Le, left; Ri, right

Table 2. Histological characteristics of hamartomas and gangliogliomas (n=17)

	No. of cases	Frequency (%)
Increased vascularization	17	100
Glial fibers	13	94.12
Contents of astrocytes	15	88.23
Contents of nerve cells	14	82.35
Vessel aberrations	12	70.59
Localization in the leptomeninges	7	41.18
Contents of oligodendroglia	5	29.41

Average size (cm)	Surgical removal	Histological diagnosis
3-4	Tumor	Astrocytoma + hamartoma
3	Medial section of Tl	Ganglioglioma and Tl
3	Tumor cyst and hippocampus	Ganglioglioma
3	Tumor and cyst	Ganglioglioma
<2	Tumor	Hamartoma
3	Anterior and medial section of Tl and the amygdala	Astrocytoma + hamartoma
3-4	Tumor	Hamartoma
3	Elastic-like tissue	Hamartoma
3	Cystic tumor	Hamartoma
3	Temporal pole up to the sylvian fissure	Hamartoma
5	Sack-like structure	Hamartoma
4	Tumor and cyst	Ganglioglioma
5	Anterior and medial section of Tl	Hamartoma
4	Temporal pole and cyst	Ganglioglioma
5	Basal section of temporal pole and hippocampus	Hamartoma
>6	Tumor and hippocampus	Ganglioglioma
<2	Capsular tumor	Ganglioglioma

Table 3. Type of positive cells with immunohistology in 11 hamartomas (GFAP, S-100, Nf, MBP)

	No. of cases
Nerve cells	11
Astrocytes	11
Oligodendrocytes	10
Glioblasts	10
Oligoastroblasts	10
Oligoastrocytes	2

Table 4. Secondary changes observed in 17 hamartomas

	No. of cases	Frequency (%)
Cysts	14	82.35
Hemorrhages	12	70.59
Vascular abnormalities	12	70.59
Calcifications	9	52.94
Macrophage contents	7	41.18
Vacuolization (edema)	4	41.18
Thromboses	4	23.53

suggest a tumor-like malformation. These characteristics may indicate a *potential malignancy* as well as those which are considered as secondary changes. The electron microscopic findings confirmed the presence of neurons and of embryonal undifferentiated and adult differentiated glial and mesenchymal cells. No recurrences were observed after complete surgical removal.

Discussion

The 17 patients studied represent a clinicopathological entity because they all suffered from focal epilepsy over a long period and had a similar histopathological substrate and localization.

When considering the criteria given by the WHO for the classification of brain tumors (17) these lesions should be considered as benign (grade I), although the cellular and nuclear polymorphism, the lack of a clear delimitation from the surrounding normal tissue, and the meningeal localization (seven cases) may be considered as potentially tumoral. These lesions resemble true semibenign and malignant gliomas. From a histopathological standpoint it is possible to classify them as "malformations" which can potentially progress and proliferate (2, 6). They are constituted by a mixture of neurons, undifferentiated and differentiated glial cells, and sometimes mesenchymal cells included in an atypical vascular net. The term ganglioglioma may be used as a synonym for hamartoma because in both cases we are dealing with a mixture of neuroectodermal elements (5, 6, 17). The secondary tissular changes, such as hemorrhages, calcifications, vascular fibrosis, the formation of cysts, and neuropilic vacuolization, may be the reason why these processes have a late clinical onset although no signs of growth are evident. The increasing secondary changes could be partially responsible for the epileptogenic focus. On the other hand the presence of neurons isolated or in groups in the hamartoma-like foci could be directly responsible for the epileptic discharges, as SCHOLZ and HAGER (14), and other authors have already pointed out (4, 11, 13, 16). Our findings would support this idea since in every case we were able to demonstrate a great number of polymorphic neurons and ectopic neuronal foci.

Summary

The cases we refer to constitute a clinicopathological entity characterized by focal epilepsy of long duration. The histopathological substrate is a benign process, classified as an hamartoma, which is po-

tentially tumoral due to its histopathological characteristics. The secondary tissular changes and the presence of isolated or grouped neurons seem to be responsible for the late onset of epilepsy. Due to the characteristics here described, a surgical resection as complete as possible is recommended to relieve patients from epileptic seizures and to avoid proliferation and malignant transformation.

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Clinical and Neuropathological Findings in a Case of Hemimegalencephaly

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Hemimegalencephaly is a rare connatal disorder clinically characterized by intractable seizures and occasional enlargement of the cranial circumference. Death usually occurs in early infancy. Very rare reports of treatment by hemispherectomy (5, 6) have been published. We would like to report another case with close relations to a connatal, highly differentiated gangliocytoma.

Case Report

A male, the second child of healthy parents without significant family history, was delivered by cesarian section in the 38th gestational week. Apgar Score was 7/8/10 and the child appeared normal except for an enlarged head circumference of 36.5 cm (above the 97th percentile for age). On the first postnatal day, generalized seizures occurred that could not be controlled by anticonvulsive medication. The frequency of seizures was up to 30 grand mal attacks per day. Ultrasound examination revealed a shifting of the middle echo to the right side. Computed tomography was performed, and pathological changes were seen in the left fronto-temporo-parietal region (Fig. 1). In the frontal area, a large tumor with contrast enhancement could have been suspected but in the temporal as well as in the parietal lobe the lesion was poorly defined.

A biopsy of the frontal tumor-like lesion was performed (NP 473/85) at the age of 6 weeks. Neuropathological examination showed numerous large multipolar and ectopic neurons of different shape (Fig. 2) with disordered polarity. Differential diagnosis was difficult and a dysontogenetic lesion with a possible blastomatous tendency was suspected with relations to a highly differentiated gangliocytoma. However, on reviewing the case in a clinical conference, the diagnosis of hemimegalencephaly seemed possible, as well.

In the postoperative period, generalized seizures continued despite anticonvulsives. Therefore, left hemispherectomy was performed, but during the operation ventricular fibrillation occurred. After resuscitation stable conditions could be established and the operation was finished without complications. Shortly after the end of the operation, a second cardiac arrest occurred and resuscitation failed.

The neuropathological post-mortem (S 455/85) examination confirmed the suspected left-sided hemimegalencephaly. Macroscopically, the cortical gyri of the left hemisphere were enlarged and the cut surface revealed thickened cortex up to 20 mm in the fronto-temporo-parietal area. The cortex-white matter junction was generally preserved; however, multi-

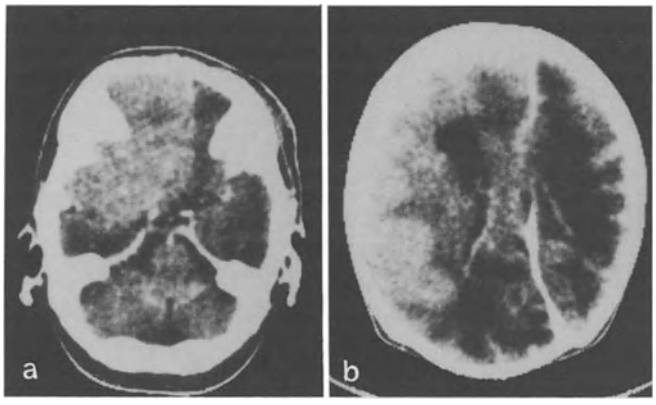

Fig. 1. Computerized tomography shows a large, left frontal space-occupying lesion (a) and a contrast-enhancing dysplastic cortex in the left fronto-temporo-parietal area (b)

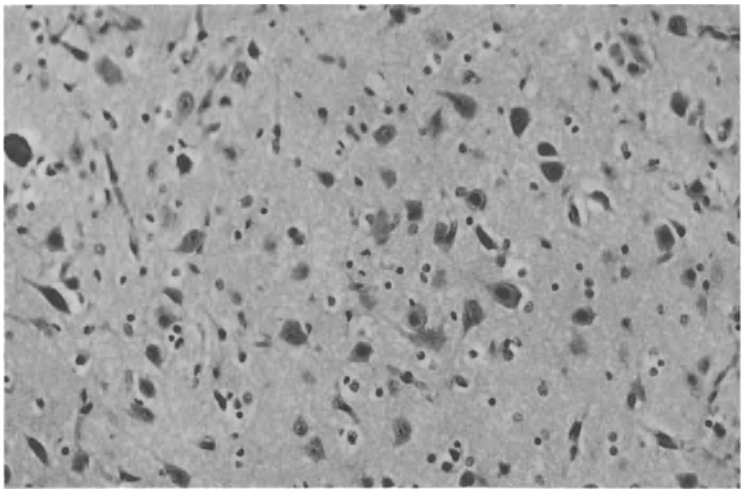

Fig. 2. Biopsy specimen of left frontal pole shows numerous large multipolar and ectopic neurons of different shape with disordered polarity. (HE, x 160)

ple ectopic islands of gray substance were seen. The basal ganglia could not be identified with certainty. In the occipital parts, cortical differentiation seemed normal. There were no macroscopic changes of the right hemisphere, right basal ganglia, brain stem, and cerebellum.

Histologically, a gangliocytoma was again found in the left frontal lobe. Immunohistochemistry showed strong reactivity of large neurons to NSE with the numerous smaller neurons being NSE negative. The parietal and temporal lobes showed a severe distortion of the normal cortical architecture with an enormously enlarged cortex and no clear cortex-white matter junction. Neurons were of different shape but often

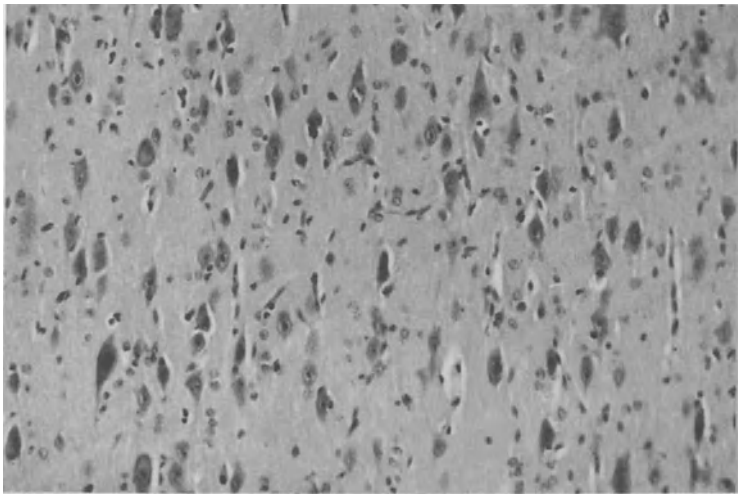

Fig. 3. Autopsy specimen of left parietal cortex shows neurons of different shape with a clear polarity toward the cortex. Normal cortical layers cannot be identified. (HE, x 160)

with a clear polarity toward the cortex (Fig. 3). However, the normal cortical layers could not be identified and the cortical pattern was disarrayed by occasional giant neurons and areas of slight gliosis. Morphometric analysis of the dysplastic cortex compared to the corresponding areas of the opposite hemisphere showed that the density of neurons per area was not much different but that the shape and size of the single neurons varied considerably on the affected side. In general, the medium size of the neurons was 70% larger than the average size of normal corresponding neurons. The neuropathological changes fitted best the diagnosis of pachygyria with local differentiation into a highly differentiated gangliocytoma. There was no normal architecture of the basal ganglia that were composed of clusters of primitive small neurons and could not be clearly identified due to the cortical hypertrophy. Heterotopias were found subependymally as well as in white matter. The right hemisphere appeared normal with respect to the neuronal architecture. However, severe hypoxic changes could be found consisting of extensive neuronal loss in Sommer's sector of the cornu Ammonis.

In summary, a severe left-sided hemimegalencephaly with pachygyria including multiple heterotopias and a frontal gangliocytoma with continuous transition into dysplastic cortex was diagnosed. The hypoxic changes of the right hemisphere were thought to be due to the uncontrollable epileptic activity.

Discussion

Megalencephaly may be subdivided into the three main categories primary, secondary, and unilateral form (4), which is commonly referred to as hemimegalencephaly. The etiology and clinical course of this pathological entity have not been fully understood. The condition is generally regarded as a developmental/proliferative disorder with a variety of morphological alterations. These include pachygyria, micropolygyria, gliosis of various degrees, and formation of giant neurons (2).

The universal finding in this condition is a severe distortion of the cortical layering and a loss of neuronal polarity. Manz et al. reported an increased DNA and RNA content as well as an increase in proteins by 66% in the hypermegalic hemisphere. This is consistent with the morphometric findings in our case, which indicate a dysplastic hyperplasia of neurons rather than a neoplastic condition with a true increase in cell numbers. However, a clear separation from highly differentiated gangliocytoma cannot be made. In order to elucidate the question of the dysontogenetic or blastomatous nature of the condition, serial sections of the whole brain with morphometric analysis of the cyto- and neuroarchitectural features would be necessary.

Although the operative results after hemispherectomy are disappointing, a single case with a favorable outcome has been reported in the literature (5). Therefore, we consider hemispherectomy to be justified as a possible treatment in this otherwise fatal condition.

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Recent Results from Epilepsy Surgery in Children and Adults

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Epilepsy surgery has been carried out in Umea, Sweden for the last 6 years. Fifty-eight patients have been operated on for intractable partial epilepsy: 23 children (aged 1.4-16 years, mean 8.6 years) and 35 adults (aged 17-51 years, mean 33.4 years). Twenty-five patients were females and 33 males. Adults and children had suffered from epilepsy for an average of 60% of their lives. Upon admission the etiology among the children was unknown in 13%, perinatal in 13%, and postinflammatory in 23%. In the adults the causes were unknown in 37%, postinflammatory in 29%, posttraumatic in 11%, and paranatal in 9%.

Among the children 43% had a glioma as the presumed cause of the epilepsy. Among the adults a glioma was assumed in 14%. Seizures with or without secondary generalization, despite adequate trials with one to four antiepileptics, occurred in the children at frequencies between 1/week to 100/day, and in the adults between 1 and 15/month.

Upon admission, neurological deficits were seen in 65% of children and in 14% of adults. Positive radiological findings on conventional screening occurred in 70% of children and in 31% of adults.

The preoperative scalp EEGs showed interictal epileptic abnormality that was unilateral or localized in 56% and bilateral in 44% of children. Additional scalp EEGs aimed at recording ictal events were useful in providing new information on the suspected lesion. Occasionally intra-arterial and intravenous barbiturate EEG tests were carried out to clarify the seizure problem (4, 5).

In adults the preoperative scalp EEG information on interictal abnormality revealed unilateral or localized changes in 72% and bilateral changes in 28%. Additional sphenoidal lead recordings from 28 patients with complex partial seizures revealed bitemporal interictal abnormality. Fivty-five percent of these patients therefore underwent stereo-EEG analysis. Two chronic depth electrodes (Rhodes Medical Instr. Inc., USA) were implanted stereotactically during general anesthesia into both amygdalae and anterior hippocampi after visualization of the temporal horns by means of air ventriculography.

Split-screen scalp and stereo-EEG - during daytime video-recording, during nights tape recording - with concomitant reduction of antiepileptic medication initially revealed bilateral interictal epileptic abnormality from the depths in 55%. Later on ictal discharges appeared which preceded the clinical attacks. The ictal sequences started unilaterally from the mesial temporal lobes.

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Pharmacological testing was at times carried out with low (5) and high (6) dose barbiturate injections (amobarbital, methohexital) to determine the regional response to the injected substance (2) and to define the most resistant cortical region in patients with bilateral ictal abnormalities.

Prior to the EEG analysis the adult patients were screened neuropsychologically with conventional discriminative tests and with intracarotid Amytal studies (1, 3, 7). Preoperative intracarotid Amytal speech testing (11) on 51 patients (35 of whom were operated upon) determined the relationship between handedness and hemisphere speech. Eighty percent of these were right-handed, 12% left-handed, and 8% ambidextrous. Left hemisphere speech dominance was found in 93% of right-handers. Three out of four of the ambidextrous and four out of six of the left-handers also had left hemisphere speech dominance. Bilateral speech representation (8) was found in four patients, two of whom were right-handed, one left-handed, and one ambidextrous. Right-sided speech was encountered in two patients, one left- and the other right-handed. The incidence of left-sided speech was 22% lower in patients with left-sided lesions than in those with right-sided lesions.

Hemisphere memory was tested by means of concrete and abstract words and pictures (3). The anterograde recognition results obtained in 11 patients with speech-dominant temporal lobe lesions were compared to those from ten patients with corresponding nondominant lesions. In both groups the nondominant hemisphere recognized concrete and abstract words, thus exhibiting language capacity. Those patients with nondominant lesions had impaired recognition of words and pictures during testing of the lesioned hemisphere, while the opposite side performed these tasks well. Lesions in the speech-dominant temporal lobe impaired word and picture recognition on that hemisphere, and also word, but not picture, recognition on the opposite side.

The operations were carried out under general anesthesia using pre- and post resection ECoGs as required. When necessary, methohexital was given i.v. to enhance interictal/ictal epileptic abnormality recorded from surface and depth electrodes. The latter was done peroperatively by means of needle electrodes placed in the amygdala-hippocampus region. Electrical stimulation was used to define the motor strip before resection.

The resections carried out in children were located in the frontal lobes in eight cases (three on the left, five on the right), in the right temporal lobe in four, and in other regions in five (two on the left, three on the right). Six patients underwent subtotal/total hemispherectomies (four on the left, two on the right). Four of them had transient postoperative meningitis. Four received a ventriculoperitoneal shunt.

Operations on adults included four stereotactic amygdalotomies, 24 classical (double staged) temporal lobectomies (eight on the left, 16 on the right) with or without removal of the pes hippocampi, and seven frontal lobe resections (three on the left, four on the right). No complications occurred.

Histopathological analysis of cortical specimens removed from children showed the following findings: gliomatous tumors 39%, mild cortical dysplasia (10) 32%, tuberous sclerosis 8%, and Sturge-Weber disease 5%. In adults the corresponding findings were: gliosis 47%, mild cortical dysplasia 22%, angioma 14%, gliomatous tumors 9%, tuberous sclerosis 3%, unknown 6%.

Surgical outcome in children, with follow-ups between 1 and 55 months (mean 2.3 years), was: seizure-free or marked improvement in 69%, less than a 50% seizure reduction in 31%. Two of seven patients in the latter category died 8 and 13 months postoperatively from seizure-related complications.

Surgical results from follow-ups of 3-78 months (mean 3.5 years) in adult patients showed 76% to be seizure-free or markedly improved, while 29% did not show a worthwhile seizure reduction. Two unimproved patients died 1.4 and 4.4 years postoperatively during episodes of seizures.

All patients were advised to remain on antiepileptic medication for 2 years postoperatively.

Postoperative neurophysiological testing is now carried out to assess the effects of surgery on IQ and memory.

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Experiences with the Treatment of Complex Partial Seizures by Selective Amygdalo-Hippocampectomy

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Introduction

Treatment of temporomesial epileptogenic lesions has gained increasingly in significance during the past 10 years. The results of neurophysiological research into the limbic system have provided us with a general idea of the pathogenesis of complex partial seizures (CPSs). Thus the term "lesion" has shifted from denoting space-occupying lesions in anatomical compartments to undefined lesions in functionally relevant areas (1, 2, 4, 5, 6). The microsurgical consequence of this neurophysiological progress in diagnosis was the development of a selective procedure for treatment of CPSs by YASARGIL and WIESER (9, 10). This paper reports our first experiences with selective amygdalo-hippocampectomy for lesions and functional disturbances in mesiolimbic areas.

Material and Methods

Our series comprises 12 patients suffering from CPSs (seven male, five female; age 9-54 years, mean 32.5 years), who were operated during the last 10 months at the Hannover Medical School (Table 1). All patients underwent detailed neurological, neuropsychological, and neuro-ophthalmological examinations. Beside a long-term EEG, enhanced CT scan, MRI, and selective and magnification angiography were performed in all cases. By these means two groups could be distinguished: (1) a group with a morphological lesion and positive neuroradiological findings (n= 7) and (2) a functional group (n= 5) with ambiguous or negative neuroimaging. In this group interventional EEG recording using foramen ovale electrodes (8) revealed an epileptogenic focus in the temporomesial area. All patients underwent transsylvian transventricular exploration of the temporomesial region using the technique of YASARGIL et al. (10).

Results

The operation led to removal of uncohippocampal tumors in seven cases. In five patients sclerotic foci were resected. In all but one patient a selective amygdalo-hippocampectomy was performed. Figure 1 shows the operative site at the end of operation. Histological findings and the influence of the selective procedure on CPSs are summarized in Table 2. The only patient in whom hippocampectomy was omitted due to a localized lesion in the amygdala (glial scar) again suffered CPSs after a seizure-free interval of 2 months. There were no deaths in our series. All but one patient could be transferred from intensive care to the normal

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Table 1. Complex partial seizures in 12 patients. Group 1: morphological lesion and positive neuroradiological findings. Group 2: functional cases with epileptogenic focus in the mesiolimbic area

General symptoms	Observed symptoms	Group 1 (n= 7)	Group 2 (n= 5)
Consciousness	Pseudoabsence, arrest reaction	5	5
Behavior	Changes in posture, mimic, affectivity, malaise	6	3
Memory	Amnestic ictus, interictal deficit	3	2
Speech	Dysphasia, verbal automatisms	2	1
Automatisms	Motor, oroalimentary	3	2
Hallucinations	Olfactory, auditory, visual	3	1
Visceromotor signs	Gastric, changes in pupils' diameter	2	3

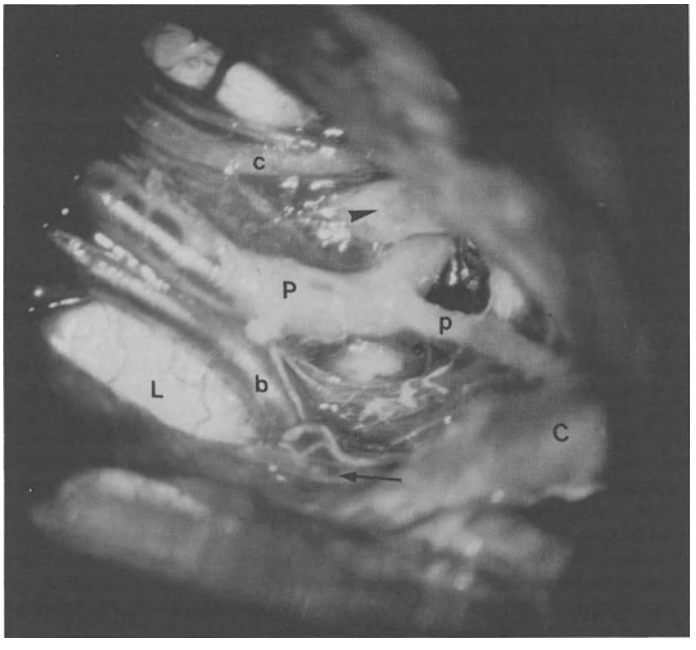

Fig. 1. Operative sites at the end of selective operation (removal of an uncohippocampal astrocytoma WHO II on the left side). *C*, internal carotid artery; *p*, posterior communicating artery; *P*, posterior cerebral artery; *c*, superior cerebellar artery; *L*, lateral cerebral peduncle; *b*, basal vein (Rosenthal); *arrow*, anterior choroidal artery; *arrowhead*, N. oculomotorius

ward 1 day after operation. Postoperative hospital stay was 9-14 days. The only complication occurred after removal of an uncohippocampal astrocytoma WHO II. This patient developed a slight contralateral

hemiparesis which completely resolved during the following month. Visual field defects could not be observed postoperatively. On postoperative neuropsychological testing, memory and performance on verbal and nonverbal learning were unchanged.

Table 2. Histological findings and influence of amygdalo-hippocampectomy on complex partial seizures in 12 patients. Group 1: morphological lesion and positive neuroradiological findings. Group 2: functional cases with epileptogenic focus in the mesiolimbic area

	Histological findings			Seizure-free	Rare seizures	Improved	Not improved
Group 1 (n= 7)	Glioblastoma	WHO IV	1			1	
	Astrocytoma	WHO III	1		1		
	Astrocytoma	WHO II	3	2	1		
	Oligodendroglioma	WHO II	1	1			
	Ganglioglioma	WHO II	1	1			
Group 2 (n= 5)	Hippocampal sclerosis		2	2			
	Old hemorrhage with gliosis		2	2			
	Gliar scar		1				1[a]

[a] Amygdalectomy only

Discussion

The transsylvian transventricular approach described by YASARGIL et al. (10) is the optimal way of microsurgically treating pathological processes and functional foci in the mesiolimbic area. Prerequisites for this operation are extensive microsurgical experience and meticulous anatomical studies of the region using dye injection techniques. Despite such preparations the selective procedure remains difficult throughout the operation. In our material the temporal fossa was found to be narrowed by abnormally convex frontobasal bone in four cases. Despite these difficulties during pterional craniotomy, the sylvian fissure can be easily opened in most cases. In one case, however, the sylvian fissure had to be dissected laterally of the sylvian veins, due to anatomical variations. The sylvian veins, nevertheless, could be preserved in all cases. The retroinsular exploration of the temporal horn poses no problems in space-occuping lesions of the middle and posterior part of the temporomesial region. In most of these cases dilatation of the tip of the temporal horn is present. Anterior processes with obliteration or dislocation of the temporal horn result in dislocation of relevant landmarks, thus endangering the anterior choroidal artery and the optic tract. In all these cases (four patients) careful central evacuation of the tumor proved useful, as well as later mobilization of its posterior part and preparation of the sulcus choroideus in a posteroanterior direction. If the ventricles were small we identified the temporal horn before extirpation of the laterobasal amygdala, in order to avoid damage to its subependymal drainage.

In operating on functional lesions the problems are the anatomy and the vascular supply of the hippocampus. Particularly microdissection of infratentorially herniated mesiolimbic structures is difficult (two cases in our series). This situation can be suspected preoperatively from the MRI and is confirmed by the position of the uncus intraoperatively. The distribution of lateral carotid branches provides important information on the vascular supply of the hippocampus. When uncal arteries are lacking, the anterior choroidal artery supplies the caput hippocampi with one first larger branch in 97% of cases (3). In patients with sufficiently developed uncal arteries, one to four tiny branches from the anterior choroidal artery can be observed, as confirmed in our material. In the first-mentioned and most frequent case, the hippocampal branch is an important landmark for early identification of the anterior choroidal artery and the optic tract.

Conclusion

Our results can be compared with those reported in the literature (8, 9). Of 12 patients with CPs, ten were seizure-free or showed significant reduction of seizures after operation, without important complications. The failure of the only selective operation in the region of the amygdala suggests that even a normal looking hippocampus should routinely be removed in cases of morphological or functional lesions. Although our short follow-up (3-10 months) does not allow any definitive conclusion, selective amygdalo-hippocampectomy seems to be a successful procedure for the treatment of drug-resistant CPSs.

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Thirty-five Years' Experience with Surgery of Nontumorous Epilepsy

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Introduction

Soon after the establishment of neurosurgery as a separate discipline at the University of Graz in 1950 the operative treatment of patients suffering from focal epilepsy refractory to medication began.

In the first 28 patients indication for neurosurgery was still vague and the methods employed variable (Table 1).

Table 1. Surgery of epilepsy, 1952-1985, Universitätsklinik für Neurochirurgie Graz

Later cases			First 28 cases	
Technique	No.	Catamneses	Technique	No.
Hemispherectomy	6	3	Sympathectomy	4
Hippocampectomy	50	34	Probatory	1
Fornicotomy	6	6	Corticotomy	18
Cingulectomy	40	17	Meningolysis (subdurography)	5
Amygdalotomy	13	13		
	115	73 (63.5%)		28

With increasing knowledge of the anatomy and function of the limbic system (2, 3, 6, 9-11) and stimulated by reports of PENFIELD et al. (12), temporal lobe epilepsy became more interesting and has been operated on in this unit since 1954. Systematic EEG screening made possible a more precise assessment of indication for surgery by providing parameters which have since become commonly accepted: episodes of convulsions for at least 2-3 years, inefficiency of anticonvulsive medication, and a constant EEG focus unilaterally localized and situated in a dispensable area of the brain. Neuroimaging must show the symmetric contralateral brain structures to be undamaged. The IQ should suffice for social rehabilitation. The aim of the operation is to achieve (a) freedom from seizures and prevention of deterioration of personality structures, (b) correction of behavioral disorders.

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Material and Methods

One hundred and fifteen patients underwent operation: 6 hemispherectomies, 50 hippocampectomies, 6 stereotactic fornicotomies, 40 cingulectomies, and 13 stereotactic amygdalotomies. Symptomatic seizures as caused by tumors, vascular lesions, etc. were strictly excluded from this study.

Between 1952 and 1962 six children (five girls and one boy, aged 3-13 years) with spastic infantile hemiplegia underwent *hemispherectomy*, the EEG showing pathological activity in the atrophic hemisphere. Indications and operative technique were in accordance with the recommendations given by Krynauw (7). In three cases the hemisphere was removed in two separate parts and in three cases in one piece. Catamnestic data were available in three patients, all of whom had remained free of seizures. In only one case had a contralateral hemiparesis persisted for 30 years. One child succumbed to a postoperative infection of the CSF. At operation in each case bioelectrical activity was recorded, both from the cortex and from the basal nuclei. Spike and wave patterns were always present until total removal of the hippocampus, which led us to discontinue this procedure in favor of hippocampectomy.

Hippocampectomy in accordance with the suggestions of PENFIELD et al. (12) was performed in 50 patients suffering from psychomotor epilepsy with a permanent focus within the depth of one temporal lobe. Thirty-seven male and 13 female patients with an average age of 26 years were operated on. At surgery in each case hypersynchronic activity was mapped by means of electrocorticography. In the first 40 patients a partial anterior temporal lobe resection with removal of the hippocampus was performed. Resection was limited in the last ten patients. To reduce the formation of scar tissue and minimize trauma a CO_2-laser was used. The available long-term results are shown in Table 2. Postoperative antiepileptic medication was continued for 2 years in all cases, independent of the occurrence of seizures.

Table 2. Long-term results after hippocampectomy, 1954-1985, Universitätsklinik für Neurochirurgie Graz (n=34)

Preoperative		Postoperative				
		No fits	Markedly improved	Improved	Unchanged	Worse
Convulsions	34	18	9	2	3	-
Mental changes	14	-	5	5	4	-

Working ability:					
Full	Partly	None	Full	Partly	None
10	18	6	24	5	5

Stereotactic *fornicotomy* was performed on six patients, five male and one female, aged between 25 and 38 years, who had shown no improvement after hippocampectomy. The method employed followed the description of UMBACH (13). No further seizures were recorded in three patients; the rest became manageable with antiepileptic medication.

A bilateral frontal *cingulectomy* as described by LeBEAU (8) in the treatment of erethitic hyperactivity was performed on 40 patients, 26 male

Table 3. Long-term results after bilateral anterior cingulectomy, 1955-1985, Universitätsklinik für Neurochirurgie Graz (n=17)

Preoperative		Postoperative				
		No fits	Markedly improved	Improved	Unchanged	Worse
Convulsions	17	4	5	3	5	-
Erethitic states	17	-	6	4	5	-
Working ability:						
Full	6		Full	8		
Partly	4		Partly	2		
None	7		None	7		

and 14 female, with an average age of 17 years. Stereotactic procedures were employed on three patients only. All others were operated on by craniotomy exposing both gyri cinguli anteriores. In the last eight cases the gyrus cinguli anterior was not removed by suction, but vaporized with a CO_2-laser. Results are shown in Table 3. Psychosurgical adjustment was achieved in ten cases (60%). Bioelectrical activity of both frontal gyri cinguli and the left exposed cerebral cortex were regularly monitored. In four patients electrocorticography of both anterior gyri cinguli showed a spike and wave pattern. In these cases no more seizures were seen after resection of the foci (4). One oligophrenic child died 4 h after operation. The postmortem findings were negative.

Stereotactic bilateral *amygdalotomy* (14) was the method chosen in the operative treatment of 13 patients suffering from epilepsy associated with an aggresive form of debility. They were inmates of mental institutions whose constant raving interfered seriously with their care. Results were satisfactory in all cases, so that patients could be looked after in a normal way.

Discussion

The fact that in all but one of the six patients who underwent hemispherectomy, no postoperative hemiplegia was observed, confirms KRYNAUW's assumption that cerebral damage sustained at a prenatal stage or in early childhood will result in moving central functions into the unaffected hemisphere. In histological investigation of tissue gained during hippocampectomy, gliotic changes could be demonstrated in 80%, confirming the etiologic importance of "incisural sclerosis" as pointed out by Penfield. In 37 patients a history of birth trauma or early trauma of the head could indeed be confirmed.

No evaluation of fornicotomy is possible after six cases only. Although in all cases the fornix was without doubt severed, in three cases seizures - even if diminished - did persist. Perhaps bioelectric impulses from the amygdala hippocampus were transferred to the other brain structures via the stria terminalis.

The operative indications for stereotactic amygdalotomy seem to be limited to inmates of asylums, when all other methods of restraint have failed.

Conclusion

1. Operative procedures seem indicated in patients resistant to anti-epileptic medication, when a constant focus can be located in a dispensable area of the cerebrum.
2. In most cases this will apply to the areas of the hippocampus and the n. amygdalae which can be resected, guided by electrocortical mapping and special techniques such as CO_2-laser to reduce the formation of scar tissue.
3. Erethitic hyperagitation in focal and/or generalized epilepsy, mostly in children or adolescents, can be calmed and intellectual improvement attained by bilateral resection of the anterior gyrus cinguli.
4. Bilateral stereotactic amygdalotomy will not influence seizures but must be considered a psychosurgical intervention only to be used as a last resort.

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Chronic Cerebellar Stimulation in the Treatment of Epilepsy

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Introduction

In the early to mid 197Os COOPER et al. (3) put to practical use the theoretical concepts of JULIEN (4), who ascertained the inhibitory action of the Purkinje cells on the motor cortex, the classical work of MORUZZI (5) about the inhibition of spasticity by the same cells, and the work of DOW et al. (2), who showed that removal of the cerebellar cortex intensifies epileptic activity and demonstrated the existence of an inhibitory mechanism in the reticular structures of the cerebellum. COOPER et al. (3) presented a rather small series with promising results. However, the method was subjected to considerable criticism. The main arguments against it included potential damage to the nervous substance and the number of complications connected with the surgical procedure, such as CSF leakage, breakage of the leads, and frequent mechanical failures.

We have tried the method, employing a new, simplified, and miniaturized stimulator developed just for cerebellar stimulation and a new surgical technique.

Materials and Methods

The series comprised nine patients (six males and three females) ranging in age from 16 to 37 years (mean 26.2 years). All had a history of epilepsy, the average duration being 10.55 years, and all had grand mal seizures, two with focal onset in many instances and two with absences in addition. In every case the patient had been treated unsuccessfully with anticonvulsants. The postoperative follow-up ranged from 1 to 6 years, with a mean of 3.7 years.

The surgical procedure was developed in experimental animals and was considerably simplified: it consists of a small skin incision and a burr hole placed over the cerebellar hemisphere. The implant is placed in the burr hole epidurally, the cerebellum is not exposed, and the subarachnoid space is not opened. The stimulation begins 10-14 days after the operation and the patient remains on the same medication as before the procedure. The implant is a disc-shaped tuned RF circuit with a rectifying diode, measuring Ø 18 x 7 mm (Fig. 1). The implant is powered via an antenna connected to a logic programming unit, a pulse generator, and a transmitter. Stimulation sequence are determined by means of binary switches. The signal from the stimulation pulse generator is added to the signal from the programming unit, and the sum is fed into the transmitter and supplied to the implant. The

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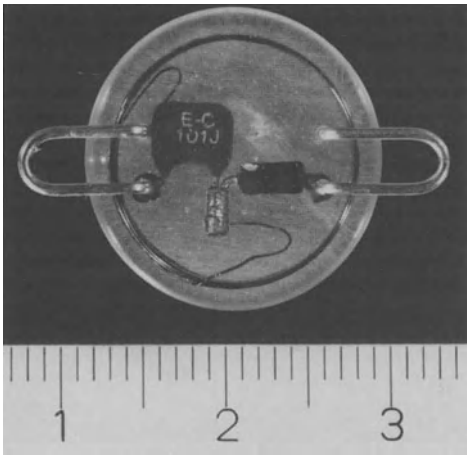

Fig. 1. The implant (scale in cm)

frequency can be set from 5 to 50 Hz, the typical value being 12 Hz. The pulse width is set at 0.6 ms.

Results

A number of experiments were performed in order to establish whether cerebellar stimulation produces any effect on the brain. It was expected, as DOW (1) has already reported, that stimulation would inhibit the photic and auditory evoked potentials. Indeed, the stimulation of the cerebellum in our patients abolished visual evoked potentials, either ipsi- or contralaterally (Fig. 2).

The EEG pattern returned to normal in some patients before the clinical improvement. The first signs were the changes in the background activity, which later reached the alpha-band pattern (Fig. 3).

Table 1 summarizes the main data and the results. Three patients should be considered as failures. One (case 1) requested the removal of the implant because of an inexplicable pain at the site of the operation. The frequency of his seizures, however, was reduced by about 70% within a few months of stimulation. Two patients, both with occasional focal onset of their grand mal seizures, did not derive any benefit from the procedure. Both stopped the stimulation and one of them (case 5) later succumbed to epileptic status.

Of the remaining six patients, three have occasional seizures, markedly reduced as compared with those prior to surgery, and three are seizure-free.

On psychological testing, performed yearly, all patients who benefited from the procedure showed considerable and sometimes quite impressive improvement in verbal expressions and vigilance and diminished aggressiveness.

The series presented is certainly too small to allow any definite conclusions; yet some patients showed a promising and even dramatic response. The simplified surgical approach, the improved stimulator, and the minimal risk of the procedure are attributes which may favor retrial of the method.

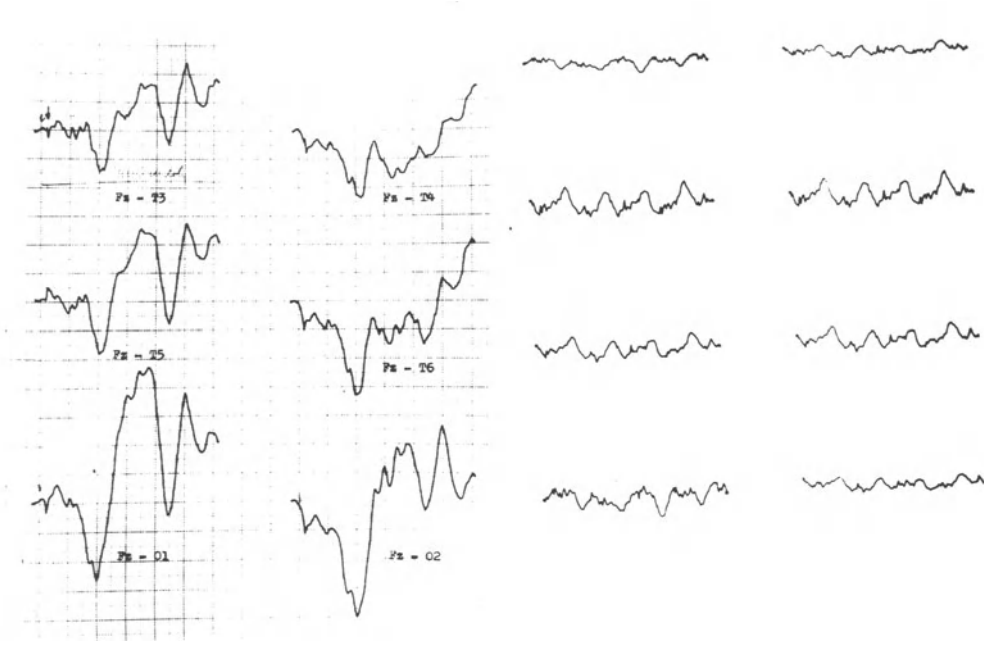

Fig. 2. Visual evoked potentials before and after the stimulation. No response during the activation of the stimulator

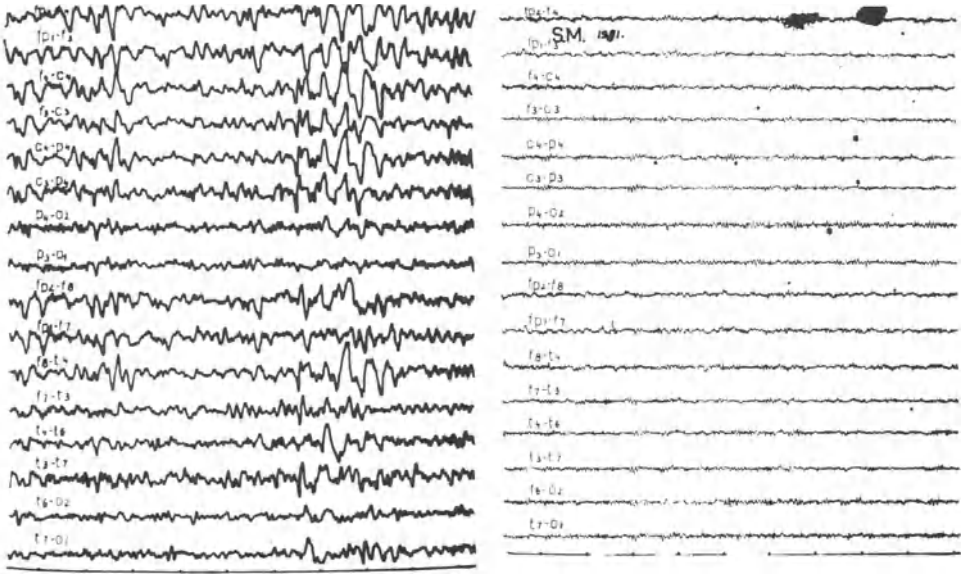

Fig. 3. EEG before and 2 years after chronic cerebellar stimulation. Same patient as in Fig. 2

Table 1. Summary of main data and results

Patient	Age	Duration of epilepsy (years)	Type of seizure	Average number of seizures per month	Results	Follow up (years)
1.	21	6	Grand mal	4-5	Requested removal of the implant because of pain. Only two seizures within 4 months of stimulation	2
2.	22	7	Grand mal	50-70	No seizures for the last 3 years	6
3.	29	13	Grand mal	5-10	No seizures	6
4.	26	10	Grand mal occasionally with focal onset	15 approx.	No or very little improvement	5
5.	16	6	Grand mal, often with focal onset	20-30	No improvement	4
6.	23	8	Grand mal	30 approx.	Three to four seizures monthly	5
7.	37	18	Grand mal Absences	10 approx. 10 or more daily	One or two grand mal seizures and up to 20 absences	3
8.	32	16	Grand mal Absences	4-5 3-10 (daily)	One seizure monthly, occasional absences	1
9.	30	16	Grand mal	4-6	No seizures	1

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Long-term Results of Stereotactic Surgery for Therapy-Resistant, Mainly Partial Epilepsies

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Introduction

When the treatment of epilepsy with drugs reaches its limits as the disease becomes resistant to therapy, the patient must be considered for surgical management. The steady increase in symptoms and the accompanying deterioration in the quality of life can be treated successfully by various forms of surgical intervention (1, 8, 9, 22). Despite refinements in microsurgical instrumentation and techniques, however, complications, including impaired memory and speech, still occur (1, 9, 14).

The stereotactic method was originally developed to manage extrapyramidal motor disorders and chronic pain. The scope of the technique was gradually broadened to include the treatment of therapy-resistant epilepsy. The technique carries relatively few risks and can be performed in patients of any age.

Since 1954, we have carried out stereotactic surgery for cases of medically intractable epilepsy in various target sites. The results of these operations have been reported in detail (2, 3, 6, 7, 12, 19-21).

Patients and Results

Between 1978 and 1984, 22 patients with therapy-resistant epilepsy and different types of seizure were operated on by the stereotactic method (Table 1).

Table 1. Patients operated on stereotactically for therapy-resistant epilepsy between 1978 and 1984

Number	Female	Male	Age at operation	Length of anamnesis
22	7	15	29 yr	11 yr

All of the operations were carried out using the stereotactic target instrument after Riechert and Mundinger. The coagulated subcortical target sites were determined according to the seizure type and EEG pattern. In the majority of cases, unilateral multilocular coagulation, i.e., amygdalotomy combined with fornicotomy or anterior commissurotomy, was performed in one session, while bilateral procedures

Table 2. Multilocular coagulation from various types of seizure

Mixed (n=13)	Generalized (n=3)	Psychomotor (n=5)	Focal (n=1)
A Fx CA CF	A Fx La.m	A Fx Thal	Ca.i Thal
13 9 4 2	3 2 1	5 4 2	1 1

required two sessions at least 6 months apart (Table 2). In some of the patients, EEG recordings were made during and after the operation.

Drug therapy was rarely changed after the operation. The average hospital stay was 7 days. Six patients had slight temperatures for a short time after surgery and suffered from drowsiness. One patient was apathetic and drowsy for days. In one patient, a slight transient hemiparesis could be observed, and in another a mild, permanent, but intermittent hemiparesis. One patient died of a thromboembolism during the course of follow-up.

Follow-up examinations were carried out from 1 year to 7 years after surgery. The catamnesis is based on examinations of the patients, as well as interviews with the patients and their physicians.

The results of the operations are compiled in Table 3. Postoperatively, two of the 22 patients were free of seizures, as were four patients who continued to receive the same medication. Three patients showed no change from their preoperative condition and only in four patients was there an increase in seizure frequency. The remaining nine patients showed improvement in terms of the type of frequency of seizure. In most cases the seizure type changed from severe to less severe.

Preoperative EEG examinations showed marked focal findings or a temporal seizure focus in 17 patients; in five patients there was a unilateral or bilateral general change. However, no correlation could be established with the operative results; in other words, an improvement of the EEG did not necessarily mean clinical improvement.

Table 3. Long-term results in 22 patients operated on stereotactically for therapy-resistant epilepsy between 1978 and 1984

Seizure-free	Seizure-free with drug therapy	Deteriorated	Unchanged	Improved
2	4	4	3	9

The effect of surgical management of therapy-resistant epilepsy, particularly focal and temporal epilepsies, has been a matter of discussion for almost 100 years (1, 4). Of the various operative methods, the most successful have been resection of the epileptogenic zone, amygdalotomy, resection of the hippocampus, and temporal lobe ablation. These techniques, following strict surgical indication and localization of the focus, bring about marked improvement.

By refining the surgical method and by employing the microsurgical technique, the rate of complications could be reduced, if not comple-

tely eliminated. The stereotactic operation can be carried out with relatively little risk for the patient. Instead of resecting the morphologically altered tissue, the subcortical structures that cause or conduct paroxysmal impulses are stereotactically coagulated in the limbic system and in the basal ganglia. These structures are only accessible to stereotactic intervention and not to open surgery.

Based on the present long-term results and on earlier studies, the stereotactic functional management of therapy-resistant epilepsies can no longer be considered an experiment.

Summary

Twenty-two patients were operated on stereotactically between 1978 and 1984 for temporal therapy-resistant epilepsy. Because of the different seizure types and patterns, multilocular coagulation was performed in the various subcortical structures such as the amygdala, fornix, anterior commissure, Forel's field thalamus, and lamella medialis. Catamnestic examinations were performed from 1 to 7 years after surgery. Six patients are still seizure-free today, four of whom continue to receive medication. Three patients show no change after the operation and in four cases the condition has deteriorated. In nine patients, the duration of the seizure has been slightly shortened, the frequency of seizures has decreased, or the seizure type has changed.

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Pharmacoresistance and Surgical Treatment in Temporal Lobe Epilepsies

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We report on 16 patients who were operated on, in the last few years, for temporal lobe epilepsy. Of these, 14 were operated on in the neurosurgical department of our clinic. Professor Vernet in Copenhagen carried out one temporal lobectomy (case 1), and Prof. Yasargil in Zürich performed one amygdalo-hippocampectomy (case 12). Out of 14 patients operated on in Berlin, nine (cases 2, 3, 6, 7, 9, 11, 13, 14, 15) were admitted for surgery through the Department of Neurology and five (cases 4, 5, 8, 10, 16) from outside (Fig. 1).

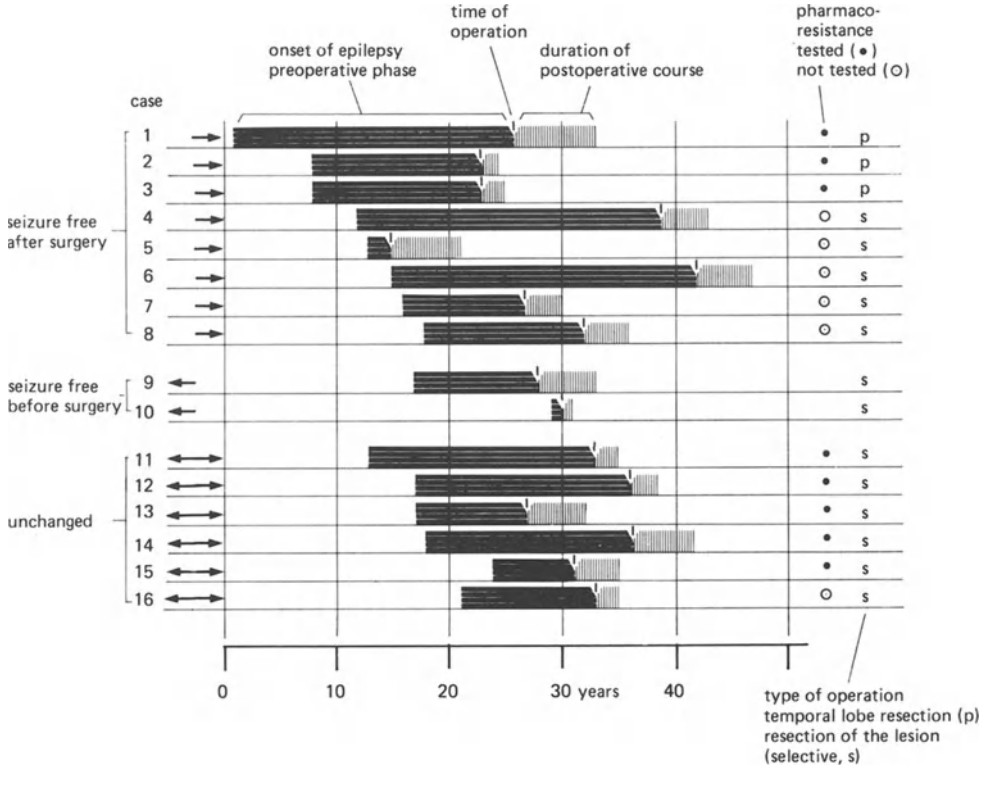

Fig. 1. Preoperative phase, postoperative course, pharmacoresistance, and type of operation in 16 patients with temporal epilepsy

A clinical diagnosis of temporal epilepsy with complex focal seizures was made in all cases. In addition, repeated EEG recordings showed consistent or predominant unilateral discharges. A morphological focus found on the CT examination of five patients who had alternating foci was decisive in deciding on the side to be operated on (cases 1, 4, 12, 14, 15).

In the 11 cases from the neurological department who were operated on, the EEG diagnosis was supplemented in two cases by nasopharyngeal recordings (cases 2, 12), in six cases by seizure EEGs (cases 2, 11-15), and in six cases by recordings made during sleep (cases 1, 2, 7, 11, 14, 15).

The patients were between 1 and 29 years of age when they were taken ill; the average age was 16.8 years. The patients were operated on between 15 and 42 years of age; the average age at operation was 31.1 years. The duration of illness before the operation ranged from 1 to 27 years (average 14.9 years).

Following the operation 10 of the 16 patients were seizure-free. However, as two patients who were admitted from outside were already seizure-free before operation, only 8 of 14 can be counted as becoming seizure-free following the operation. This result of 57% lay rather more toward the lower border of the most frequently stated success rates (2). We must, however, state that, contrary to customary opinion, a person is not to be regarded as free from seizures if aurae still occur.

Should clinical factors indicating a favorable or unfavorable surgical prognosis be sought, it appears at first sight that being taken ill at an early age and surgery at an early age were favorable in our patients. A long period of illness was not, however, generally unfavorable (Table 1), as one might have expected from the frequently expressed recommendation (1) that one should not wait too long before operating, otherwise a mirror focus will develop. We must realize that in considering the correlations between the seizure symptoms, morphological findings in CT and MRI, functional changes in the EEG and SPECT, and the results of surgical treatment, the number of patients is too small

Table 1. Clinical data and surgical treatment

	Seizure-free (n=8)	Unchanged (n=6)
Age of onset	13.6	21
Age at operation	29.5	38.1
Duration of epilepsy (in years)	19.3	18.2

Table 2. Pharmacoresistance and surgical outcome

	Seizure-free (n=8)	Unchanged (n=6)
Tested	3	5
Not tested	5	1

for a multifactorial analysis. We can nevertheless ask ourselves a question which has never hitherto been asked: Were the favorable cases really drug resistant? Or put differently, what chance do the really drug-resistant cases have of becoming seizure-free by means of surgery? This question arises since of the eight patients who became seizure-free, in five resistance to antiepileptic drugs was not tested before surgery. Pharmacoresistance exists when seizures still occur although all antiepileptic drugs of first choice in monotherapy have been given in all doses up to the point of intolerance (3). These five patients were first placed on a consequential drug regime after surgery. The possibility cannot be denied that had these patients received suitable medication prior to surgery they would have become seizure-free even without surgery. On the other hand, of the eight patients who according to all the rules were pharmacoresistant before surgery, only three became seizure-free afterward. This result is enough to establish the recommendation that no patient should be operated on without previous thorough testing for drug resistance (Table 2).

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Results of Surgical Treatment in 300 Patients with Temporal Lobe Epilepsy

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The surgical treatment of epilepsy has been applied in the Department of Neurosurgery, Academy of Medicine, Warsaw since 1957. During the past 28 years over 3000 epileptic patients have been clinically investigated in our Department and 557 of them have been submitted to various kinds of surgical treatment. In most of these patients (455), resection of the epileptogenic focus was performed. Three hundred of them underwent temporal lobectomy. Before CT investigation was introduced, in about 6% of cases small tumors were found in the pathological investigations of the specimen. All such cases were excluded from this analysis.

The indications for the operation are commonly known: long-lasting epilepsy, frequent epileptic fits in spite of pharmacological treatment, and clinical and electrophysiological signs of unilateral epileptogenic focus.

The age of our patients at the time of operation was between 16 and 25 years in 49% of cases. Children below 15 years old constituted only 16.3% of patients. However, the onset of the disease in most patients was in early childhood: in 33% of patients under 5 years of age, in 74.3% under 15 years. The patients were usually treated pharmacologically for a very long time before being referred for surgical treatment: over 80% were treated for more than 6 years, and a proportion of them for over 2o years.

The etiology of epilepsy is usually difficult to establish preoperatively; in some cases it is uncertain, in many, unknown (Table 1). Trauma at birth was well documented in the patients concerned while in patients with head trauma, the time of the injury was related to the first epileptic attack. The group with an infectious etiology included meningitis or meningoencephalitis, postvaccination encephalitis, and evident signs of cerebral damage during various viral infections. However, in about half of the patients (44.3%) the etiology remained obscure.

In all patients standard anterior (or anterior and middle in the non-dominant hemisphere) temporal lobectomy was performed in two pieces, with removal of the anterior hippocampus and the amygdala. Electrocorticography was carried out before and after resection. Almost all operations were performed under general anesthesia.

Three patients died after surgery (mortality 1%) and in two patients hemiparesis persisted (morbidity 0.7%). The follow-up of the 297 patients is shown in Table 2.

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Table 1. Etiology of temporal epilepsy

Etiology	No. of patients	%
Birth trauma	52	17.3
Head trauma	52	17.3
Infectious	58	19.4
Other	5	1.7
Not known	133	44.3

Table 2. Follow-up of 297 patients

Died during follow-up	12
Lost to follow-up	27
Follow-up less than 2 years	22
Follow-up 3-28 years	236

Twelve patients died during the 28-year follow-up period. Four of them committed suicide in spite of complete cessation of the epileptic attacks. Three patients died in epileptic status after sudden arbitrary withdrawal of antiepileptic medication after 1-2 years without seizures. In one patient the cause of death was viral hepatitis, and in one a car accident; in the other three it was unknown. Twenty-seven patients were lost to follow-up due to change of address without notification. In 22 patients the follow-up has been too short (less than 2 years after surgery). Therefore the final analysis included 236 patients followed up for 3-28 years after temporal lobectomy.

The outcome scale is as follows:
Grade 1: Very good result - no seizures
Grade 2: Good result - no more than two attacks per year or rare, non-disturbing auras
Grade 3: Poor result - less frequent seizures and some improvement of social life
Grade 4: Bad result - no improvement.

Grades 1 and 2 represent satisfactory results, grades 3 and 4 unsatisfactory results. The results in the 236 patients are shown in Table 3.

We also tried to establish the influence of various clinical factors on the result of surgery. The dependence of the result upon *age* was estimated: slightly worse results were found in the group of children below 15 years of age (satisfactory 57.4%; unsatisfactory, 42.6%), but the difference was not convincing. The *preoperative etiology* had practically no influence on the results of surgery: we obtained satisfactory results in 62.8% of patients with trauma at birth, 69.4% of patients with head trauma, and 73.9% of patients with an infectious etiology. The *preoperative duration of the disease* also had no influence on the final result of surgical treatment in our patients. In fact the only clinical feature which seems to have had an influence on the postoperative results is *mental status*, as defined by intelligence quotient (I.Q.) (Table 4). The mentally retarded patients had a much poorer prognosis. Therefore recently we have included intellectual deterioration in con-

Table 3. Final results in 236 patients

Result	No. of patients	%	
Very good	121	51.3	68.2
Good	40	16.9	
Poor	25	10.6	31.8
Bad	50	21.2	

Table 4. Operative results in relation to mental status

I.Q.	Satisfactory result (%)	Unsatisfactory result (%)
80 or more	81.7	18.3
79 or less	51.2	48.8
In the whole group	68.2	31.8

secutive psychological investigations as an additional indication for the surgical treatment of temporal lobe epilepsy.

Conclusion

In spite of the improvement in the pharmacological treatment of epilepsy (blood level monitoring, new antiepileptic drugs) there are still a number of patients in whom surgical treatment is the treatment of choice. Diminishing operative risk (in our series, mortality in the last 200 patients was 0.5%) suggests that one should take into consideration such treatment for patients with relatively rare epileptic seizures; two-third of them a favorable result can be expected. Intellectual deterioration seems to be an additional indication for early surgery.

Epilepsy Surgery in Bonn from 1950 to 1985: A Retrospective Uncontrolled Clinical Evaluation of 62 Operated Epileptics*

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Introduction

The estimated prevalence of epilepsy in West Germany is 0.5%-1% (7, 15). Most epileptics achieve remission with modern drug therapy at adequate serum levels, but one-third do not (7). Given that the main indication for surgical treatment includes drug resistance or severe side-effects and ongoing social stigmatization, currently there may be approximately 10 000 candidates for surgery in West Germany (7), and 30 000-120 000 in the United States (3, 33, 39).

Since HORSLEY's (16) report on the first three craniotomies for the cure of focal epilepsy, and the elaboration of FOERSTER's (10) ideas by PENFIELD at the Montreal Neurological Institute (27-29), refinement of the perioperative management has been continuing. In the Neurosurgical Department of Bonn (area of 2 million inhabitants) 1.75 per thousand of the 40 000 operations performed between 1950 and 1985 have been because of medically refractory seizures (cf. MÜLLER and RÖTTGEN (24) and DILL and GULLOTTA (6) for some of the early patients).

There have been two *turning points* in the frequency (see Fig. 1: diminution after 1966, increase after 1984). The *first* one followed the disappearance of posttraumatic epilepsy and the establishment of a special department for the elaboration of drug therapy, with the administration of valproinate (21) and clonazepam (2) as anticonvulsive agents. The *second* one occurred following the introduction of magnetic resonance imaging (MRI) (1, 20, 35, 36) and positron emission tomography (PET) (31). Several times MRI of durg-resistant epileptics has been found to be suspicious, even if earlier computerized cerebral tomographic (CT) scans proved normal. With regard to the question of whether these "MRI foci" correspond to the source of the seizures, and whether it is best to excise them, a retrospective evaluation of the long-term outcome of the previously operated epileptics seemed worthwhile.

Materials and Approach

Patient Selection and Population

All those patients of the last 35 years who had been operated upon owing to medically refractory seizures, including posttraumatic epilepsy (30), were evaluated. They were not followed up if a tumor (36)

*Dedicated to Prof. Dr. P. Röttgen

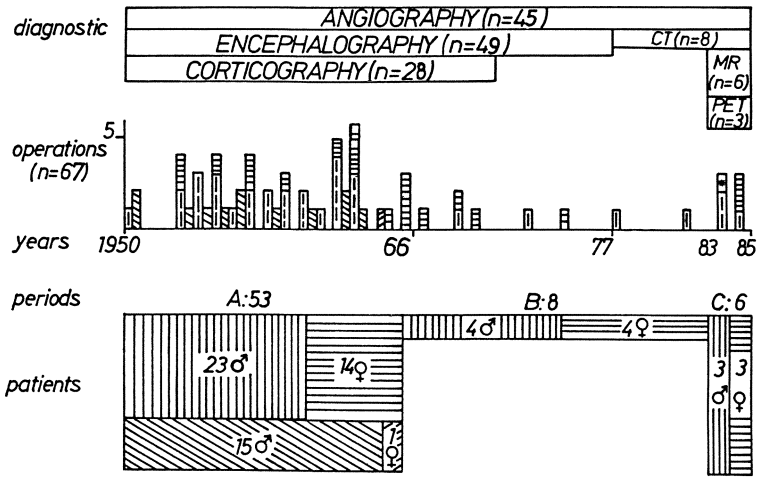

Fig. 1. Chronology of the operations (epilepsy surgery, Bonn 1950-1985, n=67). *CT*, computerized cerebral tomography; *MR*, magnetic resonance imaging; *PET*, positron emission tomography; ▥, males with nontraumatic epilepsy; ▤, females with nontraumatic epilepsy; ▨, males with posttraumatic epilepsy; ▧, females with posttraumatic epilepsy; *, hemispherectomy

or an angioma was identified preoperatively (exception: MRI focus only).

There have been *three periods* (A-C) with different diagnostic as well as therapeutic approaches (see Fig. 1):
Between 1950 and 1966, 80% of the operations were performed, a quarter of them because of posttraumatic (postabscess) cicatrices, mainly from World War II. Of the remaining three-quarters, 21% had been explored because an intracranial mass lesion (4) could not be ruled out by the then diagnostic procedures. During this period more males than females were operated upon, especially for posttraumatic epilepsy.

After 1966 the operative frequency decreased as a consequence of the scarce transfer of epileptics for surgical treatment; this did not alter in 1978 as a result of the availability of CT alone.

Data were sampled mainly from the files of the Neurosurgical and Neurological Departments of the University of Bonn and of the Rheinische Landesklinik in Bonn. By contacting the family doctors, outpatient examinations or the answering of a special questionnaire were organized. Table 1 shows the patients' profile: 62 patients (average age at op: 24 yrs) had to be observed retrospectively for an overall period of about 1143 years. The retrieval was 90%, for both patient number and evaluation years. The mean follow-up period for the whole group was 18 years (range: 1-33 yrs).

Preoperative Symptomatology and Diagnostic Procedures

The preoperative duration of symptomatology was 9 years on average (range: 1-30 yrs), with the following type of seizures: complex partial seizures with (n=24) and without (n=19) secondary generalization, absences (n=19), grand mal (n=14), partial seizures with elementary

Table 1. Patients and follow-up (epilepsy surgery, Bonn, 1950-1985, n=62)

	Sum	Male	Female
Number of all epileptics:	62	40	22
- nontraumatic (n)	50	29	21
- posttraumatic (p)	12	11	1
At operation:			
- age (yrs): average	24 (1-51)	n 26 (1-51)	n 22 (3-37)
(range)		p 24 (1-42)	p 25 (25)
- duration of symptoms: (yrs)	9 (1-30)	n 9 (1-30)	n 9 (1-20)
		p 7 (1-16)	p 17 (17)
Repeated ops: (number of all ops: 67)	5	n 1	n 0
		p 4	p 0
Lateralization: (right : left)	31:31	n 12:17	n 13:8
		p 5:6	p 1:0

A: Number of all patients	62	
B: Patients with complete follow-up (92% from A)	57	
C: Patients with incomplete follow-up (8% from A)	5	
D: Alive in 1986 (65% from A, without the 5 of C)	40	
E: Mean age of D in 1986	44	yrs
F: Dead in 1986 (27% from A, without the 5 of C)	17	
G: Mean age of F at death	37	yrs
H: Cause of death: unknown	4	
cardiopulmonary insufficiency	3	
fall, accident	3	
pulmonary tuberculosis, pneumonitis	3	
sudden unexplained death	2	
suicide	1	
perioperative complications	1	
I: Sum of all intervals from the first op to 1986	1422	yrs
K: Calculated follow-up time (if all of C were alive)	1143	yrs
L: Observed period (90% from K)	1033	yrs
M: Not observed period (10% from K)	110	yrs

symptomatology (n=8); 21 patients had more than one type of seizure. The frequencies of symptoms were: up to 10 times daily (n=4), daily (n=22), weekly (n=18), monthly (n=8), quarterly (n=8), and yearly (n=2); five of the patients intermittently suffered from epileptic status. If possible, "mental changes" (12) were classified as: none (n=18, 31%), slight (n=25, 42%), moderate (n=14, 24%), and severe with attempted suicide (n=2, 3%). The condition of 22 of the patients (35%) allowed them to have a normal education or occupation, while the condition of 36 of the patients (58%) was restrictive.

All patients had been examined by repeated electroencephalography (EEG). The use of angiography, encephalography, CT, MRI, and PET is demonstrated in Fig. 1. From 1966 on, brain scintigraphy, as well as prolonged video-EEG recordings, were added on occasion. Since 1984, an amobarbital test (37) has been performed if hemispheric dominance is unclear.

Table 2. Operative technique, complications, and histopathology (epilepsy surgery, Bonn, 1950-1985)

Technique (n=67, macroscopic)	
Subtotal anterolateral resection of the temporal lobe	21
Excision of a posttraumtatic (postabscess) cicatrix	14
Temporal pole resection, including (parts of) amygdala	8
Local excision from temporal gyrus	6
Exploration with biopsy	6
Local excision from frontoparietal gyri	4
Exploration, local procaine injection	3
Hemispherectomy (18), frontotemporal bilobectomy	2
No exact classification possible	2
Excision of posttraumatic cicatrix and occipital lobe	1
Complications	
Reoperation (bone flap removed, wound revision, CSF shunt)	6
Superior contralateral quadrantanopia	5
Permanent dysphasia	3
Inflammation (meningitis; fistula, osteomyelitis)	2
Aggravation of a preexisting hemiparesis	1
Perioperative mortality	1
Histopathology (n=54, optical microscope)	
1) Primary nosological entity	(n= 22)
Posttraumatic/postabscess cicatrix	11
Microangioma	4
Early childhood alteration	2
Postcontusional alteration	1
Micro-oligodendroglioma	1
Tuberous sclerosis	1
Heterotopia	1
Postvaccinal alteration	1
2) Pathological alteration with doubtful classification, especially whether cause or sequela of epilepsy	(n=21)
"Gliosis"	15
Arachnoidal fibrosis	3
Satellitosis	2
Hyalinosis	1
3) No pathological alterations of the excised specimen	(n=11)

The correlation of histopathology (1-3) to clinical outcome (a=better, b=doubtful, c=worse) shows no definite significance: 1a=12, 1b=8, 1c=2; 2a=10, 2b=9, 2c=2; 3a=4, 3b=6, 3c=1

Surgical Technique

Principally the procedure depended on the intraoperative sites (see Table 2). The subtotal temporal lobectomies (n=21) preserving the vein of Labbé as well as the anterior choroidal artery were anterolateral (RÖTTGEN's method (34)). None of them were as extended as recommended by FALCONER (8, 9), especially not for the removal of the temporobasal and mesial structures (40). Twenty-six percent of the operations were performed under local, and 74% under endotracheal anesthesia. A cor-

ticogram with surface electrodes (ECoG) was carried out in 42%. The resection of posttraumatic cicatrices was performed according to FOERSTER (11). There were 12 different surgeons: one of them did half of the 67 operations, and three-quarters of the epileptics were operated upon by three neurosurgeons.

Results

The perioperative mortality was 1.5% (n=1). Further complications and the correlation of histopathology to clinical outcome are shown in Table 2. On average the patients were discharged from the neurosurgical ward after 17.5 days, and 69% were allowed to go home. As shown in Table 1, it is certain that two-thirds of the patients are alive in 1986 (mean age: 44 yrs). Within the deceased group (n=17; mean life expectancy: 37 yrs, cf. 14, 19, 41, 42) the posttraumatic epileptics (n=7) showed a relative predominance ($P< 0.025$, $\chi^2=5.90$), but they did not differ significantly with regard to benefit from the operation during their lifetimes. As shown in Fig. 2, 43% benefitted from the operation while 43% showed no change; 8% proved to be worse after the operation, and 6% could not be classified. The outcome was assessed on the basis of the criteria outlined below.

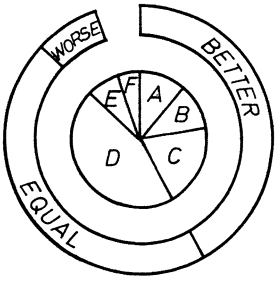

Fig. 2. Clinical outcome (epilepsy surgery, Bonn, 1950-1985, n= 62). *A*, no medication, no symptoms, no mental changes, with job: 13%; *B*, like *A*, with medication: 11%; *C*, with benefit from the operation, seizures reduced: 18%; *D*, with doubtful benefit from the operation: 43%; *E*, postoperatively worse: 8%; *F*, no data available: 6%

Seizures

Of those patients free of symptoms, eight were without (13%) and seven with (11%) medication; of those with reduced frequency of seizures, ten (16%) were without and two (3%) with intermittent loss of consciousness. Twenty-six showed no benefit from the operation with respect to the seizures, including 6 patients (10%) with later improvement from medical treatment. Three showed more seizures after the operation (5%).

Mental Changes

Of patients with severely altered behavior, one improved and one worsened. Most of those patients with slight to moderate alterations (n= 32) remained unchanged, through there were some (n=2) improvements as well as some deteriorations (n=5).

Job

Twenty patients (32%) pursued a normal occupation or school education before and after the operation; of those who had restrictive status 3 (5%) improved, 28 (45%) did not change, and 5 (8%) worsened.

Correlations of Various Parameters with Clinical Outcome

No influence on outcome was established for sex, type and frequency of the seizures, lateralization of the operation, anesthesia, intraoperative ECoG, and extent of the operation (especially not for resection of the amygdala (23)). Some patients seemed to benefit from pure biopsy.

Doubtful correlations: In both the group with the best (Fig. 2A) and the group with the poorest (2E) outcome, the mean duration of symptoms was below 9 years (2A: 5.3 yrs; 2E: 4.8 yrs; $P < 0.05$, $\chi^2 = 4.40$).

Remarkably, six out of eight of the group with the best outcome had been operated upon by one surgeon during the period (1957-1966) with the highest frequency of surgery for epilepsy (n=4/yr). There was no significant correlation between the microscopic findings and benefit from the operation (Table 2); though most of the patients with resected microangiomas had good results even in the third and fourth decades of life, was a slightly increased proportion of patients with no benefit from the resection of unclassifiable or inconspicuous specimens.

Evident correlations: Most of the patients with a restitutio ad integrum had been younger than 17 years (22) of age at the time of operation ($P < 0.05$, $\chi^2 = 5.19$). Markedly altered behavior before the operation compromises the benefit from surgery ($P < 0.05$; $\chi = 4.73$).

Discussion

In Bonn there was no neurosurgical department before 1946. For this reason one can hardly compare the results under discussion directly with those of traditional centers (5, 9, 13, 26, 38). In addition, a retrospective evaluation of 35 years with changing diagnostic, pharmacological, and surgical regimens has known limitations. It has not been easy to reconstruct the early data. Exact pre- and postoperative comparison of higher cerebral functions for the whole group is nearly impossible (especially as regards verbal and perceptual intelligence, memory, etc. (25, 32)).

The value of long-term evaluation and the necessity of scepticism toward brief observation periods can be demonstrated by one comparison: The Bonn cases of the 1950s were published by DILL and GULLOTTA (6) in 1970. In 13 of those 19 patients no tumor was known pre-operatively, and thus they fulfill our above-mentioned inclusion criteria. They were reevaluated in 1986, and six of them should be classified differently: No. 1, from "frequent seizures 8 yrs postop" to "restitutio ad integrum without medication"; No. 4, from "no change" to "aggravation and suicide"; Nos. 5 and 6, from "without seizures under medication" to "restitutio ad integrum without medication"; Nos. 14 and 15, from "no seizures 1 yr postop" to "less seizures but severe psychosis, predominantly hospitalized." Consequently at least these results, formerly referred to in JENSEN's (17) worldwide synopsis as "Bonn: free from seizures: 57.9%; no change: 42.1%," have to be amended.

A reliable assessment of our more recent patients and the influence of MRI and PET on long-term outcome is consequently not yet feasible. Overall, epilepsy surgery in Bonn, mainly with techniques of the 1950s and 1960s, proved to be a form of treatment for so-called therapy-resistant epilepsy because it did no harm in over 90%, was beneficial in over 40%, and was healing for every tenth patient. To solve the question of whether this is superior to the spontaneous course (14, 19, 41, 42) or to medical therapy, evaluation with matched controls of severe nonoperated epileptics is under way.

Conclusion

Epilepsy surgery remains a challenge. The best results in respect of drug-resistant seizures may be achieved in motivated patients in the second decade of life who have had about 4 years of unilateral focal epilepsy without mental change and who are treated in a multidisciplinary center (including epileptology, neurophysiology, neuroradiology, and neurosurgery)(n>5/yr). Exact preoperative selection of patients and careful neurophysiological management may be as crucial for postoperative benefit as the neurosurgeon's skill. The postoperative medication must be continued for at least 2 years, and the outcome cannot be judged before 3 years, or even longer.

Acknowledgments. The authors are indebted to Mrs. B. Mensching, Mrs. K. Mutlaq, and Mr. H.U. Klatt for their technical assistance and appreciate the kindness of Dr. Hild, Prof. Kersting, and Dr. Penin in consenting to the study of their files.

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Surgical Treatment of Pharmacoresistant Epilepsies in Children and Adolescents

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Introduction

Between 1980 and 1985, 24 children and adolescents (age range 1.9-18 years) suffering from pharmacoresistant epilepsies, predominantly complex partial seizures, were treated in our institution. Nearly all patients were admitted from epilepsy centers.

Presurgical diagnostic procedures were mainly CT, MRI, and angiography, but in special cases long-term EEG recordings were made by way of foramen ovale electrodes. In focal lesions intraoperative electrocorticography (ECOG) was used to define the areas of resection. Presurgical diagnostic procedures disclosed structural lesions in all children.

In four patients hemispherectomies were carried out, and in two, amygdalo-hippocampectomies. Cortical resections were performed in two of three patients suffering from epilepsia partialis continua; one patient only had a craniotomy with ECOG without resection. Gangliogliomas and low grade astrocytomas were the main tumor type in nine patients. The predominant site of tumor localization was temporal in eight and parietal in four.

The aim of this paper is to stress special neurosurgical aspects of pharmacoresistant epilepsies in children and adolescents. Postoperative time intervals are as yet too short and the developmental stages of the children too different to give exact data concerning the definite result of surgery for epilepsy.

Hemispherectomy

Following DANDY's first hemispherectomy in a patient with a glioma in 1928 (1) and McKENZIE's first hemispherectomy for control of seizures in 1938 (5), in 1950 KRYNAUW reported encouraging results in 12 patients in whom he had carried out a hemispherectomy for epilepsy (4). Special interest was drawn to infants with Sturge-Weber syndrome by HOFFMAN et al. (3). Children with gross destructive lesions in the hemisphere, pharmacoresistant epilepsies, and hemiparesis are candidates for hemispherectomy (Fig. 1).

The operative procedure is described in detail by HOFFMAN et al. (3). The results of hemispherectomy in properly selected cases are gratifying (7). Three of our four patients have been seizure-free postoperatively. The boy of 1.9 years with a hemispheric ganglioglioma improved after surgery but still has seizures (Fig. 2). One must be aware of acute postoperative CSF disturbance and late complications,

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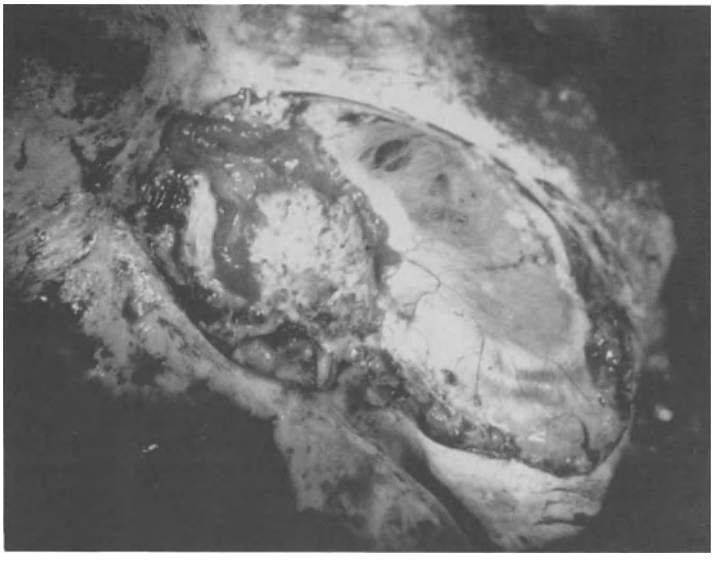

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Fig. 1. Right hemispherectomy. Plexus chorioideus still in situ

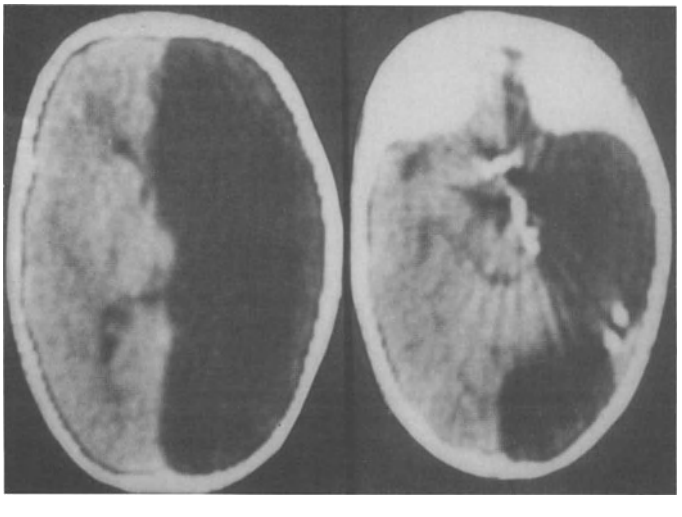

Fig. 2. Postoperative CT in a 1.9-year-old boy with congenital ganglioma

e.g., superficial hemosiderosis of the brain (8). Three of our four hemispherectomized patients needed early shunting procedures. An 18-year-old boy died 8 months after hemispherectomy from acute CSF disturbance. To prevent these acute and late complications, RASMUSSEN has been carrying out subtotal hemispherectomies since 1973 (8).

Cortical Resection

Modern use of cortical resection for epilepsy began with the work of FOERSTER (2). RASMUSSEN reported on 1407 patients who had undergone cortical excision for nontumoral epileptogenic lesions up to 1974 at the Montreal Neurological Institute. He found that 425 (33%) were seizure-free and 408 (32%) were improved (9). ECOG is essential in mapp-

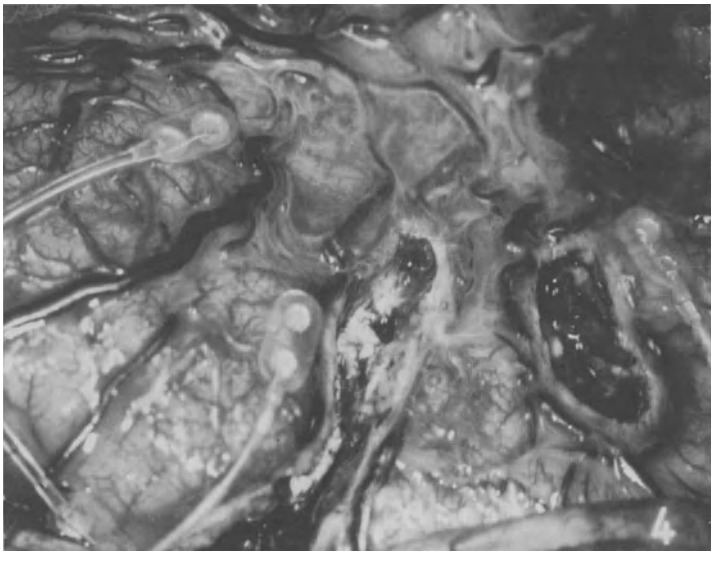

Fig. 3. Multiple cortical resections in the left central region under ECOG control

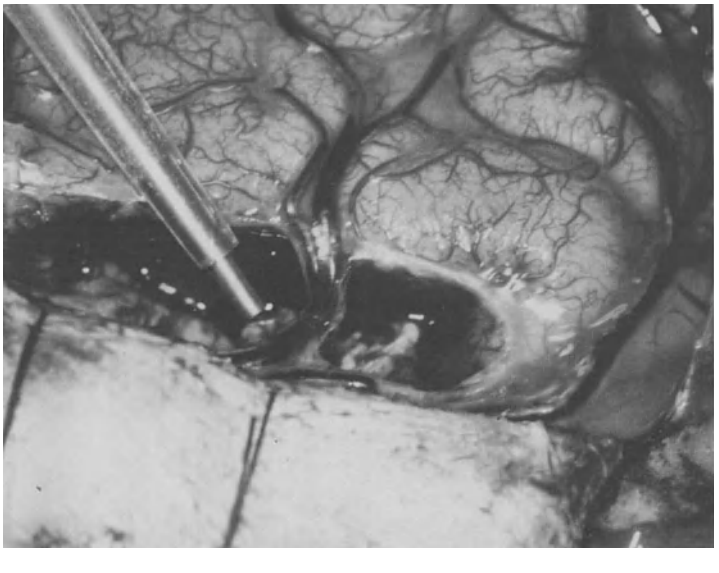

Fig. 4. Resection of a low grade astrocytoma in the right central region with the ultrasonic aspirator, leaving the bridging veins intact

ing the area to be resected. Depth electrodes have not been used by us. In one of three patients with epilepsia partialis continua and gross destructive brain lesions we carried out multiple cortical resections in the central region instead of hemispherectomy (Fig. 3).

Brain Tumors

The incidence of epilepsy as a symptom in patients with brain tumors is about 20% (9). In these patients the use of ECOG and excision of the seizure focus as well as the neoplasm has been the practice in our institution. The ultrasonic aspirator is of great value in making the procedure safe, i.e., in dealing with bridging veins in parietal lesions (Fig. 4). In our experience MRI has increased substantially the number of children who are candidates for operation because it detects some gangliogliomas which are not revealed by CT.

Selective Amygdalo-hippocampectomy

Patients with drug-resistant psychomotor epilepsy in whom mesiobasal temporal lobe epilepsy has been diagnosed are candidates for selective amygdalo-hippocampectomy (10). In two adolescents the operative approach has been transventricular (6) in one and transsylvian in the other (11); encouraging results were obtained in both cases.

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The Periosteal-Dural-Cerebral Scar, a Component of the So-called Growing Fracture: Long-term Experience of Neurosurgical Treatment

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Introduction

The genesis of a so-called growing fracture involves a sequence and combination of several typical factors, some of which are limited to the first 3 years of age. At the moment of the blunt impact, the calvaria will be impressed until it fractures; the periosteum, the dura, the arachnoidea, and the cerebral surface will be torn or lacerated. When the calvarial segments are repositioning after the impact has terminated, remnants of the periosteum are left in the fractural cleft. They may even be left in the lacerated cerebral surface - together with remnants of the dura as well. These are all common findings when a "growing fracture" is being dissected (Fig. 1). Additional factors such as pulsatile forces of CSF cysts and vessels and the low mechanical resistance of the infantile calvaria, which has not yet developed a compacta, are not discussed here.

The mixture of cerebral, arachnoidal, dural, and periosteal lacerated tissue gives rise to the development of a glial-mesenchymal scar. As this scar formation may become epileptogenic, the operative technique and the long-term results in such cases are discussed below.

Patients and Method

Twelve children aged below 20 months at the time of trauma (exception: one boy aged 7 years) were treated between 1971 and 1981 using an identical two-step procedure:

The aim of the first session was primarily the removal of the glial-mesenchymal scar (periosteal-dural-cerebral scar). This demands a careful separation from the surrounding cerebral tissue and a complete and clear-cut dissection of the dura all around the defect. Since on the side of the fractural defect the dura has generally detached from the skull at the moment of the impact and consequently has retracted from the defect on that side, it is necessary to perform an osteoclastic craniotomy that is much larger than the growing fracture. The first session is completed by the waterproof closure of the large dural defect using a piece of lyophilized dura.

After 3 months the implanted dura will be covered by a new membrane and at that time the calvarial defect is closed in a second session. In this way, the implantation of two homologous materials attached to each other is avoided, together with the subsequent nourishment and compatibility problems. The author uses a homologous calvarial bone graft.

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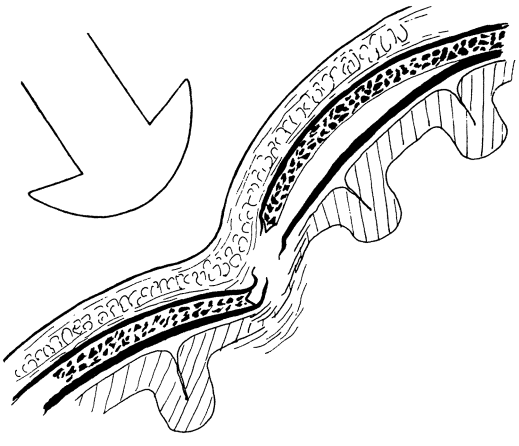

Fig. 1. Tearing and laceration of periosteum, dura, arachnoidea, and cerebral surface beneath a blunt impact, giving rise to a glial-mesodermal scar and the development of a "growing fracture"

Results

1. During the clinical follow-up of all children over 3-15 years, one child showed absences for 6 months and a second child was observed because of suspected absences. The phenomena ceased without therapy in both children. No other epileptic phenomena were observed.
2. EEG follow-up revealed no epileptic elements in five children, suspicious elements in two, and true epileptic elements in five (generalized, two; homolateral to the trauma, two; contralateral, one), starting 3-8 years after the surgical treatment. The EEGs of these children showed epileptic elements only at intervals.
3. Anticonvulsive therapy was started only in one child, when spikes became observable for the first time.

Conclusions

The described two-step operative procedure for treatment of "growing fractures" is considered a recommendable procedure in view of the good long-term clinical results that were observed 3-15 years postoperatively in this limited group of 12 patients.

Morphological Findings in Patients with Temporal Lobe Epilepsy Using Magnetic Resonance Imaging

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Introduction

Between 40% and 50% of patients with temporal lobe epilepsy are still pharmacoresistant (4). Neurosurgery is justified in such cases when there is considerable social prejudice against epileptic seizures. The success of an operation depends basically on precise topographic and qualitative diagnosis of the epileptogenic lesion before the operation (1). The use of several diagnostic methods can ensure the differentiation of the ictal focal defect. Among the various methods available today, morphological techniques which produce images have increased in importance (5). Our study verifies the value of magnetic resonance imaging (MRI) in the preoperative diagnosis of temporal epilepsies.

Altogether, 150 patients with various epileptic syndromes have been examined in our clinic using MRI. Of these, 82 were admitted to this study of temporal lobe epilepsy; patients with neoplasm of the brain or with metastases were excluded. The study was carried out using a 0.35 Tesla Magnetom (Siemens).

The EEG showed that 53 of the 82 patients had predominantly unilateral focal discharges while 29 had bilateral focal discharges. Localized changes (regional atrophy and localized lesions) were demonstrated three times more frequently by MRI than by computer tomography. Localized parenchymatous lesions with a change of the T_1 and/or T_2 signal were found almost twice as frequently with MRI than with computer tomography. It is notable that even patients with bilateral focal discharges in the EEG frequently had unilateral lesions (Table 1).

Contrary to the commonly expressed opinion that resistant cases in particular involve localized parenchymatious lesions, such parenchymatous lesions were also frequently found in the nonresistant cases. Thus, proof of a lesion using an imaging method cannot, in respect of the therapy for epilepsy, be the sole indication for surgery (Table 2).

The qualitative differential diagnosis of localized lesions using MRI showed small malformation tumors (hamartomas) (3) in ten cases and vascular defects in seven. In 12 cases qualitative classification of the changes was not possible with certainty. Computer tomography yielded no pathological findings in these 12 cases. A special signal constellation was observed with MRI, with no or a very slight signal change in the T_1-weighted image and a very much more extended area of signal increase in the T_2 mode. Neuropathological examination of the surgical specimens of a case taken from this series showed that the

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Table 1. Frequency of regional atrophy and circumscribed lesions in CT and MRI in relation to laterality of the EEG focus

EEG focus		Regional atrophy		Circumscribed lesions	
		CT	MRI	CT	MRI
Unilateral	53	4	27	9	16
Bilateral	29	1	13	7	13
	82	5	40	16	29

Table 2. Frequency of regional atrophy and circumscribed lesions in CT and MRI in relation to resistance to drug therapy

Drug therapy		Regional atrophy		Circumscribed lesions lesions	
		CT	MRI	CT	MRI
Resistant	31	1	17	6	13
Nonresistant	51	2	23	10	16
	82	3	40	16	29

extended increase of the signal in the T_2 mode was mainly caused by a gliosis (2).

Regional atrophy of the temporal lobe was a more frequent finding. this finding is marked if the results of two examiners, independently of each other and without knowledge of the EEG results, are identically classified. Morphometric control of these results was undertaken in 30 patients.

In imaging methods the size of the structure is dependent on the level of the projection (2). In order to ascertain the extent of deviation, we measured the area changes for defined levels of projection using autopsy brains. The measurements were made at the coronary level in six consecutive layers on a computerized magnetic plate. An area change of 0.3% per degree of deviation was obtained from the orthogonal level of projection. We defined an error of 2.5% as corresponding to an 8 degree deviation. Only values of the right/left comparison which fell outside of this degree of error were evaluated as significant right/left differences. Ten nonepileptic cases and those without degenerative or vascular encephalopathy were used as controls.

There was a left dominance of the temporal lobe in 80% of the controls. Left and right dominance of the temporal lobe was equally distributed in the epilepsy group.

Correlation with the side of unilateral focal discharge in the EEG showed a highly significant agreement between the smaller temporal lobe and the side of the EEG disturbance. Measurement of the cerebral circulation (SPECT with xenon 133) also indicated regional hypoperfusion in the smaller temporal lobe. That the dominant side of the disorder can also be localized in the smaller temporal lobe in pa-

tients with bilateral focal discharges in the EEG is assumed from our observation that SPECT always showed regionally reduced perfusion in the smaller temporal lobe.

An analysis of the regional distribution of asymmetry in the temporal lobes shows that in 70% of cases the whole temporal lobe is smaller. In the remaining cases a contralateral change of asymmetry, either oral (15%) or caudal (15%), occurs. By correlating these findings with the distribution of the background activity, we seek, over and above the lateralization, to characterize morphologically the spread of an epileptogenic focal disorder and thereby to make selective surgery possible.

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Cerebral Imaging in Epileptic Disease: Results of Magnetic Resonance Imaging When Computed Tomography is Within Normal Limits

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Introduction

Soon after the introduction of computed tomography (CT), numerous reports documented its usefulness in detection of cerebral abnormalities in epileptic disease (e.g., 2, 3, 8, 10, 14). The total number of abnormal findings varies considerably (7, 17, 22). Magnetic resonance (MR) imaging is superior to CT in detecting cerebral demyelination, rivals CT in imaging of brain tumors, and has tremendous potential in evaluating structural disease of the central nervous system (5, 11, 21). Therefore, we investigated the value of MR in the examination of epileptic disease when CT has been normal.

Patient Material and Methods

Magnetic resonance studies were performed at the Institute of Roentgenology, Düsseldorf, with a Diasonics MT/S magnetic resonance imager using a supraconductive magnet operating at 0.35 T. Scans were obtained with the spin-echo pulse sequence at various repetition and echo-delay times. Transverse, coronal, and sagittal sections were made.

The files of the Institute of Roentgenology, Düsseldorf, were retrospectively searched for epileptic patients in whom an MR study was requested because pre- and postinfusion CT had not shown any abnormality. We selected those patients whose epilepsy was proven; furthermore, we excluded patients whose CT scans were not obtained with a third or fourth generation scanner. We selected 73 patients according to the aforementioned criteria.

Results

We analyzed our patients according to epilepsy type (6). Most of them had predominantly grand mal epilepsy (n=37) or complex partial epilepsy (n=21). Some had focal fits (n=9) as the major manifestation of epileptic disease, while a small group (n=6) had other epileptic variants (myoclonus, absence, etc.). Sixteen patients had chronic epileptic disease; in 57 patients fits had developed recently (Table 1). In several cases the electroencephalogram (EEG) had revealed an epileptogenic focus, particularly in grand mal seizures of recent onset (Table 1). We found MR most rewarding in patients with grand mal and focal seizures who had a short history of fits. The presence of an epileptogenic focus on EEG clearly favored the demonstration of some abnormality on MR.

Table 1. Correlation between type of epilepsy, time of onset of epileptic disease, presence of EEG focus, and pathological MR findings

Epilepsy classification	No. of patients	Number of patients with Recent onset epilepsy	Chronic epilepsy	Number of patients with pathological MR findings	Number of patients with an EEG focus	Number of patients with an EEG focus and pathological MR findings
Epilepsy with grand mal seizures	37	28	-	11 of the 28	11	4 of the 11
		-	9	1 of the 9	2	0 of the 2
Complex partial epilepsy (temporal lobe epilepsy)	21	15	-	1 of the 15	4	1 of the 4
		-	6	1 of the 6	1	0 of the 1
Simple focal epilepsy (jacksonian type)	9	8	-	3 of the 8	6	2 of the 6
		-	1	0 of the 1	-	-
Other epilepsy types	6	6	-	1 of the 6	1	1 of the 1
		-	-	-	-	-
Total	73	57	16	18 of the 73	25	8 of the 25

Table 2. Correlation between hyperintense lesions seen on MR scans, epilepsy type, and differential diagnosis in epileptic patients without pathological CT findings (excluding pediatric patients)

MR finding	Epilepsy type	Number of patients	Differential diagnosis
Multiple intracerebral hyperintense lesions	Grand mal seizures	3	Ischemia/demyelinating disease
	Focal, jacksonian type seizures	2	Encephalitis/demyelinating disease
Hyperintense temporal lobe lesions	Grand mal seizures	2	Medial temporal lobe lesion of unknown etiology/low grade glioma
	Focal, jacksonian type seizures	1	Low grade glioma
	Complex partial seizures	2	Medial temporal lobe lesion of unknown etiology/mesial temporal sclerosis/low grade glioma
Hyperintense lesion of the internal capsule	Focal, jacksonian type seizures	2	Ischemia

Magnetic resonance imaging depicted multiple intracerebral hyperintense pathological findings, hyperintense areas in the temporal lobes, or pathology in the internal capsule in adult patients (Table 2). A patient with left-side focal epilepsy with occasional secondary generalization had hyperintense lesions in the right mesencephalic-diencephalic region of the brain and in the right occipital paraventricular white matter (Fig. 1). In another instance of focal, secondary generalizing seizures the hyperintense findings were restricted to the subcortical white matter of the right parietal lobe (Fig. 2). Figure 3 demonstrates a hyperintense signal in the medial parts of the right temporal lobe, suggesting mesial temporal sclerosis in a patient with psychomotor epilepsy and a right temporal focus on EEG.

Seventeen pediatric patients were studied too. In 11 cases the MR findings were within normal limits. Four children had slight signs suggesting connatal lesions of the brain such as minimal ventricular asymmetry, loss of brain substance, etc., which were not seen on CT. In one child MR demonstrated demyelinating or leukodystrophic disease, whereas in another it suggested bilateral degenerative disease involving the basal ganglia.

Although several lesions were visualized by MR, the exact diagnosis of the disease causing these alterations was often difficult. The presence of mass effect was suggestive of neoplastic disease, but in fact could not exclude an acute inflammatory, demyelinating, or ischemic process. Follow-up investigations were helpful in these cases. Involvement of both the white and gray matter of the brain was thought to exclude demyelinating disease; however, it could be seen in ischemic disease as well as in encephalitis. Ancillary investigations were generally necessary for differential diagnosis. Nevertheless, in several cases it was impossible to obtain a definite diagnosis as to the pathological entity responsible for the MR findings and the epileptic seizures.

Discussion

Although CT has been accepted as a very useful examination in epilepsy (2, 3, 8, 10, 14), no abnormality can be demonstrated in 20%-50% of cases, depending upon patient selection in the various series (7, 12, 22). MR can give supplementary information in imaging of the brain (5, 11, 21) and several authors have investigated its ability to reveal lesions of the central nervous system in epilepsy (1, 12, 13, 15, 16, 20). These reports predominantly studied highly selected groups of patients with psychomotor epilepsy: when CT was within normal limits 20%-30% of cases showed some abnormalities of the temporal lobes. Loss of volume, uncal herniation, and mesial temporal sclerosis were found; gliomas, arteriovenous malformations, and other diseases were rare. Partial complex seizures of the psychomotor type (focal epilepsy of the temporal lobe) have been studied preferentially with MR because CT of the temporal lobes is often difficult to interpret due to artifacts (4, 14), although mesial temporal sclerosis can be seen in some cases (4, 9), and because neurosurgical treatment can be offered to these patients (18, 19).

Our study involved a nonselected patient population referred to an MR practice by neurologists, hospitals, and university medical centers. All patients with proven epilepsy of whatever type and with normal CT scans of sufficiently high quality were entered in this investigation. We found MR abnormalities in 18 of 73 patients. These lesions could be correlated with seizures and EEG foci. Identification of the exact

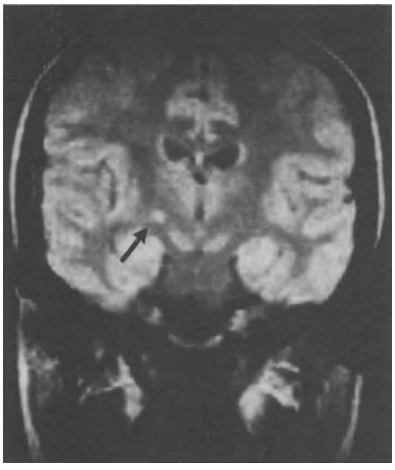

Fig. 1. Focal epilepsy of right hemispheric origin was present in a patient with a small hyperintensive lesion (*arrow*) in the right mesencephalic-diencephalic region (SE 1500/56); another hyperintensity was seen in the right occipital paraventricular white matter (not depicted)

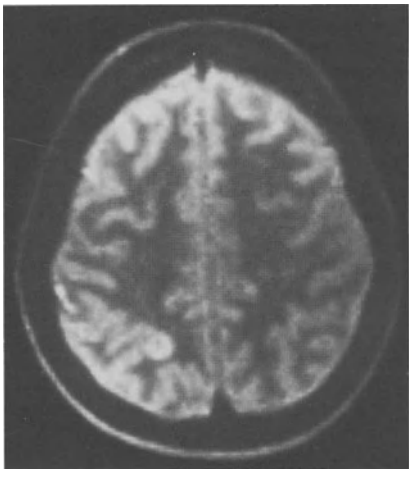

Fig. 2. This right parietal subcortical hyperintense spot (SE 2000/56) was seen in a patient with jacksonian type focal epileptic seizures of the left extremities

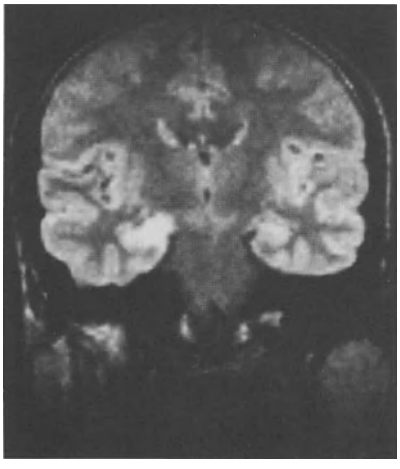

Fig. 3. The right temporal lobe is seen to be hyperintense in its mesial, hippocampal part (SE 1500/56); this patient had partial complex fits (temporal lobe epilepsy, psychomotor epilepsy)

Pathological nature of these MR abnormalities, however, is often difficult and requires follow-up examinations and other ancillary studies.

Our results indicate that MR is an essential additional technique in the diagnostic workup of epileptic patients without pathological CT findings.

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Diagnosis and Surgical Treatment of Cavernous Hemangiomas of the Speech Areas and Central Region of the Left Hemisphere

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Introduction

Vascular malformations of the cavernous hemangioma type in the central nervous system are infrequent (5, 7, 8). The series compiled by DANDY in 1928 comprised 44 cases, to which he added five of his own (4); however, it included several cases of Lindau tumors and other malformations which do not correspond to the definition of cavernous angiomas. In the case material of OLIVECRONA (2), among 941 brain tumors there were 37 angiomas (3.9%), with no case of cavernous hemangioma. Cavernous hemangioma was also extremely rare among patients admitted to the Department of Neurosurgery, University of Giessen, during a period of several years.

Histopathologically cavernous hemangiomas are characterized by a compact collection of dilated vessels which have a flat endothelium and are filled with blood. There is no parenchymatous tissue between closely apposed vascular walls. These histological features allow differentiation from arteriovenous malformations. This report concerns five patients with cavernous hemangiomas located in critical brain areas in the dominant hemisphere.

Material and Methods

Three patients were female and two male (age range: 8-42 years). The reason for admission was therapy-resistant seizures. The chief data regarding case histories and clinical features are shown in Table 1. The diagnostic workup included 16-channel EEG recording (in two cases supplemented by sphenoidal lead recording), four vessel angiography, and CT scanning before and after intravenous contrast medium infusion. The scanning was performed in 2-mm sections; reconstructed images in the coronary and sagittal planes were obtained. The location of the cavernoma was marked on the skin of the scalp (Figs. 2,3). Employing magnetic resonance imaging (MRI), a spin echo sequence was used (TR 2000 ms and TE 60 ms) in order to obtain the best possible image of gyri and sulci in the vicinity of the lesion.

Results

In only one case was a focal abnormality detected in the left temporal region with the help of sphenoidal lead recording (case No. 2). In one case (case No. 5) routine X-ray examination showed a small opacity which corresponded to the calcified part of the cavernoma.

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Table 1. Clinical data in patients with cavernous hemangiomas

Case	Age (yr)	Location	Seizures	Neurology	Follow-up
1	35 f	Operculum frontale/ frontoparietale	GM seizures	Normal	Normal, no seizure
2	24 f	Gyrus angularis	GM seizures, sensory aphasia	Sensory aphasia	Transient speech deterioration, no seizures
3	42 m	Precentral gyrus, frontolateral	GM seizures, motor aphasia	Slight arm weakness	Frequency of seizure reduced, transient increase of deficit
4	8 f	Central gyrus	Sensory jacksonian seizures	Headaches, nausea, vomiting after seizures	Normal, no seizures
5	39 m	Precentral gyrus, frontolateral	GM seizures, motor aphasia	Motor aphasia, slight arm weakness	Normal, no seizures

Angiography revealed no abnormalities whatsoever in three patients. In two patients a draining vein running from the lesion toward the ventricle could be visualized. In CT cavernomas present as a hyperdense lesion even on plain scans. The lesion is enhanced after contrast medium infusion. The draining vein can also be visualized by CT (Fig. 1). In the spin echo sequence of the MRI, a cavernoma appears as a structure with increased signal activity.

Operation

Prior to surgery the location of the lesion was marked on the scalp. The marking was later transferred onto the dura and the cerebral cortex (Figs. 2-4). The external appearance of the cortex and the sulcal relief were normal in all cases. Palpation revealed no abnormalities.

In two cases the arachnoid was found to be slightly thickened. In three cases a minimal yellowish discoloration of the cortex was found. The surface of the cerebral cortex was slightly pale in two cases. An intergyral point of entry was chosen after comparing the intraoperative appearance of the cerebral cortex with the pattern of sulci and gyri revealed by NMR. The arachnoid was cut over a distance of 1.0-1.5 cm; the surface of the lesion was visualized on the basis of the discoloration of the cortex. The cavernoma was dissected with the help of bipolar coagulation, a microsuction device, and neodymium-YAG laser. In three patients the postoperative course was completely uneventful. In one patient there was a transient increase in sensory dysphasia for 1 week and in another a transient increase in motor weakness and motor dysphasia for 3 weeks. In the follow-up period

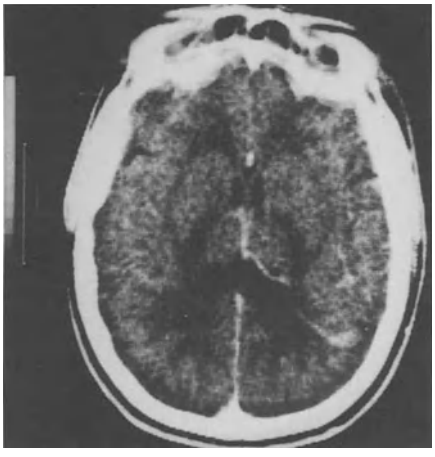

Fig. 1. Additional venous component with drainage into the ventricle and the internal cerebral vein (superimposition of four 2-mm slices)

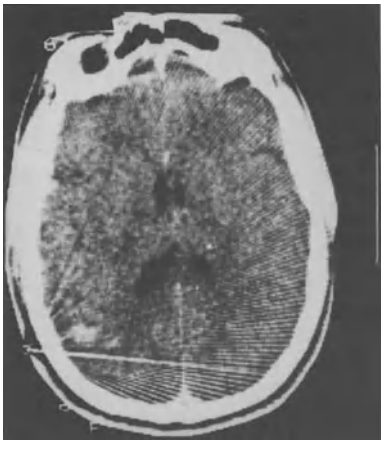

Fig. 2. Marking of the cavernoma in CT with the help of a metal rod placed on the skin of the scalp

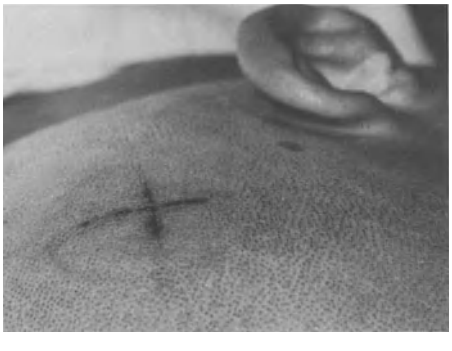

Fig. 3. Marking of the skin of the scalp

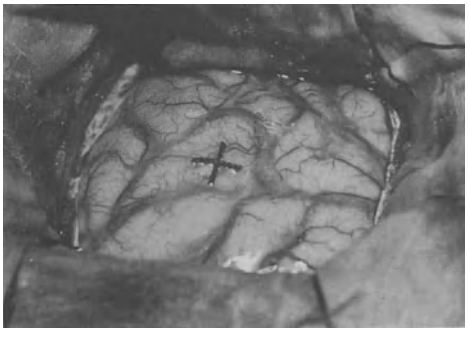

Fig. 4. Marking on the location of the lesion on the brain surface

four patients are completely free of seizures, while in one patient the frequency of seizures has been considerably reduced.

Histology

In all cases histological examination revealed typical features of cavernous angioma: a compact collection of considerably dilated vessels with a thin fibrous wall. In contrast to arteriovenous angiomas the sections of the central parts of the lesion showed only fibrous tissue in the vicinity of the vascular wall and never the presence of brain tissue. Furthermore, secondary changes were present in the form of thrombi in different stages of organization. In some parts the vascular walls were thickened, calcified, and contained hyalin.

At the periphery of the cavernous hemangioma, hemosiderin deposits and a thin wall of gliosis were found (a result of old bleedings).

Discussion

Cavernous hemangiomas are rare among patients admitted for neurosurgical treatment; however, in the autopsy material the incidence is much higher (2, 6, 7, 8, 9). One reason is probably the fact that non-space-occupying cavernomas cannot be detected by angiographic examination. Only two patients in the present series presented an atypical draining vein. This corresponds to the histological findings reported by other authors (3, 4, 6) regarding the presence of cavernous angiomas with a venous component. The venous part of the cavernoma can be visualized by computerized tomography. In all patients in our series the lesion was localized in the dominant hemisphere, while in the literature a preference for the right side has been reported (5).

In accordance with the literature, epileptic seizures were the leading neurological symptom (1, 10, 11), combined with a slight neurological deficit.

From the operative point of view the removal of cavernomas is easy. The exact location of small hemangiomas in speech areas is most important. On the surface of the brain minimal signs may be present (thickened arachnoid, slight discoloration or paleness) but are sometimes completely lacking. In order to avoid additional postoperative deficit, precise craniotomy is important. It is facilitated by projecting the location of the lesion upon the scalp with the help of CT. Exact imaging of the relief of the sulci and gyri in the vicinity of the lesion through MRI provides additional help. The combination of information provided by CT and MRI permits the exact localization of the circumscribed lesion. Thus surgery in functionally important areas is without risk of postoperative morbidity.

Summary

The diagnosis, indications for surgery, and intraoperative location of cavernous hemangiomas are discussed on the basis of five patients with cavernomas located in the speech and central areas of the dominant hemisphere. Resection of the lesions resulted in disappearance or reduction of the seizures. There were no permanent postoperative deficits.

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Seizures as an Atypical Symptom of Subarachnoid Hemorrhage

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Introduction

Subarachnoid hemorrhage (SAH) is the usual mode of manifestation of ruptured cerebral aneurysms. Seizures are considered to be uncommon as a symptom of SAH and the incidence of seizures accompanying SAH is largely unknown. We have made a retrospective analysis of patients with SAH due to cerebral aneurysm with the aim of comparing clinical and neuroradiological findings in the groups with and without seizures.

Material and Methods

Between January 1978 and December 1975, 488 patients with SAH and 30 patients with an intracranial aneurysm without prior bleeding were admitted to the Department of Neurosurgery, University of Giessen. Hospital records and CT scans were reviewed. Only the first CT scan of every patient was analyzed for this investigation. Seizures with classical symptoms which had been observed by a witness were included. Loss of consciousness without clearly defined symptoms was not considered as fit. All EEGs done in the patients with fits were reexamined for detection of epileptic foci.

Results

Of the 488 patients, 37 (7.6%) presented an epileptic fit in the acute phase of subarachnoid hemorrhage. All 37 patients had had a grand mal seizure. In seven patients focal seizure preceded generalized convulsions. In two patients transient postictal palsy was present. Focal onset of the seizure was of no help in evaluation of the site of rupture. In three of the seven patients the focal seizure was ipsilateral to the hemisphere in which the bleeding took place. Thirty of 42 seizures in 37 patients occurred initially at the onset of the signs of the bleeding. Eight fits happened within the first 2 h after SAH, and four within the first 4 days.

Mean age (43.3 ± 12.5 years) did not differ from that in all cases of SAH; the sex distribution showed a slight predominance of males (60% vs 40%).

The location of the aneurysms in patients with seizures differed from that in the whole population of patients with SAH (Table 1). Middle cerebral artery aneurysms were represented nearly twice as frequently among patients with seizures. Aneurysms of the posterior communicating artery and of the vertebrobasilar system were represented much less

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Table 1. Distribution of aneurysms, including multiple aneurysms, in patients with SAH with/without seizures

	Patients with SAH (%)	Patients with SAH and seizures (%)
ACoA AcA	41.7	36.6
MCA	20.0	36.5*
PCoA	14.3	4.9
ICA	13.0	17.1
Vertebro-basilar system	11.0	4.9

*$P < 0.05$

Table 2. CT findings in the first scan of patients with SAH with/without seizures

	Patients with SAH		Patients with SAH and seizures	
	n	%	*n*	%
Intraventricular hemorrhage	87	19.3	13	35.1*
Intracerebral hemorrhage	99	21.9	16	43.3**

*$P < 0.05$, **$P < 0.01$

frequently. EEG revealed a sharp wave focus in only two of 37 patients. Comparison of the first CT scans after the bleeding showed differences between the groups. The incidence of intraventricular hemorrhage and intracerebral hemorrhage was much higher among patients with seizures (Table 2). Among patients with intraventricular rupture of the aneurysm the frequency of seizures was almost twice as high as in patients without intraventricular hemorrhage.

Clinical outcome (classified according to the Glasgow Outcome Scale (1)) was worse in those patients with an initial fit. Mortality was increased by 8.6%. The percentage of patients with a good outcome was lower in the group with seizures (27.2% versus 43.6% among patients suffering SAH without a fit) (Table 3).

Discussion

The occurrence of epileptic seizures caused by aneurysms is well known (2, 4, 5). In contrast, fits as one of the first signs of an acute subarachnoid hemorrhage are very seldom documented (3). 7.6% of all our patients with an SAH (in a nonselected series) presented seizures as an initial symptom. This is in good accordance with another report

Table 3. Outcome of patients according to the Glasgow Outcome Scale (GOS)

GOS	Patients with SAH (%)	Patients with SAH and seizures (%)
1 (dead)	23.7	32.3
2 (apallic)	0.6	0
3 (bad)	13.5	18.9
4 (moderate)	18.6	21.6
5 (good)	43.6	27.2

of fits being among the first signs of SAH in 7% of cases (3). Intraventricular and intracerebral hemorrhages seem to be an additional factor causing fits and leading to an unfavorable clinical course.

Summary

In 37 (7.6%) of 488 patients with an acute SAH due to cerebral aneurysm, seizure was one of the first symptoms of the bleeding. In these patients intraventricular and intracerebral hemorrhage was twice as frequent as in those without a seizure and clinical outcome was worse.

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Rehabilitation in Neurosurgery

Rehabilitation of Patients with Organic Brain Damage After Diseases Requiring Neurosurgery

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In recent years, there has been further specification of the forms of therapy appropriate in neurological rehabilitation hospitals of stage II. The composition and monitoring of the therapy program (physiotherapy, ergotherapy, logopedics, neuropsychology, and occupational therapy) adapted to the functional disorders of each individual patient are of primary importance. The choice of the method of therapy is based on the clinical picture and on specific functional diagnostic methods, e.g. in the logopedic department the Aachen aphasia test, and in the neuropsychology department a group test battery with about 20 subtests. The mutual exchange of information between the various group therapists and the rehabilitation physician in regular conferences is very important. Discussion of physical treatment methods, occupational therapy, and logopedics will be dispensed with here, but the work of the neuropsychologist in the rehabilitation clinic will be briefly described.

In neuropsychology, the term *"Hirnleistungsschwäche"* (general brain deficit), which is often employed by physicians, is no longer used since the performance of the brain is not always equally affected and because there are specific functional deficits which can be subjected to specific training, just as on the physical side a paralyzed muscle group can be dealt with better by specific physiotherapeutic exercises than by general sports. POSER (8) has undertaken the validation of our group test battery for adults with brain damage. Our patients are investigated for about 2.5 h with this test battery. POSER arrived at very interesting observations with regard to the localization of neuropsychological functional disorders which are consistent with the theories on the function of the various areas within a hemisphere (7). The results of the statistical analysis were substantiated by comparison of the test results with the focus localization in CT. Accordingly, the slowing down of information processing is to be regarded as the most general neuropsychological consequence of brain damage (9). Table 1 lists the side-specific deficiencies in the neuropsychological field. Table 1 also contains some of the tests from the battery which proved sensitive for the disorder in question. In addition, it was possible to delimit regional brain damage further within one hemisphere in certain cases. It is noteworthy that the disturbed performances respond well to specific neuropsychological therapy and can often be normalized up to an average level.

Rehabilitation measures are also appropriate in slight to moderately severe traumatic brain damage without motor deficits or other neurological disorders. Above all in qualified intellectual occupations complete failure in the profession may occur when there is even minimal impairment of neuropsychological performance or a minor psycho-organic syndrome with behavioral disorders. This failure must then be evalua-

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Table 1. Side-specific neuropsychological deficiencies

Loss or disturbance in *left* hemispheric damage	Loss or disturbance in *right* hemispheric damage
Analytical information processing	Holistic information processing
Verbal memory	Visual memory
Verbal intelligence	Registration and reproduction of figures
Complex thought processes	Hemineglect
Sensitive tests:	*Sensitive tests:*
remembering a text	d 2 (2)
revision test (6)	LPS 3/4/7 (4)
numerical tests	BENTON (1)
LPS 1/2 (4)	drawing mirror images

ted retrospectively as a manifestation of organic brain damage which was not noticed before recommencement of work, but which could have been disclosed by neuropsychological diagnostics and given specific treatment.

Of 1600 patients who were admitted to our rehabilitation hospital after diseases requiring neurosurgery in 1984 (Table 2), the group with subarachnoid hemorrhages and aneurysms showed most pareses and aphasias. This may be associated with superimposed vascular syndromes; the fewest psychosyndromes and epileptic attacks were found in this group. On the other hand, epileptic attacks occurred most frequently in tumor patients (in almost 50% of those with malignant tumors). The large number of neuropsychological disorders in all groups (amounting to up to 80%) is striking. However, the patients with benign brain tumors showed a surprisingly good result, only 62% having neuropsychological disorders. These patients were even better with regard to the psycho-organic brain syndromes: only 36% showed psychosyndromes, as against about 60% of the trauma patients.

There is as yet no generally valid measurement criterion for the very difficult control of efficiency in neurological rehabilitation (10). The yes-no rating of ability to work is just as inadequate as the Glasgow Outcome Scale; the application of test batteries is also mostly related only to one subarea, which is insufficient for a total evaluation of the result of rehabilitation. CT also cannot say anything about the degree of clinically relevant brain damage, nor does it allow a prognosis with regard to the result of rehabilitation.

The percentage improvements in motor deficiency, aphasia, neuropsychological deficits, and psychosyndromes in the various patient groups we examined after an average of 7 weeks of therapy are listed in Table 3. In all four categories the best results were found in patients with subarachnoid hemorrhages and aneurysms, in which the initial findings were severe. Nevertheless, here the restoration of working ability was almost poorest of all diagnostic groups. Working ability improved most in patients with benign brain tumors or penetrating head injuries. Incidentally, according to our many years of experience both groups also had the best chance of rehabilitation. This is probably because as a rule these disorders or injuries involve localized

Table 2. Organic brain damage after neurosurgical diseases (n=1600)

	No.	Age	Lesions on admission (%)				
			Motor deficiency	Aphasia	Neuropsychological deficits	Psychosyndrome	Epileptic seizures
PHI	95	40	31	16	80	63	22
CHI	931	38	39	10	83	57	18
SAH and aneurysms	171	45	49	24	79	38	15
Benign tumors	295	45	39	13	62	36	33
Malignant tumors	108	42	43	23	79	49	47

Abbreviations: PHI, penetrating head injuries; CHI, closed head injuries; SAH, subarachnoid hemorrhages

Table 3. Results of therapy after neurosurgical diseases (n=1600)

	Improvement after 7 weeks of therapy (%)				
	Motor deficiency	Aphasia	Neuropsychological deficits	Psychosyndrome	Restoration of working ability
PHI	30	32	45	27	18
CHI	32	14	40	24	16
SAH and aneurysms	55	36	49	36	11
Benign tumors	36	20	32	22	17
Malignant tumors	30	26	39	22	6

Abbreviations as in Table 2

rather than generalized brain damage and because the neurosurgeon had also contributed to the prevention of generalized brain damage by timely intervention. As expected, patients with malignant brain tumors showed the poorest restoration of working ability, but they should not be excluded from rehabilitation (3, 5). Successful rehabilitation entails not only measurable restoration or maintenance of ability to work, but also the acceptance of a handicap by the person concerned, optimal compensation for physical and psychological restrictions, and thus an improvement in the quality of life. In practice, the road to this objective is often very long and tedious.

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Early Rehabilitation of Patients with Severe Craniocerebral Injuries. Organizational Regulation and Problems of Workmen's Compensation Insurance

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1. The activitites of the insurance institutions for workmen's compensation insurance in the area of rehabilitation have the purpose of achieving optimum results using "all suitable means" with the goal of reintegrating the accident victim in occupational life (1).

This requirement can be realized in individual cases in the medical area if
1. timeliness in guaranteed in registering and providing primary aid to the accident victim
2. a selection of those accident victims requiring special medical care for prompt and complete recovery is ensured.

The proven therapeutic procedures were based on these two principles, e.g. the insurance physician procedure and the injury-type procedure (2). In effect, these organizational forms apply only in the acute phase; for further rehabilitation current legislation calls for individual decisions.

It should also be noted that according to the law (3) the insurance institution has *sole* responsibility for performance of the therapy; this means the obligation to supervise and control the therapy. It does *not* mean that the insurance institution can or wishes to decide alone in medical matters; instead, it seeks the help of qualified physicians. But the insurance institution must ensure by means of organizational measures (also within its own administration) that the accident victim receives the necessary treatment for his injuries - also by specialists if required - not only in terms of acute care but also in the course of further therapy.

2. In the following I should like to present the measures taken by the Northwest German Association of the Employer's Liability Insurance Institutions, comprising the four northern German coastal states, in order to improve the organization of early rehabilitation of patients with severe craniocerebral injuries in accordance with the provisions of the law.

In November 1974, the workmen's compensation insurance associations presented their view of this problem in the memorandum entitled "Improvement of the rehabilitation of patients with severe craniocerebral injuries" (4), in which the entire range of rehabilitation from
first aid and transport to
acute therapy (as stage 1) to
further rehabilitation after acute or
postacute treatment (as stage 2) up to

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occupational rehabilitation (as stage 3)
was described and specific public demands formulated.

Here we will restrict ourselves to the areas of acute therapy and further rehabilitation.

In the memorandum acute therapy was subdivided into
traumatologic
neurosurgical and
neurologic and psychiatric
treatment.

Traumatologic and neurosurgical acute care (today designated as stage 1a) may be seen as largely ensured in accordance with the current state of knowledge. Special activities in this area have been developed in the framework of hospital planning of the German states. The insurance associations see virtually no need for regulations in this area today.

On the other hand, specific activities are considered necessary within the fields of "neurologic and psychiatric acute therapy" (today designated as stage 1b - early rehabilitation (5), because, according to the memorandum, facilities for this rehabilitation phase are almost completely lacking. Here measures must be taken in the institutional area, because the insurance associations have found that the required rehabilitation in special centers is often initiated too late, although it has been shown that rehabilitation therapy initiated early leads to surprisingly good results.

Understandably, it took some time for the recommendations of the memorandum to be translated into concrete plans for closing the gaps in early rehabilitation care and eliminating bottlenecks in the admission of patients for further rehabilitation. This is not the place to trace the development in this area, but a brief description of the current situation is in order.

There are a number of special rehabilitation centers available within the area covered by the Northwest German Assoaciation of Employer's Liability Insurance Institutions.

For young people and adults these are:
in *Schleswig-Holstein:* Malente, Damp and Bad Segeberg
in *Hamburg:* the Berufsgenossenschaftliche Unfallkrankenhaus
in *Lower Saxony:* Bad Bevensen, Hessich-Oldendorf, Lippoldsberg and Soltau.

For children and adolescents: Geesthacht and Bremen-Friedehorst.

We assume that with the special rehabilitation centers known to us, which, however, provide very different ranges of services, the need for special facilities is met and that with the help of these facilities care is provided that is accessible to the public and - even more importantly - close to the place of residence.

3. In a further step the object was then to improve information in the administrations of the insurance associations regarding the exact definition of the term "severe craniocerebral injury". After all, the reviewing clerks must determine - sometimes with the help of the consulting physicians - whether a rehabilitation case as such is present. This problem understandably poses special difficulties, because unlike the case of an amputation or paraplegia, the question cannot be readily answered. An exact report by the physicians is therefore of paramount importance.

In principle, it should be assumed that the insurance association is provided with the attending physician's report and the supplementary report additionally prepared by the attending physician and the chief hospital physician ("supplementary sheet and follow-up check for craniocerebral injuries", form D(H) 13a (head)) and that the report on neurologic findings (form AV 9) has been submitted.

The attending physician's report is usually submitted without delay as specified in the working contract, although the information on the necessity of special rehabilitation measures is naturally relatively scant in this initial report.

With the supplementary sheet and follow-up check things become more difficult. Apparently it is still problematic to use this report in the way the authors intended. In this context I should like to point out once again that in *every case* of an accident with head injuries and brain involvement or suspicion of brain involvement the supplementary report is to be submitted without delay.

The partners of the agreement physician/insurance institution introduced this form in 1976 so that the required information on the care chain can be provided. It is obvious that these expectations can be met only if the report is submitted in the scope intended. Yet in only about 50% of cases is the report submitted with the initial findings. Further reports as transfer findings are rare and as dismissal reports almost nonexistent.

Similar complaints are heard with respect to the submission of neurologic reports. It should be noted that the attending physician and the chief hospital physician are obliged to call upon a neurologist for consultative clarification and sometimes also for participatory treatment in every case involving head injury (i.e. also in what are deemed "minor" cases).

I should also like to point out another report which is apparently unknown to many, namely the medical form AV 9 a, the "medical report to the compensation insurance institution on a head injury with suspected brain involvement". This form, too, is intended to ensure the necessary information flow between the physician and the insurance association in a simple manner. The report is to be submitted:

1. if in the course of treatment it is found that far-reaching rehabilitation measures appear necessary in the immediate or foreseeable future
2. if in the expert review the performance of farreaching rehabilitation measures appears necessary.

This report can be used by surgeons, neurosurgeons and neurologists alike.

4. In view of these difficulties in reporting, the Northwest German Association of Employer's Liability Insurance Institutions has endeavored to establish concrete indication criteria as guidelines for the reviewing clerk in a model experiment run since the beginning of 1982 in cooperation with the Neurologic Clinic Hessisch-Oldendorf (director Dr. GOBIET) (6). The solution was offered of concentrating the administration of accident cases involving head injuries to one or several specialized employees of the insurance associations involved in order to manage as efficiently as possible the relatively time-consuming review of whether a rehabilitation case is present and whether treatment in a special center is required.

In the course of the model experiment the selection criteria were further concretized with the help of the physicians of the Neurologic Clinic Hessisch-Oldendorf.

Whether the initiation of rehabilitation measures is necessary, however, is not decided on the basis of these criteria alone but above all on the basis of the course and development of the cerebral functional disturbance in each individual case. A schematic assessment is neither possible nor indicated.

In order to take these circumstances of the individual case into account, a special medical consultation was arranged, which Dr. GOBIET was kind enough to attend.

It was often found that the documents available for assessment by the reviewing medical clerk did not always reflect the current state of the injured person. For this reason Dr. GOBIET was empowered to directly consult the attending surgeon/traumatologist and/or neurologist on behalf of the responsible insurance association. This permitted better assessment of the case and improved the necessary communication between the attending physician of the accident victim and the head physician of a possible special rehabilitation center.

5. Dr. GOBIET has just reported on the results achieved in this model experiment. In view of the positive experience gained, it appeared expedient - also in the interest of equal opportunity for all accident victims - to introduce this procedure for all compensation insurance institutions operating within the territory of our association. This was done at the beginning of 1986 (7), after Privatdozent dr. FRANK, head physician of the August-Bier-Klinik in Malente, and Dr. WOCHNIK, head physician of the Neurologic-psychiatric and Neurotramatologic Department of the Berufsgenossenschaftlichen Unfallkrankenhauses Hamburg, offered their services as further advisory specialists.

It is hoped that the positive experience gained in the model experiment will continue after the general introduction of the procedure on such a broad basis.

In conclusion, allow me to make a comment: As attending physicians, you can make a key contribution by notifying the insurance association in time of the necessity of special rehabilitation. The insurance associations will receive such information gratefully and will then initiate appropriate measures.

For there is general agreement on the goal: making possible the reintegration of your patients - our insured parties - in work life, family and society through better rehabilitation results.

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2. Sections 5 and 6 of the provisions of the earlier RVA of June 19, 1936 in conjunction with Ltnrn. 23-28 and 45, 46 of the agreement between physician and workmen's compensation insurance association
3. Section 557 paragraph and 3 RVO
4. Publisher: Hauptverband der gewerblichen Berufsgenossenschaften e.V., Lindenstrasse 78-80, D-5205 St. Augustin 2
5. Cf. 3.3 of the memorandum on page 12

6. Cf. Wesche/Gobiet "Optimierung der Rehabilitationsergebnisse von Schwer-Schädel-Hirnverletzten durch Frührehabilitation". In: Die Berufsgenossenschaft 6/1985, pp 33O-336

7. Circular A 5/1986 of January 2O, 1986

Rehabilitation of Head-Injured Patients in Edinburgh

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Introduction

The rehabilitation needs of head-injured patients are not easy to meet and differ from the needs of patients with other neurological disorders such as spinal lesions, stroke, or localized cerebro-vascular problems. Head-injured patients tend to have a varying combination of physical disability, cognitive impairment, and behavioral disturbance. The premature transfer of such patients to young disabled units, mentally handicapped institutions, or general psychiatric wards, respectively, is inappropriate as none of these facilities can cater adequately for the mixture of disabilities from which the patient suffers. Moreover, this pattern changes over a period of time, with major improvements in function over the first postinjury year and smaller though discernible improvements over the second year. In 1972, a special committee met on behalf of the Scottish Home and Health Department and presented guidelines for the organization and development of rehabilitation services, noting in particular the combination of disabilities suffered by head-injured patients. In this report it was proposed that at least two special centers be set up in Scotland for the care (1) of the severely disabled head-injured patient. Unfortunately, this recommendation has never been followed up and at the present time no special facilities exist in Scotland for head-injury rehabilitation.

In Edinburgh, there are at least facilities for general neurorehabilitation and at present it is within this facility that recovering head-injured patients are managed. The neurorehabilitation unit at the Astley Ainslie Hospital consists of a 22-bedded male ward and a 21-bedded female ward. Although some beds are designated for neurosurgical and some for neuromedical rehabilitation, an extremely close working relationship exists between neurosurgeon and neurologist so that in effect 38 of the 43 beds are jointly available for the rehabilitation of both surgical and medical neurological cases. Management is on a multiprofessional basis with medical and nursing staff, clinical psychology, social work, and the three remedial therapies (speech, occupational, and physiotherapy) represented. The professor of surgical neurology (JDM) and the neurologist (BP) hold twice-weekly team conference and ward rounds. A house officer is responsible for the daily care of inpatients while more senior training staff in rehabilitation medicine rotate through the unit as part of their training in rehabilitation medicine. A senior house officer from neurosurgery attends on a weekly basis with the professor and liaises in the assessment and transfer of patients from the head injury and neurosurgical unit to the neurorehabilitation unit. The clinical psychology service is provided by two principal clinical psychologists, each of whom have specific

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sessions in neurorehabilitation, and both of whom usually have assistants. Both wards carry a fair complement of nursing staff.

Head Injury Admissions

In the 2-year period to mid-1985, 121 severely head-injured patients had been evaluated in the unit under the joint neurology-neurosurgery program. Nine of these patients had been admitted on more than one occasion, accounting for a further 17 admissions, but these were normally for short periods of reassessment or for family relief. These additional admissions are not considered further. The 121 patients assessed comprised 98 males and 23 females; the average age was 38 years, with the median age in the 15-24 year age group. Two-thirds of the patients came from in and around Edinburgh; a further fifth of the patients came from surrounding parts of south-east Scotland, and 17% came from other parts of Scotland normally served by other neurosurgical units. These latter cases reflect the lack of any facilities for head injury rehabilitation in the other areas.

Length of Stay in the Unit

Seven percent stayed for 1 week or less, 43% for between 1 week and 1 month, 36% for between 1 and 3 months, and 14% for longer than 3 months.

Discharge from the Unit

By the end of the study period, 112 of the 121 patients had been discharged from the unit and of these, 101 (90%) had returned to their own home. Seven patients (6%) were returned to a referring neurosurgical or other unit, while three (3%) had to have long-term psychiatric care because of unremitting behavioral disorders. The remaining patient, who was a member of the armed forces, was transferred to a military hospital for further rehabilitation. Of the seven patients who were sent back to the referring unit and who might be considered to represent failures of rehabilitation treatment, four, all geriatric, were returned to our own acute head injury unit to await placement in a psychogeriatric unit. At the end of the study period there were nine patients still in the neurorehabilitation ward. Two of these have a long-term placement problem and have been in the unit for several years, long before the start of this study. The remaining seven patients were still undergoing active rehabilitation; all have since returned home.

Discussion

While the adoption of a multiprofessional joint medical and surgical neurological approach to rehabilitation of head-injured patients appears to have been fairly successful in returning most patients to their own home, it is clear that our unit caters for only a fraction of the population of head-injured patients in our region who might benefit from rehabilitation. A survey of the work of our own regional head injury unit in 1981 showed that, in that year alone, 116 of the total number of 1919 head injury admissions remained severely disabled or vegetative and an even greater number were moderately disabled (2). It has been suggested that these patients are equally likely to benefit from active rehabilitation. We believe that there is a strong case to be made for expanded and special facilities for head injury

rehabilitation in our area and in Scotland as a whole, and in partnership with our neurosurgical and neuropsychological colleagues in Glasgow we are trying to obtain support from the Scottish Home and Health Department for a national development along these lines.

Conclusions

We believe that it is important for the neurosurgeon to be involved directly in the rehabilitation of his head-injured patients because:

1. Rehabilitation must begin early, in the neurosurgical intensive care unit, as soon as survival of the patient is assured.
2. Study of recovery of function is at least as important, in understanding the pathophysiology of brain damage, as the study of loss of function.
3. The continuity of one extended team in acute and long-term care of the head injured is most reassuring to him and his family.
4. The rehabilitation team benefit from the direct and detailed information that the neurosurgeon can provide concerning early events, investigations and management and the late complications of the head injury.

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On the Need for Rehabilitating Persons with Craniocerebral Injuries of Varying Severity

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In 1977, the Minister of Labour, Health and Social Affairs of the state of Baden-Württemberg, Mrs. GRIESINGER, wrote that no "reliable data on ... accident-related craniocerebral injuries" are available, "nor on the extent to which special rehabilitation measures are required on account of these injuries..." (1). In saying this she drew on the industrial injuries insurance administration's memorandum entitled "On Improving the Rehabilitation of Persons with Severe Craniocerebral Injury" (2), drafted with our cooperation.

These industrial injuries insurance recommendations do contain general criteria for early identification of persons who require rehabilitation. Concerning the problem under discussion here, however, it has been possible for us to attempt to develop even more exact criteria for determining the rehabilitation needs of head-injured patients.

The 4303 cases of head injury studied by us subdivide into:
2809 cranial contusions without brain involvement = 65.3%
1494 cases of cerebral involvement of varying severity= 34.7%
i.e., 1301 "cerebral concussions" = 30.2%
193 "cerebral contusions" = 4.5%

Looking first at the cerebral contusions: this means a preliminary number of 193 potential rehabilitees, i.e., 4.5% of the patient population, or 12.9% of the fairly definite diagnoses of cerebral involvement of varying extent. The number of 193 potential rehabilitation cases will probably diminish only by the number of cases which were impossible to decide definitely without knowledge of the entire course but which later turned out to belong to the concussion group requiring no rehabilitation.

We hence attempted to clarify the concrete question of individual need for rehabilitation by assuming the presence of a more extensive neuropsychiatric initial syndrome, and determined the individual patient's need for rehabilitation solely on the basis of the symptom complex present - that means, totally independent of the diagnosis given (!).

The presence of a severe initial syndrome requiring early rehabilitation was assumed *in all cases* where, at first admission or even later,
- disturbance of consciousness had been severe, that is, at least marked sleepiness had occurred, or
- the period of disturbed consciousness had lasted for more than 2 h, or
- a definite diagnosis of transitional psycho-organic syndrome had been made, or

- regardless of the degree of consciousness disturbance, strong vegetative symptoms had been present, with an *additional* assumption that traumatic violence of at least moderate severity had occurred.

At least one of these criteria - severe disturbance of consciousness for the most part - had been present in 214 cases, and in most of these cases more than one had been present. These 214 patients, or 14.3% of all cases of cerebral involvement, can (as definitely as is possible on the basis of the files) be regarded as a strict selection of patients needing rehabilitation.

It should, further, be reemphasized that at least short-term inpatient treatment in the sense of early rehabilitation may have to be provided when *brief periods* of disturbed consciousness and psychopathological changes are observed; first because these may need some time to regress, and second because a persistent vegetative symptom complex is especially frequent in these less to moderately severe brain injuries. By clearly observing the initial symptoms and their course, a lot can be done toward facilitating later resolution of issues of medical opinion. Furthermore, at least for the most critical patients, this regrettably appears to be the only way to enable brain-organic or psychoreactive behavior or adjustment disorders to be prevented.

A marginal issue involved in the need for brain injury rehabilitation, which is, however, of relevance in particular to statutory accident insurance, has for the first time been investigated in such a large number of patients: the presence of a convulsive disorder - be it as a sometimes briefly observed sequela of craniocerebral injury or even (regrettably four times as frequent) as its cause! A seizure disorder was found to have ensued in six cases of cerebral involvement, i.e., 0.4%, whereas in 25 cases, i.e., 1.7% or every 60th patient, it was plausibly traced as the more or less definite *cause* of the brain injury sustained at work! Irrespective of whether it is possible for statutory accident insurance to intervene, it should, from a medical perspective, be strongly emphasized that this population in particular run an extraordinarily high risk, specifically when highly accident-prone jobs are involved (such as working on scaffoldings or with rotating machines). We would also take this opportunity to point out that when a seizure disorder is present, and even more so in combination with even a slight brain injury, psychic deficits must be expected. And these are known to contribute to rendering return to working rather problematic.

Apart from the brain-organic and psychoreactive behavioral and adjustment disorders, impairment of intellectual and other psychic aspects of functioning, and the brain-organic convulsive disorders, the memorandum cited above (2) gives various other, so far unmentioned criteria for the provision of rehabilitation, which are added here for the sake of completeness: paralyses and other disorders of motor functioning, neuropsychological disorders (such as speech/language impairments), and vegetative and vasomotor regulation disorders.

Specifically in the age of computer tomography, however, the following quotation from SCHIAN is as valid today as it was in 1977: "In a widely technology-dominated Medicine, the realization has more and more - and today we are saying: still not enough - been gaining ground in brain injury rehabilitation that, unless extraordinarily serious neurological deficits or multiple injuries are present, the course will be determined by the psychopathological deficits incurred" (3, 4, 5). "Our experience in recent years has shown that the most unfortunate courses have often not occurred in those with the most severe bodily sequelae but specifically in those patients who, in the absence of

some major physical disability, had gradually developed behavioral maladjustments, frequently of an induced nature, solely on account of the psychopathological disorders present, not to mention the losses in psychophysical tolerance that ensue in any case."

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The Rehabilitation of Aphasics in an Acute Clinic

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During recent years, experience with the rehabilitation of aphasics as well as knowledge of the brain processes relevant for rehabilitation has increased impressively. In the following those aspects of rehabilitation of aphasics will be discussed which are relevant especially to an acute clinic. Beforehand some aspects of plasticity will be brought to mind.

In 1984 Nottebohm was able to prove that birds can develop new neurons in spring (the time of singing) in the brain areas relevant for singing, which can be built up cyclically each spring. This result, which is revolutionary for our conceptions of plasticity, has not yet found any correspondence in the human brain. A further subject of great importance for the research into plasticity concerns the sprouting of axon collaterals, which in the brain do not exceed distances of 1 mm. It is still a question of dispute whether such sprouting can be functionally helpful or rather leads to the formation of irritating networks which may even develop epileptogenic activity. The heightened transmitter sensibility of partially denervated neurons also provokes new neuronal integrations, the functional significance of which is doubtful.

On the level of neurocybernetic description, a multistorage model of information processing is most adequate. According to this principle of redundant storage it is assumed that cognitive information in the brain does not get lost. Disturbances usually instead concern the processes of information retrieval. The redundancy of information storage in the brain is comparable to the situation in a library where the information in a lost book can be largely reconstructed on the basis of information in other books. Therefore the main intention of speech therapy is the activation of inhibited information and of substituting patterns of cognition. This can be achieved only by a systematic approach. It is not sufficient just to expose the patient to spoken language. In such situations the patient may disguise his deficits in speech comprehension by general remarks containing little or no information. Therefore it is of special importance to improve speech understanding. The therapy program has got to fit the special pattern of deficits. For this a specified diagnosis of aphasia (Broca, Wernicke, amnestic, global, and conduction aphasia) is especially important in cases of trauma or tumors, because in these cases mixed forms of aphasia very often occur. Also personal and educational factors have got to be taken into account. But of prime importance is consideration of the phases of the illness. The first phase concerns the 4-6 weeks immediately after the start of the illness. The second phase, the phase of consolidation, extends over 2 years. Improvements can also be seen in the third phase after 2 years.

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The first phase is of decisive importance because in it, emotional, cognitive, and behavioral patterns are established anew. Out of 280 aphasics observed by us over the last 12 years in the Neurosurgical University of Bonn, 22 were intensively analyzed in the first stage. Here we want to refer to our general experiences with therapy in the first stage. In the first week of illness one should not yet commence exercises or too much testing. Psychologically oriented communication (even nonverbal) with the patient is of greater help at this stage. The relatives should be informed about the different aspects of the illness, especially its nonpsychotic character. The psychological care has got to take account of the fact that the patient has got to cope with his speech loss. Therefore one should not force the patient into a test situation which demonstrates to him his deficits too explicity. The therapy has got to heed the linguistic character of the disturbance, which means that, for example, the missing words need not be statistically rare ones but may even be the most frequent pronouns, prepositions, articles, and auxiliary verbs. Such words can be disturbed more easily because they have only a linguistic function and not a definite meaning. On the other hand, in Wernicke patients it is usually the nouns, which do have definite meaning, that are predominantly disturbed. One should take care that in the further course of the therapy sessions natural situations are also included. Thus situations of shopping or asking the way should be imitated. In many patients, especially those with amnestic aphasia, a stimulation of the verbal engram is possible by varying the stimulated sensory channel. In many cases words may be activated by demonstrating the corresponding pictures.

Of special interest is the stimulation of the right hemisphere by prosodic intonations and melody therapy. In this way and also by tachistoscopic hemifield stimulation the nondominant hemisphere may be additionally activated even in global aphasics. We think that all these measures are of special importance in the early phase of aphasia because at this stage the spontaneous plasticity of the brain can be optimally employed and a motivational crisis prevented.

Rehabilitation After Severe Head Injuries

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Introduction

During the last 10 years a total of 2269 patients with severe head injuries have received intensive treatment in our clinic. Eight hundred and thirty patients remained in coma longer than 24 h, and of these, 425 died. The 405 survivors were in coma I, II, or III.

Ability to Work

Information about the follow-up was available for 304 patients. They are represented individually in Fig. 1 according to their age and the degree and the duration of coma. The line joining the points of the patients with the longest period of coma, followed by complete recovery for each age group, produces a curve which we call the *borderline of good recovery*. In younger age groups this borderline is near to the 5%

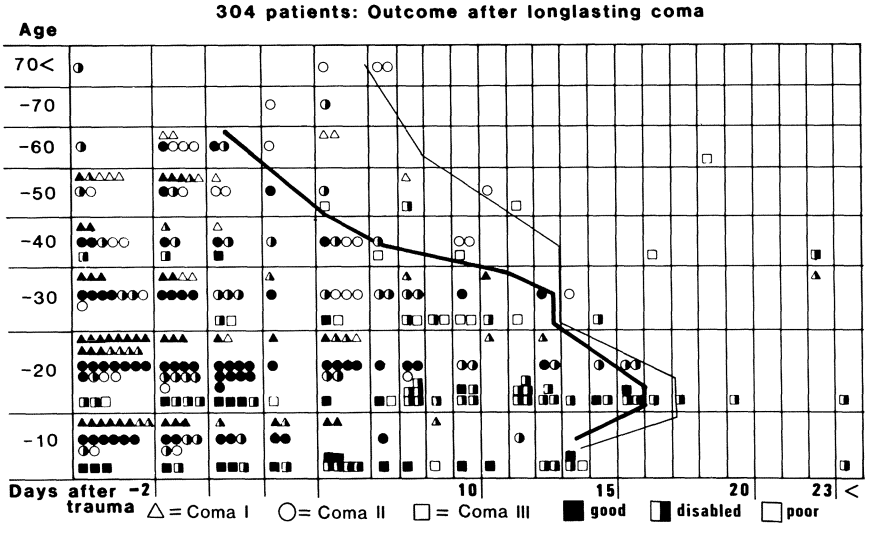

Fig. 1. Three hundred and four survivors of severe head injuries with coma of more than 24 hours' duration

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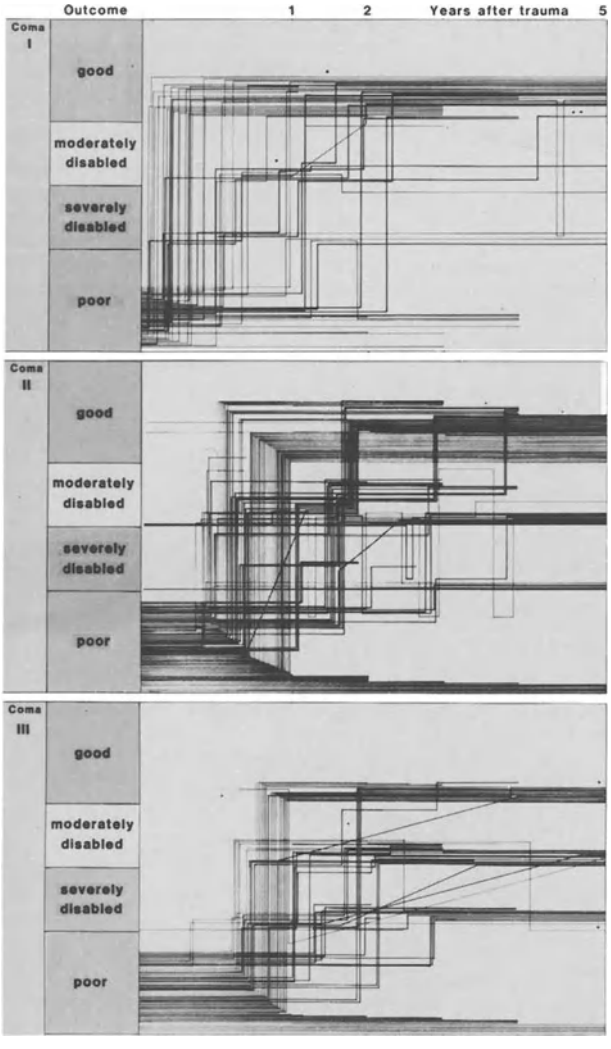

Fig. 2. Follow-ups of 267 patients with longlasting posttraumatic coma I, II, or III

survival limit, but in 40- to 60-year-old patients, the borderline of good recovery is 2-8 days shorter than the 5% survival limit. In patients older than 60 years with longlasting coma only incomplete recovery was observed.

Follow-ups

Two hundred and sixty-seven follow-ups of 1 year and 178 of up to 5 years after trauma were available for survivors of an initial coma I, II, or III lasting more than 24 h (Fig. 2).

The degree of recovery according to the Glasgow Outcome Scale (BOND 1975) - good, moderately or severely disabled, or poor - is shown in Fig. 3 on the basis of either first examinations after injury and later reexaminations or information from questionnaires.

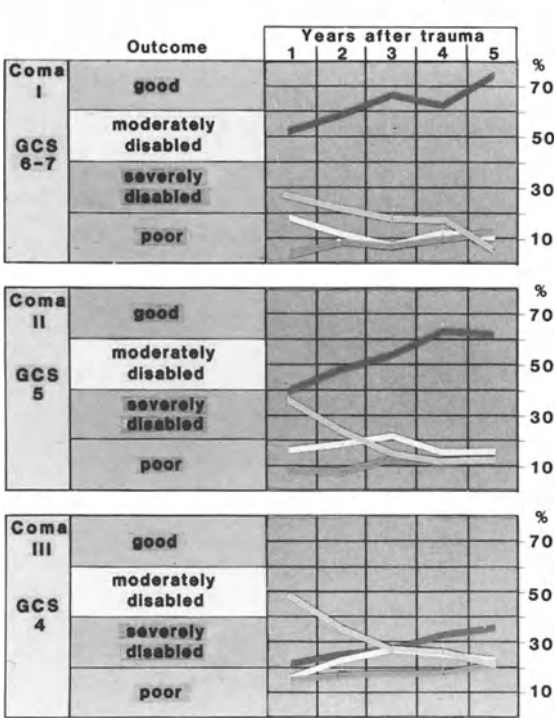

Fig. 3. Degree of recovery 1-5 years after posttraumatic longlasting coma. Percentage calculated from the findings in Fig. 2

The individual courses show that improvement usually occurred during the first year after trauma. *Improvement during the 2nd year* was documented in about 20% of the cases: in 17% of the cases after initial coma I, in 18% of the cases after coma II, and in 22% of the patients after coma III. In the third, fourth, and fifth years late improvement occurred in between 12% and 2% of the cases.

After posttraumatic *coma I lasting more than 24 h*, the percentage of full recoveries reported increased from 53% to 73% from the first to the fifth year. Partial recoveries diminished from 17% to 10% during the 5-year period, whereas the frequency with which inability to work was reported dropped from 26% to 5%.

After initial *coma II* 40% of the patients recovered completely during the first year; this percentage gradually increased to 62%. The frequency of partial recovery rose from 16% in the first year to 21% in the third and sank to 15% in the fifth year. Inability to work, which was as high as 35% in the first year, sank to 12% in the fifth year.

After initial *coma III*, which, with one exception, was survived only by patients up to 50 years of age, full capacity to work or to attend school was reached during the first year by only 21% of the patients, rising to about 32% in the fourth and fifth years. Partial recovery increased from 16% to 23%; severe disability varied between 15% and 21%. The percentage of those unable to work or attend school during the first year after coma III was 48%. At the end of 5 years this figure, based on the available information, had sunk to 21% of the patients of *all age groups*.

Age, Duration of Coma, and Good Recovery

Figures 4-6 deal only with patients with *good recovery*. We examined three different groups:
a) Patients in the same age group
b) Patients with the same length of initial coma
c) Patients with the longest period of coma

ad a) Fig. 4: After coma I 70% of young patients between 10 and 20 years of age recovered fully during the first year. In such patients with coma III, the corresponding figure was 18%, gradually increasing to 46%. Permanent inability to work after coma III diminished from 26% to 9%.

Thus it seemed that young patients recovered more quickly and more fully than the average of all patients (Fig. 3). Unfortunately, however, a follow-up was not possible in about one-third of the cases. Many of these young patients were foreigners who left the town or country. We felt it advisable to examine the influence of factors other than age.

ad b) Different age; same coma duration; good recovery: Figure 5 shows the follow-ups of 20 patients of different age at trauma, but all with the same length (4-6 days) of initial coma. The periods between trauma and full ability to work or to attend school were about 3-6 months in all patients with coma I or II. After coma III the period was usually longer, from 1 1/2 years up to 5 years.

Thus, unexpectedly, for patients in different age groups who survived the same length and same degree of coma, the period of recovery was also about the same. Older patients who survived the same length of coma recovered as quickly as did younger ones, but the incidence of these survivors was minimal in higher age groups.

ad c) Maximum duration of coma after which full recovery is possible: In Figure 6 the survivors of the *longest* periods of coma who finally achieved full recovery are entered on a chart according to their age at the time of trauma. The maximal duration of coma varied according to age.

Full recovery was reached in less than a year in patients over 40 years of age where the maximal duration of coma II was relatively short. After longlasting coma of 10-15 days some younger patients also recovered quickly, in 3-6 months. But with other young patients, rehabilitation had to continue for 2-5 years, especially in cases of midbrain syndrome.

Summary

Four hundred and five follow-ups of survivors of severe head injuries showed that the maximal duration of a restrictively defined *coma* following which full recovery can occur varies according to the age of the patient from 4-15 days. On average, 80% of the patients recover during the first year, as do the rare cases of full recovery in higher age groups. Young patients with initial midbrain syndrome sometimes need up to 5 years and more for a full recovery.

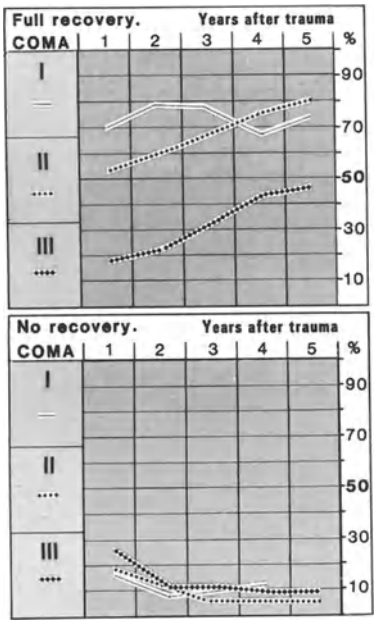

Fig. 4. One hundred patients aged 11-20 years at trauma with long-lasting coma I, II, or III. Percentage of courses with full or no recovery

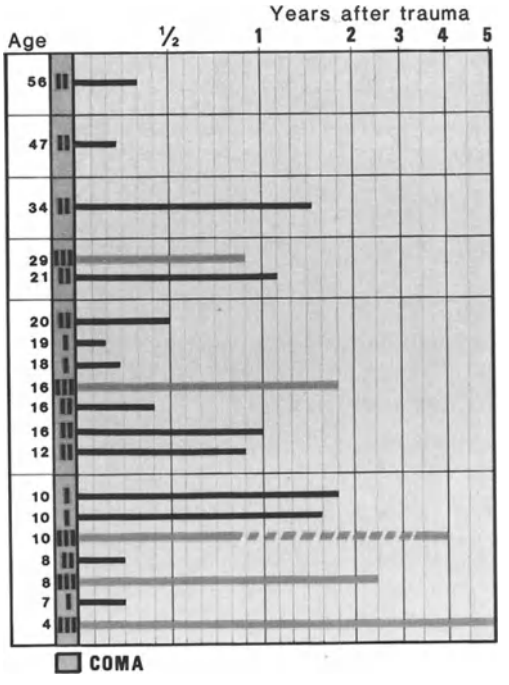

Fig. 5. Period up to full recovery of patients of all age groups with about the same duration of coma (4-6 days)

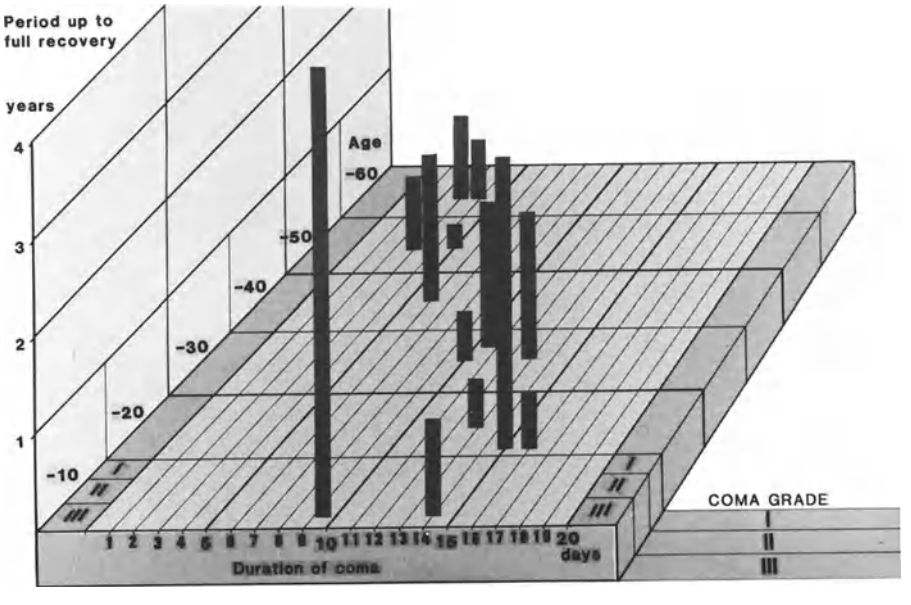

Fig. 6. Period up to full recovery of the patients with maximum duration of coma in different age groups

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Prognosis for Vocational Rehabilitation in Patients with Traumatic Epilepsy

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Introduction

Patients with traumatic epilepsy present special problems in respect of vocational rehabilitation: When seen as patients with a primary head injury they also have seizures; when seen as patients with epilepsy the sequelae of head injury have to be taken into account.

What conclusions can be drawn regarding the prognosis for vocational rehabilitation in these patients? Do the risks present in both groups combine in traumatic epilepsy, e.g. epileptic seizure frequency and psychic alterations on the one hand, disturbances of concentration, memory, and neurolcgical deficits from cerebrocranial trauma on the other? Or are there factors such as youth or intelligence that influence vocational rehabilitation more favorably than might be expected?

Patients and Methods

Over a period of 7 years, 116 patients had epilepsy out of 3824 patients participating in a 1- to 3-week vocational assessment program in a vocational training center (6). We report on 73 patients whose epilepsy became manifest after leaving school.

We transferred the records of the occupational physician, the occupational psychologist, and the master mechanic who observed the skilfulness in vocational tests onto a computerized sheet. Intellectual capacity was measured with a psychological battery testing concentration, performance independent of education, and verbal, numerical, and perceptual abilities. The mean value of these five diagnostic program parts established the intellectual capacity (7).

Practical abilities and skilfulness were evaluated by master mechanics in different vocational tests in a training workshop using metal and plastic material, soldering and wiring tasks, measuring and connecting exercises, accounting and drawing exercises, commercial correspondence, and organizing tasks. Differences were tested by the chi-square test and by the two-tailed Kruskal-Wallis test (for three groups).

Results

In 15 (20%) of the 73 patients etiology was traumatic, in 40 (55%) symptomatic, and in 18 (25%) cryptogenic. In 13 of the 15 patients with traumatic epilepsy the cause had been a penetrating head injury. With the exception of one case all patients with traumatic epilepsy

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Table 1. Social situation at vocational assessment (n=73)

		Traumatic (n=15)	Symptomatic (n=40)	Cryptogenic (n=18)	
Age (18-43)		28.9	30.9	33.9	$P<0.05$
Sex	Men	11	16	18	NS
	Women	2	4	-	
Marital status	Single/ unmarried	11	16	6	$P<0.05$
	Married	4	24	12	
Children	Yes	2	17	10	$P<0.04$
	No	13	22	8	
	No records	-	1	-	
Education	None	2	10	4	$P<0.17$
	Primary school	10	20	13	
	Secondary school	3	10	0	
	No records	-	-	1	

had traumatic late seizures, taking the first week after trauma as the boundary between early and late seizures. The mean value for the first seizure after trauma was 8 months. Four patients had been unconscious for less than 24 h and six patients for several days; in five patients no exact records could be found.

Patients with traumatic epilepsy were younger than patients with symptomatic or cryptogenic epilepsy ($P<0.05$). The former more often lived alone ($P<0.04$) and on average had fewer children ($P<0.04$), a finding certainly to be explained by their lower mean age (Table 1). Patients with traumatic epilepsy had a better education and more vocational training (80% vs 75%). Most of them had learned a manual occupation.

Looking at the stage of treatment, more than half of the patients with traumatic epilepsy had an oligo-epilepsy (i.e., hitherto fewer than six grand mal seizures) which had responded favorably to antiepileptic monotherapy.

In the year before vocational assessment, 43% of the patients with traumatic epilepsy had been seizure-free, in contrast to only 7% of the patients with a cryptogenic etiology; statistically there was, however, only a slight tendency toward discrimination ($P<0.14$). Patients with traumatic epilepsy had, not surprisingly, more additional handicaps than others, like psychic and/or neurological handicaps ($P<0.03$) (Table 2).

Suggestions for vocational retraining were made to 68% of the whole group. Sixty-six percent received concrete proposals - equivalent to 3 years of professional education - like training in telecommunications, construction engineering, or clerical/sales work. Ten percent received proposals at a level equivalent to 2 years of professional education,

Table 2. Type of epilepsy, status of treatment, and additional handicaps

		Traumatic (n=15)	Symptomatic (n=40)	Cryptogenic (n=18)	
Type of epilepsy	Primary generalized	-	20%	61%	
	Focal	100%	73%	33%	$P<0.01$
	Unclassified	-	7%	6%	
Oligo-epilepsy		53%	28%	22%	$P<0.12$
Seizure-free in the year before vocational assessment		43%	29%	7%	$P<0.14$
Seizures		57%	71%	93%	
Seizures during vocational assessment		14%	23%	50%	$P<0.07$
Antiepileptic medication	None	14%	7%	22%	
	Monotherapy	73%	58%	44%	NS
	Multiple therapy	13%	35%	34%	
Additional handicaps	None	-	13%	-	
	Neurological	40%	27%	22%	$P<0.03$
	Psychic	40%	22%	22%	
	Others	20%	38%	56%	

Table 3. Prognostic factors for suggestions and the level of occupational retraining (n=73)

	Suggestions for vocational retraining	Level of occupational retraining	Traumatic vs others
Age	$P<0.05$	$P<0.03$	$P<0.05$
Education	NS	$P<0.07$	$P<0.17$
Seizures during vocational assessment	$P<0.10$	NS	$P<0.07$
Number of additional handicaps	$P<0.003$	NS	NS
Psychopathological disturbances	$P<0.008$	NS	NS
Intellectual capacity	$P<0.0001$	$P<0.001$	NS
Concentration	$P<0.01$	$P<0.006$	$P<0.06$
Working pace	$P<0.0001$	$P<0.0001$	NS
Drawing Skills	$P<0.0001$	$P<0.002$	$P<0.07$
Manual skills	$P<0.10$	NS	NS

while for 24% labor exchange was suggested. Patients with traumatic epilepsy did not differ from others in respect of the propositions for vocational retraining. The suggestions were influenced not only by age ($P<0.05$), but also by seizures occurring during vocational assessment ($P<0.10$), by the number of additional handicaps ($P<0.003$), by psychopathological disturbances ($P<0.008$), by intellectual capacity ($P<0.0001$), by disturbances in concentration ($P<0.01$), by working pace ($P<0.0001$), and by drawing skills ($P<0.0001$) (Table 3).

When looking at the *suggestions for vocational retraining of patients with traumatic epilepsy* it becomes clear that there are favorable and unfavorable factors: favorable factors are a young age and fewer seizures during vocational assessment, while unfavorable factors are striking disturbances in concentration and in skilled motor movements (i.e., drawing). For several other factors there were also deficiencies in comparison with the other two groups, although the differences were not statistically significant (Table 3).

The level of the occupational retraining proposed seems to be influenced by similar factors as suggestions for vocational retraining, such as age and level of education (Table 3).

Discussion

Our study shows that the prognosis for patients with traumatic epilepsy does not reflect combination of factors associated with epilepsy and with cerebrocranial trauma; this is in contrast to some results reported in the literature (5). The seizure frequency is lower and psychopathological disturbances are not more frequent than in patients with epilepsy of another etiology.

The young age of these patients seems to be a favorable prognostic factor. Although the patients with traumatic epilepsy have a higher level of education and more job experience than others, they suffer from a worse intellectual capacity, lower concentration ability, and more difficulties in skilled motor movements. This is in accordance with Batzel et al. (1980), who found intellectual and motor performance to be the most consistently discriminating factors between unemployed, employed, and prevocational groups, regardless of etiology.

It must be concluded that these are specific consequences of a head injury, which underlines the significance of early neurosurgical and neurological rehabilitation in patients with traumatic epilepsy. If such rehabilitation is not achieved it seems that patients with traumatic epilepsy will have an earlier age for disability pension (4, 5) or will not be employed in accordance with their abilities (2, 3, 8).

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Neuroactive Substances Influencing Regenerative Processes in the Central Nervous System: Neurobiological and Clinical Aspects

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In his influential work published in 1928 under the title "Degeneration and Regeneration of the Nervous System," RAMÒN Y CAJAL noted: "Once development was ended, the founts of growth and regeneration of the axon dendrites dried up irrevocably. In adult centers, the nerve paths are something fixed, and immutable; everything may die, nothing may be regenerated." (39) Approximately 50 years later BJÖRKLUND and STENEVI summarized: "It is well established that the adult mammalian brain has the capacity for sprouting, synaptogenesis, and reformation of severed connections (6)." The initial "hard-wired" concept of brain organization did not exclude recovery of function of the central nervous system; early experience of restorative events after brain ischemia resulted in the classical theories of recovery, including the strategy of behavioral compensation, diaschisis (release of uninjured tissue from a temporarily suppressed state), and vicariation (the possibility that one structure can take over another's function), (for review, see 18). New neuroanatomical and neurophysiological techniques, including anterograde and retrograde tracing of axons and intracellular recordings, resulted in the modern concept of "neuronal plasticity." This term is used to refer to certain types of adjustment of the nervous system to changes in the internal of external milieu, possibly combined with changes in neuronal connectivity (28). Direct lesions and external environmental changes like abnormal sensory input, e.g., dark rearing, during the prenatal and early postnatal period of development can affect neuronal connectivity, which is just in the process of being established. The onset of these modified connections seems to be inducible only during the primary development, and is then referred to as primary neuroplasticity. An outstanding example is the rearrangement of retinotectal axons after partial ablation of the superior colliculi and monocular enucleation in Syrian hamsters at birth by rerouting of growing axons (42). Also transneuronal changes can be elicited, as shown in altered callosal projection patterns after enucleation at birth (e.g. 11, 47). The possibility of modifying neuronal connections to a wide extent based on axonal rerouting declines clearly with age, so that it will not be recognizable in adult individuals. However, experimental work since the beginning of the second half of this century has provided evidence that plastic changes can also occur in the adult stage. LIU and CHAMBERS (34) reported a significant amount of dorsal root axon sprouting in the spinal cord when axons of adjacent dorsal roots were cut. Other important examples are lesion-induced modifications of neuronal connections in the limbic forebrain of rats (38), in the red nucleus of cats (46), and in the hippocampus of rats (10). These phenomena based on partial deafferentiation and changes in already established neuronal connectivity are subsumed under the term secondary neuroplasticity.

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The adult mammalian central nervous system neurons seem to fail to show axonal regrowth over long distances, probably as a result of factors in their tissue-damaged microenvironment, i.e. unfavorable extracellular substrate conditions based on ischemic reactions (e.g., see 9), mechanical barriers due to posttraumatic scar tissue formation (40), and as yet undefined inhibitory components in the normally existing internal CNS environment (9). The onset of reactive synaptogenesis after CNS lesions can be realized by axonal sprouting of surviving neurons and free postsynaptic offerings. The axonal sprouting occurs in the form of collateral sprouting, paraterminal sprouting, and contact synaptogenesis (38). The active role of the postsynaptic cell in the reformation of synaptic contacts is suggested by the facts that (a) polyribosomes are particularly prominent under developing spine synapses and increase substantially during lesion-induced synapse growth, and (b) in parallel with the increase in polyribosomes, there are increases in the incorporation of protein precursors in the adjacent neuropil, which appear to reflect protein synthesis by the spine-associated polyribosomes (44).

Drug Treatment of CNS Lesions

In light of the above-mentioned considerations the targets of pharmacological intervention after CNS lesions should be the scar tissue formation, mediators of ischemic reactions, the microenvironment of neurons and their regrowing axons, the capacity of neurons for regrowing their axons or axon collaterals, and the induction of postsynaptic membrane thickenings (offerings).

Scar-Dissolving Agents

CLEMENTE and WINDLE (8) administered a pyrogenic substance derived from *Pseudomonas* bacteria, called Piromen, after spinal cord compression in cats. They stated that the pia-glial membrane failed to form in the treated cats; the extent of sprouting of the intraspinal neurons was the same in both the treated and the untreated group. Intraperitoneal injections of L-thyroxine were performed; histological examination of the spinal cord showed thinner or absent scar tissue formation and axons growing across the crushed area (25). Lidase, trypsin, elastase, and hyaluronidase were studied by different groups with different results, ranging from a high recovery rate of 44% down to ineffectiveness (35, 17). Because of the suggestion of WINDLE et al. (48) that pyrogens act to reduce scarring by stimulating secretion by the adrenal gland, ACTH and cortisone were also used, with the result of a reduction in connective tissue and less neuronal degeneration (7).

Drugs Preventing the Occurrence of Putative Mediators of Posttraumatic Ischemia

Recent studies regarding spinal cord function have shown an injury-induced massive cellular influx of calcium (3), followed by release of a number of substances which promote vasoconstriction and platelet aggregation, e.g., prostaglandin (30) and thromboxane (27), leukotrienes, and also the vasodilator and platelet aggregation inhibitor prostacyclin; they are induced by the arachidonic cascade. Drugs selectively interrupting this biochemical pathway are the cyclooxygenase inhibitors ibuprofen and meclofenamate, the thromboxane synthetase inhibitor U-63557 A (22), and the leukotriene synthetase inhibitor piriprost (29); stable prostacyclin can be administered in the form of ciprostene calcium HALL et al. (23) measured the drug effects in pretreated cats after a

spinal cord contusion injury. Animals treated with ibuprofen and meclofenamate showed a nearly stable spinal cord blood flow, whereas U-63557 A and piriprost could not prevent a decrease. Ciprostene calcium injection was followed by only a slight preserving effect.

Antioxidants

Ischemic anoxia is associated with oxygen-derived free radical generation which leads to possible irreversible membrane damage by lipid peroxidation. In addition to the membrane-protective effect, the antioxidants tocopherol (vit. E) and selenium also show a complete preservation of posttraumatic spinal cord blood flow (23).

Influencing the Neuronal Microenvironment

Mammalian axons regrow if severed in a peripheral nerve, but fail to penetrate the CNS (e.g., see 43). On the other hand, central axons enter a peripheral nerve segment implanted into the brain or spinal cord (e.g. see 5, 1); this leads to the assumption of the existence of growth inhibitory factors in CNS tissue which have not yet been identified. Thus any therapeutic possibilities are still unknown.

Neuronotropic and Neuritogenic Agents

Since PURPURA et al. (37) have found by electron microscopic studies that mature neurons in gangliosidoses produced new processes, including aberrant secondary neurites with occasional synapses, the gangliosides, especially monosialoganglioside (GM1; the ganglioside with the highest bioavailability in CNS (21)), were taken into account as therapeutic drugs. In vitro and in vivo studies showed both a neuronotropic effect (concerned primarily with survival and maintenance of the neuron) and a neuritogenic effect (involving a significant increase in the number, length, and branching of neuronal processes) (for review, see 33). However, experimental data in rats also indicate that ganglioside treatments reduce the severity of the initial behavioral effects after entorhinal lesions without enhancing the sprouting by septodental fibers (16), possibly based on an antiedematous effect (32). First clinical trials yielded information that GM1 is able to induce some beneficial effect, since the naturally occurring recovery after stroke is enhanced (e.g., see 4).

Thyroid Hormones

It is suggested that the intraaxonal microtubules are essential for the growth and maintenance of neurites, transporting protein from the cell soma to the growth cones at the end of the axon terminals. Administration of trioiodine-thyronine in adult rats, in which dorsal root regeneration was observed, showed an increase in the number of microtubules. Furthermore, it has been shown that T_3 has a stimulating effect on the reformation of myelin sheath (36). Improved functional recovery has been demonstrated in spinal cord injured rats after treatment with T_3 or T_4 (45).

Opiate Antagonists

Apart from the enkephalins and endorphins there exists a third group of endogenous opioid peptides, the dynorphins (20), which produce a dose-related hindlimb paralysis following intrathecal administration in the rat (12). Dynorphin accumulates in the injured spinal cord, with a remarkable intensification of neurological deficit (15). The opiate receptor antagonist naloxone, administered in high doses, improved spinal cord blood flow, somatosensory evoked potentials, and long-term neurological recovery (19, 50). Thyrotropin-releasing hormone (TRH) appears to act in vivo as a partial physiological antagonist of endogenous opioid systems without enhancing posttraumatic pain and being more effective than naloxone (14). Because of the very short plasma half-life of TRH (approx. 5 min), a number of TRH analogs have been developed, especially CG 3509, which is as effective as TRH (13). Multicenter clinical trials are being initiated.

Induction of Postsynaptic Membrane Thickenings (Offerings)

Longlasting administration of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) or sodium bromide, a substance known to produce stable hyperpolarization in sympathetic ganglion of frog (41), was capable of modifying the properties of receptive surfaces of neurons in the superior cervical ganglion of adult rat (31), thus providing postsynaptic offerings for potential regrowing axon terminals.

In conclusion, both the presynaptic *and* the postsynaptic sites in areas in which reactive synaptogenesis is worthwhile must be taken into account, also in view of the fact that CNS connectivity is a dynamic system with neurogenetic responses of excitatory and inhibitory neurons acting by changes in their input (cf. 49).

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Rehabilitative Surgery of Lesions of the Caudal Cranial Nerves

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Intraoperative lesions of the caudal group of cranial nerves with postoperative paralysis of the vagus and glossopharyngeal nerves are associated with severe disorders of swallowing and voice (9). The main problem is aspiration, with potentially life-threatening pulmonary sequelae (6, 7).

Since in the experience of many surgeons the use of a cuffed tracheal tube is of limited value for even the temporary control of aspiration, in our approach (2, 4, 5) to surgical rehabilitation of swallowing we prefer a plastic tracheostomy. This means the entire tracheostoma is lined with skin (1).

Aspiration is controlled by an intratracheal dressing consisting of a plugging gauze tamponage above the tracheal tube, which additionally is wrapped conically by a gauze strip (4). In this way it is possible to wait some time for the general condition of the patient to improve without any danger of aspiration.

The next step in our approach to correction of disorders of deglutition and voice is myotomy of the cricopharyngeal muscle with division of the circular muscle fibers of the cervical esophagus. Then the paralyzed pharyngeal wall is resected from the introitus of the esophagus up to the palatine tonsil.

By resection of a strip of the mucous membrane from the pharyngopalatine arch and by suturing the defect, we obtain an obstruction to the nasopharynx on the paralyzed side.

In cases of unilateral paresis of the vagus and the glossopharyngeal nerves, the glottal repair will be done by insertion of a cartilage implant into the paralyzed vocal cord (3) to attain a midline position of this vocal cord in order to improve voice and coughing up and additionally to protect the lower airways from aspiration. This procedure is better done before resection of the pharyngeal wall to prevent infection of the wound.

Adequate protection of the lower airways by the intratracheal dressing through the epithelialized tracheostoma is necessary until the function of swallowing is restored. The feeding tube can usually be removed 10-14 days after pharyngeal surgery. Surgical closure of the tracheostoma should be done only when laryngeal edema has subsided and when deglutition will have been recovered, i.e., about 6-8 weeks after pharyngeal surgery.

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In cases of bilateral paresis of the vagus and glossopharyngeal nerves we have to deal with many more problems, especially in the high-grade aspiration (8, 10). The surgical procedure in the pharyngeal region is nearly the same as in unilateral paresis. Only in a few cases do we have to operate on both pharyngeal walls. But in the region of the glottis there is a big difference in surgical rehabilitation. In cases of bilateral paresis of the vagus we are forced to perform a partial closure of the glottis, leaving a small fistula in the posterior commissure. This fistula enables the patient to phonate without danger of aspiration. As a rule the patients have to keep their tracheal tube, but in one case of bilateral paresis of the vagus and glossopharyngeal nerves we succeeded in reopening the formerly performed laryngeal stenosis and were able to close the tracheostoma.

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Psychological Rehabilitation of Patients with High Level Cervical Spinal Cord Lesions by Means of Automatic Bedside Projection Equipment for Reading Belletristic Literature

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The medicomechanical treatment of spinal cord lesions ought to be complemented by psychological guidance from the very beginning. ORBAAN (3) reviewed 140 traumatic cases he had managed in this way as a psychologist over a period of 12 years. Some rules can be cited in respect of the psychological adjustment process, which involves several phases, such as denial, depression, aggression, and acceptance. It is essential to have created a relationship of mutual trust between the therapist and the patient, who sometimes rejects the seriousness of the inescapable reality as a means of self-defense against the psychological shock and emotional crisis which threatens the personality. An empathic, more fractionated and gradual approach aimed at enlightening, as suggested by ROGERS (4), has proved better than an objective scientific declaration. The patient often needs an emotional catharsis, the opportunity to tell his life story, to explain his educational, familial, professional, and social background and his intellectual and cultural interests. These personal details and the achieved level of coping with the immense psychological problems should be noted in his medical report for the benefit of all the doctors, nursing staff, and physiotherapists who will be involved during the various stages of rehabilitation. Together with a listening, sympathetic approach, which does not prematurely destroy unrealistic hopes of the possibilities of rehabilitation, the patient wants badly to receive proposals regarding alternatives in his way of life, with new or renewed objectives. We must try to give the patient the chance to prove to himself his own worth, to learn how to make more of his new situation, and how to stay in communication. The situation is strained in cases with high-level cervical spinal cord lesions because a real handicap with loss of motility of both arms and hands will exist, especially in tumor cases with a bad final prognosis. These patients are condemned to stare at the ceiling, dependent on the friendly help of attendant persons in operating their cassette recorders or TV sets.

For this category of severely disabled patients, which is fortunately small, we have tried to make accessible the magic agency of literature, which opens up the world of mental culture, with its touching and enriching intimacy, binding the reader temporarily to the fate of poetical figures and stories according to an individual measure of reading and reflecting. Books are copied on long band micro films, which are then projected half automatically on a bedside screen with automatic focusing. The go-on switch can be operated by the patient himself. Problems regarding security and the film strip transport were solved by use of the PENTACON system PRACTICA 150 AFT from Dresden, completed by the compatible *"Automatische Bildbandführung."* According to our inquiries it was the only system on the market in the East and West which has the properties to manage up to 17 m film band, which means 850

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pages a spool. Authors' and publishers' copyright regulations were easy to meet, for hitherto nobody wanted to earn any fee from this film library. The projection screen can be fixed in an oblique and upward direction at the foot of the bed so as to facilitate a good view from the supine or dorsally elevated position of the reader. This equipment can be transported and used, free of charge, at home too. Our experiences were amazing and encouraging. A new level of conversation and interrelationship between physician and patient was achieved, the latter even reading books which the former had just read. There was also a response from authors who wanted to provide reading for such people and to organize a centralized lending department with the help of the Braille Bibliothek in Leipzig, which until now has offered tape archieves for blind people. The handicapped patient obtains great help from his own reading; it helps him to overcome his depression and he no longer needs "luxurious service" for as many hours as the day has. New interests are awakened and life becomes a little more worthwhile. The benefits for personality which accrue from access to belletristic literature, including poetry, have been analyzed in detail by CHRIST (1). GIEBEL and ARNOLD (2) examined problems of sexuality in para- and quadriplegics. Sexuality lies waste, whereas libidinous feelings and dreams of love continue to exist. Literature can help to neutralize and "platonize" this deep conflict.

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Arteriovenous Malformations in Childhood: Clinical Presentation, Results After Surgical Treatment, and Long-term Follow-up

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The following study presents the results after surgical treatment of arteriovenous malformations in childhood. Special emphasis is given to the clinical presentation and the effect of morphological factors, such as the site and size of an AVM, on the postoperative results.

Clinical Material and Methods

In a series of 159 arteriovenous angiomas recently published (1) we found 33 children aged 1-16 years, 18 boys and 15 girls. For the site of the AVMs see Table 1. Twelve of the angiomas were described as "small" with an angiographic diameter less than 2 cm, 14 as "medium-sized" (2-4 cm), and seven as "large" (diameter more than 4 cm).

Clinical Presentation

We found 28 bleeding and five nonbleeding malformations. Twenty-three of the bleeding malformations showed intracerebral bleeding with clot formation, and only five subarachnoid hemorrhage. Of those who did not bleed, three presented with epileptic seizures, one showed a hemiparesis of the infantile type, and one had extracranial extension.

Surgical Treatment

For 31 AVMs total excision was possible. Two malformations seemed not to be excisable but had to be treated by ventriculoperitoneal shunting due to hydrocephalus. We had one postoperative death, for a mortality of 3%. (Mortality in our complete series of 159 surgically removed angiomas was 10.3%.)

One child with a large midline angioma of the basal ganglia died 1 year after a ventriculoperitoneal shunting procedure due to intracerebral hemorrhage.

Follow-up

All but two children have been followed up by personal examination in our clinic (seven from 1 to 5 years after operation, 12 from 5 to 10 years, six from 10 to 20 years, and four from 20 to 30 years). Twenty-one patients showed no or minimal neurological deficit and were completely able to work when school was finished. Six of our patients were working although a greater neurological deficit, such as hemiparesis

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or aphasia, had remained. Two were not able to work due to severe neurological deficit.

Twenty-two patients were able to do the jobs they had intended to do before operation. Seven were not able to do so.

Twenty-four patients reported no epileptic seizures more than 1 year after operation. Most of them did not take any drugs. Four patients had seizures controlled by anticonvulsive drugs. One child had severe epilepsy with marked personality changes.

We classified the results in four groups: "excellent" (1), "good" (2), "fair" (3), and "poor" (4). Table 1 shows the importance of the size of an AVM for the final result. It is obvious that angiomas located in functionally important brain areas (parietal lobe, central region) have worse results after operation. However, it has to be kept in mind that bleeding in these cases led to a greater neurological deficit even before operation.

Table 1. Localization of angiomas and operative results

	Result/no. of cases					
Localization	1	2	3	4	+	Total
Frontal	5	1	-	-	-	6
Temporal	5	2	-	-	-	7
Parietal	-	3	-	1	1	5
Occipital	-	2	-	-	-	2
Sylvian fissure	1	-	-	-	-	1
Central region	1	3	3	-	-	7
Lateral ventricle	-	1	-	-	-	1
Corpus callosum, basal ganglia, and midbrain	1	-	-	1	1	3
Cerebellum	-	1	-	-	-	1
Total	13	13	3	2	3	33

Table 2 shows the importance of the size of an angioma for the postoperative result. Although small and medium-sized angiomas have a smaller risk of postoperative deficits, it has to be emphasized that even large angiomas with many arterial feeders can be excised with little postoperative deficit. Compared to the adults in our complete series of 159 surgically removed AVMs, the postoperative deficits after removal of large AVMs or AVMs located in functionally important brain areas are markedly less. Surgical excision of AVMs in childhood is less dangerous than in adults, and provides excellent results in long-term follow-up. If it is possible, total surgical resection of AVMs can therefore be recommended as a safe and effective procedure.

Dedication. This paper is dedicated to Kurt Schürmann, who operated upon most of the patients presented in this study.

Table 2. Size of angiomas and operative results

Result	Diameter (cm) <2	2-4	>4	Total
1 - Excellent	6	6	1	13
2 - Good	4	6	3	13
3 - Fair	1	1	1	3
4 - Poor	1	-	1	2
Died	1	-	1	2
Total	13	13	7	33

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How Good Are the Good Results in Aneurysm Surgery? Psychological Aspects of Rehabilitation of Early and Late Operated Patients with Cerebral Aneurysm

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Introduction

Since 1979 patients with subarachnoid hemorrhage (SAH) from a ruptured aneurysm have been acutely operated on within the first 72 h in the Neurosurgical Clinic of the Medical School of Hannover. Between 1979 and 1983 327 patients were admitted with definite clinical SAH. In 256 (78%) an aneurysmal malformation could be established angiographically. Fifteen patients (4.6%) died before surgical intervention. Of the remaining 241 patients (73.7%), 88 (36.5%) underwent early surgery and 153 (63.5%) late surgery (Table 1).

Table 1. Glasgow Outcome Scale

I	Good recovery: patient can lead a full and independent life with or without minimal neurological deficit
II	Moderately disabled: patient has neurological or intellectual impairment but is independent
III	Severely disabled: conscious patient but totally dependent on others to get through the activities of the day
IV	Vegetative survival
V	Dead

Referring to the Glasgow Outcome Scale, 55 (62.5%) of the early operated patients could be classified as grade I at the postoperative follow-up 6 months later. One hundred and three late operated patients (67.3%) achieved this postoperative result. Altogether, 158 (65.6%) patients were classified as grade I.

Questions

1. Which psychological alterations do patients show who were classified as grade I on the Glasgow Outcome Scale?
2. What is the situation regarding occupational rehabilitation in this group of patients?
3. Are there different results in early and late operated patients?

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Patient Random Samples

Of the 158 patients, 44 have been examined:

Sample

23 male	= 52%	102 male	= 43%
21 female	= 48%	139 female	= 57%
17 early op.	= 39%	88 early op.	= 36.5%
27 late op.	= 61%	153 late op.	= 63.5%

Mean value of time after operation: 3.5 years; range 2-5.5 years.

The Psychological Methods

1. The patients underwent a "structured interview." Systematically the following points were discussed: general condition, description of pre- and postoperative job situation, present complaints.
2. Patients were asked to mark on a time scale from which point after the operation their condition showed no further improvement.
3. On a scale patients were asked to indicate their postoperative physical and mental ability in relation to their preoperative situation.
4. The psychometric tests included the following parameters: memory (with special regard to short term memory), ability to concentrate, and quick reaction.

4.1 ZVT - Zahlenverbindungstest (number sequence test) according to OSWALD and ROTH (7) is a simple test in order to establish the ability to concentrate, the "speed of reaction," and an idea of the general intelligence.

4.2 DCS - Diagnosticum für Cerebralschädigung (diagnosticum for cerebral damage) according to WEIDLICH and LAMBERTI (8) for recording the visual memory and concentration. The test is also used to discriminate the potential reason for dysfunction (neurotic vs physical).

4.3 Test to establish the speed of learning or short-term memory - TÜLUC (Tübinger Luria-Christensen-Neuropsychologische Untersuchungsreihe) (4). The formula for the test was established by ourselves. The test consists of ten words used in everyday life and a nine digit telephone number. The results of the sample were compared with the results of patients from the Neurosurgical Clinic who were treated for lumbar disc problems.

5. With the FPI (Freiburger Persönlichkeitsinventar (2)) the following important comparisons regarding personality could be made: satisfaction with everyday life, social norms, performance orientation, inhibition, excitability, aggression, stress, physical complaints, health worries, extraversion, emotionality.

Although the tests were selected for their practicality the examination lasted about 2-5 h. Other similar examinations have employed more complicated and large-scale test methods (1, 6).

Results

Ad 1. In all tests the sample's gain in mean value was clearly below average values. In comparison to the disc patients a highly significant difference was present.

All psychological data and self-evaluation data were listed and evaluated. Patients were attached to a remission group in accordance with their psychological conspicuousness.

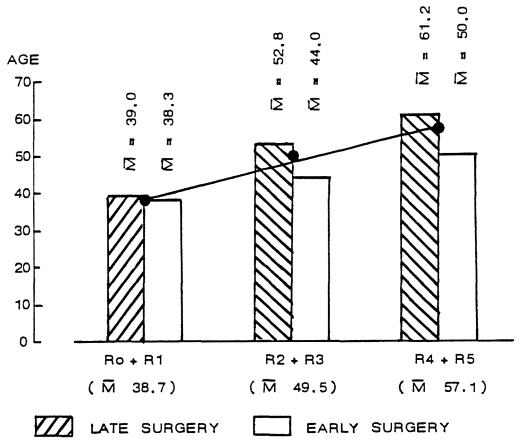

Fig. 1. Overall results in relation to age of surgery. $R_0 + R_1$ = full remission; $R_2 + R_3$ = clear conspicuousness; $R_4 + R_5$ = severe conspicuousness endangering rehabilitation

Group R_0 represents full remission without any conspicuousness; R_5, remission with severe conspicuousness. As illustrated in Fig. 1, age at the time of surgical intervention was a predictor of remission grading.

Self-description, test results, and the personality questionnaire revealed the following disturbances: memory disturbance 90%, physical weakness 85%, lack of concentration 75%, changes of mood 70%, emotional instability 60%, diminished tolerance 55%, increased need for sleep, awkwardness, health worries, low level of life satisfaction, and voracity.

Ad. 2. Judgment of occupational rehabilitation had to be based on the background of the job market. Of all 55-year-old and older patients, 90% had to go into early retirement regardless of their postoperative recovery. Excluding from this study the group of housewives (9 patients) and one preoperative pensioner, 34 patients remained for review: 12 patients (3 early, 9 late) had to take early retirement (35%); 6 (2 early, 4 late) worked postoperatively on reduced hours (18%); and 12 (6 early, 6 late) worked under the same or similar conditions as before (35%). Four patients (12%) lost their job postoperatively or did not take up their job again for different reasons.

Ad 3. Of the 44 patients examined, only 10 (22.7%) achieved full remission: they completely fulfilled the criteria of grade I of the Glasgow Outcome Scale. Among these were four early and six late operated patients. Twenty-four patients (54.5%) showed clear conspicuousness either in the test results or in their self-description. Ten patients (22.7%) showed severe impairment in nearly all tested areas (Fig. 2).

There was no significant difference between early and late operated patients in any of the three groups.

Discussion

From a recent clinical study (6) it has been suggested that early aneurysm surgery might be an additional trauma to the brain which has already been severely injured by SAH, and may lead to permanent disturbances of mental qualities even in patients with a good surgi-

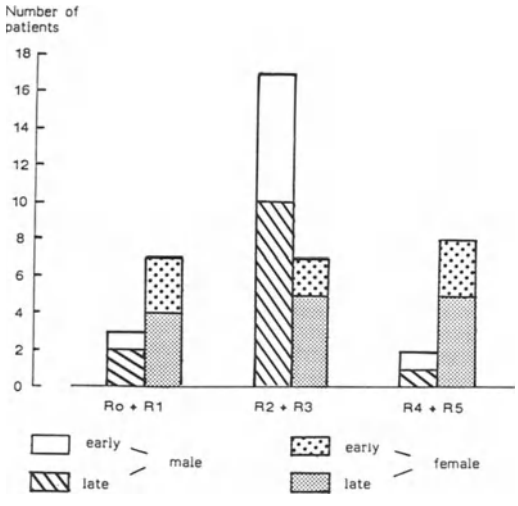

Fig. 2. Remission groups. Abbreviations as for Fig. 1

cal outcome. Our results do not support this thesis. In fact, early operated patients seem to recover quicker than late operated patients. However, it can be verified that the age of the patient at the time of SAH and surgical treatment substantially determines the grade of recovery.

In order to achieve a more adequate classification of patients postoperatively we propose the discussed tests because better rehabilitation might be possible on the basis of these complementary postoperative data. The study also shows that the Glasgow Outcome Scale might not be sensitive enough for profound postoperative evaluation, especially regarding mental disturbances and individual rehabilitation.

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Plasticity of the Brain After Extensive Cerebral Infarction: Report of a Case and Discussion

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The following case is intended to illustrate the exceptional extent to which neuroplastic processes are possible in the mature central nervous system.

Case Report

In 1969, a 28-year-old male was involved in a traffic accident and suffered injury to the visceral cranium. After 8 months completely free of symptoms, this right-handed patient suddenly had an infarct in the left hemisphere with global aphasia, high-grade hemiparesis, hypoesthesia, and hyperpathia on the right, as well as recurrent jacksonian seizures.

Carotid angiography (Fig. 1) revealed a traumatic aneurysm of the left internal carotid artery below the base of the skull as the cause of this embolic cerebral infarction. Cerebral embolism due to aneurysms of the cervical segment of the internal carotid artery have been described previously (1, 2, 10, 11). Moreover, a distinct postembolic rarefaction of the left branches of the middle cerebral artery was shown on angiography.

Cerebral CT scanning (Fig. 2) in 1980 showed an extensive complete cerebral infarction in the area supplied by the left middle cerebral artery. Despite the unfavorable prognosis, especially of such a large embolic infarction, progress control showed continuous regression of the neurologic deficit over a period of years, i.e., even long after the critical time limit of 3 months (8). The global aphasia largely regressed over a period of months, but the regression was only complete after 5 years.

The patient was initially unable to walk, but now displays normal strength in his right limbs. His gait is entirely normal. The fine motor activity is undisturbed, even including the writing style. Only a discrete tendency to pronation and right emphasis of the deep tendon reflexes throughout were found neurologically.

On the other hand, a hemihyperpathia on the right side progressed over the course of the years. Finally, the patient was impaired to such an extent by this condition that a stereotactic hypophysectomy was carried out.

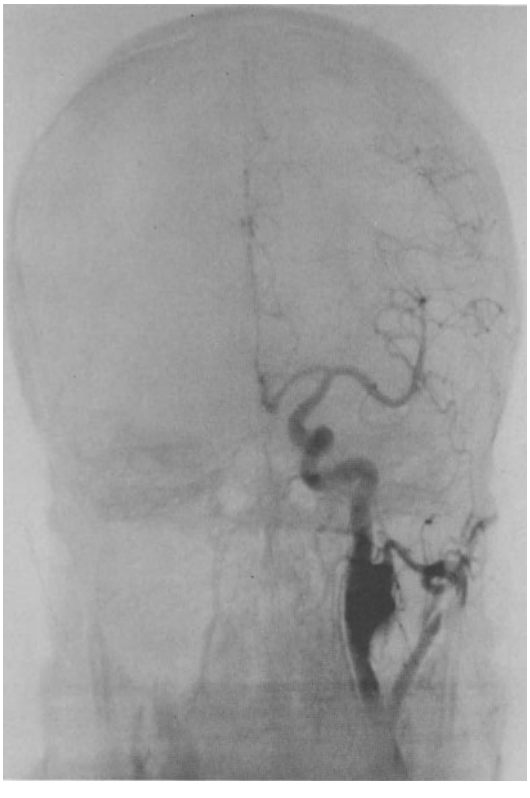

Fig. 1. Left carotid arteriogram demonstrating traumatic aneurysm of internal carotid artery. Note post-embolic rarefaction of left middle cerebral artery branches

Discussion

The excellent recovery from global aphasia cannot be explained solely by premorbid inverse representation of the speech center, but displays pronounced processes of plasticity extending over years, including activation of homotopic areas of the right hemisphere (4, 5, 6).

The motor restitution processes are most likely explained by functional substitution of pyramidal tract systems which had been lost, by pyramidal fibers running ipsilaterally to the paretic side (3, 6, 7). The degree of recovery in extensive cortical lesions as in this case would accordingly sometimes depend on as intensive as possible an activation of nondecussating pyramidal tract fibers. Moreover, the development of nervous facilitating processes within the damaged hemisphere is conceivable.

The hyperpathia is attributable to a lesion of the thalamoparietal radiations due to the infarct (9). The progression of the hyperpathia might be attributable to an improvement in function of the pain-processing system, and thus to neuroplastic processes.

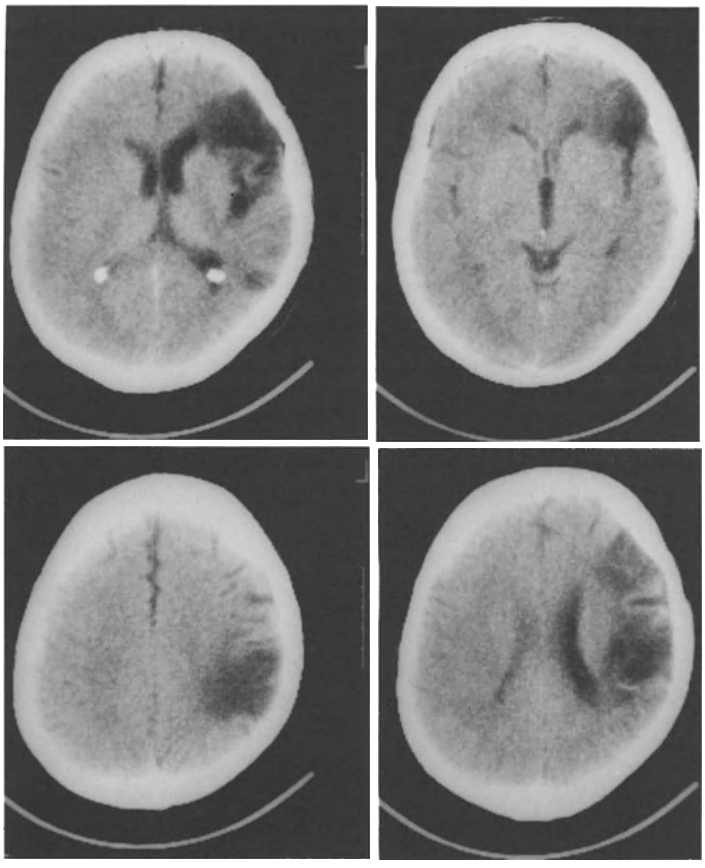

Fig. 2. CT scan 11 years after embolic infarction in the left middle cerebral artery territory

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Autogenic Training as a Means of Early Rehabilitation of the Nucleotomy Patient: A Model Showing the Integration of Autogenic Training into the Patient's Neurosurgical Treatment During His Hospitalization

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The effects and physiological changes attainable through the standard exercises of autogenic training, as they are postulated by J.H. SCHULTZ, have been studied and set on a broad scientific basis (10). The relevant physiological changes achieved by autogenic training in regard to the nucleotomy patient are a decrease in muscle tension and an increase in blood supply in intentionally selected body regions (6, 7). Autogenic training as a useful method of dealing with chronic pain patients will not be further discussed in this paper (2, 13).

As long ago as 1975 BENSON proved that various relaxation techniques, e.g., autogenic training, progressive muscle relaxation, hypnosis, Zen, yoga, and other kinds of meditation, produce similar physiological responses, such as decreasing oxygen consumption, decreasing blood pressure, decreasing muscle tension, and an increase in alpha waves in EEG (1). A number of experimental studies focusing on changes in blood flow and body temperature have been reported (4, 6, 12). The first standard exercise - a passive concentration on heaviness of the limbs - brings about a variety of bodily changes within a very short time, mainly feelings of relaxation, warmth, and heaviness (9, 10).

In contrast to rehabilitation centers, where relaxation techniques are being taught to nucleotomy patients for 3-4 weeks, surgical units rarely employ autogenic training during the patient's hospitalization. Its application, however, is repeatedly reported in inpatients suffering from somatic pains (3, 7, 10, 15). This article presents a model showing how autogenic training can be integrated into the standard treatment plan for nucleotomy patients during their 1-week stay in a neurosurgical hospital.

The gradual introduction of autogenic training is divided into three stages. Each stage is followed by a careful evaluation, the results of which are taken into consideration in the planning of the next stage stage. This procedure ensures that autogenic training, once applied according to a sophisticated plan, will subsequently be accepted by the patients, that it will show the expected effects, and that it will fit into the daily or weekly timetable of the surgical unit without hindering routine work.

In stage 1 the application of autogenic training takes place once a week for only 30 minutes. In small groups of three to nine, the patient is given a short introduction into the method of autogenic training and is taught the first standard exercise. After a short practice phase he is encouraged to share and discuss the experienced sensations with the other trainees and to ask questions. Back on the ward, each patient does his exercises by himself.

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In stage II the number of trainers increases. Therefore more patients can benefit from autogenic training. The teaching sessions take place more often a week. Additional teaching material, such as timetables and instruction papers, is provided. A comparison with matched controls should take place.

After a thorough evaluation of the results, the autogenic program is offered to all patients: stage III. Research work have to ascertain whether autogenic training has additional long-term effects, i.e., whether it improves the overall outcome of the surgical treatment of nucleus pulposus prolapse.

First results: from March to August 1985 76 patients were taught the first standard exercise in the neurosurgical hospital of Würzburg (FRG). Five persons had already had basic knowledge of relaxation techniques. Eighteen patients attended the introductory session repeatedly. Table 1 shows the distribution according to sex and age. Sixty-six patients practiced on the ward (Table 2), 52 of them at least once a day. The compliance rate of 86% is relatively high. The individually experienced effects regarding feelings of heaviness, warmth, and relaxation are presented in Table 3: relaxation ranked highest with 92%, followed by heaviness with 72%; warmth appeared in 48%.

Other autogenic discharges are listed together with their frequency in Table 4. Outstanding are intruding thoughts (n=50), tingling (n=42), difficulties in concentration (n=32), circulatory sensations, (n=20), and borborygmus (n=20). Really disagreeable feelings were reported only seven times during the investigation period.

Table 1. Distribution according to sex and age of 76 patients taking part in autogenic training

	Female	Male	Total
Patients	41	35	76
Average age	40.28	43.53	41.90
Std. dev.	8.82	9.73	9.12

Table 2. Individual features concerning training conditions (n=76)

	Female	Male	Total
Participation before operation	4	3	7
Repeated participation	12	6	18
Previous knowledge	3	2	5
Practicing on the ward	37	29	66

Discussion

The effects reported by the patients who attended our tuition of autogenic training coincide with the literature on the subject (5, 8, 9, 10). The usual side-effects, called autogenic discharges, decrease the longer autogenic training is practiced (5, 9). Because of the high

Table 3. Frequency of feelings of relaxation, heaviness, and warmth during the first standard exercise of autogenic training (n=76)

	Female	Male	Total
Relaxation	38	32	92%
Heaviness	30	25	72%
Warmth	20	17	48%

Table 4. Autogenic discharges during the first standard exercise of autogenic training (n=76)

Autogenic discharges	Total no.
Intruding thoughts	50
Tingling	42
Difficulty in concentration	32
Circulatory sensations	20
Feelings of tension and swelling	20
Borborygmus	20
Sleeping	12
Motor discharges	10
Floating	7
Dizziness	5
Feeling of detachment	5
Increased salivation	5
Twitching of eyelids	4
Pain-like sensations	3
Disagreeable heart sensations	2
Itching	2

compliance rate and the satisfactory results in the first stage of the model, stage II was started in December 1985 so that now six trainers teach autogenic training for half an hour three times a week. Up to now 187 out of 850 nucleotomy patients have received an introduction into the relaxation techniques of autogenic training.

Advantages of such relaxation techniques are that, firstly, the costs are kept relatively low due to group tuition, and secondly, it is a mental device which supplements medical treatment in reducing muscle tension and increasing blood flow. Compared with surgical or pharmacological intervention, harmful side-effects are negligible.

Possible disadvantages are the difficulties in obtaining objective data on the actual physical effects during clinical routine and the dependence on the patient's readiness to learn and regularly practice autogenic training, which is subject to his individual personality structure.

Up to now the results and experiences during clinical application of autogenic training show that relaxation techniques are a promising additional method in the routine treatment of the nucleotomy patient.

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Early Results of Systemic Extension Therapy in Patients with Herniated Lumbar Discs and Similar Conditions

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Introduction

The degenerating intervertebral disc within its spinal segment is softened, narrowed, and deranged. It may protrude or prolapse toward neural structures. The intervertebral foramen and the spinal canal may be narrowed (1-3). The spinal segment in question may become destabilized and is then subjected to temporary or constant asymmetric strain, possibly resulting in subluxation and laterolisthesis (Fig. 1).

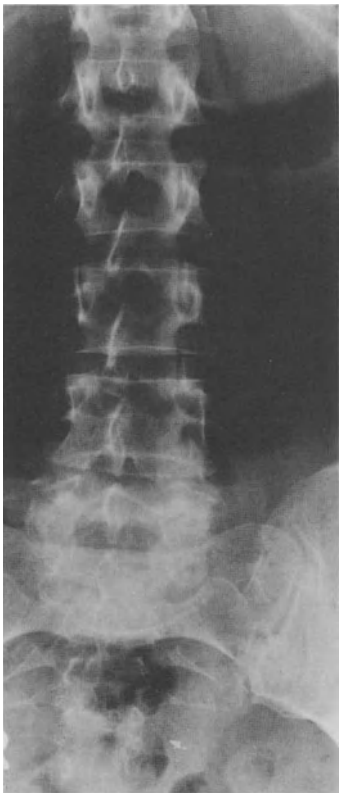

Fig. 1. Anterior X-ray of lumbar spine in a 41-year-old woman: Degenerate segment L4/5 is lowered and unstable with laterolisthesis to the left, resulting in slight rotation scoliosis of the spine. Osteoporosis is noted. Complaints were lumbosacral pain with alternating left and right sciatica under stress and strain, which was improved by rest and by extension therapy. There was no neurological deficit

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To compensate for these deficiencies, the following treatment steps seem necessary in sequential order:
1. Elongation by lengthening
2. Symmetrization
3. Stabilization
4. Mobilization

These principles appear valid for conservative and postoperative treatment alike. For operative cases it should be kept in mind that every disc operation creates a wound within and applies trauma to the spinal segment, excavates the disc space to a greater or lesser degree, and thus may increase segment instability.

Material and Methods

In this series, 250 hospitalized patients (193 after microneurosurgical lumbar operations, 57 with conservative therapy) were treated by daily physiotherapeutic application of short-term lengthening (5 s) of the lumbar spine, allowing the body to hang suspended by the hands from a bar rack (in German: *passiver Aushang*), followed by prolonged (up to 15 min) intermittent traction in a 20°-30° head-down position with fixed feet on an inclined board (in German: *schiefe Ebene*). Each individual treatment was registered and documented as to its effect: beneficial, no effect, or deleterious. The total result was summarized at the end of the hospital stay in four categories: no more symptoms, much improved, unchanged, worsened.

Bar rack lengthening and inclined board traction were applied to fulfill the first two principles of treatment as postulated above: elongation and symmetrization of the lumbar spine. These physiotherapeutic measures were to be continued daily by the patient after being discharged.

The patient groups included are shown in Table 1.

Results

The early results of the treatment are published here. It is intended that the late results in the same patient groups will be published at a later date.

Operated patients left their bed on the 1st postoperative day and walked with assistance. The application of spinal column lengthening and extension measures was begun on the 7th postoperative day in operated patients and on the 1st day after admission in patients with conservative treatment. This form of treatment was generally *tolerated well* by almost all patients, including the operated patients: only 10 out of 193 operated patients (i.e., 5%) definitely refused continuation of these measures after primary or repeated trials, usually because of increased lumbar pain and less often because of increased radicular pain.

The results are shown in Table 2.

Table 1. Patient groups

Microneurosurgical disc operation (n = 193)[a]		Conservative treatment (n = 57)		
Disc prolapse	45%	Lumbar sciatica		52%
Disc perforated	40%	Lumbago		22%
Recurrent disc with adhesions	18%	Postoperative residual pain		9%
Hypertrophy of ligamentum flavum	26%	Fracture of lumbar vertebra		9%
Lateral recess stenosis	15%	Spondylolisthesis	1 patient	8%
Segmental stenosis	9%	Disc, operation refused	2 patients	
Osteoporosis	13%	Others	2 patients	
Spondylolisthesis	4%			
Others	2%			

[a] Percentages add up to more than 100 because of patients with more than one condition

Table 2. Results

Patients with microneurosurgical disc operation (n = 193) Extension therapy end result (%):	No more symptoms	Much improved	Unchanged	Worsened	
Disc prolapse	32	52	10	6	
Disc perforated	23	58	13	6	
Recurrent disc with adhesions	24	40	24	12	!
Hypertrophy of ligamentum flavum	31	49	14	6	
Lateral recess stenosis	21	39	36	4	!
Segmental stenosis	28	44	22	6	
Osteoporosis	30	62	4	4	
Spondylolisthesis	43	43	14	-	
Patients with conservative treatment (n = 57) Extension therapy end result (%):	**No more symptoms**	**Much improved**	**Unchanged**	**Worsened**	
Lumbar sciatica	33	56	11	-	
Lumbago	31	31	31	7	
Postoperative residual pain	20	40	40	-	
Fracture of lumbar vertebra	20	20	40	20	

Discussion

From the results, it is important to note that among the different conditions of segmental degeneration, operated recurrent disc patients (! in Table 2) and operated patients with lateral recess stenosis (! in Table 2) were improved less frequently (about 60%) than other operated patients. It is suggested that the cause may be that adhesions and lateral recess stenoses are not being sufficiently decompressed by extension procedures alone.

On the other hand, the positive effects of these procedures in some 75%-90% of all other conditions, especially osteoporosis and spondylolisthesis, are stressed. In general, results were better in the operated than in the conservatively treated patients.

Summary

1. Extension therapy is a beneficial form of physiotherapy in degenerate lumbar spine conditions.
2. It is innocuous in conservative as well as in early postoperative treatment.
3. It should be applied more often to teach patients to continue these forms of therapy by themselves after being discharged home.
4. Early improvement is seen in 75%-90% of operated patients with lumbar discs, hypertrophy of ligamenta flava, osteoporosis, and spondylolistheses. It is less effective in bony segmental and spinal stenoses and lateral recess syndromes, and in recurrent operated discs with adhesions.
5. It is suggested that *continuous regular application* of these measures may constitute a substitute for chemonucleolysis in a number of patients with soft disc disease of the lumbar spine.

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Post-traumatic Syringomyelia: Results of Seven Shunt Operations in the Light of Pre- and Postoperative MRI Findings

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The enormous increase in the life expectancy of paraplegic individuals during the last 20 years has led to a relatively high rate of late complications. The published cases increased between 1959 and 1986 from 10 to 403. In 1985 ROSSIER et al. (29) reported an incidence of 3.2% and in the subgroup of complete quadriplegic patients even 8%.

When MRI was developed it at once became the best method in the diagnosis of syringomyelia (12, 13, 14, 19). In the literature we found 122 reported cases of MRI findings, but no systematic studies of *postoperative* cases (1, 3, 8, 9, 12, 15-22, 31, 33, 34).

During the last 2 1/2 years we have operated on seven patients with post-traumatic syringomyelia and were able to investigate six of them postoperatively with MRI, sometimes repeatedly. Besides the expected collapse of the syringes, which correlated well with improved clinical condition, we documented (1) a catheter-introduced cord tethering, a complication which has not been descibed previously, and (2) an additional arachnoid cystic structure which had to be shunted. We also disproved the popular opinion that small syringes could not profit from operation (29, 38, 39).

As Tables 1 and 2 show, the time of onset of *new* symptoms varied from 4 months to 18 years; these symptoms included the typical syndrome with pain in the neck and shoulder, sometimes provoked by coughing and sneezing, segmental dissociated sensory disturbances in four cases affecting the trigeminal nerve territory, and atrophic pareses of the upper limbs (5-7, 28).

Six of the seven patients improved: two showed complete remission, two extensive remission, and two fair results. Case 6, who was operated on twice without permanent stabilization in another clinic, showed further progression.

Pain is best influenced as reported elsewhere (4, 36). Myelotomy is performed via a median approach through the fasciculus medialis, which is without function in paraplegic patients.

We were not able to use the most promising technique of intraoperative spinal sonography, which is useful in detecting the size of syringes and in controlling complete intraoperative collapse, and which is reported to be superior to MRI in discovering septa and very small cysts (10, 12, 23, 26, 27, 30).

Case 1: A large syrinx (C2-T8) was firstly successfully drained to subarachnoid; a sneezing attack induced a recurrence, but there was

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Table 1. History, length of latency, and *new* symptoms

Case, age at accident	Latency	Level of spinal cord injury	Pain	Dissociated sensory disturbances				Atrophic pareses of upper limbs	Vegetative	Cranial nerves
				Therm.	Alg.	Aesth.	Pall.			
1 24 yr	8 yr	T11 incomplete	++	(+)	(+)	+	-	+++ left + right	Horner	-
2 26 yr	4 month	T4 complete	++	++	++	+	-	++ right	-	-
3 20 yr	7 yr	C6 left C7/8 right	++	++	++	+	-	++ right	Horner Hyperhidrosis	
4 11 yr	7 yr	T8 complete	++++	+++	+++	++	+	+ right	Horner Scoliosis	V 1-3 r.
5 25 yr	3 yr	T12 complete	+++	++	++	+	-	+ left	-	V 1-3 l.
6 34 yr	5 yr	T5 complete	+++	+++	+++	+	-	+++ left + right	Horner Arthro-pathy	V 1-3 l. X l.
7 20 yr	18 yr	T4 complete	+++	++	+++	+	-	++ left + right	-	V 1-3 l. XI l.

Table 2. Pre- and postoperative MRI findings

Case	Preop. finding Syrinx from ... to ...	Shunt to ...	Result after 3 months			Postop. MRI finding	Follow-up
			Pain	Sensory	Motoric		
1	C1/2-T8 (CT-assisted myelography)	Subarachnoid	++	=	+	Collapsed	After 6 months improvement, recurrence
	MRI after recurrence: syrinx refilled	Peritoneal	++	=	+	Collapsed Cord tethering	After 6 months new kind of neck pain with lower intensity; after 1 year very slow progression
2	C5-T1 (CT assisted myelography)	Subarachnoid	+++	+++	+++	-	Complete remission for past 2 years
3	C5-C7	Subarachnoid	+++	+++	+++	Collapsed	Complete remission for past 14 months
4	Medulla-T8	Subarachnoid	+++	++	+	Collapsed ventral arachnoid Cyst?	At first good remission. After 5 months recurrence; after arachnoid-peritoneal, shunt, extensive remission
		Arachnoid peritoneal	+++	++	+		
5	C1-T11	Subarachnoid	+++	+	+	Collapsed	10 months extensive remission
6	Foramen magnum-T4	Peritoneal (3rd op.)	(+)	=	=	Unchanged	2 months improvement, then progression. Trigeminus improved.
7	C2-T4 Septa?	2 x subarachnoid	+++	+	=	Collapsed	Free of pain, slow motoric improvement in spite of syringomyelia for 13 years

renewed improvement after peritoneal shunting. After 6 months there was onset of another kind of lower level pain in the neck, dependent on flexion and moving. After arrest of progression for 1 year, a very slow decline ensued. MRI showed the sufficiently drained cervical syrinx and lower, at the level of laminectomy, a classical *cord tethering* which we regard as the probable cause of the current myelopathy.

In the 1005 cases of operated syringomyelia reported in the literature we found no comparable complication. Given the nature of the cervicothoracic junction, it is evident that a rigid catheter may cause an unphysiological fixation and finally tethering of the cord.

Case 4: A haustrated syrinx extending to the medulla was drained to subarachnoid. There was arrest of lancinating pain in the neck and occiput, and extensive remission. Five months later pain and ascending sensory disturbances reappeared. Control MRI showed a cervical collapsed syrinx; in fact the ventral subarachnoid space was extraordinarily extended. Unfortunately myelography was not permitted. We assumed there was a blockage of arachnoid CSF flow or a cyst; therefore we drained from subarachnoid to peritoneal. Clinical remission followed.

Cases 2 and 3: The two patients with the less extended syringes showed the best results, with complete remission and freedom from pain.

The problems of the diagnosis of syringomyelia can be solved by MRI, CT-assisted myelography, and high resolution intra- and postoperative sonography.

Since 1981 drainage operations, sometimes in combination with cordectomy, have resulted in improvement in 61% of patients and prevented further progression in 23%; 16% worsened in spite of surgery (Table 3).

We consider shunt operation to be a useful method in cases of syringomyelia, although it is still undergoing improvement.

Table 3. Syringomyelia: operations performed between 1981 and 1986 (selection of comparable studies)

Year	Authors	Cases	Operative methods
1981	Philips et al.	4	Syringo-peritoneal shunt
1981	Pecker et al.	4	Syringo-peritoneal shunt
1981	Shannon et al.	13	Myelotomy 10 x, cordectomy 3 x
1982	Tator et al.	20	Syringo-subarachnoid shunt
1984	Barbaro et al.	39	Syringo-subarachnoid shunt 15 x, syringo-peritoneal shunt 19 x, myelotomy 2 x, combination with craniocervical decompression 7 x
1984	Alvisi et al.	26	Marsupialization
1985	Steven et al.	27	Syringo-subarachnoid shunt 11 x, syringo-periotoneal shunt 12 x, myelotomy 4 x
1985	Suzuki et al.	29	Syringo-peritoneal shunt
1986	Lesoin et al.	8	Syringo-peritoneal shunt
		165[a]	

[a] 69 post-traumatic

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Early Rehabilitation in Neurosurgery: Summary and Future Prospects

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The term rehabilitation is usually restricted to describe social security aspects of medical reintegration into the vocational and social environment. In reality rehabilitation means more than that. It is derived from the Latin word *habilitare*-to enable. This means that it should be initiated sooner than at present, i.e. in the form of early rehabilitation in the emergency department, including the intensive care unit.

Rehabilitation in the speciality of neurosurgery includes all of the nervous system, i.e., skull and brain, spinal cord, and peripheral nerves. The neurosurgeon therefore cannot withdraw from this task and believe himself to be responsible for "operative procedures" only. If as a neurosurgeon I start with a capital "A," I will have to continue with a capital "B" which is looking after the further recovery of the patient. Most departments of neurosurgery have instituted an excellent follow-up of spina bifida and hydrocephalic children. Early rehabilitation in all other diseases is far from satisfactory. The concepts of rehabilitation as practiced in some areas tend to neglect patient-oriented care. This is why MILLER and PENTLAND in their chapter emphasize the insufficient number of acute neurotraumatological rehabilitation units when reporting on the Edinburgh center. The importance of providing early rehabilitation beds was also mentioned in BUSCH's paper from Gailingen.

The presentation by FROWEIN and HAAR of the outcome of rehabilitation in previous years clearly shows that new concepts will lead to considerable improvement. Several papers showed that during the early phase necessary measures are not duly considered, such as speech therapy (LINCKE and DURWEN) or observation of the risk of epilepsy (SCHULTZ and THORBECKE). STOLKE et al. emphasized the value of psychological tests.

In his presentation at the meeting, FÖRSTER, from the point of view of social insurance for occupational accidents, mentioned the November 1974 memorandum for the improvement of rehabilitation of the severely head injured. There are three stages:

1) Resuscitation, transportation, and acute therapy
2) Further rehabilitation following acute or postacute therapy
3) Vocational rehabilitation

Early rehabilitation is to be considered as neurological and psychiatric acute care (stage 1b). The neurosurgeon required for this task is not mentioned. Thus early rehabilitation does not lie in the hands of those primarily concerned with the patient's care.

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To improve results early rehabilitation must begin with intensive care. We have to overcome arbitrary frontiers imposed for reasons of organization. Only after completion of phase 1b), or early rehabilitation, should phase 2), or later rehabilitation in an adequate center, be instituted to prepare the patient for reintegration into family and job. Demands on beds in a neurosurgical intensive care unit, however, frequently require early return to a general surgical department from which the patient was referred. This carries a major risk. Both the hazzards of transportation and discontinuation of intensive care measures frequently lead to the patient being referred back to neurosurgery, often as an emergency, or to the patient's death. Therefore early stage 1b) treatment is only possible in close association with a neurosurgical department or, as a compromise, close to this unit.

A far better solution is undoubtedly to institute beds for this phase of treatment with sufficient equipment within the neurosurgical departments. The Edinburgh unit is an example in the United Kingdom (cf. MILLER and PENTLAND). This approach is the most economical as well. The institution of adequate early rehabilitation units associated with the departments of neurosurgery in sufficient numbers is one of the most important tasks in the future therapy of head injuries.

The establishment of rehabilitation centers far away in the country must be considered medical mismanagement if a reasonable and efficient reintegration is to be achieved with the help of relatives. To achieve this aim as early as possible, other institutions concerned with rehabilitation, i.e., the social security authorities concerned with occupational accidents, the Federal and Länder Social Insurance Boards, and the CNS Board, have to be involved.

We intend to extend cooperation in the future. Practical concepts toward this aim are originating in the field of neurosurgery, and our joint efforts should be successful in achieving it.

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Surgery in and around the Brain Stem and the Third Ventricle

Edited by M. Samii

1986. 370 figures. XXIII, 599 pages.
ISBN 3-540-16581-9

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Every neurosurgeon should record the difficult or unusual cases he encounters in his practice. Dr. Sugita's precise documentation of 100 technically difficult microneurosurgical operations more than does justice to this precept. This selection includes the unsuccessful cases as well, since, in the author's own words, "they taught me more than the successful ones". Each case is color illustrated by the author, with pre- and postoperative x-rays and brief operative notes complementing the hand-drawn illustrations. Each case also exemplifies the use of neurosurgical instruments which have contributed to the improvement of surgical results in various procedures.

The style of this beautiful atlas, a kind of surgical diary, will help familiarize the reader with new refined operative techniques and be of particular interest to all working in this field.

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