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Preface

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

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

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

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

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

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

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

regarded as standard. Our aim throughout is to promote contacts among neurosurgeons in Europe and throughout the world neurosurgical community in general.

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

The Editors

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A. Advances

Proton Spectroscopic Imaging in Cerebral Ischaemia
Where we Stand and What Can be Expected

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Introduction

Cerebrovascular research is traditionally focused on the effects of changes in blood flow on neurological function. With the improvement of technical developments it became possible to correlate local cerebral blood flow (CBF) with focal neurological deficits. From local CBF measurement we learned that perfusion above the threshold of 20 ml/100 mg/min does not

always mean that metabolism and function are still intact. Over the past ten years research interest in cerebral ischaemia showed a gradual shift towards cellular biology and pathophysiology. Changes in brain metabolism were considered to be more important than differences in blood flow. The development of new techniques in vitro and in vivo allowed to investigate many different aspects of cellular metabolism. Positron emission tomography was the first in vivo technique which proved that it was possible to obtain regional metabolic information with an acceptable local resolution. Nuclear magnetic resonance, which was introduced in medical research only fifteen years ago, has become a major tropic in brain research. Actually it has become an entire research field with many aspects, including imaging, angiography, and CBF-, energy metabolism-, and intracellular pH-measurement. Several brain metabolites, among which lactate (Berkelbach v. d. Sprenkel 1988 a), can be studied in vivo with proton nuclear magnetic resonance imaging (MRS). The same technique used for magnetic resonance imaging (MRI), has been developed into a technique to visualize metabolite concentrations in the milimolar range with still improving resolution.

Historical Overview

In 1946 Bloch and Purcell received the Novel prize for their description of the principles of nuclear magnetic resonance. For thirty years the technique was used for structural analysis in biochemistry. The reason why magnetic resonance was considered valuable, was that it is a quantitative technqiue. In the early seventies the first biological applications were described (Hoult 1974). The breakthrough of nuclear magnetic resonance in medicine, which provided general acceptance of the technique came after the first imaging applications (Damadian 1976). In less than ten years the clinical application of MRI was realized and in a few years, MRI became the most powerful diagnostic technique in neurology and neurosurgery. MRI is based on proton magnetic resonance spectroscopy (MRS) of water in an array of very small volumes in the area of interest. The signal intensity of the proton resonance in the spectra, represented as a gray tone, is the basis for the image. Looking at MR-images it seems controversial to state that NMR in principle is a very insensitive technique. However when we realize that the proton concentration in water is about 110 mole/L, it becomes clear that measurements in the milimolar range may be difficult. The resolution of in vivo measurements of brain metabolites is a problem indeed. Therefore research foxused on improvement of spectral resolution. The introduction of the surface coil has been of extreme importance for the development of MRS in experimental brain research (Ackerman 1980). In 1983 a research team at Yale university showed that it was possible to

visualize proton signals in brain metabolites by suppression of the signal evoked by protons in water. Lactate accumulation was demonstrated in several pathophysiological conditions (Behar *et al.* 1983). Several years later localized single point spectra in a patient with cerebral ischaemia demonstrated lactate in the surrounding area of an infarct (Berkelbach van der Sprenkel 1988 b; Bruhn *et al.* 1989). Small amounts of lactate were also demonstrated under physiological conditions during hyperventilation (van Rijen 1989). In time, high field proton MRS in experimental models was developed in a sophisticated research tool (Allen *et al.* 1988; Moseley *et al.* 1990; Bosman *et al.* 1990; de Graaf and Bovée 1990; Houkin *et al.* 1990; van Rijen *et al.* 1991). Clinical applications of proton spectroscopic imaging at 1.5 Tesla are still on their way to become a selective and sensitive technique for in vivo investigation of brain metabolism (Luyten *et al.* 1990).

Methodology of Proton Magnetic Resonance Spectroscopy (MRS)

General Aspects

Protn MRS enables to visualize metabolites in the milimolar range. Assignments using in vitro and in vivo MRS, have been made to aspartate, (phospho)creatine, glutamine, glutamate, alanine, glycine, inositol, taurine, choline, N-acetyl aspartate, GABA and lactate (Petroff *et al.* 1989; de Graaf and Bovée 1990).

Several aspects determine the sensitivity of proton MRS obtained metabolic information. In the first place intrinsic factors. Concerning the magnetic properties of the molecule under investigation, protons have optimal properties for MRS. Protons are for instance 6 times more sensitive for magnetic resonance than phosphorus atoms. In the second place several extrinsic factors play an important role in MRS. The spectral resolution is determined by the peak intensity (metabolite concentration, T 1 and T 2) and the line separation, which depends on magnetic field strength, measurement time and magnetic field homogeneity. The higher the magnetic field, the longer the measurement time and the better the homogeneity, the better the resolution of the spectra. It is therefore clear that more accurate metabolic information can be obtained in experimental high field MRS at 4.7 Tesla than in human studies at 1.5 Tesla, where measurement time is a limiting factor. The resolution is also dependent on the quality of the detection coil. Surface coils have improved the signal-to-noise ratio, but have the major draw-back that quantitative information is lost. The quantitative character, which is so essential for this technique is also lost when pulse sequences with a selective excitation profile are used. These pulse sequences are necessary to suppress the signal of two metabolites with abundant availability in biological systems, that mask the signal of metabolites in the milimolar range: water and fatty acids.

Water Suppression

In order to visualize other metabolites than water in the proton spectrum it is necessary to suppress the water signal which is about 10,000 times stronger than that of the metabolites of interest, that are resonating at a slightly higher frequency. Water suppression can be performed with binomial sequences (Hore 1983), pre-saturation of the water signal by Dante-pulses (Morris and Freeman 1978), dephasing of the water signal after selective excitation (Haase *et al.* 1985) and by adiabatic inversion of the water signal (Luyten *et al.* 1989), thereby continuing the sequence at the moment of zero-crossing of the water resonance (Patt and Sykes 1972).

Fat Suppression

Not only water, but lipid signals in mammalian tissue may obscure the metabolite resonances as well. Editing sequences, using the effect of J-coupling, have been developed to suppress the lipid signal and study single metabolites (Williams 1986). Lipids in myelin can not be visualized since only mobile fractions of fatty acids can be detected by NMR. Fortunately, all NMR visible lipid signal in human brain studies is confined to bone marrow and subcutaneous fat around the skull. By accurate localization techniques the lipid signal may be suppressed completely, resulting in NMR spectra which show several well resolved metabolite signals (lactate) which resonate in the same spectral range as the intense $-CH_2-$ and CH_3-proton from fat.

Localization

Several techniques of localization have been published. The most simple method is localization by means of a surface coil, which has a half spherical sensitive volume with the same radius as the surface coil used (Ackerman *et al.* 1980). If the surface coil is combined with a spin echo sequence a further selection is made of a slice within the sensitive volume of the coil (Bottomley *et al.* 1984). Other techniques use the gradient coils in a way they are used in imaging techniques. By subsequent excitation of three perpendicular slices a volume is selected for proton spectroscopy. The volume is selected on a previously made MRI. The advantage of this technique is that areas with pathological changes can be selected with great accuracy. In the beginning stimulated echo's were used for volume selection (Frahm *et al.* 1987 and 1989; den Hollander and Luyten 1987). The disadvantage of this sequence is that 50% of the proton signal is lost during the sequence. Recently a Carr-Purcell spin-echo volume selection technique (Ordidge *et al.* 1985; Jung *et al.* 1990) has been used which has doubled the sensitivity.

Spectroscopic Imaging

Spectroscopic imaging combines volume selection with two dimensional phase encoding. In this way 1024 volumes with a nominal size of 7 × 7 mm and a section width of 25 mm can be studied simultaneously in 34 minutes (Luyten 1990). Fourier transformations in the two spatial directions and along the chemical shift axis of the metabolite of interest, results in chemical-shift images representing the density distribution of specific biochemical compounds. Metabolite maps of choline, (phospho)creatine, N-acetyl aspartate, and lactate have been reconstructed in this way. By mathematical means it is possible to calculate the ratio between the signal intensity of two metabolites in each volume. This can be represented as an image as well.

Quantification of Spectra

Quantification of proton spectra is a complicated problem. MRS is, as stated above a quantitative technique; after correcting for T 1 and T 2 losses the integral of the peak corresponds to the concentration of the metabolite. However peak height – as well as peak integral – analysis have been used with moderate success. The main problem is that there is a considerable peak overlap of different metabolites in spectra obtained by in vivo MRS at 1.5 Tesla. Incorporating the in vitro obtained prior knowledge about positions, width, and relative amplitudes of peaks into the quantification of in vivo spectra has proved to be useful in achieving reliable results for spectra with several overlapping lines (de Graaf and Bovée 1990).

Pulse Sequence and Computer Analysis

In fact all aspects of proton MRS discussed separately in the previous sections are united in one pulse sequence. The local metabolic information is obtained by subsequent filtering and Fourier transformation of the free induction decay that is assigned to a previously designed area of interest. Especially in the case of chemical-shift imaging the reconstruction is a potential source of methodological inaccuracies that have not all been overcome yet. Recent results of image guided proton spectroscopy and chemical shift imaging in patients with cerebral ischaemia are presented here to demonstrate that lactate accumulation can be observed in acute as well as in more chronic cerebral ischaemia. Chemical shift images of a healthy volunteer are shown to compare with. Evaluation of the spectra reveals that not only lactate but also other brain specific compounds are affected by impairment of the cerebral circulation.

Materials and Methods

H-1 MR Spectroscopic Measurements; Data Accumulation

All proton MR spectroscopic measurements were performed on a 1.5 Tesla Gyroscan (Philips Medical Systems, Best, The Netherlands) at the Utrecht University Hospital. A standard 1-H 30 cm diameter head coil was used for MR imaging and spectroscopy. Axial spin-echo images (TR/TE = 2,000/50, 100 ms) were made to establish the region of interest. A rectangular volume of interest was defined, within the margins of the field of view (FOV), to exclude lipid signals from the skull; typical dimensions were 80 × 80 × 25 mm. The magnetic field homogeneity was optimized over this volume with the proton MR signal of tissue water, measured with the Carr-Purcell double-spin-echo volume selection technique. The typical line width obtained by shimming was 4.5 Hz. Water suppression was done by selective inversion of the water signal, followed by the volume selective spin-echo sequence (TE = 272 ms/TR = 2 s) at the zero crossing of water (Patt and Sykes 1972). For 1-H spectroscopic imaging measurements, volume selection and water suppression were combined with gradient phase encoding in two dimensions. A region of interest was selected as described above, while a field of view for the spectroscopic imaging was chosen to be larger than that of the selected volume (typically 225 × 225 mm). The H-1 MR spectroscopic images were obtained at TR/TE values of 2,000/272 ms. A two-dimensional spectroscopic image was obtained from a 25 mm thick slice over the selected volume with 32 × 32 phase encoding steps and a FOV of 225 × 225 mm, which led to a nominal voxel size of 7 × 7 × 25 mm. Four measurements were accumulated for each profile, which resulted in a measurement time of 34 minutes.

H-1 MR Spectroscopic Measurement; Data Processing

The data were processed by applying Lorentz-Gauss windowing in the time domain (exponential narrowing of 4 Hz and Gaussian broadening of 5 Hz) for noise reduction and spectral resolution enhancement. The water suppression was further improved by the data shift accumulation method (Roth *et al.* 1980). To reconstruct the chemical shift images, zero filling to a 128 × 128 array was applied in the two-dimensional k-domain. Three-dimensional fast fourier transformation resulted in a set of 128 × 128 magnitude spectra. Integration boundaries were selected by visual inspection of the frequency domain spectra. Because of volume selective shimming, the peak positions did not vary more than 10 Hz across the image. Cross-contamination of different metabolite maps was therefore minimized. The spectra were not re-aligned to compensate for spectral inhomogeneity. Metabolite maps were reconstructed for choline, creatine, N-acetyl aspar-

tate, and lactate, by calculating the integral of the three-dimensional data set. The integrals were displayed on a linear gray scale of 128 × 128 voxels to obtain metabolite maps. Conventional MR images obtained previously were used to interpret the metabolic images. Reconstruction of ratio maps was performed by calculating the ratio between integrals from metabolites included, with subsequent processing as described above.

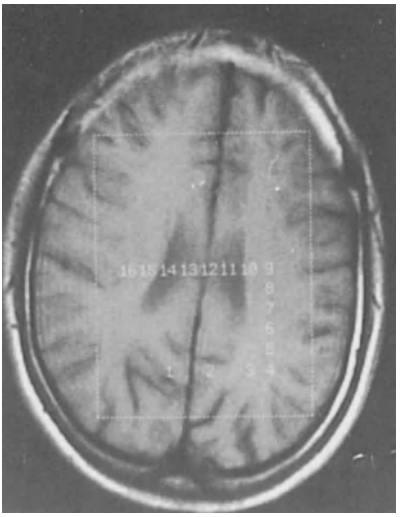
Patient Material

One healthy volunteer was studied in order to demonstrate the differences between normal variation and pathological alterations. Patient G. is a 62 year-old male who was a healthy man until the 22 of November 1990. That day his left leg felt like it slept. The symptoms disappeared but reappeared the next day when he was admitted to the department of Neurology. On examination there were slight pyramidal symptoms of the left leg. On the 29th he had subsequent TIA's with a 10–15 minutes duration, that finally resulted a progressive symptoms. There was a central facial palsy and a slight hemiparesis on the left side. Duplex scanning demonstrated a small vessel wall irregularity of the right internal carotid artery, without haemodynamic significance. On the next day, the proton spectroscopic imaging experiment was performed.

Results

Metabolite maps of the volunteer are demonstrated in Fig. 1. A completely normal MRI is shown with the corresponding volume that was selected for spectroscopic imaging of N-acetyl aspartate, choline, and (phospho)creatine. Figure 1 b shows the spectra from the voxels with corresponding numbers. The spectra show a rather uniform pattern at first sight with N-acetyl aspartate as the main signal and lactate which would appear in the spectrum on the right side of NAA is not visible. For that reason spectroscopic images of lactate are not shown. Figure 1 c shows metabolite maps of NAA, choline, and (phospho)creatine and an image of the mathematical ratio of the choline over NAA singla intensity. In all three metabolite maps the ventricles can be seen easily. It should be kept in mind that the MRI has a slice thickness of 1 cm whereas the spectroscopic images represent a slice of 2.5 cm. A rather homogeneous distribution of the metabolites is observed in the extraventricular area. The representation of the mathematical ratio between NAA and choline concentration shows a uniform image with exception of one artifact close to the left margin of the image.

Figure 2 shows the MRI and the metabolite maps of NAA and lactate in patient G., together with the representation of the ratio between choline and NAA peak integral. The MRI shows distinct changes in the area just



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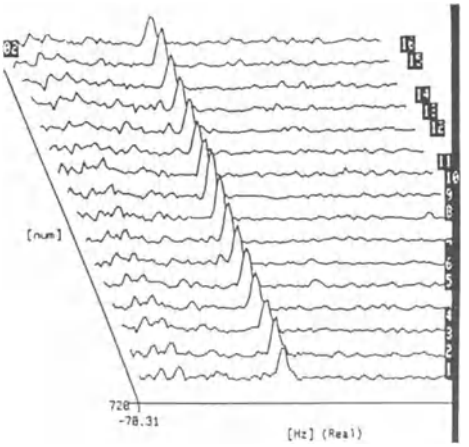

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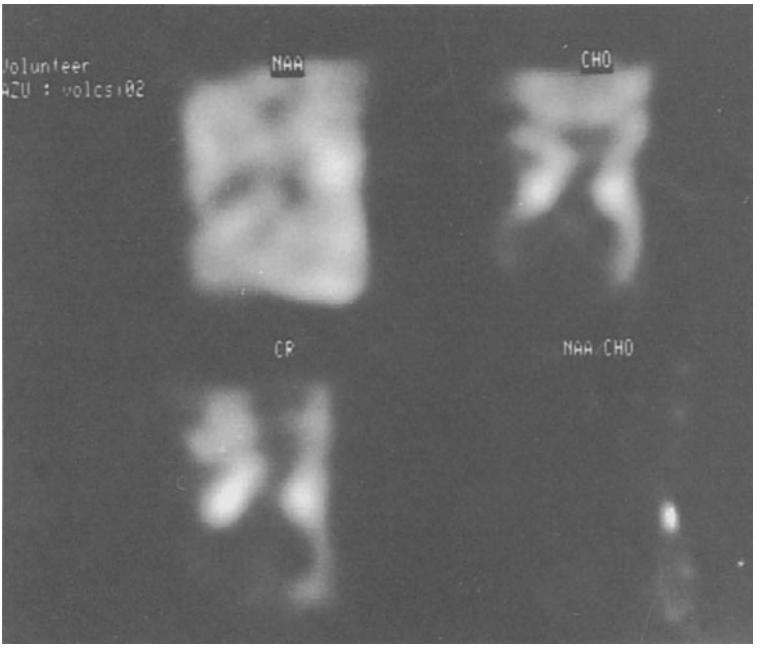

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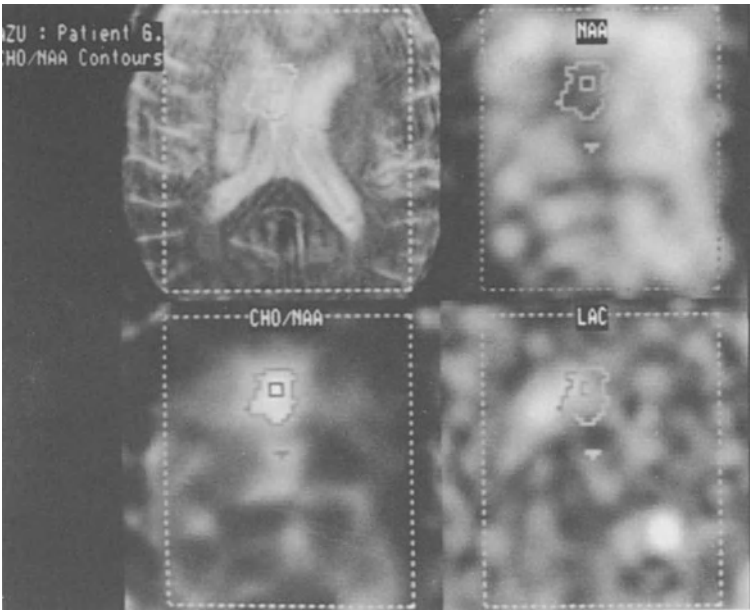

Fig. 2. Proton spectroscopic images obtained from patient G. with a seven day history of a minor paresis of the left leg and a progressive hemiparesis of the left side over the past 24 hours before this examination. The scout MR image obtained with a spin-echo sequence shows distinct abnormalities in the basal ganglia of the right hemisphere. The white box in the MRI corresponds to the selected volume for proton spectroscopic imaging. Metabolite maps of NAA and lactate show changes with a slightly different anatomical distribution (for discussion see text). In order to facilitate the comparison of corresponding metabolic maps, the contour of the area with an increased Cho/NAA ratio is depicted in all images

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Fig. 1. Proton spectroscopic images obtained from a healthy volunteer. a) Scout Magnetic Resonance image obtained with a spin-echo sequence. The slice thickness of the MRI is 10 mm. The white box corresponds to the selected volume for spectroscopic measurement. The white numbers correspond to the spectra from selected voxels. b) Spectra obtained from selected volumes with reference to the MRI. The numbers on the right side of the spectra correspond to the numbers in Fig. 1 a. c) Metabolite maps of NAA, choline, (phospho)creatine, and the ratio between NAA and choline. The slice thickness of the metabolic images is 25 mm. The metabolic information of 32 × 32 volumes of 1.5 cm^3 is represented in images of 128 × 128 voxels. There is a clear reflection of the ventricles, which is most clear in the choline and (phospho)creatine images. Except for one small artifact on the left the representation of the ratio shows no specific inhomogeneity

lateral to the right ventricle. The NAA image shows a decrease of NAA in the paramedian right frontal cortex, overlapping in part with the hyperintense area on the MRI. Furthermore the signal of NAA is less homogeneous in the right hemisphere when compared to the left side. The ratio between NAA and choline is also clearly abnormal in the same area. In order to facilitate the comparison of regional metabolic changes the area where the Cho/NAA ratio is elevated, is projected in all other images. The lactate image shows two areas with an increased signal. The largest area is located between the area with severe changes in NAA/Cho and the cortex. A second area is observed close to the left occipital ventricular horn. At the moment of measurement, the patient had no other symptoms than stated above.

Discussion

The results obtained in this study demonstrate that spectroscopic imaging has become a technique with clinical relevance. The two-fold increase in signal to noise, compared to previous studies (Berkelbach van der Sprenkel 1989 b), was obtained by the use of a spin-echo-instead of a stimulated echo-sequence. Is its now possible to obtain 1024 proton spectra simultaneously with a nominal sensitive volume of 1.5 cm^3 in 34 minutes. Spectroscopic imaging makes quantitative comparison of metabolite concentration possible between different areas in the brain, since spectra are obtained from a similar volume with the same pulse sequence. Absolute quantitative measurement of metabolite concentrations is however not yet possible with magnetic resonance spectroscopy because of the lack of a reference.

With repeated measurement in the same subject a highly reproducible signal is obtained. The interpretation of a decrease in metabolite levels however may be very difficult. An observed decrease could mean several things and can be due to a partial volume effect with the CSF in the ventricle or a real decrease in metabolite level. Besides this, white matter and gray matter may contain different a concentration of the metabolite under investigation. Another possible error can be caused by the fact that lipids from subcutaneous fat and bone marrow have an overlapping resonance with lactate. This makes the choice of the volume of interest crucial.

Proton magnetic resonance spectroscopy has proved to be a powerful technique to investigate physiology and pathophysiology of the brain. In physiological conditions lactate is available in the brain at a concentration below 1 mmol. During hyperventilation lactate was demonstrated in combination with alkalosis (van Rijen *et al.* 1989). In cerebral ischaemia there is a close correlation of lactate accumulation and the pHi (Hope *et al.* 1988; Berkelbach van der Sprenkel 1989 a). Modulation of the serum glucose

level affects the lactate accumulation in a very significant way (Chopp *et al.* 1988; Berkelbach van der Sprenkel *et al.* 1991). Lactate accumulation is the first metabolic escape pathway during ischaemia and is of major interest because it is an early marker of ischaemia, even before permanent damage has occurred (Crockard *et al.* 1987). Lactate however has also been observed in the surrounding area of ischaemia until 18 days after the onset of cerebral ischaemia (van Rijen *et al.* in press). Interestingly the proton spectrum also provides information on damage of neuronal metabolism. NAA has been identified in neurons but not in astrocytes (Nadler and Cooper 1972; Birken and Oldendorf 1989) and the amount of NAA is therefore a marker of metabolism in cortical and subcortical gray matter. A decrease in NAA may reflect a permanent or a reversible neuronal metabolic deficit. Choline is supposed to be a marker of metabolism of membrane structures probably in astrocytes as well as neurons. In old infarcts the level of choline is decreased (Berkelbach van der Sprenkel *et al.* 1988 b), whereas it may be less decreased then NAA during the active process of infarction. The ratio of NAA/choline has proved to be a sensitive parameter to study metabolic damage in cerebral ischaemia, especially during ongoing membrane degradation (van Rijen *et al.* in press).

The results in our patient clearly indicate that the observed metabolic changes show a heterogeneous pattern. These results stress the importance of a high spectral resolution. The lesion observed on the T 2 weighted MRI reflects permanent damage as well as oedema. Changes in NAA and NAA/Cho ratio are observed on the medial aspect of this hyperintense MRI lesion. Lactate accumulation is observed on the lateral aspect of the changes on the MRI, between the basal ganglia and the cortical structures. These results may suggest that there is an ischaemic area in the core with (ongoing) permanent damage. On the lateral aspect of the infarct the lactate level is elevated, which may suggest the existence of a penumbra. With the anatomical distribution of blood vessels in mind, the region where the lactate level is elevated is a watershed area, where the distribution of arterial blood may have been taken over by cortical arteries after occlusion of the perforating arteries.

The meaning of the second area with lactate is not clear; on MRI and CT there were no changes in this area, even on the adjacent MRI slices there were no abnormalities observed. The area might be located in the posterior horn of the left ventricle or in the periventricular white matter. Although it is well known that the lactate concentration is elevated in the ventricle during ischaemia (Prockop 1986), it seems unlikely that a concentration gradient exists in the cerebrospinal fluid.

A visual control of the spectra in this region showed a broad signal, which might in part be due to contamination of the spectra with a lipid signal. A periventricular area with a local alteration of metabolism is

therefore more likely. Damage in this area probably will not cause neurological impairment, as was the case in our patient.

In conclusion, the results of proton spectroscopic imaging are promising. Further improvement can be expected from hard ware developments like an improved coil design and more powerful gradients. Software improvements may enable to eliminate the disturbing fat signal, to improve the processing of the regional spectra and their quantification. It remains questionable whether it will be possible to detect other metabolites in the human brain. The use of the proton spectroscopic imaging technique in animal studies at 4.7–7 Tesla may enable to study metabolic effects of cerebral ischaemia in much more detail. The metabolites currently studied may then be visualized with an improved spatial resolution and other metabolites with a lower tissue concentration may become detectable. Future developments in the field of spectroscopic imaging and magnetic resonance imaging of CBF may prove that it is possible to measure regional metabolite concentrations and blood flow without the use of ionizing radiation.

Abbreviations

MRI Magnetic Resonance Imaging
MRS Magnetic Resonance Spectroscopy
NMR Nuclear Magnetic Resonance
CBF Cerebral Blood Flow
TIA Transient Ischaemic Attack
NAA N-acetyl-aspartate
(P)CR (Phospho)creatine
Cho Choline
TR Repetition Time
TE Echo Time
1-H Proton
31-P Phosphorus

References

1. Ackerman JJH, Grove TH, Wong GG, Gadian DG, Radda GK (1980) Mapping of metabolites in whole animals by 31-P NMR using surface coils. Nature 283: 167–170
2. Allen K, Busza AL, Crockard HA, Frackowiak RSJ, Gadian DG, Proctor E, Ross Russel RW, Williams SR (1988) Acute cerebral ischaemia: Concurrent changes in cerebral blood flow, energy metabolites, pH, and lactate measured with hydrogen clearance and 31-P and 1-H nuclear magnetic resonance spectroscopy. III. Changes following ischaemia. J Cereb Blood Flow Metabol 8: 816–821
3. Behar KL, den Hollander JA, Stromski ME, Ogina T, Shulman RG, Petroff OAC, Prichard JW (1983) High resolution 1-H nuclear magnetic resonance study of cerebral hypoxia in vivo. Proc Natl Acad Sci USA 80: 4945–4948

4. Berkelbach van der Sprenkel JW (1988 a) Functional and metabolic aspects of cerebral ischaemia, Thesis
5. Berkelbach van der Sprenkel JW, Luyten PR, van Rijen PR, Tulleken CAF, den Hollander JA (1988 b) Cerebral lactate detected by regional proton magnetic resonance spectroscopy in a patient with cerebral infarction. Stroke 19: 1556–1560
6. Berkelbach van der Sprenkel JW, van Echteld CJA, Bénabid AL, Decorps M, Tulleken CAF (1989 a) Marginal ischaemia in the rat: a model with bilateral carotid artery occlusion studied with 31-P and 1-H NMR spectroscopy. In: Meyer JS, Lechner H, Reivich M, Toole JF (eds) Cerebrovascular disease 7. Excerpta Medica, Amsterdam, pp 289–296
7. Berkelbach van der Sprenkel JW, van Rijen PC, Luyten PR, den Hollander JA, Tulleken CAF (1989 b) Clinical applications of proton magnetic resonance spectroscopy. In: Meyer JS, Lechner H, Reivich M, Toole JF (eds) Cerebrovascular disease 7. Excerpta Medica, Amsterdam, pp 143–151
8. Berkelbach van der Sprenkel JW, van Rijen PC, Verheul HB, van Echteld CJA, Tulleken CAF (1991) The in vivo relationship between serum glucose and energy rich phosphates, pHi and lactate during progressive forebrain ischaemia in the rat. J Cereb Blood Flow Metabol 11: S 333
9. Birken DL, Oldendorf WH (1989) N-acetyl-L-aspartatic acid: a literature review of a compound prominent in 1H-NMR spectroscopic studies of the brain. Neurosci Biobehav Rev 13: 23–31
10. Bosman DK, Deutz NEP, De Graaf AA, Vd Hulst RWN, van Eijk HMH, Bovee WMMJ, Maas MAW, Jorning GGA, Chamuleau RAFM (1990) Changes in brain metabolism during hyperammonaemia and acute liver failure: Results of a comparative 1H-NMR spectroscopy and biochemical investigation. Hepatology 12: 281–290
11. Bottomley PA, Edelstein WA, Hart HR, Schenck JF, Smith LS (1984) Spatial localization in 31-P and 13-C NMR spectroscopy in vivo using surface coils. Magn Reson Med 1: 410–413
12. Bruhn H, Frahm J, Gyngell ML, Merboldt KD, Hanicke W, Sauter R (1989) Cerebral metabolism in man after acute stroke: New observations using localized proton NMR spectroscopy. Magn Reson Med 9: 126–131
13. Chopp M, Welch KM, Tidwell CD, Helpern JA (1988) Global cerebral ischaemia and intracellular pH during hyperglycaemia and hypoglycaemia in cats. Stroke 19: 1383–1387
14. Crockard HA, Gadian DG, Frackowiak RS, Proctor E, Allen K, Williams SR, Russel RW (1987) Acute cerebral ischaemia: concurrent changes in cerebral blood flow, energy metabolites, pH, and lactate measured with hydrogen clearance, 31-P and 1-H nuclear magnetic resonance spectroscopy. II Changes during ischaemia. J Cereb Blood Flow Metab 7: 394–402
15. Damadian R, Mink L, Goldsmith M, *et al* (1976) Field focussing nuclear magnetic resonance (FOWAR): Visualisation of a tumor in a live animal. Science 194: 1430–1432
16. de Graaf AA, Bovée WMMJ (1990) Improved quantification of in vivo 1-H NMR spectra by optimization of signal acquisition and processing and by

incorporation of prior knowledge into spectral fitting. Mag Reson Med 15: 305–319
17. den Hollander JA, Luyten PR (1987) Image guided localized 1-H and 31-P NMR spectroscopy of humans. Ann NY Acad Sci 508: 386–398
18. Frahm J, Bruhn H, Gyngell ML, Merboldt KD, Hanicke W, Sauter R (1989) Localized high resolution proton NMR spectroscopy using stimulated echoes: initial applications to human brain in vivo. Magn Reson Med 9: 79–93
19. Frahm J, Merboldt KD, Hanicke W (1987) Localized proton spectroscopy using stimulated echoes. J Magn Reson 72: 502–508
20. Haase A, Frahm J, Hänicke W, Matthei D (1985) 1-H NMR chemical shift evidence (CHESS) imaging. Phys Med Biol 30: 341–349
21. Hope PL, Cady EB, Delphy DT, Ives NK, Gardiner RM, Reynolds EO (1988) Brain metabolism and intracellular pH during ischaemia: Effects of systemic glucose and bicarbonate administration studied by 31-P and 1-H nuclear magnetic resonance spectroscopy in vivo in the lamb. J Neurochem 50: 1394–1402
22. Hore PJ (1983) Solvent suppression in Fourier transform nuclear magnetic resonance. J Magn Reson 29: 283–300
23. Houkin K, Kwee IL, Nakada T (1990) Persistent high lactate level as a sensitive MR spectroscopy indicator of complete infarction. J Neurosurg 72: 763–766
24. Hoult DI, Busby SJ, Gadian DG, Radda GK (1974) Observation of tissue metabolites using 31-P nuclear magnetic resonance. Nature 252: 285–287
25. Jung W-I, Grodd W, Lutz O, Petersen D (1990) Localized 1-H in vivo NMR spectroscopy of small volume elements in human brain at 1.5 T. Magn Reson Med 15: 320–326
26. Luyten PR, Groen JP, Vermeulen JWAH, den Hollander JA (1989) Experimental approaches to image localized human 31-P NMR spectroscopy. Magn Reson Med 11: 1–21
27. Luyten PR, Marien AJH, Heindel W, van Gerwen PHJ, Herholz K, den Hollander JA, Friedman G, Heiss WD (1990) Metabolic imaging of patients with intracranial tumours: H-1 spectroscopic imaging and PET. Radiology 176: 791–799
28. Morris GA, Freeman R (1978) Selective excitation in Fourier transform nuclear magnetic resonance. J Magn Reson 29: 433–462
29. Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR (1990) Early detection of regional ischaemia in cats: Comparison of diffusion- and T2-weighted MRI and spectroscopy. Magn Reson Med 14: 330–346
30. Nadler JV, Cooper Jr (1972) N-acetyl-L-aspartatic acid content of human neural tumours and bovine peripheral nervous tissue. J Neurochem 19: 313–319
31. Ordidge RJ, Bendall MR, Gordon RE, Connelly A (1985) Volume selection for in vivo spectroscopy. In: Govil, Khetrapal, Saran (eds) Magnetic resonance in biology and medicine. TATA Mc Graw Hill Publishing company Ltd, New Delhi, pp 387–397
32. Patt SL, Sykes BD (1972) T1 water eliminated fourier transform NMR spectroscopy. J Chem Phys 56: 3182–3184

33. Petroff OA, Spencer DD, Alger JR, Prichard JW (1989) High field proton magnetic resonance spectroscopy of human cerebrum obtained during surgery for epilepsy. Neurology 39: 1197–1202
34. Prockop LD (1986) Cerebral spinal fluid lactic acid. Neurology 18: 189–196
35. Roth K, Kimber BJ, Freeney J (1980) Data shift accumulation and alternate delay accumulation techniques for overcoming dynamic range problems. J Magn Reson 41: 302–309
36. van Rijen PC, Luyten PR, Berkelbach van der Sprenkel JW, Kraaier V, van Huffelen AC, Tulleken CAF, den Hollander JA (1989) 1-H and 31-P measurement of cerebral lactate, high energy phosphate levels and pH in humans during hyperventilation: associated EEG, capnographic, and Doppler findings. Magn Reson Med 10: 182–193
37. van Rijen PC, Tulleken CAF, Marien AJH, den Hollander JA, Luyten PR (1991) Brain metabolite mapping using 1-H NMR spectroscopic imaging in patients with focal cerebral ischaemia. Stroke (in press)
38. van Rijen PC, Verheul HB, van Echteld CJA, Balazs R, Lewis P, Tulleken CAF (1991) Effects of dextromethorphan on rat brain ischaemia and reperfusion assessed by magnetic resonance spectroscopy. Stroke 22: 343–350
39. Williams SR, Gadian DG, Proctor EA (1986) A method for lactate detection in vivo by spectral editing without the need for double irradiation. J Magn Reson 66: 562–567

Radiosurgery

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Introduction

Stereotactic surgery destroys or affects small intracranial targets and it can be carried out with a number of different physical agents: heat or cold, chemical or radioactive solutions, radioactive sources, ultrasound or laser beams. In all these cases, the physical agent is carried to the target through a burr hole. Leksell, 1951, had the idea of using stereotactically directed narrow ionizing beams which can reach the target through the intact skull. He coined the term radiosurgery. We define radiosurgery as a neurosurgical procedure where narrow ionizing beams, given in a single high dose fraction, are used either to destroy a predetermined target volume or to induce a desired biological effect in the target volume without opening the skull and with minimum risk of damage to the surrounding non target neural tissue.

Radiosurgery differs from radiotherapy in principle and technique. Radiotherapy relies on the difference in biological radiosensitivity between the cells of the pathological and the surrounding normal tissue. In radio-

surgery, the accurate stereotactic localization and the fields of radiation with steep gradients make such biological differences to irradiation less critical. The physically determined concentration of the radiation on the target becomes one of the important factors of treatment as it allows the delivery of a high single dose with a sharp gradient to a well-delineated tissue volume with little effect on the surrounding normal brain tissue.

History

The idea of radiosurgery and its tool the Gamma Knife was a logical step in the creative endeavour of Leksell. The closed stereotactic system was a replica of his open stereotactic instrument (Leksell 1949). His stereotactic system of the "arc radius" type is an elegant application to neurosurgery of the cartesian principle for defining the location of a point in space by relating it to three planes intersecting at right angles to each other. It consists of a semicircular arc with a probe carrier. By placing the arc on the skull of the patient according to the X, Y and Z coordinates, the target will be in the center of the arc and can be reached by the electrode or probe from any angle.

In radiosurgery, ionizing beams are used instead of the electrode, probe or cannula. Ionizing beams can transport energy from an external source through an intact skull to a predetermined intracranial target inducing lesions of different size and shape or triggering planned biological responses according to the treatment parameters selected. In principle, different types of energy carrier could be used. Leksell *et al.* systematically investigated the advantages and disadvantages of a number of possible sources from both theoretical and practical points of view. They first reported the use of 280 kV X-rays in the treatment of a case of compulsive neurosis (Leksell *et al.* 1955). For "cerebral surgery" they used a Bragg peak or intersecting non-Bragg peak proton beams from a synchrocyclotron (Larsson *et al.* 1963, Leksell 1960), and looked at linear accelerators as a potential radiation source.

After these initial physical laboratory and clinical tests, Leksell concluded that, although heavy particles from a synchrocyclotron and the photons from a linear accelerator had a number of attractive qualitative characteristics, the machines were either impractical for clinical purposes or did not meet the requirements of precision and ease of handling. This lead to the decision to design and build the Gamma Knife, a dedicated compact radiosurgical apparatus with fixed sources and target (Leksell 1968, 1971, 1987).

The fact that Leksell and most of his associates were neurosurgeons undoubtedly played an important role in this decision. The goal was to construct a neurosurgical tool that was easy to handle by the neurosurgeon

himself, without a large number of technicians. The Gamma Knife was installed in Stockholm in 1968. Biomedical research and clinical application of narrow beams of accelerated charged-particle radiation started in the 1950s in the University of California at Berkeley, Lawrence Berkeley Laboratory (Tobias *et al.* 1952) and later in Harvard, Boston (Kjellberg *et al.* 1961). However, the first trials with such charged particles were not stereotactic. The relatively high cost of the Gamma Knife and cyclotrons led to a number of neurosurgeons adapting linear accelerators for radiosurgery (Betti *et al.* 1983, 1984; Colombo *et al.* 1985, 1987; Lutz *et al.* 1988; Friedman *et al.* 1989; Hartman *et al.* 1985; Podgorsak *et al.* 1988, 1989).

Radiosurgery Systems. Tools and Methods

The Gamma Knife

The equipment known as the Gamma Knife is an integrated system consisting of (Fig. 1):

1. The unit with the beam sources
2. The collimator system
3. The treatment couch
4. The stereotaxic frame: an orthogonal three-dimensional coordinate system
5. A computerized dose-planning system.

The beam sources are embedded in a heavily shielded shell – the central body of thick cast iron (Figs. 1 and 2). A remote controlled shielded door opens and closes to allow the remote controlled treatment coach with the patient to move into treatment position and to move out of the treatment space after the procedure has been completed. The treatment is monitored and manoeuvered from the control panel. A two way intercom secures the verbal communication between patient and neurosurgeon. The beam source consists of 201 $Cobalt^{60}$ rods. Each rod is 20 mm in length and 1 mm in diameter and contains 12 to 20 cylinder-shaped pellets of $Cobalt^{60}$. Each pellet is 1 mm long and has a diameter of 1 mm. The pellets are hermetically sealed in a stainless steel capsule. The latter is introduced in a second stainless steel capsule and then in an aluminium rod container. The activity of each source capsule is specified to be 30 Ci ± 10% at the time of installation. The total activity in the existing Gamma Unit can vary between 5400 Ci (3.30 Gy/min) and 6600 Ci (4 Gy/min), in other words 6000 Ci ± 10%. The sources are radially distributed over a segment of a sphere so that their Gamma beams intersect at the center of the sphere (isocenter). The radiation emitted by a pellet is attenuated when it penetrates through other pellets. Therefore, the dose rate measured at the Unit Center Point depends on the number and position of the $Cobalt^{60}$ pellets in the sources, in addition to the total activity. The beams are individually col-

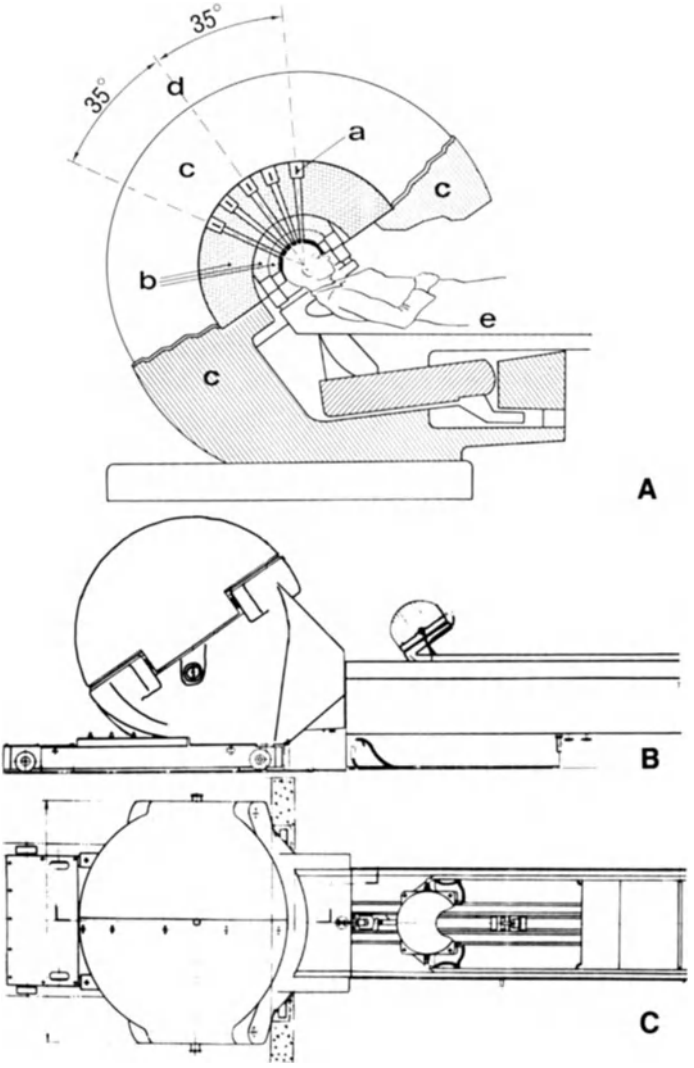
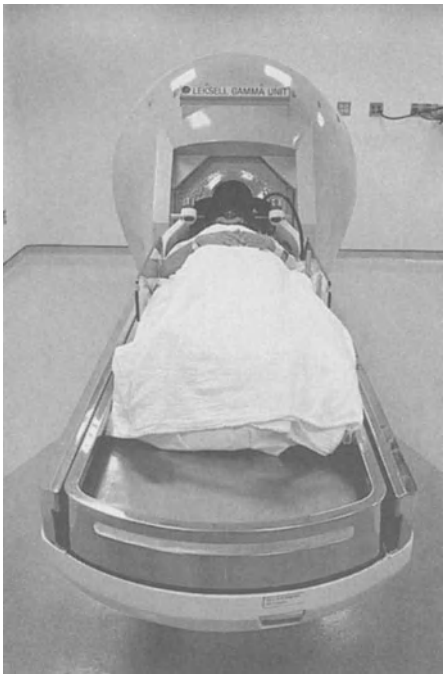
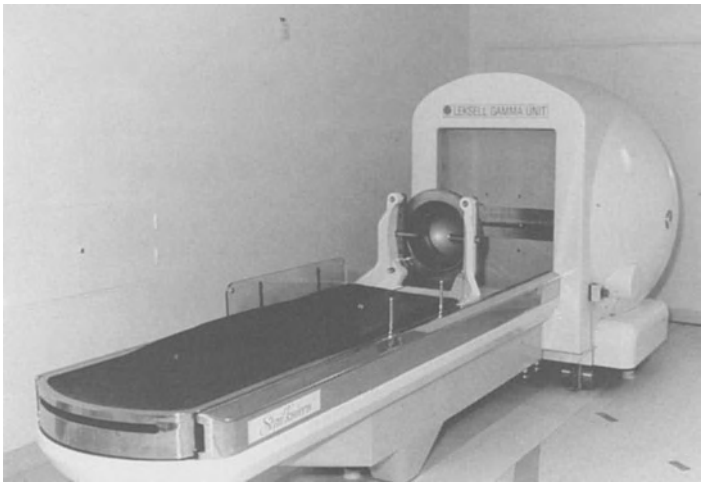


Fig. 1. A, B, C Schematic drawing of the Gamma Knife: *a* ^{90}cobalt source; *b* the twin collimators; *c* shielding; *d* the center of the system; and *e* remote controlled operating couch

limated in a collimator system – with two collimators in the central body and the collimator helmet, attached to the treatment coach. The collimator closest to the patient and the one closest to the source are made of tungsten with a density of 17.8 grams per cm^3. The intermediate collimator is of lead. The collimator helmet (Fig. 3) is provided with axis rods (trunnions). The head of the patient, with the Leksell base instrument rigidly fixed on the skull and with the slide-adjustable socket bearings set according to the



A



B

Fig. 2. (A) The Gamma Knife: prototype A, (B) the Gamma knife: prototype B (shielding, collimator helmet, remote controlled operating couch)

Y and Z coordinates of the target, is suspended in the collimator helmet with the trunnions inserted in the socket bearings. The head is positioned according to the X coordinate by right to left adjustment of the trunnions.

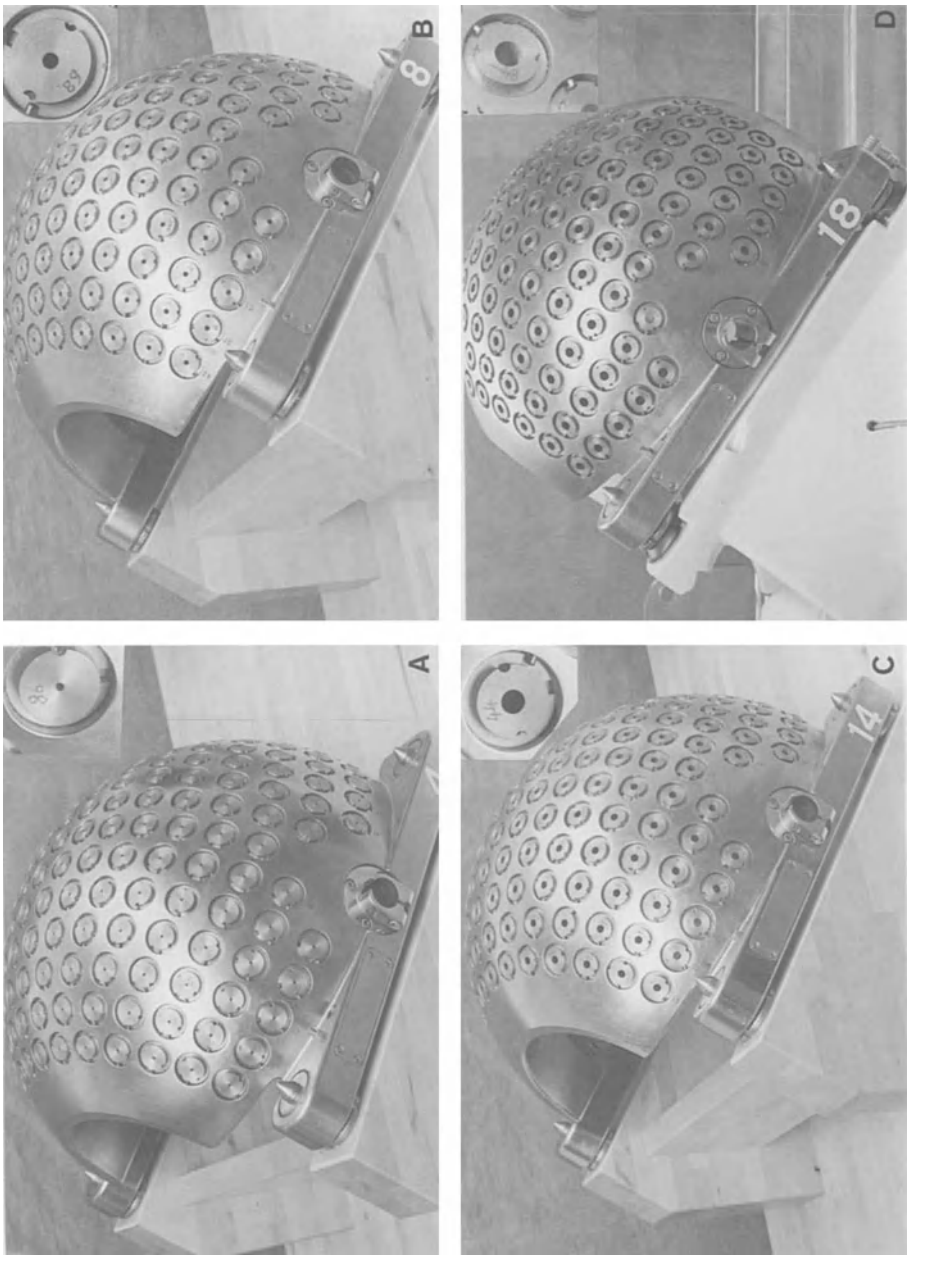


Fig. 3. (A) Collimator helmet 4 mm and single channel (insert right corner), (B) collimator helmet 8 mm and single channel (insert right corner), (C) collimator helmet 14 mm and single channel (insert right corner), (D) collimator helmet 18 mm and single channel (insert right corner)

The docking precision between the collimators is controlled by microswitches. When the couch is in the treatment position and the 3 collimators are aligned, the beam channels become patent and the beams are collimated toward the common focal point (isocenter). This focal point remains in a fixed position since the radiation sources are in a fixed position. When a helmet is in the treatment position, its beam defining collimators are located halfway between the sources and the Unit Center Point. The distribution of radiation around this center is dependent on the size of the 201 orifices in the collimator system through which the beams have to pass. The size of the collimator is defined as the diameter of its circular aperture as projected on a surface placed perpendicularly to the beam axis at the Unit Center Point. So defined the standard collimator sizes are 4, 8, 14, and 18 mm. With these collimator helmets a volume of 0.07 cc, 0.5 cc, 3 cc and 6 cc, respectively, receives 50% of the dose in the isocenter (Fig. 3).

The dose gradients are very steep within the 90, 70, and 50 percent isodose configuration (Fig. 4). By using collimators singly or combined, isodose configurations of any size and shape can be obtained. In addition, single-beam channels can be plugged if a particular structure in proximity with the target must be protected.

Radiosurgery with Heavy Particles

Radiosurgery using heavy particles like protons or helium is based on the Bragg peak principle (Bragg *et al.* 1904). The heavy particles penetrate the neural tissue inducing first scarce ionization; then interacting with the tissue they lose velocity and the ionization is enhanced. Finally when the particles hit the target they release the whole radiation energy they carry. This ionization pattern is known as "Bragg curve" and the maximum energy is released at the "Bragg peak". With the focused peak delivery of the energy at the predetermined depth in brain tissue a steep dose gradient is obtained.

In Harvard the proton beam is generated in a 160 million electron volt cyclotron. The beam is extracted, focused and directed to the target. It is absorbed to leave 12 cm working range. It is collimated by 3 brass collimators to make the beams nearly parallel. The beam passes through a nitrogen ion chamber to measure the amount of proton radiation. It then passes through a variable water absorber which automatically compensates for individual portal paths (Kjellberg *et al.* 1979, 1983).

At the Lawrence Berkeley Laboratory, a 184-inch 230 MeV Synchrocyclotron providing helium ions beams is used for Bragg peak therapy (Lyman *et al.* 1986, Fabrikant *et al.* 1984). The range of the Bragg ionization peak and the width of the peak are determined by interposing appropriate absorbers in the beam path, thereby creating a three-dimen-

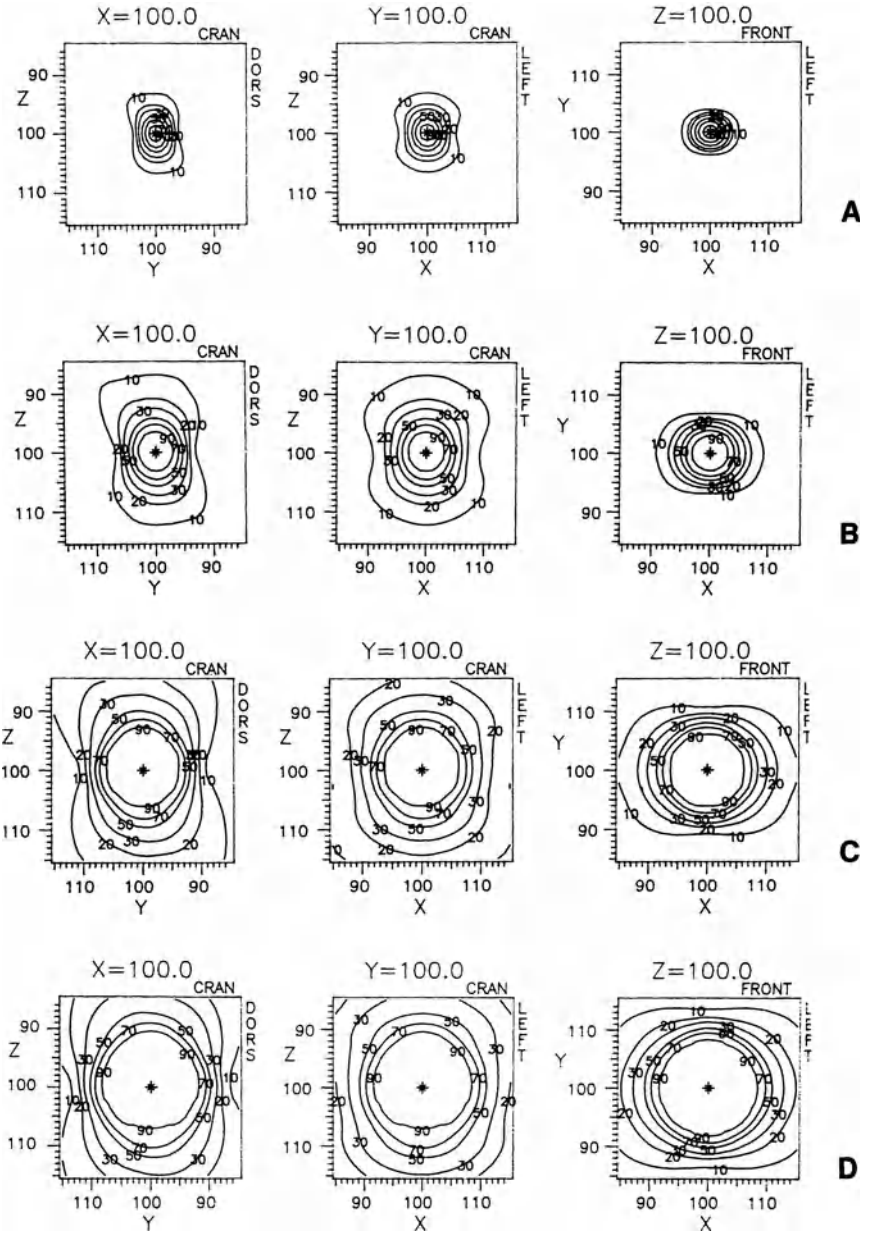


Fig. 4 (A) Isodose configurations obtained with the 4 mm collimator: lateral, frontal and axial projections. (B) Isodose configurations obtained with the 8 mm collimator: lateral, frontal and axial projections. (C) Isodose configurations obtained with the 14 mm collimator: lateral, frontal and axial projections (D) isodose configurations obtained with the 18 mm collimator: lateral, frontal and axial projections

sional high dose volume of desired shape placed stereotactically within the brain. Multiple entry angles and beam parts are selected so that the high dose Bragg-peak regions of the individual beams converge within the lesion.

Recently a proton synchrotron at Loma Linda University and another one in Upsala, Sweden, have been installed for treatment of patients. Russia, Switzerland, and Japan have a number of installations either already in use for patients or in blue prints. The University of Washington (Seattle) has started to use neutrons for radiosurgery.

Radiosurgery with Photons from Linear Accelerator

Components of electromagnetic radiations acting as corpuscles of energy without mass, deliver their energy in the form of small amounts called quanta or photons. Because they have no charge, the photons ionize indirectly producing secondary electrons as a result of interaction with the penetrated tissue. The technique of linear accelerators used for radiosurgery involves, unlike the Gamma Knife, rotations of both the gantry and the couch – hence of both the source and the target. The advantages of rotating therapy are the reduction of the irradiation time and the sharper deep isodose by infinite entrances. However, this technique is less accurate due to the instability of energy emission, to the vagueness of the mechanical isocenter (± 2 to 6 mm) and to the variability of the skin target distance (Podgorsak 1989). The dose delivered by modern linear and circular accelerators can vary per degree of rotation, guided by microprocessor and change of the form and size of a multileaf collimator during arc therapy, but these accelerators are not available for small radiosurgical targets (Podgorsak 1989).

Three linear accelerator based radiosurgical techniques have been used clinically so far:

a) The single plane rotation
b) The multiple non-coplanar converging arcs
c) The dynamic rotation

The single plane rotation technique uses one beam directed to the target and moved through an arc. Optimal dose fall-off occurs outside the target volume.

The multiple non-coplanar converging arcs technique was first described by Betti and Derechinsky (1983, 1984). The patient is seated in a treatment-chair, the target receives the beams through a series of 140° arcs each for a different treatment-chair angle (Betti *et al.* 1989). Colombo *et al.* developed a multiple converging arcs technique with the patient in the supine position. Five 110° arcs deliver the radiation energy. For each arc the position of the treatment couch is different. A spherical sector of 160° × 110° is covered (Colombo *et al.* 1985). Hartmann *et al.* use 11 arcs

of 140° each either from 20° to 160° or from 200° to 340° (Hartmann *et al.* 1985). Lutz *et al.* use 4 arcs. One arc is in the transverse plane with 0° as couch angle from 50° to 310° and a 100° arc is given with the couch angle of 90°, 45° and − 45° (Lutz *et al.* 1988). Friedman and Bova use a 6 MeV Phillips linear accelerator. Tertiary collimation is achieved with circular cerrobend collimators, ranging in size from 5 to 35 mm. A portable add-on stereotactic device controls all patients and gantry movements, in order to improve the radiation beam accuracy (Friedman and Bova 1990). With the dynamic rotation technique the patient is treated in the supine position with both the couch and the gantry rotating continuously and simultaneously during the treatment.

The multiple non-coplanar arcs techniques deliver the dose through gantry arc rotations at various stationary couch positions, while the dynamic rotation delivers the dose through a simultaneous rotation of the gantry and the couch. These techniques stretch the requirements for the mechanical approach of the gantry isocenter and the couch rotation axis to levels which are beyond what was until recently expected of manufacturers of medical linear accelerators. Nevertheless, according to Podgorsak (Podgorsak 1989), in spite of the complexities in experimental design and the considerable weight in the gantry and the couch, manufacturers of modern linear accelerators are capable of delivering an isocenter/couch rotation axis accuracy within $\sim \pm 1$ mm. Podgorsak concludes that even though the precision of dose delivery with the Gamma Knife is higher, the spatial precision of dose delivery attainable with modern linear accelerators is adequate for radiosurgery and is of the same order as the precision of the target localization.

Radiobiological Principles in Radiosurgery

Radiobiological data on radiosurgery are scarce. Bjorn Larsson's experience in the field is unique. I have heavily borrowed material for this section of my chapter from his report at the Symposium on Radiosurgery in Charlottesville (1989). Radiosurgical lesions seen in healthy tissue have been qualitatively and quantitatively similar in animals and patients. Larsson (1962), Rexed *et al.* (1960), Leksell *et al.* (1960) and Andersson *et al.* (1970) studied the early and late lesions produced with single high doses of proton in the central nervous system of rats, rabbits and goats. Collimated proton beams have also been used to study structure-function relationship. Small hypothalamic lesions selectively blocked the central regulation of milking in goats (Gale *et al.* 1963) and the pigeon's corpus striatum was functionally isolated (Fabricius *et al.* 1962).

In man, histopathological study of a single dose proton produced lesion in the brain of a cancer patient treated for pain (Larsson *et al.* 1963) was

obtained. The absorbed radiation dose, given by cross-firing with a 2 cc × 5 mm, 185 MeV proton beam, was 200 Gy at the center of the lesion.

Cancer pain has also been treated with the Gamma Knife. Steiner *et al.* (1980) and Dahlin *et al.* (1975) described the lesions produced in the Centrum medianum. The threshold dose for production of a lesion was estimated to be 140 Gy and with doses of 180–250 Gy reproducible necrotic lesions have been obtained in 3 weeks (Fig. 5). At the target dose of 200 Gy there was circumscribed destruction of the nervous tissue with only small perivascular haemorrhages and slight cellular reaction at the edge of the lesion. A striking feature was the paucity of cellular reaction at the periphery of the lesion. There was slight wide-spread tissue response and no swelling of the irradiated hemisphere.

Fig. 5. Gamma lesion in a patient with cancer pain. Coronal section made in the plane through the isocenter in the target. Fifty-three weeks after the treatment with 200 Gy, the lesion in the thalamus is necrotic, bloodless and well demarcated

The changes following the short period of rapid degeneration, observed during the first year after irradiation, may be divided into three stages:

1. Necrotic stage. At a dose level of 200 Gy this stage covers approximately the third and fourth weeks after irradiation when necrosis and acute degenerative inflammatory reactions can be observed.

2. Stage of resorption. This stage is characterized by more or less intense cellular activity. There is resorption of cellular debris with the beginning glial scar formation. Phagocytic cells eliminate necrotic debris from the central part of the lesion. This activity is maximal at the end of the necrotic stage and decreases gradually. The stage of resorption is also characterized by astrocyte proliferation around the necrotic area and occasional giant cells which sometimes have large lobed nuclei. The marginal zone of the lesion also shows a chronic inflammatory reaction with congested vessels and formation of new capillaries, often with endothelial thickening, and round cell proliferation. The length of the stage of resorption is not very well known. It may well last more than 1 year after irradiation.

3. Late stage. This stage covers the period from about 1 year after irradiation and is characterized by prominent glial scar formation. The lesion is now well stabilized. There are no inflammatory reactions, giant cells, increase of vessels, teleangiectasis or haemorrhage, and there has been no evidence of cellular elements resembling those of neoplasms in an early stage.

For a given target structure, radiation quality and dose distribution, the important parameters that determine the radiation response are absorbed radiation dose and, to a lesser extent, the dose rate. The cellular response to irradiation has been studied with radiation induced inactivation of cells in culture, measured as decreased "proliferative cellular survival". The DNA is the main target in the cell. The initial chemical damage yields in base alterations, cross-links within the DNA itself (or between DNA and a near-by protein), and DNA strand breaks.

Reparative processes due to enzyme systems may occur. It is the unrepaired, or misrepaired, double strand breaks that are believed to play a dominating role in the development of proliferative cell death, with subsequent tissue degeneration and brain necrosis. A distinct correlation exists between the frequency of DNA double strand breakage and mitotic death.

The dose required to produce radionecrosis, through direct or indirect inactivation of "critical" tissue elements, depends on the existence and physiological role of proliferative cells within the target volume. The cell subpopulations that are likely to suffer first, due to high-dose irradiation, are those with the highest rate of mitosis and subsequent cell loss.

In healthy central nervous tissue subject to radiosurgery, two such critical subpopulations have been identified: endothelial cells and oligodendroglia (van der Kogel 1986). Relatively low levels of cell depletion

may result in glial and endothelial damage (Hopewell *et al.* 1970). Tumour tissue and vascular malformations often respond to a much lower dosage, because of the higher proliferative activity of the pathological cell populations, as compared with the healthy brain.

The high doses typical of clinical radiosurgery (20–200 Gy) may considerably decrease the probability of survival of irradiated proliferative cells, down to 10^{-6}, or less. Analysis of data for cell lines derived from tumour or healthy cells from a study by Hall *et al.* (1988), and Nilsson *et al.* (1980), indicates that dose-survival curves can vary significantly, even for cells of similar types. In radiosurgery, the response of any tissue (healthy or pathological) depends not only on the reproductive death of proliferative cells in critical cell populations, but also on the extent to which repopulation occurs.

Demyelination and white matter necrosis are caused by the loss of oligodendroglia, sometimes in combination with damage to endothelial cells, and by circulatory deficiency. Depending on the volume irradiated, doses of 20 Gy or more are required to cause such alterations in the adult human brain. Evident neuronal degeneration, and gray matter necrosis require slightly higher absorbed doses and are probably directly related to damage to endothelial cell loss and damage to the blood-brain barrier system. There may be significant differences in the doses required to achieve a given end point, but it is typical of radiosurgery that necrosis occurs inside the steep gradient zone of the dose distribution, without significant tissue changes outside that zone.

The effect of radiation on normal tissues is either acute, occurring within days or weeks, or late, taking many months or years to develop. In slowly proliferating cell-populations, as in the brain, it takes very high doses (such as in functional radiosurgery as described above) to achieve an acute effect. With the possible exception of acute oedema, that can sometimes be seen during the first week after irradiation, all undesired effects of radiation surgery are late. Demyelination and associated functional defects may occur many months and even years after irradiation.

Dose-rate Effects

For radiation of low linear energy transfer, i.e., photons or protons used with cross-fire techniques, the rate at which the single dose is given affects the radiation response: if repair allowed to occur during the treatment, the probability of cell survival increases. As this effect is most pronounced at dose-rates less than 1 Gy/minute (Hall *et al.* 1988), it should not affect the response of tissues in the target volume where the dose is usually delivered at a higher dose-rate. In tissues outside the high dose-gradient zone, however, it helps to reduce the risk for undesirable late radiation damage.

Radiosensitivity of Vessels

In radiosurgery, a dose-distribution with a steep gradient at the borderline of the target volume, in the neighborhood of the 50% isodose curve should be used. The center dose is then chosen so that the desired degeneration in the target volume occurs at a convenient time, say 1–6 months after irradiation. The precision at which this delay can be predicted is partly dependent on individual variations of radiosensitivity, within the group of patients under consideration.

In a group of patients treated by radiotherapy for malignant tumours, a congenital variation in individual radiation sensitivity has probably been demonstrated (Ågren *et al.* 1990). Similar variation should be expected to exist among radiosurgery patients (Dahlin *et al.* 1975). A predictive assay of healthy tissue radiosensitivity would be of value, for identification of particularly sensitive or resistant individuals.

Radiation has long been known to induce damage in small vessels in the skin (Windholz 1927), in larger pulmonary vessels (Wolbach 1909), and in the human aorta (Thomas and Forbus 1959). Regardless of the form of ionizing radiation used, the qualitative effects in the tissue of vascular lining of an AVM appear to be the same. The early changes consist of perivascular or endothelial cell swelling with increased nuclear basophilia, endothelial cell degeneration with necrosis, diapedesis of leucocytes into the interstitial space and increased colloids. Fissuring of the walls, spot haemorrhages, and thrombi may occur. In response to the injury, fibroblastic activity increases and there is reparative proliferation of surviving endothelial cells with increased deposition of collagen in the media of vessel walls. The adventitia undergoes a process of fibrosis.

In the early phase, the changes may be slight and appear diffusely in small vessels, whereas later they involve increased areas of the vessel wall. The proliferation of endothelial and media cells and of the subendothelial connective tissue as well as the deposition of homogenous collagenous and hyalinic material increases in the long term the progressive reparative endothelial and medial thickening leads to the fibrosis and occlusion of small vessels that culminates in the obliteration of the AVM.

Total obliteration of medium sized vessels was demonstrated in an AVM specimen excised when only partial obliteration following Gamma Knife treatment was achieved (Steiner 1984). In specimens treated with proton beams similar changes have been reported (Nielson *et al.* 1972).

Biological and Chemical Modification of the Radiation Response

Interference with the oxygen supply has little importance in radiosurgery. Radioprotective drugs are also of limited value, since the blood-brain barrier system prevents their penetration into the brain tissue. There are

indications (Cerda *et al.* 1983), however, that the vascular endothelium may be protected through injection of sulphydryl compounds like cystamine before irradiation. Larsson suggests the use of radiosensitizers such as drugs that interfere with DNA repair, for reducing cell survival in neoplasms that are not protected by an intact blood-brain barrier system. Larsson also advocates the systemic injection of cell-seeking compounds, loaded with the light boron isotope, boron-10, and subsequent irradiation with slow neutrons, that makes the boron atom disintegrate into two cell-killing nuclear fragments (Gabel *et al.* 1984). A boron-10 concentration of some 10 microgram per gram target cells is sufficient to double the cell-killing efficacy of slow neutrons. Neutron capture therapy based on neutron capture in boron is of interest in the context of radiosurgery as a possible adjuvant that may be used for a coordinated whole organ or regional treatment of infiltrating malignancies or disseminated tumour cells (Larsson 1989). Such a strategy would be particularly relevant when there is a need, both for stereotactic surgery for treatment of targets visible by computerized imaging methods, and for the eradication of undetectable growth in larger anatomical structures. Larsson also plans the use of blood-born boronated macromolecules or boronated substances with affinity for endothelial cells, for adjuvant neutron capture therapy in the radiosurgical treatment of larger arteriovenous malformations.

Neutron capture therapy is described here as an example of possible treatment modalities that may be used to increase the efficiency of narrow beam stereotactic radiosurgery, by damaging critical tissue components. Since the probability of local control is a steep function of the absorbed dose, even a modest specific exposure of pathological endothelium (or other regimes that permit specific cell-killing) would significantly increase the chances of cure, without complications.

Radiosurgery with the Gamma Knife

Although the theme of this Chapter is Radiosurgery in general, the vehicle of the theme is the Gamma Knife. Radiosurgery with the Gamma Knife is the quintessence of the concept of Radiosurgery giving it its philosophy, its history, and its achievement.

Radiosurgery was the idea of a neurosurgeon, its tool – Gamma Knife – was devised by a neurosurgeon, and was used and improved by neurosurgeons. Neurosurgeons – by trial and error – found out the indications, the results and failures of the method. Mastering both the microsurgery and the radiosurgery, they were less biased in their decision making of which technique to use for an AVM or an acoustic neuroma and they incorporated the Gamma Knife in their armory considering it no more than a tool and not a panacea. The Gamma Knife has remained until now

a neurosurgical instrument. The linear accelerator or cyclotrons, have been adapted to radiosurgery by neurosurgeons. However they are installed in Departments of radiotherapy or physics and used by radiotherapists, the neurosurgeon playing a secondary role in the team. In the future this may, if not now, influence decision making and the selection of patients for treatment.

In the following review of radiosurgery with Gamma Knife, we discuss the pathologies treated and the results obtained. The results available with photons and heavy particles and pertinent future developments in the field will also be discussed.

Method

The base ring (Leksell *et al.* 1987) is fixed to the skull with aluminium screws or carbon fiber pins inserted in 4 shallow burr holes drilled 3 mm in the skull bone. The Leksell stereotactic coordinate frame is attached to the base ring. Children are treated under general endotracheal anaesthesia. With the base ring and the stereotactic frame fixed to the patient's head, the appropriate stereotactic imaging – computer tomography, magnetic resonance image or arteriography – is carried out to visualize the target lesion (Figs. 6 and 7).

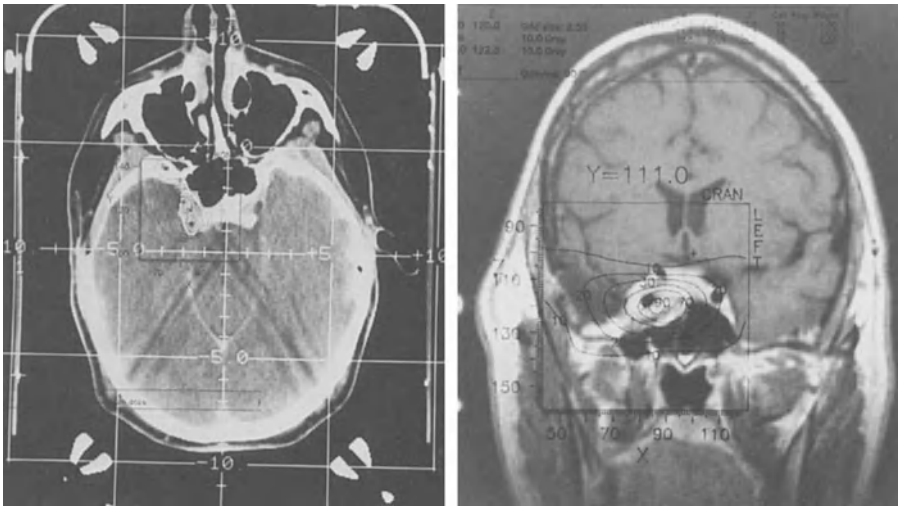
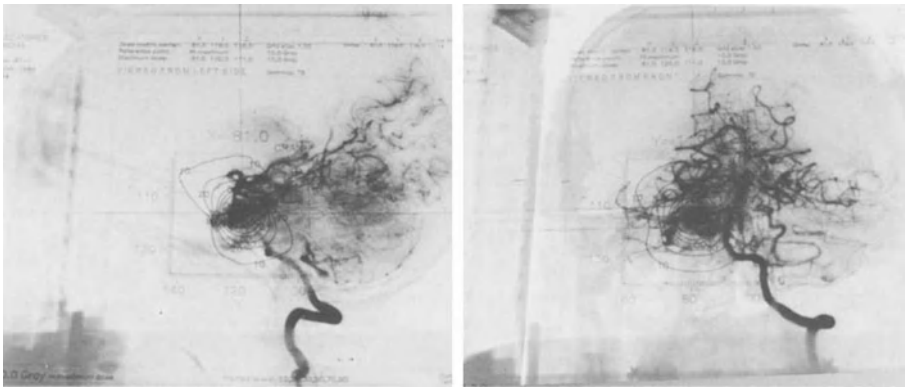


Fig. 6. (A) Stereotactic coronal MRI of residual meningioma in the left cavernous sinus. Status after microsurgery. The isodose configuration is superimposed on the MRI image. (B) Stereotactic transaxial CT scan of residual meningioma involving the left cavernous sinus. Status after microsurgery. The isodose configuration for the given slice is superimposed on the CT film



A B

Fig. 7. Vertebral angiogram: (A) lateral and (B) frontal view in an arteriovenous malformation of the brain stem. The isodose configurations are superimposed on the malformation

Angiography

Biplane rapid-serial subtraction stereotactic angiograms are carried out to define the AVM nidus and determine target coordinates. The study should be complete and of high quality. Substraction should be used. In some cases in order to better define the target, superselective catheterization is useful. It might clarify the contribution from different arterial territories to the different parts of the AVM. Concomitant stereotactic angiography and MRI may facilitate a better definition of the nidus.

CT and MRI Imaging

The stereotactic instrument used for the determination of target coordinates is compatible with CT, MR, PET or Magnetoencephalography imaging equipment. Special Plexiglass boxes with fiducial markers for CT or MRI are attached to the base ring. When a CT scan is used, following the injection of the contrast medium, 1.5 mm cuts are carried out through the target. The target coordinates are determined directly from the films (Bergström *et al.* 1980) or by digitization using the software of the CT scanner. More recently gadolinium-enhanced MRI has been used more and more frequently for visualization of tumours and similar computing techniques are also available for MRI. MRI offers the advantage of orthogonal imaging in three different, or even any, arbitrary plane. There are several pitfalls in performing coordinate determinations from MRI images. One problem is the lack of homogeneity of the magnetic field which may cause distortion, particularly in the periphery of the visualized field and thus interfere with

the accuracy of the coordinate calculation, since the fiducial markers on the stereotactic frame are peripherally located. The magnitude of distortion due to field inhomogeneity can be studied by scanning a phantom containing paramagnetic markers with known positions. The information thus obtained may be used to correct the distorted stereotactic image. However, in our experience using the Siemens Magnetom, this problem has been negligible after careful shimming of the magnetic coils. Other potential problems with MRI are the relative thickness of the image slices, chemical shift artefacts and artefacts related to flow. In critical treatment situations, it is advisable to check a coordinate determination from an MR-image by one from a CT-image, which remains more reliable.

Dose Planning

The dose-planning program gives the radiosurgeon a plot of the distribution of radiation around the target point in any plane of his choice. Fig. 4 points in the selected plane receiving equal amounts of radiation are connected to produce isodose lines. They are usually given as percentages of the maximal dose delivered to the tumour. To perform the calculation of the dose distribution, the dose-planning computer (Microvax) needs information not only on the position of the target in the skull as given by the stereotactic coordinates but also data allowing an estimate of the radiation absorption. The dose distribution is calculated within a three-dimensional matrix with a size of $31 \times 31 \times 31$ points. The distance between the points or the "grid size" is determined by the surgeon and is usually 1 to 3 mm, depending on the size of the target treated. The targets first selected from the stereotactic images are tentative, and minor adjustments of their position in stereotactic space may be needed, depending on the isodose distributions plotted by the computer. For optimal results and minimal risks, it is essential that the target volume receives the required dose without radiation damaging to the non-target surroundings. This implies that the steepest isodose gradient of the dose distribution coincides with the periphery of the target. In other words, this means that the density of isodose lines in any plane should be maximal at the periphery of the target on the corresponding plane of the stereotactic image through the target. If this requirement is met, a high dose may be given to the target, the surrounding normal tissue receiving a low dose. The steepest dose gradient usually falls around the 50–70% isodose lines, hence it should be planned that one of these isodose lines coincides with the periphery of the target. This may require several overlapping fields of radiation, each with a separate stereotactic focal point. Optimization may demand the use of different collimator sizes for the different targets. The isodose distribution may also be changed by changing the relative time of radiation at each target-weighting.

Finally, the radiation field may be altered by occlusion of some of the radiation sources: so called plugging. The latter procedure mainly affects the distribution of the volumes of low radiation. Plugging is often useful in the treatment of skull base lesions to avoid unnecessary radiation to the brain stem or cranial nerves.

Marginal changes in the position of the field of radiation may also be made by changing the incidence angle of the radiation relative to the skull base. This could be crucial in the treatment of skull base lesions close to the sella, where the irradiation of the optic chiasm should be avoided.

The dose-planning provides a treatment protocol which in two simple parameters encodes the treatment plan. These parameters are the stereotactic coordinates from one or more target points and the radiation time at each point for the dose decided by the surgeon.

Dose Selection

Our accumulated experience consists of some 2000 treatments with the Gamma Knife, 1) in AVM and other vascular malformations, 2) in patients with cancer pain, 3) in severe obsessive-compulsive neurosis by anterior gamma-capsulotomy, and 4) in patients with Parkinson's disease treated by gamma-thalamotomy. The results and side effects of this large material gave some insight into the radiation tolerance of the normal brain to high doses delivered in a single session to small volumes of brain.

Radiation effects are volume-dependent in the sense that a lower average dose is sufficient to achieve the same radiation response in a large volume. In other words, a high dose to a large volume creates a proportionally larger lesion than a high dose to a small volume. For example, it was noted that a 1 cc lesion corresponding to the volume of the 50% isodose line was obtained in the internal capsule using the 4 mm collimator in a psychosurgical case with a maximal dose of 200 Gy, whereas the lesion was several cc and the spread into the volume of the 20% isodose line with 180 Gy when using the 8 mm collimator. For cerebral AVMs treated by the Gamma Knife, we have been able to clarify the relationship between risk of undue radiation effects in the normal brain and the volume treated. The dose needed to achieve the desired therapeutic results, i.e. the obliteration of the AVM, has also been established. We have found that a peripheral dose of 25 Gy is needed to reach an up to 90% chance of cure in small AVM. On the other hand, the risk of radiation-induced unwanted effects increases in proportion to the volume irradiated. For this reason, the dose has been reduced and a smaller chance of success has been accepted in cases with larger AVMs to keep the treatment morbidity below 10%. For practical purposes, we have rarely treated AVMs larger than 20 cc in order to keep a reasonable balance between risks and chances of success. The major part

of our series includes AVMs with a volume of less than 6 cc and permanent side effects have been seen in 3% of the patients (Steiner 1985; Lindquist, Steiner 1987).

The desirable dose is often restricted by the proximity of cranial nerves and eloquent brain regions. Concerning the radiosensitivity of the cranial nerves, there is some experience available from the analysis of AVM treatments, but also from the treatment of acoustic neuromas, where the total number of treatments now performed in the existing Gamma Knife centers is close to 400, and of pituitary tumours of which more than 200 have been treated. It is not possible to give the maximal tolerable dose for individual cranial nerves. It seems likely that the sensitivity of the nerves is increased in pathological cases due to mechanical compression and/or poor vascular supply. In this context, we can only give information on doses which have been tolerated and on those which have not.

In the large number of pituitary tumours and parasellar lesions treated to date, there are very few incidents of radiation damage to the optic nerve. No problems have occurred in cases where the nerve received 10 Gy, and even 15 Gy given to small segments of the nerve seem to be tolerated. In 1 case of parasellar AVM, a visual field defect resulted from a calculated dose of 20 Gy. The radiation dose to the optic chiasm and tracts has been kept below 10 Gy.

The nerves of the ocular muscles were estimated to receive 20 Gy in patients treated for spontaneous carotid-cavernous fistulas and tumours in the cavernous sinus. In only 1 of these cases was there uncertainty as to the possibility of radiation damage to the abducens nerve. In cases of AVM the trochlear nerve has also received with impunity 20 Gy in its course through the paramesencephalic cisterns.

Even the trigeminal nerve seems to withstand 20 Gy in the cavernous sinus, but approximately 15% of the patients radiated for acoustic neuromas have experienced some mild numbness in the ipsilateral face when only a small volume of the trigeminal root entry zone has received 14–20 Gy. In radiation of acoustic neuromas, the facial nerve is regularly given 15–20 Gy and partial damage to this nerve has been seen in 3–20% of the cases. There are a few examples of cases where this nerve received 40–50 Gy with no resulting function disturbance (Norén *et al.* 1987).
Experience from radiation of the VIII cranial nerve is only available from cases of acoustic neuromas when the function of the nerve has already been jeopardized. From these cases, it can be concluded that it is possible to save useful hearing even after delivering up to 15 Gy to the nerve.

There is not yet sufficient information on the vulnerability of the lower cranial nerves. The brain stem has often been irradiated with 20 Gy in connection with the treatment of AVMs in the brain stem or in the surrounding cisterns. It must, however, be emphasized that in these cases we

have been careful to limit this dose to a very small tissue volume. Furthermore, there are some unfortunate experiences which indicate that the brain stem is more vulnerable if it is compressed. Thus, in two cases of cavernous angiomas of the brain stem, radionecrosis with concomitant neurological deficits developed despite the fact that less than 18 Gy were delivered to the surface of the lesion and subsequently to a small volume of brain stem. In another case, an unexperienced colleague included too large a volume of the brain stem within 20 Gy when treating a clival meningioma resulting in radionecrosis of the brain stem and death of the patient 6 months after treatment.

The stereotactic instrument used for the determination of target coordinates is compatible with modern imaging equipment. Short-distance exposures are used and magnification is corrected. Software to compute the correction is available. A software program is incorporated in the treatment planning to determine the correct values of the target's X, Y, and Z coordinates which have been read directly off the films. The distortion due to field inhomogeneity on MRI images can be corrected. By using the Siemens Magnetom the problem has been negligible after shimming of the magnetic coils. The relative thickness of the image slices, chemical shift artefacts and artefacts related to flow are other potential pitfalls when using the MRI. It is often advisable to check the coordinate determination from an MR-image with one from a CT image.

The dose-planning program provides a plot of the distribution around the target point in any desired plane. Points receiving equal amounts of radiation are connected to produce isodose curves. Additionally to the information on the location of the target in the skull as defined by the X, Y, and Z coordinates, we use data allowing an estimate of the radiation absorption for each individual beam on its way to the target and also the distance from the collimator.

In a number of meningiomas, the vascular supply was included in the same radiation field that covered the tumour or, if this was not feasible, in a small additional radiation field. Both a stereotactic CT scan and a stereotactic angiogram were carried out. The angiogram revealed the vascular supply and the vascular target was calculated on the angiogram.

In the treatment of larger meningiomas not amenable to complete coverage with an effective radiation dose, sometimes only the vascular supply of the tumour was included in the radiation fields.

Gamma Knife in Arteriovenous Malformations

The use of radiation for AVM during the period 1914–1950 failed to achieve clear-cut results (Wegmann 1969, Krayenbühl 1957, Olivecrona *et al.* 1957, McKissock *et al.* 1957, French *et al.* 1969, Pool 1965, Jefferson 1948, Ray

1941), and the failure led to an almost unanimous consensus in the assessment of radiation as being worthless in the management of AVM. A measure of this skepticism was the initial refusal of Leksell to allow me to try the Gamma Knife for the treatment of AVM. He finally changed his mind when I showed him an illustration of an obliterated AVM following fractionated radiation carried out by Johnson (1969). The first case of AVM treated with the Gamma Knife was carried out in April 1970 (Steiner *et al.* 1972). The patients entering the project in progress were treated according to a protocol which – although it has been revised over the years, with the advent of modifications in the radiosurgical or in the imaging techniques – retains its basic principles.

Decision Making

In untreated AVM, the risk for repeated haemorrhages, disability and death, documented in a wealth of reports, provides the rationale for microsurgical, radiosurgical or endovascular elimination of the AVM. The decision making should be based on (a) the natural history of the disease; (b) the anticipated results of the available therapeutic alternatives; (c) the patient's parameters including age, medical and neurological status; (d) the presenting symptom – haemorrhage or epilepsy, headache or no symptom – the malformation being diagnosticated accidentally; (e) the variables of the AVM, including its location, size, the number and pattern of feeding and outflow vessels (as estimated by four vessel rapid serial angiography); (f) the presence of haematomas; g) the relationship of the malformation to surrounding brain structures (as determined by MRI or CT scan); and, h) the results of blood volume studies.

In a patient presenting with epilepsy, headache or with an accidentally discovered asymptomatic AVM, we advise radiosurgery. The rationale for this is the fact that in an AVM which has never bled, the latency period between the time of irradiation and the susequent obliteration of the AVM involves relatively little risk of bleeding in the interim. For a patient with a ruptured AVM, microsurgery is considered unless the location of the AVM or the condition of the patient implies high surgical risks.

The Target

As in open surgery, the aim of radiosurgery is the elimination of the nidus – the pathologic shunting vessels – from the normal cerebral circulation. This should be achieved without damaging the nutritive arteries to the brain. In an optimal radiosurgical treatment, like in microsurgery, the nidus is identified and the beam geometry fitted to the periphery of the malformation including the small non-nutritive feeding vessels while their parent vessels – nutritive arteries to the brain – are left beyond the isodose

line with the steepest dose gradient. In a number of cases in our series, the nidus was not totally included within an irradiation field considered optimal. From the beginning, in our initial protocol the patients have been grouped according to the following:

1) The nidus is totally included in the 50% or higher periphery isodose.

2) The nidus is only partially included in the 50% or higher periphery isodose.

3) Only feeding vessels are included in the 50% or higher periphery isodose.

Only the first group is considered as receiving an optimal treatment. However, this warrants some qualification. So far radiation of the feeding vessels has led to the successful obliteration of the AVM in only a few cases, but the method should not be totally discarded and research in refining the method should be continued. The problem is that during the stereotactic treatment arteriogram not all feeding arteries are functional and therefore they are not visualized. Thus, they are not treated and failure is the result. If all, but *all*, feedings vessels are radiated and occluded, the treatment can result in total obliteration of the AVM. If visualization of all feeding vessels could be obtained in a high percentage of cases, the number of cured large AVM following radiation of the feeding vessels could be increased.

Another way to approach the problem of large AVMs is to include in small radiation fields the embryologically determined strategic sites of the pathologic shunts. Occasional cures of only partially irradiated AVM were due presumably to accidental inclusion of the "shunt" in the radiation field.

Visualization of a shunt is possible today in a good number of cases. However usually there are several shunts in the nidus determining the peculiar flow pattern with complex character of its blood supply. Only obliteration of all "shunts" could secure total obliteration of the AVM. Developments in neuroimaging will hopefully improve the chances of visualization of the direct fistulas and make possible their radiosurgical treatment.

Patient Population

We treated the first arteriovenous malformation using the Gamma Knife in April 1970 and up to March 1991 eleven hundred forty-one patients (546 women and 595 men) with AVM referred from 34 countries underwent Gamma Knife radiosurgery (Table 1). Until clinical experience was accumulated we treated few cases. Only when an angiogram carried out 19 months after the treatment revealed that the first case treated with the Gamma Knife had been cured was a second case treated. After another

Table 1. *Patients with AVM Treated by Gamma Knife 1970–1990*

Nr cases	Age	F	M	Diameter	Volume range	Nr feeders
1,141	3–73	546	595	5–65 mm	1–40 cc	1–7

year and with the second case cured, a further 3 cases were treated. In 1977 we reported 30 AVM treated with the Gamma Knife (Steiner *et al.* 1977). Between March, 1989, and March, 1991, 364 of 1600 referred AVMs have been accepted for radiosurgery. It is pertinent to mention that the majority of cases have been referred by leading neurosurgeons around the world with a large experience in the microsurgery of AVM. Hundred and seventeen patients were treated for residual AVM following microsurgery. Hundred and twelve patients had embolization of their AVM, one patient had radiotherapy and 3 had Bragg-peak proton beam treatment prior to the Gamma Knife radiosurgery.

The presenting symptoms were haemorrhage in 89%, seizures with or without haemorrhage in 8%, minor or no symptoms in 3% of the cases treated (Table 4).

The age of the patients ranged from 3–76. There were 101 children in the age group 3–12 and 107 teenagers 13–17 years old (Table 1).

Table 2. *AVM Treated by Gamma Knife 1970–1990*

Treatment parameters				
Target dose	Periphery dose	Nr isocenters	Isodose line	Dose rate
12–125	10–62	1–7	50–90	1 Gy/min–3.5 Gy/min

Table 3. *AVM Treated by Gamma Knife 1970–1990*

Treatment prior to radiosurgery			
Microsurgery	Embolization	Charged heavy particles	Radiotherapy
117	112	3	1

Table 4. *AVM Treated by Gamma Knife 1970–1990*

Presenting symptoms		
Haemorrhage	Seizures	Minor symptoms/Accidental discovery
89%	8%	3%

AVM Location

Hundred and seventeen AVMs were located in the thalamus and basal ganglia, 170 in the limbic system and 94 in and around the brain stem. An additional 162 cases were located in the corpus callosum, in the hypothalamus, in the posterior fossa, periventricular, and intraventricular. If we add the 248 cases in the deep left frontal parietal temporal and occipital region, 73% of the cases treated were located deep or in eloquent cerebral regions (Table 5).

The majority of cases treated had a volume less than 8 cc. The largest AVM was 60 × 65 × 60 mm.

Table 5. *AVM Treated by Gamma Knife 1970–1990*

Most frequent localization				
	Nr	Right side	Left side	Midline
Frontal	97	55	39	2
Parietal	112	73	37	–
Temporal	159	110	47	–
Occipital	90	52	38	–
Periventricular	47	18	25	4
Vermis	8			
Basal ganglia	186			
Cerebellar hemisphere	29			
Brainstem	73			
Corpus callosum	47			
Fissura chorioidea	26			
Midbrain	21			
Intraventricular	31			

The Procedure. Pre and Peri-treatment Management

The patient is hospitalized the day before the treatment. An intravenous line is inserted on the ward and anticonvulsant medication is optimized, if required by overload. A mild sedative such as diazepam (10–20 mg po for an adult) is given. In persons with vaso-lability atropine 0.4 mg is given to block the vasovagal reflex.

Using local anaesthesia in adults and general endotracheal anaesthesia in children, the base ring with the stereotactic frame is attached to the skull of the patient either with carbon fiber pins inserted in four shallow holes drilled in the bone or using aluminium screws. Since the space in the collimator helmet is limited, the alignment of the base ring on the head is critical and should therefore be carefully planned. If the target is close to the midline the base ring should be in the midline. If the target is laterally situated, the base ring should be shifted laterally with the ear contralateral to the target close to the Y side bar of the respective side (Fig. 6). In this way the collimator will accommodate the head with the base ring without difficulty.

The arteriography is carried out with the base ring fixed in a frame holder attached to the angiographic coach. Biplane rapid film sequence with three films is carried out. Depending on the location of the AVM and the available information from previous diagnostic angiograms, 1–4 vessels are injected. Subtraction films with good visualization of the nidus and the scales of the stereotactic frame are required. Usually a digital angiogram is also carried out. Replaying the sequences on the screen helps to define the nidus better. In selected cases, superselective catheterization of small distal vessels gives additional information.

A stereotactic MRI or CT scan may help in the determination of the coordinates in cases where the nidus is not visible clearly enough on one of the arteriogram views. The MRI or CT cuts should cover the region of the nidus as defined by the coordinates on the arteriogram. The magnification factor is obtained by digitization. The coordinates of the target are either digitized or determined by using a graphic method (Bergström *et al.* 1980).

The dose planning is computed. Adjustment of the coordinates to obtain a match as close as possible between the beam geometry and the shape and size of the target is achieved by changing the coordinates either on the printed isodose configuration or on the screen with the display of both the isodose configuration and the target. When an appropriate isodose configuration is achieved, it has to be superimposed on the angiogram, but not only on the planes of the target points (Figs. 6 and 7). It should also be checked in as many planes as possible along the segments of the coordinate scales that correspond to the extension of the AVM. These

isodose configurations in successive cuts will reveal whether or not the decided isodose line covers the nidus completely.

The peripheral and maximal doses are decided considering the tissue volume within each isodose line covering the AVM and the surrounding neural tissue as well as the proximity of eloquent structures. The coordinates are transferred to the base ring. The head of the patient is positioned in the collimator helmet, the time of radiation is set and the treatment is started. Once the treatment is completed, the base ring is removed and the wounds from the attachment of the base ring are dressed with sterile cotton pads. Corticosteroids are administered for 24 hours. The patient is allowed to eat and is discharged the morning after the day of treatment.

Follow-up

At the start of the project follow-up arteriography was repeated at 3, 6, 9, 12, 24, and 60 months after radiosurgery. Later, when the postoperative course in pilot series was clarified, CT scanning without and with contrast medium was used for the early follow-up. With the introduction of the MRI, either this or CT scanning every 6 months was considered appropriate. The post-treatment CT or MR studies detect radiation induced changes in the normal neural tissue and, if the AVM was visible on pre-treatment MRI or CT scan, the postoperative studies monitor the changes in the shape and size of the AVM. When the AVM is no longer visible on the CT or MRI, an arteriogram is obligatory before declaring the patient as cured. At present an MRI arteriogram is still not good enough to assess the final result of radiosurgery. Digital angiography of good quality is now accepted. However, not many of the digital angiographies seen by us are of an acceptable quality. AVMs which have not obliterated 2–3 years following the treatment should be retreated. Even in cases where this, for some reason, did not happen, the follow-up has been continued.

In a group of 30 patients we did obtain a follow-up arteriogram 5–8 years after the occlusion of the AVM was demonstrated by an angiogram. No recanalisation of the AVM and no further obliterative processes of the normal vessels could be observed.

Clinical follow-up continues every 6 months for those patients who still are not cured and yearly for the cured patients. In an effort to obtain a follow-up we occasionally recruited the help of the Red Cross or the Salvation Army to reach patients who moved from their previous addresses.

Treatment Variables

During the project in progress we strictly adhered to the initial protocol. This specified whether the entire AVM nidus or part of it or only the feeding vessels have been included in the radiation field and whether the

treatment was considered satisfactory. It has been considered that in 90% of the patients the entire nidus has been treated with optimal dose. However in the first years this was not checked along the entire coordinate scale. Recently, when we controlled the treatment planning of these early series using the presently available planning system, a number of the AVMs of moderate and large size should be considered as non optimally treated. This could explain some of the failures.

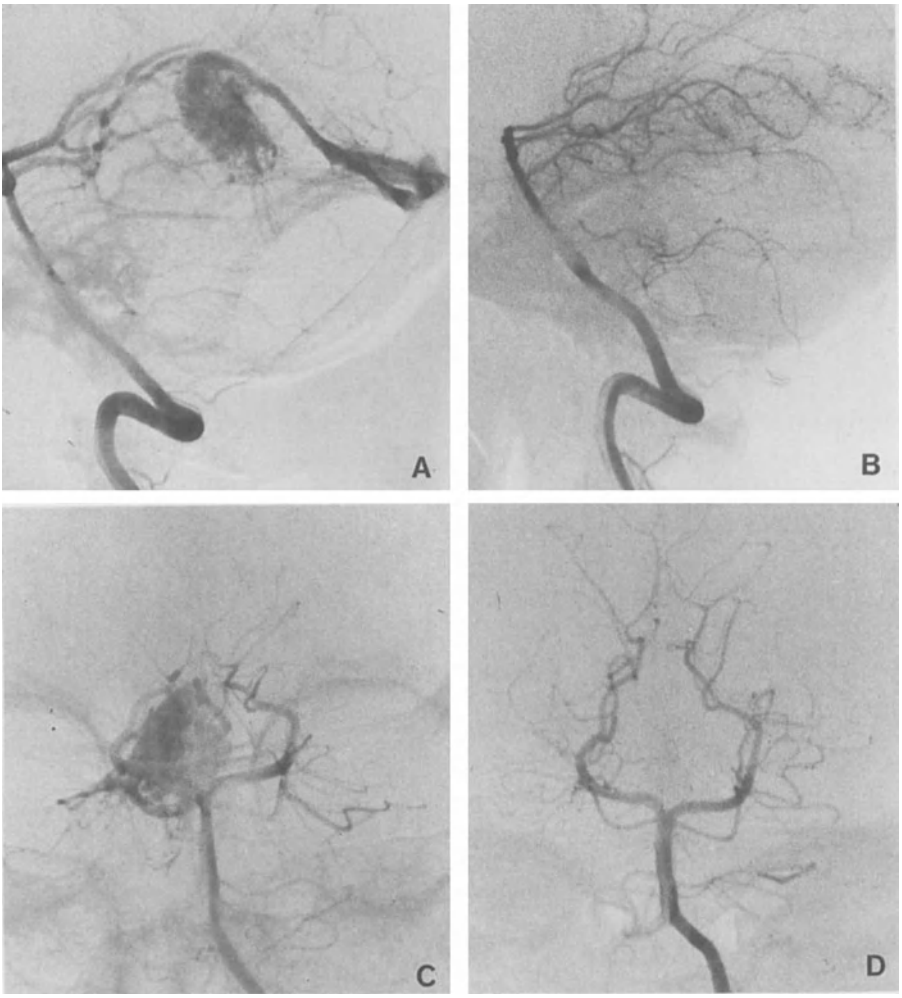


Fig. 8. Vertebral angiography. (A) Lateral and (C) frontal views of an AVM in the superior region of the vermis fed by branches of the right superior cerebral artery. (B) and (D) Two years after Gamma Knife treatment, subtotal obliteration of the malformation. No nidus is revealed; however, a tiny early filling vein still persists

In 600 cases one isocenter was used, in 541 cases overlapping fields were used, with two isocenters in 383, 3 in 115, 4 in 25, 5 in 9, 6 in 5, 7 in 3 cases and 8 in 1 case. The 14 mm collimator was most frequently used, followed by the 8, the 18 and the 4 mm collimator in the named order. The rationales I had for the use of 50 Gy as maximum and 25 Gy as peripheral dose proved not to be pertinent. Nevertheless the decision to use 25 Gy as the marginal dose was fortunate and at least in our material it still seems to be the optimal dose. Maximal doses of 15–125 Gy and periphery doses of 10–62 were tested (Table 2). Respecting the basic principle of radiosurgery – a steep dose gradient at the borderline between the

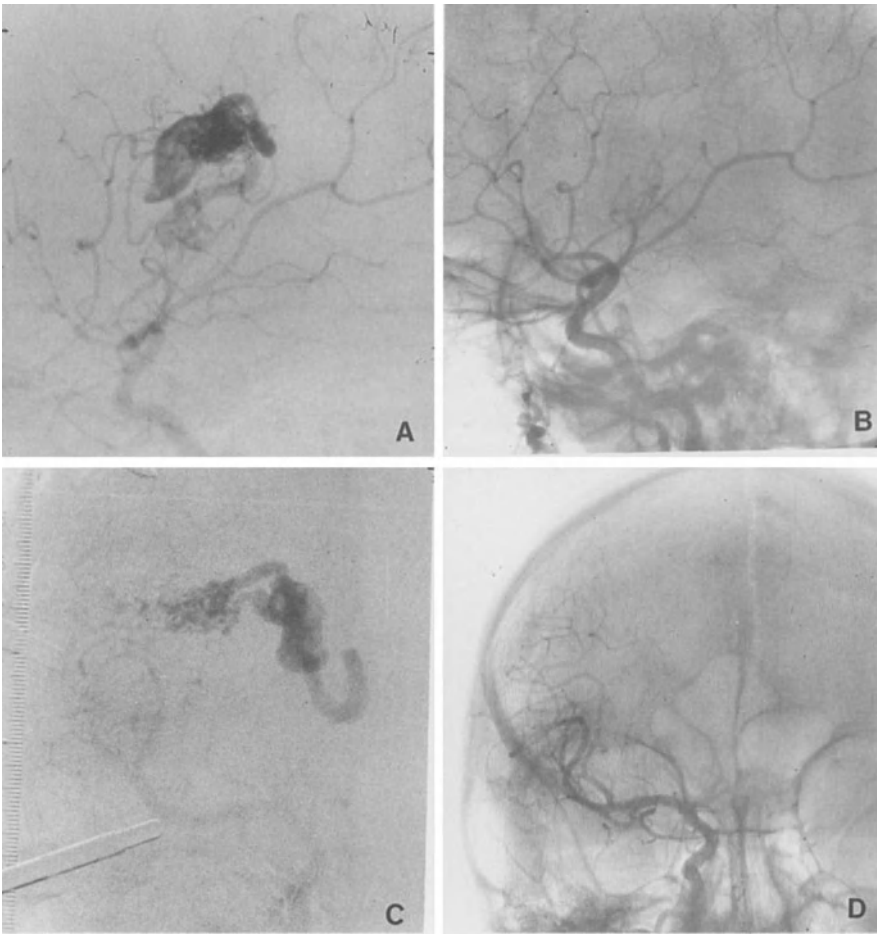


Fig. 9. (A) Lateral and (C) frontal views of AVM fed by branches of the right middle cerebral artery. The drainage is to the internal cerebral vein which is ectatic. (B) and (D) Two years following the Gamma Knife treatment. The AVM disappeared

target periphery and surrounding normal structures – peripheral isodose levels of 50%, 70%, and 90% in the named order have always been used (Table 2).

Results

Changes in the Angiogram

Subsequent to radiosurgery, changes as observed on the angiogram were:

1) Haemodynamic changes occurring usually before changes in the size

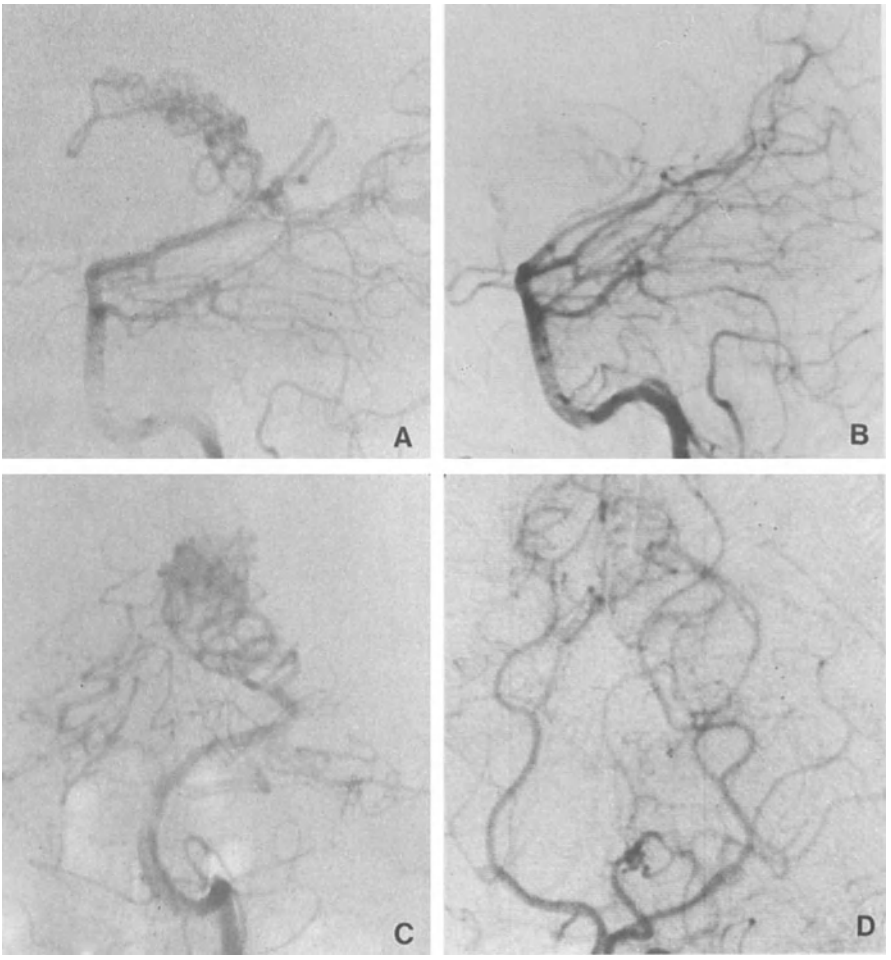


Fig. 10. Vertebral angiography. (A) Lateral and (C) frontal views of AVM around the posterosuperior part of the left thalamus, fed by choroidal arteries. (B) and (D) One year after Gamma Knife treatment, total obliteration of the AVM

and shape of the AVM. The flow-rate decreases progressively. Sometimes the size of the feeding arteries and outflow veins decrease too.

2) Partial obliteration of the AVM.

3) Subtotal obliteration of the AVM. We define as subtotal obliteration of the AVM a total disappearance of the nidus, but persistence of early filling tiny or still enlarged vein or veins (Fig. 8).

4) Total obliteration means no longer filling of the nidus, normal cir-

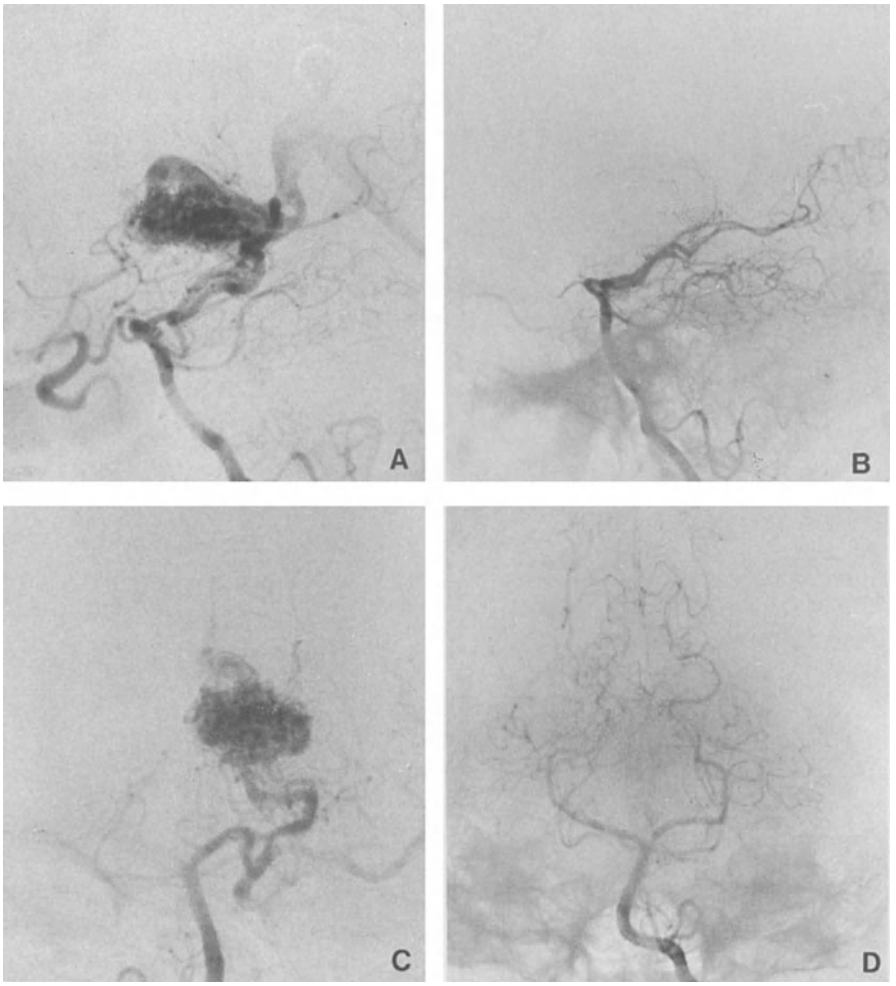


Fig. 11. Vertebral angiography. (A) Lateral and (C) frontal views of AVM in the posterior part of the left thalamus fed by thalamo-perforating and psoterolateral choroidal arteries. The drainage is to the vena magna Galeni and sinus rectus. (B) and (D) Three years after Gamma Knife treatment total obliteration of the AVM

culation time and normalization of the afferent and efferent vessels (Figs. 9, 10, 11, 12, 13).

Of 880 patients with the AVM considered as optimally treated, 461 had an appropriate angiographic follow-up. The relatively low percentage (52.3%) of follow-up is explained by the fact that while in the first 7 years (1970–1977) only 30 patients with AVM have been treated, from March 1989–March 1991 364 had Gammay Knife treatment and in the majority, the angiographic follow-up is not yet due. Of 461 AVMs with a satisfactory

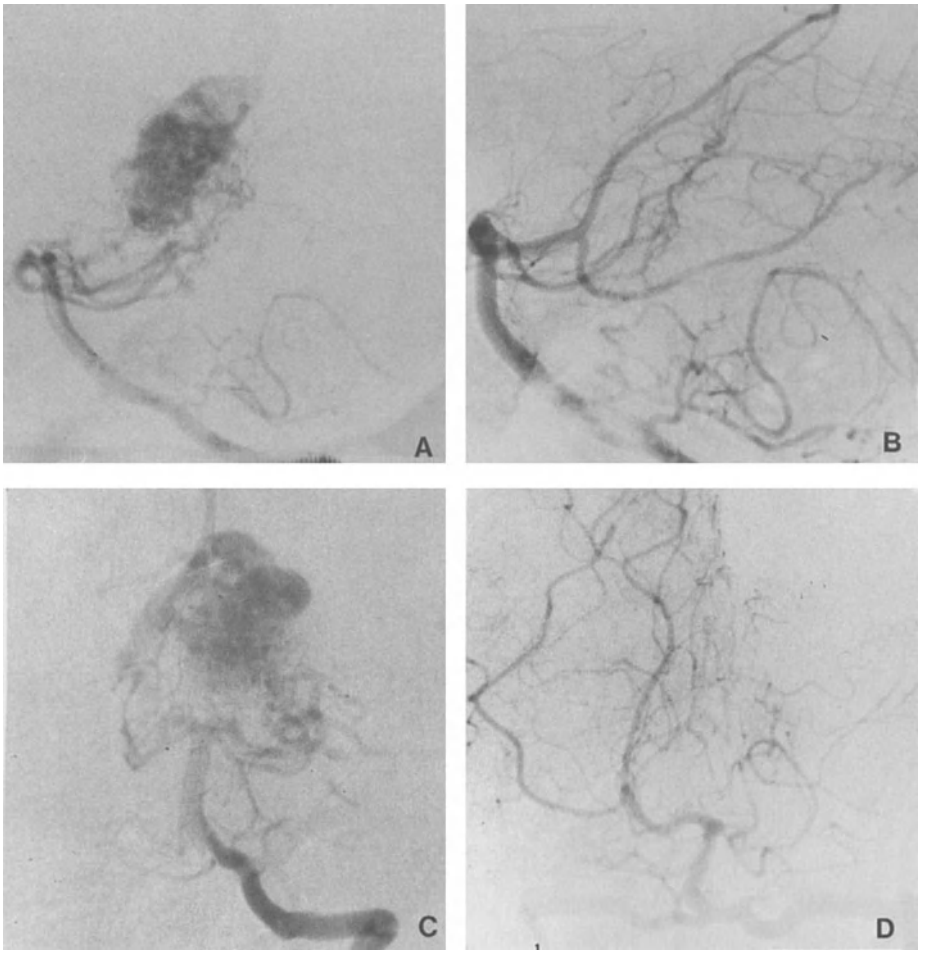


Fig. 12. Vertebral angiography. (A) Lateral and (C) frontal views of AVM at the level of the midbrain. The malformation is fed by dilated branches of the left superior cerebellar and by thalamo-perforating arteries. There is contribution from the posterior cerebral artery too. After the Gamma Knife treatment (B) and (D) no filling of the AVM two years later

angiographic follow-up, 369 (80%) were totally obliterated within 2 years following the treatment. Complete obliteration of the AVM within 1 year following the treatment occurred in 230 of 306 cases (75.1%) (Tables 6 and 11).

MRI follow-up was carried out in 198 cases – in 1 case in 1986, in two cases in 1987, in 9 cases in 1988, in 18 cases in 1989, in 150 cases in 1990, and in 18 cases in the first 3 months of 1991. No flow void pattern in the region of the treated AVM could be seen in 55 cases. Comparison between

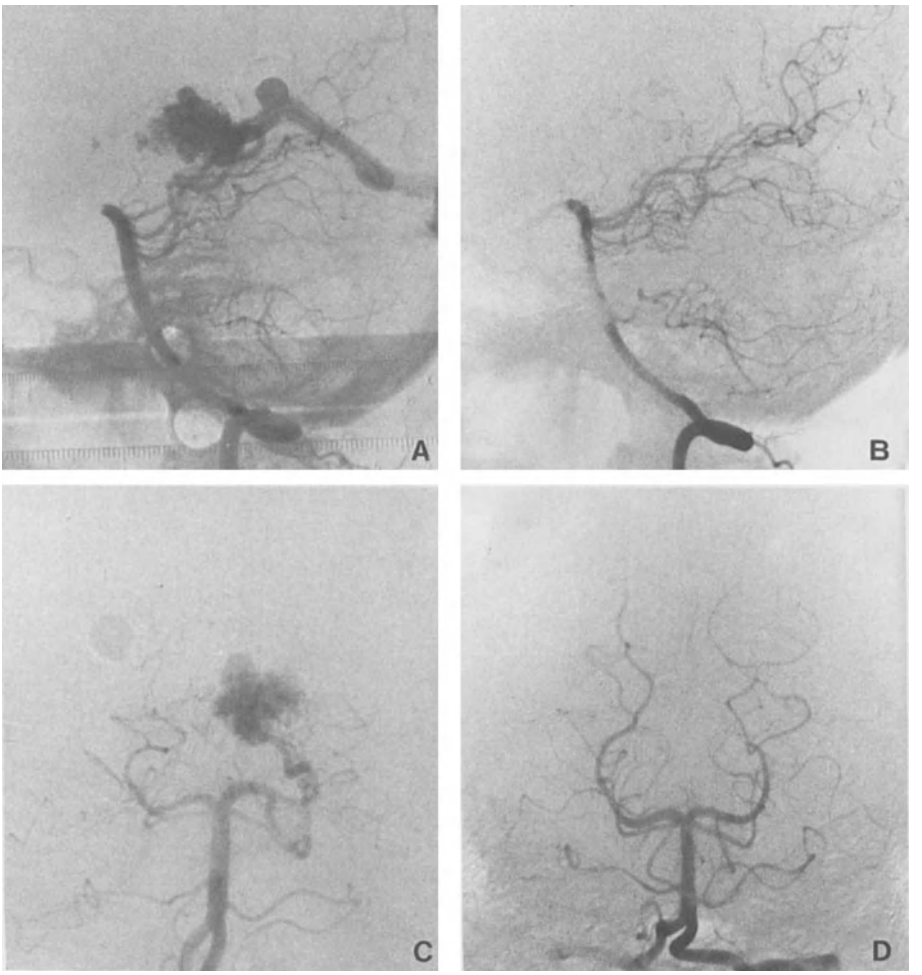


Fig. 13. Vertebral angiography. (A) Lateral and (C) frontal views of AVM at the level of the superior part of the midbrain and posterior part of the thalamus. The malformation is fed by posterior choroidal and thalamo-perforating arteries. The drainage is to the vena Galeni (B) and (D) Three years after the Gamma Knife treatment

MRI and angiogram results was possible in only 21 cases. The arteriogram finding agreed with the MRI finding in 7 cases of obliterated AVMs. In 14 cases where the MRI indicated total obliteration, the arteriogram revealed subtotal obliteration in 6 and partial obliteration in 8 cases.

If the results are related to the volume of the AVM and to the peripheral dose delivered in 161 cases, the findings show that with a dose of at least 25 Gy to the periphery of an AVM no larger than 1 cm^3 the incidence of total obliteration was 88%, in AVM of 3 cm^3 78% and in AVMs larger than 8 cm^3 50%. In the group of AVMs 4–8 cm^3 in size 50% were obliterated (Table 7). With a peripheral dose between 16–24 Gy studied in 101 cases the incidence of total obliteration was 70% if the AVM was between 1–3 cm^3 in size. In the group of AVM 4–8 cm^3 in size 14 of 18 AVMs obliterated (78%). This illustrates the fallacy of small numbers. In a larger number of cases it is improbable that the incidence of total obliteration in large AVMs would be higher than in smaller AVMs.

A total of 208 pediatric patients have been treated since 1970. Of the 208 patients in the series, 106 had a 2 year follow-up arteriogram. Fifty-nine children were treated since 1989. Hence, the majority have had no appropriate angiogram follow-up yet. Total obliteration occurred in 88 (83%) cases, subtotal obliteration in 5.8%, partial obliteration in 6.7%; in 2.9% no changes were observed. If only the 97 patients who have been optimally treated and had a 2 years' angiography study are considered, the AVM obliterated in 85 cases (87.6%). Subtotal obliteration occurred in 12 (12.5%) patients (Table 8).

Table 6. *AVM Treated by Gamma Knife 1970–1990*

Nr optimally treated cases	Results				
	Angio FU	Oblit	Subtotal	Partial	Unchanged
880	461	369 (80%)	46 (10%)	25 (5%)	23 (5%)

Table 7. *AVM Treated by Gamma Knife 1970–1990*

Results related to size	
Size	Obliteration
1 cc	88%
1–3 cc	78%
4–8 cc	50%
>8 cc	50%

In 68 patients radiosurgery was repeated when the AVM did not obliterate totally 2 or 3 years following the treatment. In 38 cases two years follow-up angiography is available and shows that 31 patients (81.5%) are cured (Table 9).

Hundred and twenty-one patients had embolization before radiosurgery (Table 3). Since the majority of these cases was treated in the last two years; follow-up angiography is available in only 24 cases. Total obliteration of the AVM occurred in 7 patients (26%). Subtotal obliteration occurred in 2 cases (8.3%).

Neurological Outcome

In 247 consecutive cases of AMVs treated by the senior author prior to January 1, 1984, the long term neurological outcome has been assessed. A questionnaire was sent to each patient, his/her family and the referring physician. Follow-up could be obtained in this way in 239 out of 247 cases (97%). Eleven of 239 patients had died. Recurrent haemorrhage was the cause of death in 5 patients. The causes of death in 5 patients were unrelated to the AVM or its radiosurgical treatment. One patient had committed suicide because of intractable thalamic pain syndrome originating from his initial bleeding.

Headache. Ninety-eight (43%) of all the patients in this series complained of headache prior to gamma irradiation. In 65 (66%) of these patients the headache subsequently disappeared and in another 9 (9%) cases it improved significantly.

Seizures. Fifty-nine patients had seizures at some time during the course of their illness. Eleven of those patients became seizure-free after radio-

Table 8. *AVM Treated by Gamma Knife 1970–1990*

Gamma Knife in paediatric patients					
Nr	Angio FU	Oblit	Subtotal	Partial	Unchanged
208	97	87.6%	12.4%	0	0

Table 9. *AVM Treated by Gamma Knife 1970–1990*

Repeated Gamma Knife surgery					
Nr	Angio FU	Oblit	Subtotal	Partial	Unchanged
68	38	31 (80%)	6	1	0

surgery and could stop the anticonvulsant medication. Thirty patients became seizure-free after the treatment however they continued with the anti-seizure medication. Eleven patients developed seizures which they did not have before the treatment. It should be noted that all these patients had intracerebral haemorrhages before the treatment with brain tissue damage of variable degrees. Therefore it is unclear whether the seizures were related to the post haemorrhagic brain tissue damage or to the radiation.

Speech Dysfunction. Thirty-five (15%) patients had some speech disorder prior to radiosurgery. This subsequently resolved fully in 21 and improved significantly in another 5 cases.

Motor Function. Seventy-four patients presented with motor deficits caused by the initial haemorrhage. The motor deficits resolved in 40 cases, and improved in 13 patients.

Sensory Function. Subsequent to radiosurgery, 19 patients recovered sensation in previously hypoesthetic areas. Twenty-seven patients showed no improvement of their sensory deficit.

Memory Disturbance. Before treatment, 44 patients experienced some degree of memory dysfunction. In 23 patients this symptom subsequently improved considerably and disappeared completely in 17 cases.

Other Neurological Symptoms. Of 10 patients with diplopia before the treatment, 6 were asymptomatic at the time of the follow-up.

A pulsating exophthalmus in a dural AVM disappeared following the obliteration of the malformation.

In a patient with a thalamic AVM, an extra pyramidal movement disorder persists despite radiosurgery.

Functional Recovery. One hundred and sixty-two patients (71%) were reported to have a full working capacity at the time of the follow-up. In 35 (22%) of these patients, this represented improvement over their condition prior to their radiosurgical therapy. In another 15 patients the working capacity increased from "not all" to "partial".

Eight patients with normal working capacity prior to treatment described themselves as occupationally handicapped. The deterioration was caused in 3 cases by rebleeding and in 2 instances by radiation-induced neurological deficits. Severe depression was the cause of disability in one more case and chronic epilepsy in another case.

Employment. One hundred and fifty-eight patients (69%) were employed or functioning well as students or housewives (11 cases) both prior to and after radiosurgery. In 16 instances patients who were previously unemployed are now working. Meanwhile, 12 patients who were working at the time of radiosurgery are currently not doing so. In this group is a man with a rebleed of the AVM. One patient sustained a traumatic arm injury and is now employable. Four older patients retired after their treatment.

In conclusion many patients experienced resolution of pre-existing neurological deficits. It seems most probable that this improvement is only the natural recovery which is expected in many patients who have suffered recent intracerebral haemorrhages and that radiosurgery does not interfere with this process. However, it is also plausible that vascular steal was responsible for some of the patients' symptoms. In such cases, neurologic deficits could potentially improve if radiosurgical treatment leads to obliteration of the AVM with subsequent normalization of the haemodynamic condition.

Rebleed

In this series of 239 patients, haemorrhages before complete obliteration of the AVM occurred in 17 patients. Six of the 17 patients experienced the rebleed within 1 year of the treatment, with the earliest happening after only 3 weeks. One patient died of a rebleed. In prior clinical reports it was contended that heavy particle irradiation of AVMs was by itself protective against AVM rupture (Kjellberg *et al.* 1984).

To determine whether we could find, in our material of patients with nonobliterated AVMs, facts to support the above contention, our data were scrutinized with this function in mind. Probability estimates were calculated using two methods: 1) The person-year method which calculates risk on the total period of follow-up, and 2) the Kaplan-Meier life-table method which calculates the risk based on the time of follow-up to the event. Analysis by Kaplan-Meier life-table estimates demonstrated increasing risk at nearly 3.7% per year until 62 months after radiation at which the last bleed occurred. The overall risk was 3.4% at 36 months, 7.2% at 48 months, and 11.2% at 72 months. The upper and lower bounds of the 95% confidence interval at 72 months were 4% and 18%, respectively. Consequently, within the limits of the life-tables estimates, radiosurgical treatment does not appear to confer any significant protection against rebleed in the non-obliterated AVM in the first 6 years following the treatment. However after this period, the life table ends in a plateau which could be interpreted as a proof of a sustained decrease in the risk of haemorrhage in late follow-up.

There are serious arguments against such a conclusion from the life table that pertains to the risk of haemorrhage in the latent period before total obliteration of the AVM following radiosurgery (Peto *et al.* 1976). These authors contend that "it must be emphasized that any conclusion based on the fine detail of such a graph (life table) is likely to be wrong. Particularly, long flat regions at the right hand end of the table do not imply that the real risk of death (or other event such as bleeding) among patients who are still alive then is negligible, unless a large number of patients have trial times well into or beyond the flat region".

Undue Effects

Sixty-seven (6.7%) of 1000 patients developed imaging changes in the neural tissue surrounding the target treated by radiosurgery.

The changes seen in MRI or CT could be described as:

1) Ring enhancement – 16 cases
2) Irregular marginal enhancement – 7 cases
3) Regular homogeneous enhancement – 13 cases
4) Irregular homogeneous enhancement – 4 cases
5) No enhancement – 27 cases

Thirty-five patients (3.5%) presented with neurological deficit while 32 patients (3.2%) of 1000 never developed symptoms. In 3 patients the deficits were transitory (Table 10). The latency between the treatment and the onset of radiation induced changes varied from 4 months to 56 months (in 1 case) (mean 9.9 months). The radiation induced changes as shown on CT or MRI lasted from 1 month to 29 months (mean 9.5 months).

The larger the volume treated the higher was the risk for the radiation induced changes. In the group of AVMs treated twice, in 6 patients (10%) radiation induced changes could be seen on the MRI or CT scans. Three patients (5%) developed a permanent neurological deficit. These were: moderate hemiparesis in 1 case, slight hemiparesis in 1 case, and papilloedema in 1 case.

Coffey and Lunsford (1990) report 213 cases with AVM treated with the Gamma Knife. Thirty-five had follow-up angiography and the rate of total obliteration was 49%. The majority of the follow-up angiograms were carried out less than 2 years after the treatment. Presumably the incidence of total obliteration will be higher when the patients have had their second angiogram (Table 11).

Cavernous Hemangiomas

Sixteen cases were treated – 13 patients with cavernomas and 2 patients with cavernomas and venous angiomas. One case was diagnosed as cav-

Table 10. *AVM Treated by Gamma Knife 1970–1990*

Radiation Induced Undue Effects				
Nr trt	Nr cases	Changes CT/MRI	Neurological deficits	
			Transient	Permanent
1	1,000	6.7%	3%	3.2%
2	60	10%	5%	5%

Table 11. *Available Data on AVM Treated by Gamma and Photon Beams and by Charged Heavy Particles*

	Source of radiation	Nr pts treated	Diameter in mm	Target doses	F/U 1 yr after trt		F/U 2 yr after trt		Rebleed		Radiation induced imaging changes			
					Nr pts	AVM oblit	Nr pts	AVM oblit	Percent	Deaths fr rebleed	Nr cases	Percentage	Neurol deficit	
													Transient	Permanent
Steiner *et al.* (1991)	Gamma	1,141	5–65	12–125	306	74%	461	80%	3.3%	9	1,000	6.7%	3%	3.2%
Bunge *et al.** (1991)	Gamma	212	18–60	18–60	11	–	156	73.5%	–	–	–	–	–	5.1%
Coffey/Lunsford (1990)	Gamma	213	–	20–50	–	–	35	49%	–	–	–	–	–	–
Kjellberg *et al.* (1984)	Proton	260**	–	–	–	–	148	22%	–	9	439	–	–	–
Fabrikant *et al.*	Helium	350***	–	–	–	–	–	80%	10%	–	–	–	–	–
Steinberg *et al.* (1990)	Helium	89	–	–	–	–	71	62%	12%	1	65	36	5.6%	13.5%
Betti *et al.* (1989)	Linac	186	12–60	–	56	82%	–	–	–	2	–	–	1	2
Colombo *et al.* (1989)	Linac	127	5–40	18.7–40	120	49.5%	92	74.6%	–	–	–	–	5.5%	3.1%
Sturm *et al.* (1990)	Linac	78	31	–	–	44%	–	–	–	–	–	–	–	–
Oliver *et al.***** (1990)	Linac	33	–	–	21	38%	–	–	–	1–	–	–	3	–
Friedman *et al.* (1990)	Linac	33	–	–	10	20%	–	–	–	–	–	–	1	1
Loeffler *et al.* (1990)	Linac	16	–	–	11	45%	22	36%	–	–	–	–	–	–

* Personal communication.

** Kjellberg up to now has treated 1300 vascular malformations, including 98 angiographically occult vascular malformations.

*** Included are 35 angiographically occult vascular malformations.

ernoma which at surgery turned out to be a thrombosed AVM. Five cases were infratentorial and 10 were supratentorial. Partial regress of the cavernomas occurred in two cases at 15.5 and 35 months after radiosurgery. There were no visible changes in 13 cases. There was one rebleed. Six cases developed radiation induced changes (37.4%). In two of them the MRI or CT images disclosed blood-brain barrier damages. In the other 4 cases the blood-brain barrier was intact. Four patients (12.5%) remained with permanent neurological deficits. Cryptic AVMs should presumably benefit from radiosurgery, but in the majority of cases a differential diagnosis is impossible. This fact convinced us not to use radiosurgery in low flow vascular malformations until the cause of the poor response to radiosurgery and of the high incidence of complications has been elucidated.

Linear Accelerator in Arteriovenous Malformations

The numbers of patients treated to date are small compared to the series treated with the Gamma Knife or the Bragg peak heavy particle method. The follow-up is relatively short. Initial reports do not match completely the results with the Gamma Knife but they confirm roughly its success. Colombo (personal communication 1991) (Colombo *et al.* 1989) treated 127 patients with AVM (58 males and 69 females) aged from 6 to 70 years (mean 32.1 years). The diameter of the nidus varied from 5 to 40 mm. Target doses given varied from 18.7–40 Gy (mean 29.1 Gy). Mean follow-up was 34.5 months (range 1–72 months) (Table 11). Of 120 patients with more than 1 year follow-up, 101 (84.1%) had a 12 month control angiography. In 50 patients (49.5%) complete obliteration of the AVM occurred. In 40 patients the AVM decreased in size and in 11 no changes occurred.

In the group of 40 patients with incomplete obliteration at 12 months, an increase in size of the persisting draining vein was observed in 8 cases. This was interpreted as an effect of increased intraluminar pressure due to blood flow derouting. The risk of rebleed seemed to be higher in this group. Of 92 patients followed for more than two years, 67 (72.8%) had angiographic follow-up and in 50 the AVM was completely obliterated (74.6%). Rebleed occurred in 12 patients. Four died, 3 required emergency surgery, 2 remained with neurological deficits and 6 had normal neurology. Radiation induced neurological deficits occurred in 7 cases (5.5%). Four of the patients had hemiparesis or a hemisensitive syndrome. One patient developed a diencephalic syndrome, 1 patient had a confusional episode and another a fifth nerve deficit. Four (3.1%) of the 7 patients remained with permanent neurological deficits.

Betti treated 186 AVMs between December 1982 and April 1987 (Betti *et al.* 1989). Of 58 cases with 1-year follow-up and a diameter less than 30 mm, 82% were occluded. One patient developed a transient neurological

deficit. He also reported 66 AVMs treated between September 1982 and October 1985. The size of the AVM ranged from 12 to 60 mm in diameter. A target dose from 20–70 Gy was used. Two patients rebled and died. Forty patients were followed for more than 24 months. Of these, 27 (67.5%) had complete obliteration on angiography. Two patients remained with permanent neurologic deficits (Table 11).

Sturm reported data on 78 AVMs treated with the linear accelerator (Friedman 1990). The mean diameter of the AVMs was 31 mm and the mean dose delivered was 20 Gy. Forty-four percent of the AVMs were totally occluded after 1 year (Table 11).

Forty-five AVMs were treated with a linear accelerator by Oliver *et al.*, however only 33 of them have been reported (Friedman 1990). Twenty-one had 1 year angiographic follow-up and total occlusion was seen in 38%. Three patients presented with treatment related complications and 1 of the patients rebled (Table 11). Loeffler *et al.* treated 16 AVM (Friedman 1990). Complete obliteration occurred in 5 of 11 after 1 year, and in 8 of 22 after two years (Table 11).

Friedman reports on 33 AVMs ranging in size from 10 to 30 mm (average 17.2 mm) (Friedman 1990). Ten patients had a 1 year angiographic follow-up. Two showed complete obliteration. Two neurologic deficits (6%) were observed, however only 1 had a permanent deficit (Table 11).

Charged-particle Radiosurgery in Arteriovenous Malformations

Levy *et al.* states that approximately 2,000 vascular malformations worldwide have been treated using charged particle radiosurgery (Levy *et al.* 1990). Kjellberg *et al.* treated more than 1300 patients with vascular malformations of the brain, including 98 with angiographic occult vascular malformations, using Bragg peak proton radiosurgery (Levy *et al.* 1990) (Table 6). Kannov *et al.* treated 187 AVM, and Minakova *et al.* treated 50 patients with brain AVM both using proton radiosurgery (Levy *et al.* 1990). Ogilvy (Ogilvy 1990) reviewed the available information from Kjellberg. The dose used for treatment is adjusted according to the size of the AVM. Current dose protocols are below the estimated 0.6 percentile complication curve. For lesions 50 mm in size less than 10 Gy are given.

Of 260 patients treated and reported in 1984 (Kjellberg *et al.*, 1984, 1986) 148 patients had follow-up angiography, two or more years after the treatment. Total obliteration was observed in 33 (22%) patients. Ogilvy notes that the percentage of lesions demonstrating angiographic obliteration from patients treated with doses below the estimated 0.6 percentile complication isoeffective dose is not yet available. Of 439 patients followed up clinically after proton beam therapy, death from haemorrhage occurred in 8 patients within two years of treatment. Two years or more after

treatment death occurred in 3 patients who had elective craniotomy for residual AVM. Two of these patients had complications with abrupt or progressive hemiparesis related to proton beam therapy. It is unclear whether death resulted from surgery. Of 248 patients in the group followed up for two or more years after proton-beam therapy, death from haemorrhage occurred in 1 patient, excluding the 3 patients mentioned above. In 665 patients life table analysis is used to compare mortality and incidence of haemorrhage after proton beam therapy to the natural history of AVM (Ogilvy 1990).

At the University of California at Berkeley, Lawrence Berkeley Laboratory, more than 350 patients with AVM have been treated using helium Bragg-peak radiosurgery (Fabrikant *et al.* 1984, 1985, 1989; Levy *et al.* 1989, 1990; Steinberg *et al.* 1990) (Table 11). Selected for the treatment are surgically inaccessible vascular malformations, history of intracranial haemorrhage, progressive neurological dysfunction without haemorrhage, intractable vascular headaches or seizures. Ten percent of the treated cases were angiographically occult vascular malformations. The age of the 316 patients (155 males, 161 females) with AVM ranged from 6 to 69 years. Forty-five patients were 18 years or younger. Volumes treated ranged from 0.08 to 60 cc. The total obliteration rate for all volumes up to 60 cc was 80%. Rebleed occurred in 10% of patients. Some neurological dysfunction occurred in about 15% of the patients, the majority in the earlier high dose group of the initial protocol. More than one half of these patients had complete or partial improvement. Moderate or severe symptomatic vasogenic oedema occurred in about 10% of cases. In some cases histological studies revealed radiation necrosis. Symptomatic occlusion of vessels occurred in 2 to 3 percent. Overall, significant and permanent neurologic deficits occurred in approximately 10% of the cases.

Steinberg *et al.* 1990 presented a detailed clinical and radiological follow-up in 86 patients treated between July 1983 and January, 1984, for an AVM using the helium Bragg-Peak radiation in the same Lawrence Berkeley laboratory. The doses ranged from 8.8 to 34.6 Gy delivered to tissue volumes of 0.3 to 70 cc. Seventy-one of 86 patients had angiographic follow-up from 11 to 48 months after treatment. The overall findings were complete obliteration of the lesion in 44 (62%); partial obliteration in 10 (28%); and no change in 7 patients (10%). Two years after radiation treatment, the rate of complete obliteration of the lesions was 94% for lesions smaller than 4 cc; 75% for those of 4–25 cc; and 39% for those larger than 25 cc. After 3 years, the rates of obliteration were 100, 95, and 70%, respectively (Table 11).

Permanent neurological complications occurred in 12 patients (13.5%) and 5 patients (5.6%) had transient neurological complications. Haemorrhage occurred in 10 (11.6%) patients between 4 and 34 months after

treatment. The angiographically occult vascular malformations were treated with doses ranging from 10 to 45 Gy. Current dose schedules range from 15 to 25 Gy. Thirty-one of 35 patients had a 12 to 72 months follow-up. Two patients died, 6 had rebleed within 13 months after radiosurgery and 1 at 19 months. There were permanent complications in 1 case and reversible complications, in 2 cases.

Discussion

In our first reports we insisted that microsurgery should be considered as the first choice in the management of AVM in the brain. This policy seems to persist in the majority of the most recent publications on radiosurgery (Friedman 1990, Steinberg 1990) while we changed our indications. We want to underline that we no longer consider radiosurgery the second choice in the treatment of AVM. Radiosurgery is an alternative to microsurgery and in selected cases it is the first choice. The decision making is based on the natural history of the AVM, on presenting symptoms, on the parameters of the patient and the variables of the AVM. We use Gamma Knife radiosurgery for ruptured AVMs in the limbic system and in the basal ganglia, and for nonruptured AVM in all localizations. The rationale for the use of radiosurgery for non bleeding AVM even in microsurgically easily accessible localizations is the fact that the chances for total obliteration of the AVM within two years is high while the risk for a haemorrhage within two years is low.

The goal of radiosurgery for AVM is to eliminate the risk for haemorrhage. This is obtained by total obliteration of the AVM. Anything falling short of total obliteration should be considered as an unsatisfactory result. Even a tiny early filling vein indicates the persistence of shunting. The best method of assessing the obliteration of the AVM is an angiogram of good quality which should demonstrate a normal circulation time, complete absence of pathological vessels in the former nidus, and normalization or disappearance of draining veins.

One may argue that the criteria for angiographic complete response may be fulfilled by untreated cryptic AVM and which may be at risk for haemorrhage; however, in our material no haemorrhage occurred in patients declared as cured on angiographic evidence. Controversy exists concerning whether or not radiosurgery decreases the risk for haemorrhage in still patent AVM (Ogilvy 1990). There is a consensus among neurosurgeons and we share it – that only total obliteration of the AVM gives protection against rebleed. This contention is borne out by "person year probability estimate" while the result using the "Kaplan-Meier life table" method is equivocal suggesting that some protection in a radiosurgically treated but still patent AVM, cannot be excluded. This incongruency is

presumably due to a small number of patients observed for a relatively short period. A definite answer will be possible only when large series with long observation time become available. If any protection against bleeding in still patent AVMs exist, it would occur late, 6–8 years after radiosurgery. Hence its value would be questionable.

The degree of protection conferred on complete responders, partial responders and non responders as emphasized by Larsson and Gutin must be "determined from mature clinical data". According to them such a determination is difficult. To illustrate the problem, Larsson and Gutin give the example of a stratified, prospective randomized trial, designed to quantify the protective effect of radiosurgery. Two hundred patients are to be followed for 2 years to demonstrate a statistically significant protective effect (Larsson and Gutin 1990).

In their thought provoking review Larsson and Gutin also illustrate the difficulty in determining the relative efficacy of radiosurgery performed by different groups with different apparatus or techniques. According to them, 200 patients must be followed for 10 years to demonstrate a statistically significant difference in risk of haemorrhage between methods. In their example a rigorously controlled scientific study was assumed. However, today a scientific comparison is impossible. In prior studies, grading systems for AVM were not used and even today different centers use different grading systems. The patient and AVM parameters as well as the technical procedures of the treatment vary and the criteria for the assessment of complete response at angiography may vary. Therefore the comparison in Table 11 is of limited relevance.

The treatment of low flow vascular malformations remains controversial. Kjellberg treated 98 cases; however, results are not yet available. The group in the Lawrence Berkeley Laboratory treated 35 patients (Levy *et al.* 1990), and the Pittsburgh group reported 24 cases treated with the Gamma Knife (Coffey and Lunsford 1990). In 16 cases treated by us with the Gamma Knife, follow-up of 4–7 years is available. In 2 cases partial decrease of the lesion as assessed on MRI images occurred. There was rebleed in 1 case and radiation induced changes in normal neural tissue as assessed on MRI and CT scan were observed in 6 cases. Four remained with permanent neurological deficits. Thus an unfavourable course occurred in 43 percent of the cases.

Of 35 patients treated with helium (31 of them followed 12–72 months), Levy reports death in 2 cases, 7 rebleeds, and 3 radiation related complications. Hence unfavourable course was observed in 38.7%. Nevertheless, Levy cryptically considers "the preliminary clinical results [to be] promising".

We feel that the present results do not warrant a place for radiosurgery in the treatment of cavernomas. This contention was challenged, and it

was argued that only long term observation will tell us whether or not radiosurgery is appropriate for cavernomas. It has also been stated that we used too high doses and this would explain the high incidence of complication. However, we gave the same doses as for AVM and the incidence of radiation induced damages were 4 times higher than in AVM. Furthermore, we observed a case treated with low dose heavy particle. In spite of the low dosage, the patient developed a radiation induced damage of the surrounding brain tissue. But let's assume that by giving lower doses the rate of radiation induced damage will decrease. The important fact of the lack of response to treatment will persist, since it is improbable that the therapeutic effect will be better than with the high doses.

The slow-flow vascular malformation cannot be visualized on the angiogram. Therefore, long term clinical follow-up is required to assess any change in the natural history of the disease. Until imaging techniques with greater diagnostic specificity permit differentiation between those lesions that represent a true AVM and those that represent other occult malformations like cavernous angiomas, which seem not to be an indication for radiosurgery, we feel that low flow vascular malformations should not be treated with radiosurgery.

Radiosurgery in Tumours

Intracranial tumours of small and moderate size, if accurately delimited, can be treated by single high dose irradiation. However, the traditional criteria for assessment of the results cannot be applied. Radiosurgery does not eradicate a meningioma or an acoustic tumour since it only causes them to shrink or arrests their growth. This can be obtained without mortality and with a low incidence of side-effects if the basic principle of radiosurgery – a steep dose gradient at the border-line between the tumour periphery and surrounding normal structures – is respected.

Craniopharyngiomas

Radiosurgery is an appealing alternative to radiotherapy in craniopharyngiomas. It permits precise irradiation of the solid component of the tumour. More than 20 years after the first cases treated by Backlund, it still has not been possible to determine the optimal single dose necessary to induce necrosis of a solid craniopharyngioma. It seems that a peripheral dose of 10 Gy is sufficient for satisfactory results (Backlund 1979) (Table 12).

Backlund reported the results from combining intracystic radionuclide treatment with radiosurgery to solid tumour portions in 11 patients. In 3 patients radiosurgery was the primary treatment. The diagnosis was routinely secured by open or stereotactic biopsy. The target dose varied between

Table 12. *Craniopharyngioma*

	Source	Nr cases	Decrease in size	Unchanged size	FU/mos.	Complications	Death
Backlund *et al.* (1979)	Gamma	11	11	0	12–42	1	0
Coffey *et al.* (1990)	Gamma	3	1	2	–	2	0

20 and 50 Gy and the dose at the periphery of the tumour was limited to 10 Gy, in some cases even to as little as 2–5 Gy. The usual course after the irradiation was a progressive decrease in the size of the tumour and regression of clinical symptoms. The majority of the patients were in good condition and working at follow-up periods of 1 to 3.5 years.

It was difficult to establish a definite cause-effect relationship for symptoms that occurred after irradiation in a young girl who had open surgery previously and had impaired sight in her right eye (finger counting). This improved following injection of radiocolloid into a large cyst and the visual acuity in her affected eye was 20/100 at the time of radiosurgery. One year later she became blind in the same eye and after another 6 months she developed a left-sided transitory occulomotor paresis as well as a transitory hypothalamic syndrome. Subsequently, progressive recovery occurred and the patient is now well except for right-sided amaurosis. Backlund suspected that the pronounced shrinkage of the tumour may have induced untoward effects as a result of traction; however, a late radiation effect cannot be excluded as a cause of the patient's deterioration.

Coffey reported 3 craniopharyngiomas treated by radiosurgery (Coffey *et al.* 1990) (Table 12). One small residual tumour in the third ventricle after microsurgical resection disappeared 1 year after radiosurgery. The other 2 patients had residual solid tumour after intracystic ^{32}P treatment. One of these patients had received radiotherapy and had undergone two attempted tumour resections prior to radiosurgery. Thirty-three point three Gy with an 18 mm collimator were given as target dose; the peripheral dose was 16.67 Gy. The optic chiasm received less than 10 Gy. This patient experienced transient vision deterioration. The third patient received a target dose of 28.6 Gy. The peripheral dose was 20 Gy. This patient had a delayed visual loss.

Pituitary Adenomas

Since the early 1950's a large number of pituitary adenomas have been treated by heavy charged particles at the Harvard Medical School in Boston,

in Leningrad, in Moscow and at the Lawrence Berkeley Laboratory in California (Levy *et al.* 1990) (Table 13). The treatment involved at least 3 or 4 fractions delivered over 5 days and it was therefore not a radiosurgical treatment as defined by Leksell. However, it demonstrated the advantage of reduced fractionation in patients with Cushing's syndrome and it actually was the rationale for the use of Gamma Knife radiosurgery for the treatment of pituitary adenomas.

Pituitary Dependent Cushing's Disease

Eighty patients with Cushing's disease were treated with helium-ion plateau irradiation (Levy *et al.* 1990) (Table 13). Mean basal cortisol levels and dexamethasone suppression testing returned to normal values within 1 year after the treatment and remained normal during more than 2 years of follow-up. Doses to the pituitary gland ranged from 50 to 150 Gy. All 5 teenage patients were cured by doses of 60 to 120 Gy without inducing hypopituitarism or neurologic sequelae; however, 9 out of 59 older patients subsequently underwent bilateral adrenalectomy or surgical hypophysectomy following recurrence. These patients were treated with 60 to 150 Gy in 6 alternate day fractions. When the same doses were given in 3 or 4 daily fractions, 40 of 42 patients were cured. One patient developed visual field deficits 18 months after treatment. Two patients developed rapid progression of ACTH – secreting pituitary adenomas, i.e., Nelson's syndrome, following bilateral adrenalectomy that had been performed after helium irradiation failed to control the tumour growth. Two patients developed transitory partial third nerve palsies 6 to 7 years after helium – ion treatment.

Kjellberg performs the Proton beam Bragg-peak treatment in a single setting in the Harvard 160 MeV cyclotron (Kjellberg *et al.* 1979) (Table 13).

Table 13. *Cushing's Disease*

	Source	Nr cases	FU/years	Complications	Cured
Kjellberg *et al.* (1979)	Proton	180	12	–	153
Levy *et al.* (1990)	Helium	42	–	5	40
Rähn *et al.*	Gamma	8	–	–	8*

* Personal communication. Rähn has treated 120 cases with Cushing's disease. These 8 cases belong to a series treated recently, MRI with Gadolinium being used for localization.

The proton beam diameter and configuration is selected smaller than the size of the sella turcica so that a rim of pituitary tissue is preserved at the margins to avoid hypopituitarism. Patients with Cushing's disease have been treated since 1954. Of 180 patients with Cushing's disease, 93% had follow-up. Fifteen patients have died of diseases not related to the treatment. One visual field defect and 5 oculomotor disturbances with partial regression were observed as complications. Hypopituitarism occurred in 2.5% to 5% of the patients. "Cure" was obtained in 85% of patients followed up to 12 years. Failure beyond the 5 year interval occurred in the cases treated below the 85th isoeffective dose centile. The failures in the 2 to 5 year interval were treated up to the 99th centile of isoeffective dose. Findings of life table analysis were as follows: in groups of isoeffective doses: < 50 centile, 22 years; 51–85 centile, 18 years; 86–95 centile, 15 years; > 95 centile, 7 years. All four centile groups have a 75% "cure" rate at the 5 year interval (Kjellberg personal communication 1991) (Table 13).

In the Department of Neurosurgery, Karolinska Hospital, Stockholm, 112 patients with Cushing's disease were treated since 1974 with radiosurgery using the Gamma Knife (Rähn *et al.* 1980, 1979, and personal communication 1991) (Table 13). The total dose was given in a single session. In an early series of 29 patients with Cushing's disease only 14 of 29 were cured after the first treatment, 4 additional patients after 2 treatments, 2 after 3 treatments, and 2 patients required 4 treatments. Eleven of the 22 patients in remission in this series presented hypopituitarism after the treatment. An additional 37 patients with Cushing's disease have now been included in a long term follow-up by Rähn and the number of patients requiring hormonal replacement therapy was 11 of 59 (19%) and clinical remission has been achieved in 42 cases (82%).

The crude localization techniques (stereotactic plane skull films) used in Berkeley and in the early Karolinska series presumably account for the pituitary insufficiencies observed. It is of particular interest that all 8 patients in Rähn's series where gadolinium enhanced MRI has been used for target localization are cured and without need for hormonal substitution.

No recurrencies were reported in patients treated with heavy particles or with the Gamma Knife. For comparison, Laws reported a 10% recurrence rate after transphenoidal surgery in his series of patients with Cushing's disease.

Acromegaly

Helium ion beam irradiation has proven to be very effective in acromegaly. In 314 patients treated the maximum dose ranged from 30 to 50 Gy, most often delivered in 4 fractions over 5 days. Clinical improvement was observed within the first year, even before a significant fall in serum growth

hormone level occurred (Levy *et al.* 1990) (Table 14). The mean growth hormone level usually decreased nearly 70% within 1 year. Normal levels were sustained during more than 10 years follow-up. Most of the treatment failures resulted apparently from not including the extrasellar tumour extension in the radiation field.

Variable degrees of hypopituitarism were observed in about one third of the patients. No diabetes insipidus occurred. In 298 acromegalic patients, complications were limited to those patients who had received photon treatment prior to radiosurgery. Three patients developed seizures due to limited temporal lobe necrosis; 3 patients presented transitory extraocular palsies and 2 patients had partial visual field deficits.

Kjellberg reports 577 acromegalic patients treated with proton beams. The mean value of hGH showed a reduction of 80% in 2 years and 98% in 20 years. The long term course as assessed by the life table method of statistical analysis is the following: cure with hGH less than 10 ng/ml occurred in 50% of patients in 2 years, in 80% of patients in 8 years, and in 97.5% in 20 years. Cure to less than 5 ng/ml hGH occurred in 50% at 5 years, in 80% at 10 years, and in 87.5% at 20 years (Kjellberg personal communication 1991, Kjellberg *et al.* 1968) (Table 14).

Visual field defects occurred in 6 patients and blindness in 2. Fifty-one of 510 patients died (10%), more than half of them due to cardiac or cerebral vascular disease. Two patients had adenocarcinoma of the pituitary and another patient who also had X-ray therapy, developed wide spread fibrosarcoma of the base of the brain.

More than 10 years following the treatment, late failure with hGH greater than 5 ng/ml, occurred at doses below an 80% isoeffective dose centile. Five to 10 years following treatment failures with hGH. 10 ng/ml occurred below the 80th centile. Dose centiles and intervals – at 10 ng/ml were: less than 50 centile dose, 18 years; 51–85 centile, 18 years; 86–95

Table 14. *Acromegaly*

	Source	Nr cases	Complications	Improved	Cured
Levy *et al.* (1990)	Proton	318	–	Most pts.	–
Kjellberg *et al.* (1991)	Helium	577	8	–	50% after 2 yrs FU 80% after 20 yrs FU
Rähn *et al.** (1991)	Gamma	7	–	5	–

* Personal communication.

centile, 9 years; greater than 95 centile, 4 years. The one hundred percent "cure" rate to 5 ng/ml for the 4 centile groups ranged from 10 to 20 years.

Sufficient clinical, radiological and laboratory follow-up of acromegaly patients treated with the Gamma Knife in Karolinska Hospital is available in only 21 cases (Lindquist personal communication, 1991). Only 7 patients received Gamma Knife treatment as the sole treatment and complete coverage of the tumour by the intended dose was accomplished in 7 of the 21 cases. A significant drop in plasma growth hormone level resulted in 5 of 7 patients treated with the Gamma Knife alone, and neural pituitary function was preserved in all (Table 14).

Nelson's Syndrome

Backlund reported 3 cases of Nelson's syndrome treated by radiosurgery. In 2 cases 50 to 70 Gy was delivered to an isocenter at the middle of the anterior lobe of the pituitary. In a third case, the maximum dose was placed in the right half of the anterior lobe. Twenty-five to 30 months later the hyperpigmentation seen in this disorder was markedly reduced in 2 patients and disappeared completely in 1 patient and the laboratory findings normalized. A small unilateral visual field defect occurred 1 year after the treatment in a patient who had received 70 Gy. A follow-up encephalogram revealed that the volume of the sellar contents had decreased and that there had been an increase in the herniation of the suprasellar cisterns into the sella.

Prolactin-Secreting Tumours

In 22 patients with prolactin-secreting pituitary tumours, serum prolactin levels were successfully reduced following helium-ion irradiation Levy, Fabrikant *et al.* Of 20 patients followed 1 year after irradiation, 19 had a marked fall in prolactin level (12 had normal levels). Treatment dose and function were comparable to that in the Cushing's disease and Nelson's syndrome groups. Helium-ion irradiation was the sole treatment in 17 patients; the remaining patients were irradiated after surgical hypophysectomy had failed to provide complete or permanent improvement.

Tumours in the Pineal Region

Tumours in the region of the pineal gland and the quadrigeminal plate, of appropriate size and shape, can be treated by radiosurgery, irrespective of their histologic character. Stereotactic biopsy should always precede the treatment.

Backlund reported 3 pineocytomas, 2 ependymomas, 3 astrocytomas, and 1 medulloblastoma subjected to radiosurgery. The average tumour

diameter among these cases varied between 1–3 cm and target doses of 20 to 75 Gy were delivered to the lesions. The average duration of follow-up was 5 years. In 3 pineocytomas and in 2 cases in which the biopsy had failed to provide the histologic diagnosis, the therapeutic results were excellent. In 1 ependymoma and in 2 astrocytomas, the results were also good 1–3 years after the treatment. One ependymoma and 1 astrocytoma increased in size following treatment. A patient with a medulloblastoma and a patient with a tumour erroneously classified as a pineocytoma died 2 and 3 years, respectively, after treatment. Our results could confirm those of Backlund (Fig. 12). Benign tumours of the pineal region should be treated by radiosurgery whereas malignant tumours of the pineal region should be treated by conventional radiotherapy. However, if the size and shape of the malignant tumour permits the use of radiosurgery, this is probably advantageous because the results are comparable with those of radiotherapy without the systemic side-effects of the latter. Radiosurgery has the additional advantage that the treatment is completed in 1 day instead of several weeks.

Meningiomas

There is a general consensus that surgical removal is the treatment of choice in meningiomas and only in special cases such as old age or illness precluding surgery should radiosurgery be the primary treatment. It is widely acknowledged that meningiomas along the medial sphenoid wing, the petroclival ligament and the cavernous sinus are difficult to remove and prone to recurrencies even when radically removed (Mirimanoff RO, *et al.* 1985) (Adegbite *et al.* 1983, Marks *et al.* 1986). Every effort should be made to totally extirpate the tumour. The goal of surgery, however should also be to preserve the quality of life of the patient, even if this means leaving residual tumour.

Residual tumour left after microsurgery of meningiomas should be treated by radiosurgery. There is a wealth of observations that indicates that radiation may stop the growth of a meningioma or even lead to a decrease in the size of the tumour (Barbaro *et al.* 1987, Taylor Jr *et al.* 1988, Carella *et al.* 1982, Petty *et al.* 1985). Questions concerning treatment variables are still not completely answered. Target surface doses of 10–25 Gy were used. The level of the dose was restricted by the proximity of cranial nerves and the brain stem. The dose to the optic nerve, to the chiasma and to the tracts should be kept below 10 Gy. The nerves to the ocular muscles can receive up to 20 Gy. In only 1 of the cases treated with this dose was there uncertainty as to the possibility of radiation damage to the abducens nerve. The trochlear nerve has also received 20 Gy without undue effect. The trigeminal nerve seems to withstand 20 Gy in the cavernous sinus but 15% of patients treated for acoustic neuromas have ex-

perienced symptoms when only a small volume of the trigeminal root entry zone has received 14–20 Gy. An undue effect appeared in 3–20% of the cases where the facial nerve had received 15–20 Gy. Experience with radiation of the eighth cranial nerve is available only from cases of acoustic neuromas, where it seems that this nerve can be exposed without high risk to around 15 Gy. There is not yet sufficient information about the vulnerability of the lower cranial nerves. Concerning the brain stem, only a small tissue volume should be exposed to 20 Gy. The results and side effects still remain to be estimated in long term follow-up.

The longest follow-up times were reported by Rähn in a series of 62 patients treated with the Gamma Knife, in 23 follow-ups ranging from 3 to 153 months (Steiner *et al.* 1991) (Table 15). Radiosurgery was carried out as a primary treatment in 17 (73.9%) cases. The majority of these tumours involved the cavernous sinus. In 12 of the 23 patients the tumour decreased in size. In 3 patients tumour growth was observed. In 8 cases the tumour size remained unchanged. Twenty of these patients had cranial nerve symptoms prior to the treatment. In 7, the symptoms resolved completely and in 5, partially. Two patients had the follow-up imaging 14 and 10 years respectively after the radiosurgery and the tumour size was unchanged compared with the pretreatment volume. Luchin *et al.* reported 33 cases of cavernous sinus meningioma treated with proton Bragg peak at the Burdenko Neurosurgical Institute (in Levy *et al.* 1990). Using 50 to 70 Gy delivered in 2–4 fractions, local control was obtained in 84% of cases with improvement or stabilization of clinical symptoms (Levy *et al.* 1990). Richard Levy *et al.* mention the treatment of meningiomas with charged particles in Berkeley; however, no results are given. Kondziolka (Kondziolka *et al.* 1991) reported an initial 30-month experience using the Gamma Knife in 50 patients with meningiomas. Twenty-four patients had an imaging follow-up 12–36 months after the treatment. Thirteen (54%) showed a reduction in tumour volume while 9 (38%) showed no change. Two patients had delayed tumour growth. Between 3 and 12 months after radiosurgery, 3 patients developed neurological deficits that gradually improved (Table 15).

Steiner (Steiner *et al.* 1991) reports less favourable results. He treated 34 cases. Twenty-nine patients had a follow-up of up to 62 months. Four tumours decreased and 3 increased in size. Neurological symptoms improved in 4 cases (Table 15). A similar discrepancy exists between the results of Colombo and Valentino, both of them using a linear accelerator. Valentino reports that 69 of 87 meningiomas shrank with clinical improvement of different degrees (Valentino *et al.* 1990) versus Colombo's 3 decreases in size in 15 meningiomas (Steiner *et al.* 1991) (Table 15).

It is difficult to explain such differences other than by different ways in assessing the results.

Table 15. *Meningiomas*

	Source	Nr pts	Decrease in size		Increase in size	Unchanged size	FU/nr pts	FU/mos	Complications	Improved neurol symptoms
			Slight	Significant						
Rähn *et al.** (1991)	Gamma	82	11	1	3	8	–	3–120	–	12
Kondziolka *et al.* (1991)	Gamma	50	13	–	2	9	24	12–36	3	–
Steiner/Lindquist	Gamma	34	4	0	3	22	29	1–62	–	4
Bunge *et al.*	Gamma	16	3	0	1	7	–	6–36	–	–
Forster *et al.*	Gamma	3	2	0	1	0	–	up to 24	–	–
Colombo *et al.*	Photon	15	2	1	0	12	–	up to 36	–	–

Table 16. *Acoustic Neuromas*

	Source	Nr pts	Unilat	Bilat	Decrease in size	Increase in size	Unchanged	FU/mos	FU/nr pts	Complications		
										Facial palsy	Trigem neuralgia	Death
Norén *et al.* (1991)	Gamma	209	159	50	58%	15%	27%	2–206	–	–	–	2**
Flickinger *et al.* (1991)	Gamma	107	–	–	55%	2%	42%	1–37	40	36%	30%	–

* Personal communication.

** Both patients had neurofibromatosis.

Acoustic Neuromas

In the management of acoustic neuromas success is no longer measured in terms of survival and absence of gross neurological deficits but in terms of preservation of complete facial nerve function and hearing. This is true for both microsurgery and radiosurgery. Leksell had the idea to treat acoustic neuromas with the Gamma Knife, and the first acoustic neuroma patient with bilateral tumours was treated in June 1969 (Leksell 1971). I assisted with the first cases but I did it reluctantly. When I declined to be coauthor because I did not feel that the Gamma Knife had a place in the treatment of acoustic neuromas, Leksell mentioned my help in a foot note of his report. In the perspective of over 20 years, I acknowledge that I was wrong. Since then several hundred radiosurgical procedures for acoustic neuromas have been performed. The largest material is that of Norén, consisting of 325 patients with 336 Gamma Knife radiosurgery procedures. Norén recently reported 227 procedures with a follow-up period of at least 12 months (Norén 1991) (Table 16).

The surface dose of 25–35 Gy delivered to the first cases was gradually reduced over the years to levels of 10–15 Gy. In 209 patients with 219 tumours, 50 patients had neurofibromatosis. Ten of these patients had both sides treated. Ninety-one tumours had maximal intracranial diameters of 4–15 mm; 98, 16–25 mm, and 30, 26–33 mm. The mean follow-up time was 54 (range 12–206) months. In 70% of the cases a loss of contrast enhancement or lowering of the signal on the imaging films developed in the tumour.

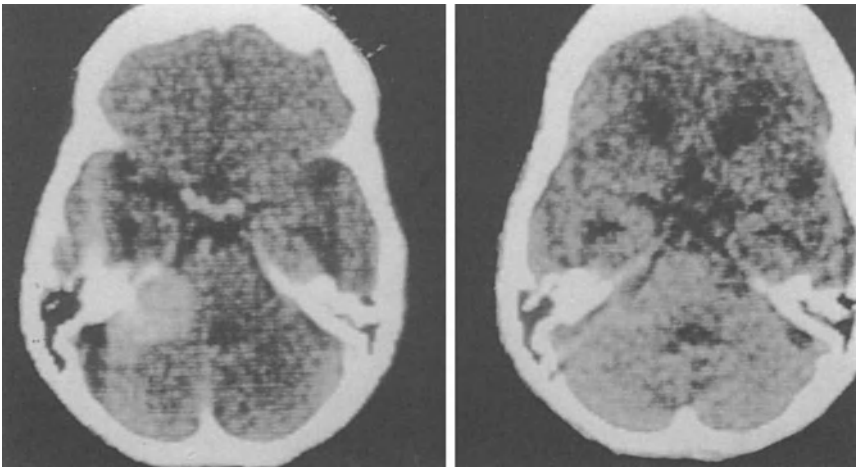


Fig. 14. Acoustic neuroma. CT scans obtained before (A) and 2 years after (B) radiosurgery with Gamma Knife

This pattern was visible 6–12 months after the treatment and became less evident over the next 12–18 months. Shrinkage occurred in 31% of the cases during the first 24 months after the treatment and in 58% later in the course (Fig. 14).

In 79 acoustic neuromas, growth before the treatment was documented by at least two separate imaging studies. Of these, 42 tumours (53%) decreased in size and 22 (28%) remained unchanged for 12–117/mean 42/ months.

The significance of the lack in change in tumour size after radiosurgery is still discussed. It might not necessarily mean that the treatment arrested the growth. To establish whether or not it is the normal behaviour of an acoustic neuroma, the growth rate of the tumour before the treatment should be known.

A study of Laasonen and Troupp (Laasonen and Troupp 1968) shows that growth occurs in about 90% of untreated acoustic neuromas if followed for a period of 12–26 months. Therefore, unchanged size of a radiosurgically treated tumour 12–24 months after the treatment reflects presumably a response to the Gamma Knife treatment.

In 20 tumours, no signs of growth were seen on two subsequent imaging examinations at least 12 months apart prior to the Gamma Knife treatment. After radiosurgery 10 neuromas (50%) decreased in size and 8 (40%) remained unchanged for 23–88 (mean 36/months) following radiosurgery. Out of the 20 neuromas of this group, 8 had a follow-up period of at least 48 (range 48–167, mean 96) months. Six of these (75%) decreased in size; 2 remained unchanged.

Thirty-four tumours (15%) increased in size. In 13 tumours (5.5%), most of them with neurofibromatosis, an initial increase was followed by arrest of growth or some shrinkage. Two patients (1%) with neurofibromatosis died. The cause of death was not related to the treatment.

Untoward Effects Following Radiosurgery of Acoustic Neuroma

Peritumoural oedema developed in 16 patients (7.5%). In 4 cases the oedema induced CSF circulation disturbances. A shunt operation was carried out in 3 of these cases. Hydrocephalus was observed in 17 patients (8%). In 47% of these 17 patients, the hydrocephalus was present before the radiosurgery.

Facial nerve function. Varying degrees of facial weakness occurred in 16% of patients within 6–8 months after the treatment. However, in the cases treated after 1975 the incidence of facial nerve damage was only around 5%. The weakness was temporary in all patients and the recovery of the nerve function occurred 6–12 months after the onset. After the reinnervation, synkinesias could be seen.

Hearing. Twenty-four percent of the patients with a pure tone average of less than 9 dB before treatment showed improvement of hearing or no change within narrow limits. When comparing hearing 1 and 5 years after the treatment the percentage of patients with unchanged hearing was roughly the same, 24% and 27%, respectively.

Vestibular function. In 65% of the ears, a caloric response was present before the treatment. Two and 4 years later the response was still there in 46% and 32%, respectively.

Trigeminal nerve function. Slight facial numbness was seen in 12% and more severe numbness in 8% of the patients. Mild numbness was usually temporary but severe sensory loss tended to persist. After 1975 the incidence of trigeminal damage was reduced to 5%.

The results of Norén have been reproduced by the radiosurgical centers of Buenos Aires, Charlottesville, Pittsburgh and Sheffield. Flickinger reports that out of 7 patients with average tumour diameters less than 10 mm, none developed hearing loss, facial or trigeminal neuropathies (Table 16).

To evaluate the value of radiosurgery in the treatment of acoustic neuromas, further study of tumour control, undue effects and dose-volume effects is needed. Nevertheless, there is a consensus among Gamma Knife experts that radiosurgery has a place in the management of selected patients with acoustic neuroma. The discussion whether radiosurgery should be used primarily or only when microsurgery fails or when the condition of the patient precludes open surgery still continues. Those who compare the results of radiosurgery with the average results of microsurgery in acoustic neuroma advocate the primary use of radiosurgery as an alternative to microsurgery. However, if one would compare radiosurgery with the best results of microsurgery achieved only by certain neurosurgeons – and the authors feel that the comparison should be with the best available microsurgical results – then radiosurgery should be carried out only for residual acoustic neuromas following surgery or in elderly patients and patients with conditions precluding surgery.

Metastatic Brain Tumours

Autopsy of patients who died of cancer reveals intracerebral metastases in 50% of the cases. Forty percent are single lesions. Untreated patients with metastatic brain tumours have a median survival of roughly 1 months. Patients treated with whole brain radiotherapy die 3–6 months later. The cause of the death is the systemic disease. However, many times despite surgery and radiotherapy patients die of a solitary metastases and not of the systemic disease. Saloman reports in a series of 208 cases (Saloman 1990) treated with surgery, a mean survival time of only 6 months. Patchell (Patchell *et al.* 1990) reported 48 cases divided in two groups. In one group,

patients with surgery and radiotherapy had a mean survival of 40 weeks and recurrencies in 20% of the cases. In the second group 23 patients received only radiotherapy and had a mean survival of 15 weeks with recurrence of the brain metastases in 52% of the cases. Brain metastases are usually well circumscribed lesions and can therefore be a good object for radiosurgery. The first solitary metastatic tumour was treated by Gamma Knife surgery in 1975 at the Karolinska Institute. Today metastatic tumours in the brain are treated in all radiosurgical centers.

Sturm reported 12 patients with solitary brain metastases treated with the Heidelberg linear accelerator system (Sturm *et al.* 1987). In 7 patients followed for 3 months or longer, all had arrest of tumour growth after a 20–30 Gy irradiation. In 4 cases significant shrinkage occurred (Table 17). At the radiosurgery symposium in Miami, Sturm reported 74 brain metastases treated with linear accelerator radiosurgery (Friedman 1990). Stockholm treated 240 metastatic tumours using the Gamma Knife (Karlsson, personal communication 1991). Small series were treated in Buenos Aires, Charlottesville, Gainesville, and Montreal. Valentino, using a linear accelerator, reports in 52 of 58 cases of metastatic tumours both imaging and clinical improvement. Six showed no improvement (Valentino *et al.* 1990) (Table 17). Mirri, using a linear accelerator, treated 95 cases of single or multiple cerebral metastases. The dose given to the periphery of the tumour was 30 Gy delivered in one or two sessions. An additional 10–

Table 17. *Metastatic Tumours*

	Source	Nr pts.	Growth Arrest	Dec Size	FU/mos	Disap-peared	Inc	Death from tumour
Sturm *et al.* (1987)	Photon	12	7	4	–	–	–	–
Valentino *et al.* (1990)	Photon	58	–	52	–	–	–	–
Mirri *et al.* (1990)	Photon	95	–	65	10.69*	12	–	–
Eben *et al.* (1990)	Photon	43	–	41	–	2	–	–
Coffey *et al.* (1990)	Gamma	24	8	11	1.5–13	–	–	3**
Kihlström *et al.* (1991)	Gamma	52	–	25	6–84 (mean 11)	23	1	–

* Mean survival time.

** 3–7 weeks after treatment.

15 Gy were given if the lesion appeared unchanged (Mirri *et al.* 1990) (Table 17). Complete disappearance of the lesion was observed in 12 patients and progressive decrease in the tumour volume in 65 cases. The mean survival time was 10 months. No complications have been observed. In a group of 11 patients where radiosurgery followed surgery the mean survival period was 18.9 months.

Eben *et al.* 1990 select patients for radiosurgery with Karnovski performance status of 70% or greater, with no evidence of systemic disease and potential survival of greater than 6 months. They report 35 patients with 43 recurrent or persistent brain metastases following radiotherapy and treated with linear accelerator radiosurgery (Table 17). The size of the tumours ranged from 12.5 mm to 37 mm (mean 27 mm). Doses between 9–25 Gy (mean 15 Gy) were given and the follow-up was 9 months. All 43 lesions have been controlled in the treatment volume as defined by a decrease in the size of the lesion on CT or "stabilization of the enhancing volume". Metastatic adenocarcinoma responded rapidly (6 weeks). In two cases it disappeared completely. Melanoma, renal cell carcinoma and sarcoma lesions have had minimal reduction in size.

Kihlström (Kihlström *et al.* 1991) treated from 1975 to June 1991 44 patients with metastasis in the brain using the Gamma Knife (Table 17). These patients have been followed clinically and by CT scan for 6 to 84 months. The dose rate was 0.7–5 Gy/min. The median maximum dose was 53 Gy and the median minimum dose was 31 Gy. The volume of the treated metastatic lesions varied between 0.3 and 13 cm^3 with a median volume of 4.4 cm^3. There was no difference in response between the tumours related to histology. In all cases but there was a striking shrinkage of the tumours starting 2–4 months after the treatment. Twentyfive metastases decreased in size and 23 disappeared completely 2 months-1 year following treatment. The only non-responder had metastasis to the brain stem from an ovarian carcinoma and received only 13 Gy as minimum dose. With the exception of this case, there were no cases in which neurological symptoms or signs progressed after radiosurgery and there were no "neurological deaths".

Coffey *et al.*, treated with the Gamma Knife 24 cases with small solitary brain metastases: melanoma (10), non small cell lung carcinoma (6), renal cell carcinoma (3), colorectal carcinoma (1), oropharyngeal carcinoma (1), metastatic adenocarcinoma (3). The size of the metastatic tumours was less than 30 mm in patients aged 24–81 (mean 51.6). Eleven patients had a fixed neurologic deficit. Seven patients had seizures (Coffey *et al.* 1990) (Table 17). Twenty patients received a combination of 30–40 Gy whole brain radiotherapy with a single radiosurgical "boost" of 16–20 Gy to the tumour margin. One patient had only radiosurgery and 3 patients were treated after the metastasis recurred following radiotherapy. Follow-ups between 1.5 and 13 months were available. No mortality and no new

neurological deficits from growth of radiosurgically treated metastasis occurred. Shrinkage of the lesion (11 patients) and tumour necrosis or arrest of tumour growth (8 patients) were documented by follow-up imaging (16), post mortem (2), and surgical specimen (1). Three patients died between 3 and 7 weeks after radiosurgery. Complete disappearance or marked shrinkage of two renal cell metastases occurred between 3 and 20 months after the treatment. Five of 9 metastatic melanomas decreased in size between 3 and 8 months after radiosurgery. Three melanomas had not grown during 13 months. One cystic metastatic carcinoma decreased 6 weeks after stereotactic biopsy and aspiration followed by boost radiosurgery. Fourteen patients were alive at the time of the report and relatively independent at home between 1.5 and 13 months after treatment.

Pittsburgh limited the radiosurgery to patients presenting with solitary metastases to the brain. Most of the other radiosurgical centers were less restrictive accepting patients with multiple lesions for treatment. Davey and O'Brien (1991) in a recent study simulated isodose configurations and made integral dose calculations for radiosurgery treating up to 3 metastases in separate areas of the brain. They concluded that the integral dose calculations of these radiosurgery dose distributions provide reasonable tolerance guidelines. This contention seems to be borne out by the radiosurgical results in series with multiple cerebral metastases. Nevertheless the value of radiosurgery in multiple metastases still remains questionable since growth control of the radiologically visible lesions does not stop the growth of the radiologically not yet detectable metastatic tumours. On the other hand, even in solitary brain metastases, reseeding from extracerebral tumour is possible.

Glial Tumours

Colombo reported the use of linear accelerator radiosurgery in 16 patients with low grade gliomas (Colombo *et al.* 1989) (Table 18). They were all

Table 18. *Glial Tumours*

	Source	Nr pts	Decrease in size	Growth arrest	Increse in size	FU/mos
Colombo *et al.* (1989)	Photon	16	–	–	–	12–71
Eben *et al.* (1990)	Photon	13	–	–	–	2–17
Coffey *et al.* (1990)	Gamma	33	14	15	4	1–25

deep seated tumours and less than 35 mm in diameter. At the time of the report, the follow-up was 12–71 months. Significant clinical improvement occurred in 9 patients, deterioration in 2 and death in 2 patients. The condition of 2 patients became stable. CT scanning revealed marked reduction or complete shrinkage in 5 cases. The results were preceded by a massive transitory increase in size at 6 to 9 weeks. In 4 cases decrease was seen without prior increase in size.

Eben *et al.* (1990) treated 13 recurrent glioblastomas and 4 astrocytomas using a linear accelerator (Table 18). The mean dose of prior radiotherapy was 59.4 Gy. The interval between prior radiotherapy and radiosurgery ranged from 3 to 120 months (median 7 months). Three patients with biopsy-proven or angiographically diagnosed glioblastomas were treated primarily with the linear accelerator radiosurgery. Periphery doses varied ranging from 10 Gy to 20 Gy. Follow-up was 2 to 17 months. Ten of the 13 patients are still alive without clinical radiographic progression at a median of 10 months after radiosurgery. After surgery and conventional radiotherapy, patients presenting with recurrent high grade glioma had a life expectancy of 2–3 months. Six patients had complications between 2 and 7 months following treatment. Of 9 high grade glioma patients treated with a stereotactic radiosurgery "boost" to standard fractionated radiation, 6 are alive with a median follow-up time of 17 months.

Loeffler *et al.* (1990) used linear accelerator radiosurgery in the treatment of 22 children with recurrent brain tumours. The histology of the lesions included ependymoma, 9 cases; astrocytoma, 6; medullo-blastoma, 2; dysgerminoma, 1; and pineoblastoma, 1. All but 2 patients had received prior radiotherapy (median dose 54 Gy). Thirteen of the 22 patients (59 percent) had also received previous systemic chemotherapy. The interval from radiotherapy to radiosurgery was 12 months median (range 5–12 months). Radiosurgery doses presented to the 70–90 isodose line at the tumour periphery ranged from 10–25 Gy. With a median follow-up period of 9 months (range 1–37 months) 11 of 19 patients are alive and 12 are free of symptoms. Imaging studies have shown reduction in enhancement volumes as early as 6 weeks following radiosurgery for ependymomas and medulloblastomas, while only slight reduction in enhancement volume has been seen in the majority of astrocytomas. Despite prior radiotherapy and systemic chemotherapy, radiosurgery was well tolerated in the majority of patients. Long term complications have occurred in 1 patient with anaplastic astrocytoma which required surgical resection of necrotic tissue.

Coffey and Lunsford, using the Gamma Knife radiosurgery, report shrinkage of the tumour in 14 of 33 malignant tumours and arrest of tumour growth in 15 patients during a follow-up period of 1–25 months (mean 5 months). Tumour progression occurred in 4 patients (Table 18). In 28 patients with available follow-up clinical data the presenting neu-

rological deficits improved in 4 patients, remained unchanged in 20 patients, and worse in 4 patients after treatment. Seven patients with malignant tumours died between 1 and 39 weeks postoperatively; however, death was not related to the radiosurgical treatment. Tumour progression as the cause of death occurred in 2 patients. Postmortem examination revealed complete necrosis of the treated tumour in 1 patient who eventually died of diffuse tumour spread within the neuraxis, 39 weeks after radiosurgery (Coffey and Lunsford, 1990).

Treatment of anaplastic astrocytomas and glioblastomas by Gamma Knife radiosurgery has been performed at the Karolinska Institute in 15 patients as an adjuvant to surgery and/or radiotherapy. High doses have been used; nevertheless, this treatment modality has added little to the therapeutic arsenal for the malignant tumours. In spite of the more optimistic interpretation of their results in other centers, significant treatment benefit of radiosurgery remains to be shown.

Discussion

Radiosurgery was originally developed by Leksell to treat functional disease, but because of pharmacological developments in the treatment of functional disease, the AVMs and tumours became the main objects for the new method from the very beginning of the radiosurgical activity. Very soon it became obvious that a number of factors promoted the treatment of the AVM while the interest in using the Gamma Knife for tumour cooled down. The fact that the results in AVM were clear-cut while the effect on tumour was less spectacular channeled the resources of the single existing radiosurgical center to the treatment of AVM. Nevertheless, there were exceptions, namely the acoustic neuromas and, in less measure, the pituitary tumours.

The recent proliferation of radiosurgical centers has already changed this trend and an increasing percentage of the treated cases represents both benign and malignant tumours. The fact that a large number of benign tumour patients are referred for radiosurgery is surprising. This could be explained partly by unsatisfactory overall results with microsurgery for tumours in difficult locations. For example, in a survey conducted by the Association of Acoustic Neuroma patients in the U.S.A., only 20% of several hundred interviewed said they were satisfied with the outcome of microsurgery. It is well known that only a few neurosurgeons operate on a sufficient number of acoustic neuromas and meningiomas involving the cavernous sinus or clivus meningiomas to acquire the necessary skill to eradicate these lesions preserving at the same time the quality of life of the patient. Therefore, the number of recurrences, the number of facial palsies, the loss of hearing, damage of other cranial nerves, and the number of

patients asking for radiosurgery is increasing, and this in spite of serious efforts on the part of those performing radiosurgery to inform the patient that, in good hands, microsurgery should not be easily discarded, and that radiosurgery should be reserved for selected cases.

In principle, we require surgical exploration prior to radiosurgery in tumours. The aim of surgery is two-fold:

1) to secure the histology and

2) to try to eradicate the tumour if this is feasible without damaging the quality of life of the patient.

A patient with a mass diagnosed as a meningioma involving the cavernous sinus by both MRI and an exploration without biopsy, was referred for radiosurgery. We advised new surgery with an effort to extirpate the tumour and if this proved impossible, to secure a specimen for histology. The patient has been reoperated and a cavernoma was found in the cavernous sinus and radically extirpated. If this patient had been accepted for radiosurgery, a cavernoma would have been irradiated, and cavernomas do not respond to radiosurgery. The cure by microsurgery would have been missed.

The second case was referred for radiosurgery with a diagnosis of an astrocytoma Grade I. It was a well-localized lesion in the uncus and instead of radiosurgery we operated and resected the uncus. The histology secured the diagnosis of dysembryoplastic neuroepithelial tumour. By performing the resection, we cured the patient. Radiosurgery was not indicated in this case.

Radiosurgery in benign tumours should be reserved for cases where surgery in skilled hands fails, for the elderly, for patients with medical conditions precluding surgery, and for patients who, in spite of adequate information, refuse surgery.

Theoretically, any tumour cell could be killed with high-enough dose of radiation. Nevertheless, in practice, there are narrow limits for using high-enough doses. In spite of the fact that the dose gradient in radiosurgery is steep, the use of tumour necrotizing doses could lead to damage of cranial nerves or other important brain structures close to the periphery of the tumour. The close vicinity of cranial nerves or brain stem to the tumour is a serious limitation of the therapeutic potentials of radiosurgery. Research should focus on the possibility to protect these structures or to increase the tumour cell killing faculty of lower doses.

Conceptually, it is difficult to accept the use of highly focused beam in infiltrating tumours. The more so since the changes seen on the MRI or CT scan do not represent the whole truth – tumour cells spreading beyond the limits of these pathological changes visible on the imaging films. One may argue that an additional apparently normal tissue volume, surrounding the pathological changes can be included, reaching, thus, the tumour cells

that infiltrate the neural tissue like the sand that penetrates the forest between the trees, when driven by the wind. However, expanding the radiation field, the volume to be irradiated would increase too. Moreover, the effect of radiation in the tumour compared to that in normal tissue will in this way become less favourable, not more favourable, as one proceeds from multi-fractionated to single fractionated irradiations. And since the twilight zone around the visible changes on the MRI could contain a significant amount of normal tissue, the possible maximum radiation dose that can be safely given will be limited. On the other hand, there may exist a subpopulation of patients in whom the tumour cells are within the limits of the pathological enhancement on the imaging study. These may benefit from radiosurgery. An additional argument for radiosurgery instead of radiotherapy could be the advantage of a single treatment. However, the main argument for the use of radiosurgery could be the necessity not to abandon the field, to persevere in research, to explore new development avenues. Some radiosensitizers that interfere with DNA repair or some other "second factor" may improve the outcome in the malignant tumours. Whether these or cell-seeking compounds loaded with Boron[10] (Gabel *et al.* 1984) or the neutron capture therapy will improve the results of radiosurgery in tumours remains to be proven.

The Gamma Knife in Functional Radiosurgery

At the time when Leksell introduced radiosurgery, this was synonymous with functional neurosurgery. Consequently, the radiosurgical method without trephination and without the hazards of intracerebral bleeding and infection was first applied in this field. Crossfiring of a thalamic target by stereotactically focused protons was initially used to treat tremor in a few cases of Parkinson's disease. After the introduction of the Gamma Knife in 1968 only this device was used in functional radiosurgery.

Gammathalamotomies were made not only for tremor but also for intractable pain (Steiner *et al.* 1980). The Gasserian ganglion was radiated for trigeminal neuralgia and gammacapsulotomies were performed to interrupt fronto-limbic connections in the treatment of intractable anxiety and obsessive-compulsive disorders (Rylander 1979, Mindus *et al.* 1991). It was demonstrated that the Gamma Knife could indeed produce the well circumscribed small lesions required in functional neurosurgery. Despite the attraction of a bloodless method for making brain lesions, the use of the Gamma Knife in functional neurosurgery abated. There were two major reasons for this development. The first was the general decline of the need for stereotactic ablative procedures with the introduction of better drugs for the treatment of tremor and pain as well as the introduction of alternative treatment methods such as stimulation procedures for pain, per-

cutaneous cordotomy, morphine pumps etc. The other reason was that there were initially no imaging methods for target localization which could match the precision and accuracy of the Gamma Knife. Crude indirect localization methods such as stereotactic pneumoencephalography were available but the accurate placement of the lesion could not be corroborated by physiological methods which necessitate trephination.

The test of time has, however, partly disavowed drug therapy in some functional disorders and there is now a resurgence of interest for neurosurgical procedures. Furthermore, the considerable developments in imaging techniques have greatly supported the advancement of stereotactic techniques. Imaging techniques for "functional imaging" such as positron emission tomography (PET) and magnetoencephalography (MEG) are now emerging to help the return of the Gamma Knife as a useful surgical tool in the field of functional neurosurgery. A reassessment of the indications and possibilities for functional radiosurgery seems, therefore, appropriate.

Cancer Pain

Gammathalamotomy for intractable pain was one of the first procedures performed with the Gamma Knife and in cancer patients it was confirmed that sharply circumscribed lesions could indeed be produced at the selected target point. The experience of treating 52 cancer patients for pain by gammathalamotomy was reported by Steiner (Steiner *et al.* 1980). All treatments were performed using the first Gamma Knife prototype. With this apparatus 2 collimators were available to produce disc shaped lesions sized 3×5 and 3×7 mm respectively. The lesion volumes were somewhat smaller than those which can be produced using the 4 mm collimator of the commercially available Gamma Knifes today. Targets were localized by using stereotactic pneumoencephalography and were related in the conventional manner to the intercommisural plane. Imaging methods for confirming the presence of a lesion were not available at the time but could be confirmed by postmortem brain examinations in 21 cases. In these cases it was shown that the intended target within the thalamic CM-Pf complex was hit with a mean error of 1 mm. This is remarkable considering the fact that a plaster cap was used for fixation of the stereotactic frame to the patient's head and for fixation of the patient's head during the treatment. Important clinical as well as radiobiological information could be extracted from this early experience. Good pain relief was achieved in 8 patients and moderate in 18. This modest success "reduced the readiness to perform this operation". This may have been a correct conclusion at a time when *in vivo* demonstration of the radiosurgical lesion was impossible. However, bearing in mind that the lesion could only be assessed at autopsy in 21 of 36 examined brains, the relatively poor results may very well have been

due to failure of creating a lesion in some of the cases. The best results were achieved by lesions placed close to the wall of the third ventricle at the level of the posterior commisure. Better effect was observed in pain located in the face or arm area. In these areas pain was difficult to attack by neurosurgical techniques well suited for lower parts of the body such as percutaneous cervical cordotomy. Surprisingly, in two thirds of the patients the pain amelioration noted was immediate and complete but lasted only for 2 to 4 days. A longer lasting effect appeared with a latency of 2 to 3 weeks. In 5 of the 8 patients with good pain relief it lasted until the patient's death 13, 10, 7, 4, and 1 months after the procedure, respectively.

In 3 cases, the pain relief lasted for 9, 6, and 13 months respectively and then returned with preoperative intensity. It was concluded that medial thalamotomy may be tried as a last resort in the treatment of cancer pain in selected patients with a short life expectancy. This conclusion is probably valid even today, but it cannot be ruled out that better results may now be achieved by the new target localization techniques and with the possibility of *in vivo* check of the volume of the resulting lesion.

From the treatment of the pain patients we got useful radiobiological information. The time course of the development of the clinical effect has already been mentioned. It is interesting to compare these data with the time course of the development of clinical effects and signal changes of the MR-image as seen in cases of gamma-capsulotomy and -thalamotomy reported below. It may be hypothetized that the threshold of radiation effects is different for morphological and physiological effects and also for different physiological effects. Such conclusions are obviously not warranted by available information but may well be worth exploring.

Maximal doses of 100 to 250 Gy were used. Lesions were consistently observed only with doses over 160 Gy. Within the volume of the lesion, approximately 200 mm^3, there were parts which had received a considerably lower dose. In our subsequent experience it has become clear that the threshold dose for radionecrosis is strongly influenced by the volume of brain receiving that dose (cf. below). The extremely high signal doses can be delivered with impunity only with the smallest available collimator, i.e., the 4 mm collimator.

Trigeminal Neuralgia

A series of 46 patients with trigeminal neuralgia was subjected to radiation of the Gasserian ganglion by the first Gamma Knife (Håkansson, personal communication). Bony landmarks were the only means of target localization in 24 cases and in 22 cases localization was made by stereotactic cisternography. Skull fixation in the Gamma Knife was provided by metal sockets stereotactically fixed according to the target coordinates onto a

plastic helmet molded to the head, as a collimator helmet could not accommodate the stereotactic frame. The radiated volume was small and the imperfections in the target localization and fixation techniques may thus have contributed significantly to inaccuracies and less than satisfactory results. Nevertheless, of 22 patients with targets localized by cisternography, 13 were completely pain free after 6 months but only 4 after 2.5 years. It is, however, noteworthy that 1 patient with a 12 year history of trigeminal neuralgia has remained pain free for 15 years without any sensory loss. The seemingly discouraging result of Gamma Knife radiosurgery for trigeminal neuralgia indicates, nevertheless, that gamma-irradiation can affect the mechanisms responsible for the painful condition. An inadvertent effect resulting in numbness similar to that after radiofrequency coagulation of the Gasserian ganglion for tic douloureux has also been noted in some patients treated by Gamma Knife surgery for acoustic neuromas (Norén 1991). The improved localization technique offered by stereotactic MRI should be employed to further study the possible utility of radiosurgery in trigeminal neuralgia. Target and doses need to be better defined.

Movement Disorders

Thalamotomy for tremor in Parkinson's disease remains one of the most gratifying procedures in functional neurosurgery and defends its place in the therapeutic armoury for those frequent cases in whom drugs fail to stop the tremor. To avoid the potential risks with invasive procedures the prototype of the Gamma Knife was used for the production of thalamic lesions in 5 cases of tremor (1968–1970). At that time the intended target could not be visualized but was indirectly determined by pneumoencephalography. Verification of lesion production could not be obtained since neither CT scan nor MRI was available. The fixation of the patient for the radiosurgical procedure was also unsatisfactory as the stereotactic frame used for target localization was too space occupying to be introduced into the collimator helmet. Instead fixation devices were applied onto a plaster of Paris helmet previously molded on the patient's head. It is therefore not surprising that beneficial results were lacking. Following the introduction of stereotactic MRI better anatomical visualization of the target volume became possible. Even a new stereotactic frame compatible with MRI and used also as a fixation device in the Gamma Knife was introduced (Leksell *et al.* 1987). These improvements paved the way for new attempts to relieve Parkinsonian tremor by gammathalamotomy and the first case using the improved methodology was treated (Lindquist *et al.* 1991) (Fig. 15). For the MRI localization procedure an IR sequence with averaging of 16 acquisitions was used (Siemens Magnetom operating at 5T). To correct for geometric distortion in the MRI image, a phantom was also run in the

MRI scanner and a corrective algorithm was used to produce an undistorted image (Sched *et al.* 1987). Furthermore, a stereotactic CT scan was also used to corroborate the correct anatomical position of the target. The irradiation was performed using an 8 mm collimator and the volume of the resulting lesion was much larger than intended. The tremor began to dwindle after 2 months but a transient hemiparesis ensued secondary to oedema. The eventual outcome was, however, satisfactory and 4 years following the treatment the patient returned free of tremor contralateral to the side of the thalamic lesion asking for a contralateral procedure to stop the tremor which had developed on the other side.

The second patient was treated using a 4 mm collimator which gave a correct volume for the thalamic lesion. In this case the clinical result was not satisfactory. It is not clear whether the lack of effect was due to the atypical clinical picture in this patient or due to the lack of physiological corroboration of the target. Recent experience from centers active in this field indicate that modern imaging techniques, especially MRI may obviate the need for physiological target definition.

Psychosurgery

Despite therapeutic progress in recent years conventional treatment of anxiety disorders fails or has only a temporary effect in 20% of patients. These disorders are often severely disabling and are associated with rates of suicide comparable to those of depression. Psychosurgery targeting the

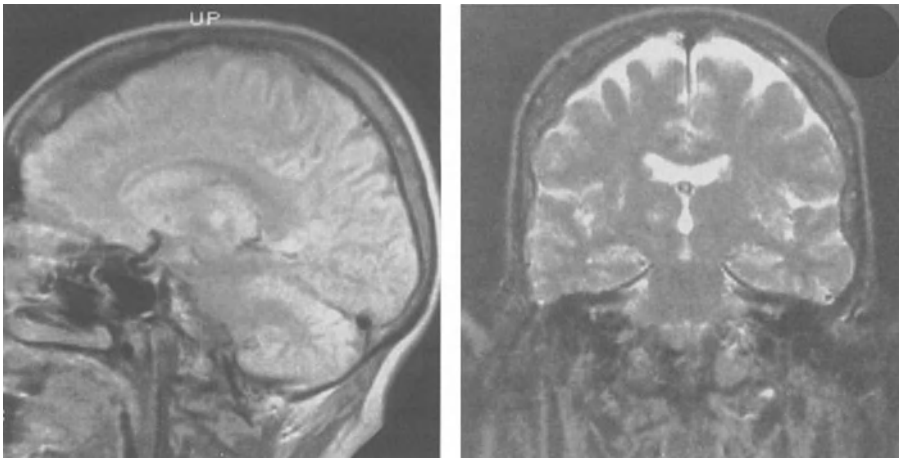


Fig. 15. Right thalamotomy, (A) coronal and (B) sagittal T2-weighted MRI images from a patient treated by right-sided Gamma Knife thalamotomy 3 months earlier. Note bright signal area in the right thalamus

fronto-limbic connections in both anterior internal capsules is considered by protagonists as a valuable therapeutic method for selected severe cases.

In a recent dissertation, studies of the effects of such procedures on the anxiety symptoms and personality characteristics were presented in conjunction with results of imaging studies performed by MRI and PET (Mindus 1991). The patient material comprised 2 series of patients with a mean duration of their psychiatric illness of 15 years and in all of whom various extensive trials of treatment had previously been made. One group included 24 patients subjected to capsulotomy by a conventional thermocoagulation technique and was followed for 1 year and the other, 7 patients treated by Gamma Knife surgery and followed for 7 years. The clinical effects of these treatments were evaluated subjectively by 2 independent observers and also rated on the "Comprehensive Psychopathological Rating Scale (CPRS)". Ratings were performed 10 days before and 2, 6, and 12 months after surgery. The effects on the personality were evaluated by the "Karolinska Scales of Personality (KSP)". These scales have been developed to measure traits related to frontal lobe dysfunction and to reflect different dimensions of liability to anxiety. At the 12 months follow-up, statistically and clinically significant improvement was noted in all assessments of symptomatic and psychosocial function. Freedom from symptoms or considerable improvement was noted in 79% of patients and none were worse after the operation. There was no deterioration in personality indices. Behind these numbers are numerous examples of dramatic improvements in individual lifestyles. A number of patients were preoperatively unable to work or function socially due to preoccupation with personal cleanliness or inability to use public transportation etc. with resulting domestic confinement, aggravation of psychological problems, deterioration of family relationships and devastation of personal finances. Postoperatively these patients could return to their previous occupation and to a normal social function. The results of gamma capsulotomy were found to be comparable to capsulotomy performed by the thermocoagulation technique. Only in 5 of the 7 patients could a lesion be demonstrated by MRI and they were the patients who benefited from the procedure. The lowest effective target dose was 160 Gy while 100, 120, and 152 Gy failed to produce lesions. Treatment of a new series of 10 patients was started in 1988 using stereotactic MRI for more accurate anatomical target localization and the new Gamma Knife model B for producing the radiolesions. In this series the lesions were produced by using a 4 mm collimator and 3 isocenters on each side for overlapping fields creating a cylindrical lesion. The maximum dose within the target volume was 200 Gy. Although it is too early to evaluate the long term psychological effects in this series of patients, important radiological information, which will serve to plan future treatments, is already available. The development of the lesions has been followed by

MRI and CT scans every 3 months. As expected, the MRI has been found to be particularly valuable for these follow-up studies. On T 2-weighted MRI images a high signal appears in the target area after approximately 3 months (Fig. 16). This signal is produced probably by local oedema. This oedema progresses in extent to include a maximal volume at around 9 months and then slowly subsides. The oedema is directly related to the dose and volume radiated. The preliminary impression is that the results equal those obtained in the former series of cases. A comparison of the radiobiological effects between the two series is unfortunately not possible as neither MRI nor CT was available when the lesions developed in the first series of patients. In the current series, the oedema was extensive in a few patients and it may therefore be wise to adjust the dose or decrease the volume exposed to necrotizing doses in future patients. It may be sufficient to use only 1 isocenter and the 4 mm collimator. With these treatment parameters and a maximal dose of 200 Gy a lesion measuring

Gamma capsulotomy offers several important clinical as well as scientific advantages over making capsulotomy with an open technique. The most important is patient tolerance. It is our experience that this psychologically vulnerable group of patients is much more willing to undergo a closed stereotactic procedure which leaves no external marks in contrast to open surgery. Theoretically, the gradual development of the radiolesion

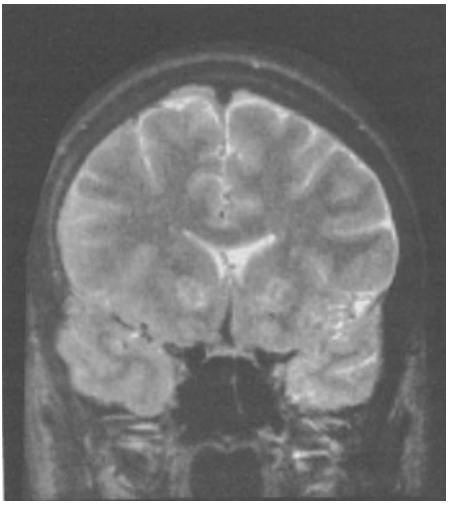


Fig. 16. Gamma Knife capsulotomy for anxiety neurosis. Coronal T2-weighted MRI image in a patient subjected to bilateral capsulotomy using the Gamma Knife. Three months follow-up with the lesions visible in the anterior internal capsule both right and left

may also allow the patient better to adjust psychologically to his new situation. The psychological rehabilitation phase is an important part of any psychosurgical procedure.

If ethically acceptable, a control group of patients could be subjected to spending time in the collimator helmet without radiation. At a later stage, if it is proven that this sham procedure gives no result in contrast to the real procedure, the control group would receive the appropriate treatment. Such a controlled study is probably necessary before the capsulotomy procedure is generally accepted among psychiatrists. Further efforts should also be made to study the biology of the developing lesions. Important questions are, *when* does the functional effect of the radiation start, and *what* are the characteristics of the MRI and CT images at this time. Even questions of dose-volume relationships need to be addressed further. The PET scanner may help to answer some of these questions and sequential studies of cerebral glucose metabolism are planned for further series of patients.

Epilepsy

Seizure was the presenting symptom in 59 of the 247 patients with arteriovenous malformations of the brain treated by Gamma Knife radiosurgery at the Karolinska Institute between 1970 and 1984. The treatment resulted in cessation of seizures in 52 of these patients. Eleven of them were also taken off anti-convulsant medication. Interstingly, in 3 patients the seizure disorder stopped altogether while the AVM itself was unaffected by the radiation (Steiner *et al.* 1991). These observations and the observations of others (Elomaa 1980, Barcia Salorio *et al.* 1985, Rossi *et al.* 1985), prompted the idea of testing focal radiation as a treatment modality for focal epilepsy. Development of the idea was, however, hampered by the difficulties in defining the area where epileptic seizures start. Conventional preoperative localization techniques, including the recording of discharges from implanted subdural and intracerebral electrodes, although better than surface EEG recordings are still deficient in this respect. Furthermore, an operative procedure is required both for the implantation and for the removal of such electrodes. Extensive resections are often necessary to achieve the required therapeutic results based on information provided by the conventional preoperative evaluation. Nevertheless, epilepsy surgery is today considered an underutilized form of therapy for drug resistant intractable seizure disorders. The new functional imaging techniques PET and MEG seem to offer improved possibilities to anatomically localize the origin of focal epileptic discharges. These methods also offer the advantage of being non-invasive. Magnetocephalography (MEG) involves the recording of the magnetic fields in the brain created by shifting electrical signals by volume conduction in the brain. This fact improves

the possibilities of their 3-D localization in the brain. Simultaneous recording of magnetic fields from a large part of the brain has now been realized by the introduction of MEGs which can record activity from 37 cannels. Preliminary studies by different groups indicate that interictal MEG recordings can supplant the recording of electrical activity during frank seizures. The place for MEG in preoperative evaluation must still be considered to be at the investigational level. However, should the investigations fulfill the expectations, MEG will provide a completely non-invasive preoperative interictal evaluation in a single recording session. Hence, it seems logical to combine such a non-invasive assessment with radiosurgery.

Since carefully planned Gamma Knife radiosurgery has been proven to be a form of treatment with a very low risk, it already seemed justified to apply the outline concept of evaluation and treatment in a few selected patients with intractable epilepsy who otherwise would be candidates for conventional epilepsy surgery. Four patients in the Karolinska Hospital and 2 in the Lars Leksell Radiosurgery Center in Charlottesville were offered and accepted this treatment option. These patients were subject preoperative evaluation protocol which includes conventional EEG, elec-

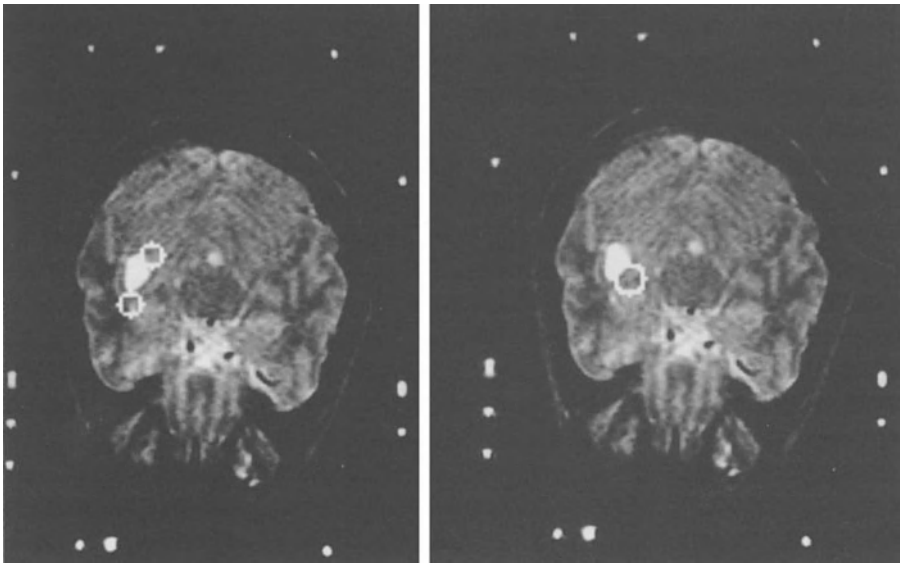


Fig. 17. Stereotactic MRI in the patient with partial complex seizures. (A) Before Gamma Knife radiosurgery. The two rings indicate origin of interictal epileptic activity revealed by MEG and digitally transferred to the MRI image. (B) Six months after radiosurgery when the patient was seizure free. Note absence of one interictal seizure focus and diminished volume of cyst

trophysiological recordings by subdural or intracerebral electrodes and PET scan. In addition, MEG investigations were performed on the Krenikon™ biomagnetic system at the Siemens research laboratory in Erlangen, Germany and Biomed Institute San Diego respectively. To make possible the transfer of the MEG data onto an anatomical image, the MEG was obtained using a stereotactic frame which remained fixed to the patient's head for a subsequent MRI study (Fig. 17). Only interictal biomagnetic activity was recorded but it was shown in all patients that clusters of dipolar activity occurred in areas where long term subdural (3 patients) or depth-electrode recordings (1 patient) recorded epileptic discharges. The dose-planning of the radiosurgical treatment was done on an MR image on which the interictal pathological biomagnetic signals had been superimposed and the treatment was subsequently carried out. Five of the patients had structural lesions in the medial temporal lobe. In one of these cases the radiological diagnosis was a low-grade astrocytoma but a biopsy was inconclusive and in another there was a partly calcified cystic lesion in the medial temporal lobe. A biopsy from this lesion was, however, negative. In a third case there were no pathological findings on CT or MRI and in a fourth patient the MRI arose suspicion of a low grade astrocytoma, which was subsequently confirmed by stereotactic biopsy. Two patients had a cavernous angioma.

The first patient was a 25 year old woman who had suffered from partial complex seizures since the age of 17. During the year before treatment the seizures were not well controlled by drugs and occurred 3–4 times a week. The epileptic focus was located at the perimeter of the low grade astrocytoma. The tumour and the focus were included in the field of radiation. Three months following treatment the patient started to notice amelioration of the seizure activity; after another 2 months there were no further seizures during a follow-up period of 11 months.

A similar schedule of preoperative evaluation and treatment was followed for the other 3 patients. For the second patient, too, 11 months have elapsed since the time of treatment. This 34 year old male had also suffered from temporal lobe fits and they had become progressively harder to control by drugs over the year prior to treatment. During the 6 months after radiosurgery this patient has experienced considerable amelioration of his seizure activity. The most recently treated patients have only a follow-up time of 2–3 months and no conclusions can yet be drawn about the therapeutic efficacy. The first two patients were re-examined by MEG following treatment at a time when their seizures had stopped. At this time the pathological interictal activity could not be traced despite the fact that the previously recorded abnormal signals were used as templates for pattern recognition in the computer program.

The encouraging results of the pilot cases will be followed by a series of cases with focal epilepsy but without structural lesions. A number of

parameters regarding radiosurgical treatment strategies need to be worked out. For example, the dose requirement remains to be settled. The possibility of severing pathways for the spread of epileptic activity could be explored as well as "undercutting" of cortical foci. In the long term perspective, the radiosurgical alternative may be an option for treating epilepsy originating in eloquent areas of the brain such as the motor cortex.

Conclusions

The explosive development in imaging and computer science, together with the increase in the number of neurosurgeons interested in stereotaxy will expand the role of radiosurgery in functional diseases. The results of early series treated for pain, movement disorders, and refractory anacastic neuroses should be reassessed and new trials with now available logistics presumably will give better results. However, the success in the treatment of functional diseases is closely related to the advances in neurophysiological research. For the time being, we still do not have a clear cut target for pain, and without such precise knowledge of the physiology and anatomy of the thalamic nuclei, the results of pain radiosurgery and of pain surgery in general, cannot improve. Furthermore, non-invasive recording identical to that provided by open stereotactic surgery is mandatory. Whether MEG will fulfill the expectation for this role still remains to be proven.

If one were tempted to prophesy, one might contemplate precise mapping of hypothalamic centers like the appetite center for example. Obesity might be treated by manipulating this center with radiosurgery instead of resecting segments of intestine.

Discussion

Radiosurgery, like many new ideas, was ignored or misunderstood for many years. Today, it seems that it is accepted by the broad church of the neurosurgical establishment. The problem is no longer the lack of legitimacy but rather euphoria leading sometimes to exaggerations, overstatements, and unrealistic expectations.

What will be the place of radiosurgery in neurosurgery? This will depend both upon the development of microsurgery and the development of radiosurgery. In the last two decades, microsurgery has expanded its boundaries and the basal ganglia or brain stem are no longer beyond its limits. Radiosurgery will have to match the results of microsurgery in order to have any role in the management of acoustic neuromas or difficult meningiomas. It is unlikely that radiosurgery will ever supplant microsurgery as first choice for the treatment of the benign tumours. However, there are a good number of meningiomas where radical extirpation is impossible. Residual tumour following surgery should be treated with radiosurgery. In an analysis of 225 meningiomas operated on at the Massachusetts Gen-

eral Hospital between 1962 and 1980, it was found that, following total resection, 93% of patients were recurrence free after 5 years, but only 68% after 15 years. However, the corresponding figures following subtotal resection were only 63% and 9% respectively (Mirimanoff *et al.* 1985). In a Canadian study from the University of Saskatchewan of 114 surgically treated patients, the overall recurrence rate after 5 years was 80%. In this patient group only the degree of radicality in initial surgery determines the risk of recurrence (Adegbite *et al.* 1983). From the University of Manchester in England, it was reported that in 53 consecutive cases operated over a ten year period, the recurrence rate over an average period of 5.3 years was 9.5% in the cases in which a complete removal including the dural attachment had been achieved, but it was almost twice as high (18.4%) when total removal was accompanied by coagulation only of the dural attachment (Marks *et al.* 1986). At the University of California in San Francisco, the recurrence rate over 5 to 15 years has been only 4% among the 51 patients who had total resection of their intracranial meningiomas during the period 1968 to 1978. However in the same Institution, 84 patients had only subtotal resection during this period (Barbaro *et al.* 1987).

Subtotal resection only was accomplished in 80 (of 224) patients at the Massachusetts General Hospital, 26 (of 53) in Manchester, and 81 (of 114) at the University of Saskatchewan. In 132 benign intracranial meningiomas treated at the University of Florida in Gainesville between 1964 and 1985, total removal was accomplished in 90 patients, resulting in postoperative death in 4 and recurrence in 8 of the surviving 86 (9%) (Taylor *et al.* 1988).

The follow-up of the 659 patients with benign intracranial meningiomas in these 5 series clearly demonstrates the importance of radical removal for cure. It is equally obvious from these studies that the size of the meningioma determines the success of surgery. The sphenoid wing and convexity were the two most frequent sites for meningiomas of this series, 20.3% and 18.4%, respectively. Whereas 90% of the convexity meningiomas were completely removed with a correspondingly high rate of cure, less than 34% of the sphenoid wing meningiomas could be totally resected. Meningiomas in the posterior fossa and in other parts of the base of the skull are notorious for being difficult to remove.

The probability of not having a second operation after an initial subtotal resection, was 75% within 5 years and 56% within ten years, but only 16% within 15 years in the series of the Massachusetts General Hospital.

In two studies from California and Florida, a retrospective comparison could be made between matched groups of patients subjected to partial resection only or partial resection followed by radiotherapy. In the California series with patients treated by subtotal resection, the tumours started to grown again in 60% of the non-irradiated cases. In the cases treated by subtotal resection followed by radiation, tumour growth was observed in

only 32% of the patients. The median time for recurrence was also significantly longer for the radiated group (125 vs. 66 months). The Florida study supported this observation and added that radiation was also effective when used after surgery for the first recurrence.

In principle, tumours sensitive to conventional radiotherapy could also be treated by radiosurgery with the advantage that the treatment is completed in one session and that the occurrence of systemic side effects is less likely compared with fractionated radiation. It has also been proved that radiosurgery may affect both meningiomas and acoustic neuromas.

Since reduction in size can be observed only in some of the treated patients, while in many patients the tumours remain unchanged, the question is whether this is due to the natural history of the lesion or if it is an effect of radiosurgery. We started recently a study with PET and Magnetic Resonance spectroscopy to determine whether pre- and repeated post-treatment metabolic studies could monitor the effects of radiosurgery in benign tumours.

Microsurgery in arteriovenous malformation can be carried out today with practically no mortality and very low morbidity. To prevail, radiosurgery should achieve at least similar results.

The trend in medicine is toward less traumatic procedures. In addition to mortality and morbidity rates, the atraumatic character of a treatment modality influences the decision making of the surgeon.

The physical agent of the radiosurgical tool is the ionizing beam; observations from radiotherapy are too often automatically applied to radiosurgery. Growth hormone disturbances have been observed following radiotherapy of children. The conclusion was drawn that there is a risk of growth hormone deficiency after radiosurgery. With 206 paediatric patients treated with the Gamma Knife and with follow-ups as long as 15 years, we have never observed any disturbance in growth hormone. As mental retardation and psychological problems were observed following radiotherapy, it was thought that mental retardation may occur after radiosurgery. We have never seen any undue effects concerning attention, concentration, or any other intellectual activity following radiosurgery. This can be explained by the fact that in radiotherapy large tissue volumes are irradiated, while in radiosurgery tissue volumes included in the radiation fields are relatively small.

The problem of the carcinogenic effect of radiosurgery crops up in every discussion and is, of course, considered in every case we treat. It is pertinent that after 23 years, we have never seen a cancer in over a thousand patients treated. Of course, the latency for the development of cancer is 26 years. However, tumour formation following radiotherapy has been observed 3 years, 7 years, or more, after the treatment, while we did not observe any radiation-induced tumour from 1968 to 1991. High single doses delivered

over a short period may be less carcinogenic than small doses administered over a long period. Presumably given enough time, a number of cancers will occur in the radiosurgical patient population. However, a population receiving no radiosurgery will probably also present a number of cancers. Hence, it will be very difficult to prove statistically a relationship between radiosurgery and cancer. In other words, as articulated by Sheline, "the occurrence of cancer will be so low that when a case will be observed it will be considered a curiosity".

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References

1. Adegbite AB, Khän MI, Paine KWE, Tan LK (1983) The recurrence of intracranial meningiomas after surgical treatment. J Neurosurg 58: 51–56
2. Ågren A, Brahme A, Turesson I (1990) Optimization of uncomplicated control for head and neck tumours. Int J Rad Onc Biol Phys 19
3. Andersson B, Larsson B, Leksell L, Mair W, Rexed B, Sourander P, Wennerstrand J (1970) Histopathology of late radiolesion in the goat brain. Acta Radiol Ther Phys Biol 9: 385–394
4. Backlund EO (1979) Solid craniopharyngiomas treated by stereotactic radiosurgery. Inserm Symposium 12: 271–283
5. Backlund EO (1979) Stereotactic radiosurgery in intracranial tumours and vascular malformations. In: Krayenbühl H, *et al* (eds) Advances and technical standards in neurosurgery, vol 6. Springer, New York, pp 3–37
6. Barbaro NM, Gutin PH, Wilson CB, Sheline GE, Boldrey EB, Wara WM (1987) Radiation therapy in treatment of partially resected meningiomas. Neurosurgery 20: 525–528
7. Barcia-Salorio JL, Roldan P, Hernandez G, Lopez-Gomez L (1985) Radiosurgical treatment of epilepsy. Appl Neurophysiol 48: 400–403
8. Bergström M, Greitz T, Steiner L (1980) An approach to stereotaxic radiography. Acta Neurochir (Wien) 54: 157–165
9. Betti O, Derechinsky V (1983) Irradiation stereotaxique multifaisceaux. Neurochirurgie 29: 295–298
10. Betti O, Derechinsky V (1984) Hyperselective encephalic irradiation with linear accelerator. Acta Neurochir (Wien) [Suppl] 3: 385–390
11. Betti O, Munari C, Rosler R (1989) Stereotactic radiosurgery with the linear accelerator: Treatment of arteriovenous malformations. Neurosurgery 24: 311–321
12. Bragg WH, Kleeman RD (1904) On the ionization curves of radium. Philosoph Mag 8: 726–738
13. Carella RJ, Ransohoff J, Newall J (1982) Role of radiation therapy in the management of meningioma. Neurosurgery 10: 332–339
14. Cerda H, Rosander K (1983) DNA damage in irradiated endothelial cells of the rat cerebral cortex. Protective action of cysteamine in vivo. Radiat Res 95: 317–326

15. Coffey RJ, Lunsford LD (1990) Stereotactic radiosurgery using the 201 Cobalt^{60} source Gamma Knife. In: Neurosurgery clinics of North America, vol I, no 5. Friedman Saunders, pp 933–954
16. Colombo F, Benedetti A, Pozza F, *et al* (1985) Stereotactic radiosurgery utilizing a linear accelerator. Appl Neurophysiol 48: 133–145
17. Colombo F, Benedetti A, Pozza F, *et al* (1985) External stereotactic irradiation by linear accelerator. Neurosurgery 16: 154–160
18. Colombo F, Benedetti A, Zanardo A, *et al* (1987) New technique for three-dimensional linear accelerator radiosurgery. Acta Neurochir (Wien) [Suppl] 39: 38–40
19. Colombo F, Benedetti A, Pozza F, *et al* (1989) Linear accelerator radiosurgery of cerebral arteriovenous malformations. Neurosurgery 24: 833–840
20. Dahlin H, Larsson B, Leksell L, Rosander K, Sarby S, Steiner L (1975) Influence of absorbed dose and field size on the geometry of the radiosurgical brain lesion. Acta Radiol Ther, Phys, Biol 14: 139–144
21. Davey P, O'Brien P (1981) Disposition of cerebral metastases from malignant melanoma: Implications for radiosurgery. Neurosurgery 28(1): 8–15
22. Eben A III *et al* (1990) Linac radiosurgery in malignant tumors. In: Eben A III *et al* (directors) Harvard Medical School Radiosurgery Update
23. Elomaa E (1980) Focal irradiation of the brain: an alternative to temporal lobe resection in intractable focal epilepsy. Med Hypoth 6: 501–503
24. Fabricius E, Larsson B, Steen L, Åkerman B (1962) Observations on pigeons with prethalamic radiolesions in the nervous pathways from the telencephalon. Acta Physiol Scand 56: 286–298
25. Fabrikant JI, Lyman JT, Hosobuchi Y (1984) Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders: Method for treatment of deep arteriovenous malformations. Br J Radiol 57: 479–490
26. Fabrikant JI, Lyman JT, Frankel KA (1985) Heavy charged-particle Bragg peak radiosurgery for intracranial vascular disorders. Radiat Res [Suppl] 104: S 244–S 258
27. Fabrikant JI, Frankel KA, Phillips MH, *et al* (1989) Stereotactic heavy charged-particle Bragg peak radiosurgery for intracranial arteriovenous malformations. In: Edwards MSB, Hoffman HJ (eds) Cerebral vascular diseases of children and adolescents. Williams & Wilkins, Baltimore, pp 389–409
28. Flickinger J (1991) Treatment of meningiomas and acoustic neurinomas with the Gamma Knife. Symposium Sloan Kettering, New York
29. French LA, Chou SN (1969) Conventional methods of treating intracranial arteriovenous malformations. Prog Neurol Surg 3: 274–319
30. Friedman WA, Bova FJ (1989) The University of Florida radiosurgery system. Surg Neurol 32: 334–342
31. Friedman WA (1990) Linac radiosurgery. In: Neurosurgery clinics of North America. Friedman Saunders, pp 991–1008
32. Gabel D, Fairchild RG, Larsson B, Börner HG (1984) The relative biological effectiveness in V 79 Chinese hamster cells of the neutron capture reactions in boron and nitrogen. Radiat Res 98: 307–316
33. Gale CC, Larsson B (1963) Radiation-induced "hypophysectomy" and hypothalamic lesions in lactating goats. Acta Physiol Scand 59: 299–318

34. Hall EJ, Marchese M, Hei TK, Zaider M (1988) Radiation response characteristics of human cells in vitro. Radiat Res 114: 415–424
35. Hartmann GH, Schlegel W, Sturm V, *et al* (1985) Cerebral radiation surgery using moving field irradiation at a linear accelerator facility. Int J Radiat Oncol Biol Phys 11: 1185–1192
36. Hellstrand E, Abraham-Fuchs K, Jernberg B, Kihlstrom L, Knutsson E, Lindquist C, Schneider S, Wirth A (1991) MEG localization of interictal epileptic focal activity and concomitant stereotactic radiosurgery. A new non-invasive approach for patients with focal epilepsy. Clinical Physics and Physiological Measurement. In press
37. Hopewell JW, Wright EA (1970) The nature of latent cerebral irradiation damage and its modification by hypertension. Br J Radiol 43: 160–167
38. Jefferson G (1948) Les hemorrhagies sous-arachnoidiennes par angiomes et aneurysmes chez le jeune. Rev Neurol 80: 413–432
39. Johnson RT (1969) Surgery of cerebral haemorrhage. In: Recent advances in neurology and neuropsychiatry. Churchill, London, pp 102–128
40. Kihlström L, Karlsson B, Lindquist C (1991) Gamma Knife surgery in brain metastases. International Radiosurgery Symposium in Pittsburgh June 1991
41. Kjellberg RN, Preston WM (1961) The use of the Bragg peak of a proton beam for intracerebral lesions. In: Second International Congress of Neurological Surgery, Washington, DC (International Congress Series no 36), p E103. Excerpta, Amsterdam
42. Kjellberg RN, Shintani A, Franzt AG, *et al* (1968) Proton beam therapy in acromegaly. N Engl J Med 278: 689–695
43. Kjellberg RN (1979) Isoeffective dose parameters for brain necrosis in relation to proton radiosurgical dosimetry. In: Szikla G (ed) Stereotactic cerebral irradiation. INSERM Symposium No 12. Elsevier, Amsterdam, p 157
44. Kjellberg RN, Kliman B (1979) Lifetime effectiveness – a system of therapy for pituitary adenomas, emphasizing Bragg peak proton hypophysectomy. In: Linfoot JA (ed) Recent advances in the diagnosis and treatment of pituitary tumours. Raven Press, New York, pp 269–288
45. Kjellberg RN, Davis KR, Lyons S, *et al* (1983) Bragg peak proton beam therapy for arteriovenous malformation of the brain. Clin Neurosurg 31: 248–290
46. Kjellberg RN, Hanamura T, Davis KR, Lyons SL, Adams RB (1983) Bragg-peak proton-beam therapy for arteriovenous malformations of the brain. N Engl J Med 309: 269–274
47. Kjellberg RN (1986) Stereotactic Bragg peak proton beam radiosurgery for cerebral arteriovenous malformations. Ann Clin Res 18 [Suppl 47]: 17–19
48. Kondziolka D, Lunsford LD, Coffey RJ, Flickinger TC (1991) Stereotactic radiosurgery of meningiomas. J Neurosurg 74: 552–559
49. Krayenbühl HA (1957) Discussion des rapports sur "les angiomes supratentoriels". Ier Congrès International de Neurochirurgie, rapports et discussions. Bruxelles
50. Laasonen EM, Troupp H (1986) Volume growth rate of acoustic neurinomas. Neuroradiology 28: 203–207

51. Larsson B (1960) Blood vessel changes following local irradiation of the brain with high-energy protons. Acta Soc Med Upsaliensis 65: 59–71
52. Larsson B (1962) On the application of a 185 MeV proton beam to experimental cancer therapy and neurosurgery. Acta Universitatis Upsaliensis. Abstracts of Uppsala dissertations in science, No 9
53. Larsson B, Leksell L, Rexed B (1963) The use of high energy protons for cerebral surgery in man. Acta Chir Scand 125: 1–7
54. Larsson B, Lidén K, Sarby B (1974) Irradiation of small structures through the intact skull. Acta Radiol Ther Phys Biol 13: 512–534
55. Larsson B, Leksell L (1986) Operate without the knife (in Swedish). In: Kosmos. Liber Publishing Co, Stockholm, pp 179–185
56. Larsson B (1989) Neutron capture therapy in support of other radiation treatment. In: Fairchild RG, Bond VP, Woodhead AV (eds) Clinical aspects of neutron capture therapy. Plenum Publishing Corporation, New York, pp 21–26
57. Larson DA, Gutin PH (1990) Introduction to radiosurgery. In: Friedman WA (ed) Stereotactic neurosurgery, neurosurgery Clinics of North America, I 4. WB Saunders Company, Philadelphia, pp 897–908
58. Leksell D (1987) Stereotactic radiosurgery. Neurol Res 9: 60–68
59. Leksell L (1949) A stereotaxic apparatus for intracerebral surgery. Acta Chir Scand 99: 229–233
60. Leksell L (1951) The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102: 316–319
61. Leksell L, Herner T, Lidén K (1955) Stereotaxic radiosurgery of the brain. Report of a case. Kungl fysiolog Sällsk. Lund Förhandl 25 (17): 1–2
62. Leksell L, Larsson B, Andersson B, *et al* (1960) Lesions in the depth of the brain produced by a beam of high energy protons. Acta Radiol 54: 251–264
63. Leksell L (1968) Cerebral radiosurgery. Acta Chir Scand 134: 585–595
64. Leksell L (1971) Stereotaxis and radiosurgery: An operative system. Ch C Thomas, Springfield, Ill
65. Leksell L, Lindquist C, Adler JR, Leksell D, Jernberg B, Steiner L (1987) A new fixation device for the Leksell stereotaxic system: technical note. J Neurosurg 66: 626–629
66. Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT (1989) Stereotactic heavy-charged particle Bragg peak radiosurgery for the treatment of intracranial arteriovenous malformations in childhood and adolescence. Neurosurgery 24: 841–852
67. Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT (1990) Charged-particle radiosurgery of the brain. In: Neurosurgery clinics of North America, vol 1, no 4. Friedman Saunders, pp 955–990
68. Levy RP, Fabrikant JI, Lyman JT (1992) Clinical results of stereotactic heavy-charged particle radiosurgery of the pituitary Gland at Lawrence Berkeley Laboratory. In: Steiner L *et al* (eds) Radiosurgery: Baseline and trends. Raven Press, New York
69. Lindquist Ch, Steiner L, Hindmarsh Th (1992) Gamma Knife thalatomy for tremor: Report of two cases. In: Steiner L *et al* (eds) Radiosurgery: Baseline and trends. Raven Press, New York

70. Linskey ME, Lunsford LD, Flickinger TC (1990) Radiosurgery for acoustic neurinomas: Early experience. Neurosurgery 1990 26(5): 736–745
71. Loeffler YS, Nedzi L, Kooy HM, Tarbell N, Scott M, Black P McL, Eben A III (1990) Results of radiosurgery in the management of recurrent paediatric brain tumours. Harvard Medical School Radiosurgery Update. Directors: Eben A, Crowell RM, Loeffler Y, Chapman P
72. Luchin Y, Minakova Y, Krymsky VA (1989) Proton beam irradiation of cavernous sinus meningiomas. In: International Workshop on Proton and Narrow Photon Beam Therapy, Oulu, Finland, pp 99–100
73. Lutz W, Winston KR, Maleki N (1988) A system for stereotactic radiosurgery with a linear accelerator. Int J Radiat Oncol Biol Phys 14: 373–381
74. Lyman JT, Kanstein L, Yeater F, *et al* (1986) A helium-ion beam for stereotactic radiosurgery of central nervous system disorders. Med Phys 13: 695–699
75. Marks SM, Whitwell HL, Lye RH (1986) Recurrence of meningiomas after operation. Surg Neurol 25: 436–440
76. McKissock W, Hankinson J (1957) The surgical treatment of supratentorial angiomas. Raports et discussions. Ier Congrès International de Neurochirurgie, Bruxelles
77. Mindus P, Bergström K, Levander SE, Norén G, Hindmarsh T, Thuomas K-A (1987) Magnetic resonance images related to clinical outcome after psychosurgical intervention in severe anxiety disorder. J Neurol Neurosurg Psychiatry 50: 1128–1293
78. Mindus P (1991) Capsulotomy in anxiety disorders, a multidisciplinary study. Dissertation for doctorate in medical sciences. Karolinska Institute
79. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL (1985) Meningioma: analysis of recurrence and progression following neurosurgical resection. J Neurosurg 62: 18–24
80. Mirri MA, Pavin G, Schinaia G (1990) Radiochirurgia delle metastasi cerebrali. Riv Neuroradiol 3: 291–298
81. Nielson SL, Kjellberg RN, Asbury AK, Koehler AM (1972) Neuropathologic effects of proton-beams in man. Acta Neuropath (Berl) 21: 76–82
82. Nilsson S, Carlsson J, Larsson B (1980) Survival of irradiated glia and glioma cells studied with a new cloning technique. Int J Radiat Biol 37: 267–279
83. Norén G, Arndt J, Hindmarsh T, *et al* (1987) Treatment of acoustic neurinomas. In: Lunsford LD (ed) Stereotactic techniques. Grune & Stratton, Orlando
84. Norén G, Greitz D, Hirsch A, Lax T (1991) Radiosurgery in acoustic neurinoma. Symposium, Charlottesville, 1989
85. Norén G (1991) Gamma Knife radiosurgery in acoustic neurinomas. In: Haid CT (ed) Vestibular diagnosis and neuro-otological management of the skull base. Demeter Verlag, Gräfelfing, pp 43–47
86. Ogilvy CS (1990) Radiation therapy for arteriovenous malformations: A Review. Neurosurgery 26 (5): 725–735
87. Olivecrona H, Ladenheim J (1957) Congenital arteriovenous aneurysms of the carotid and vertebral arterial systems. Springer, Berlin Göttingen Heidelberg, p 91

88. Patchell RA, Tibbs PA, *et al* (1990) A randomized trial of surgery in the treatment of single metastases to the brain. Eng Med 22: 494–500
89. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG (1976) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 34(6): 585–612
90. Petty AM, Kun LE, Meyer GA (1985) Radiation therapy for incompletely resected meningiomas. J Neurosurg 62: 502–507
91. Podgorsak EG, Oliver A, Pla M, *et al* (1988) Dynamic stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 14: 115–126
92. Podgorsak EG, Pike GB, Oliver A, *et al* (1989) Radiosurgery with high energy photon beams: A comparison among techniques. Int J Radiat Oncol Biol Phys 16: 857–865
93. Pool JL (1965) Aneurysms and arteriovenous anomalies of the brain. Diagnosis and treatment. Hoeber Medical Division, Harper and Row, New York
94. Rähn T, Thorén M, Hall K, *et al* (1979) Stereotactic radiosurgery in the treatment of MB Cushing. INSERM Symposium 12: 207–212
95. Rähn T, Thorén M, Hall K, *et al* (1980) Stereotactic radiosurgery in Cushing's syndrome: Acute radiation effects. Surg Neurol 14: 85–92
96. Ray BS (1941) Cerebral arteriovenous aneurysms. Surg Gynec Obstet 73: 614–648
97. Rexed B, Mair W, Sourander P, Larsson B, Leksell L (1960) Effect of high energy protons on the brain of the rabbit. Acta Radiol 53: 289–299
98. Rossi GF, Scerrati M, Roselli R (1985) Epileptogenic cerebral low-grade tumours: effect of interstitial stereotactic irradiation on seizures. Appl Neurophysiol 48: 127–132
99. Rylander G (1979) Stereotactic radiosurgery in anxiety and obsessive-compulsive neurosis. In: Hitchcock ER, Ballantine HT Jr, Meyerson BA (eds) Modern concepts in psychiatric surgery. Elsevier/North-Holland Biomedical Press, Amsterdam, pp 235–240
100. Saloman M (1990) Metastatic brain tumours. Diagnostic and therapeutic management. Contemp Neurosurg 26: 1–5
101. Sched L, Lott S, Schmitt F, Sturm V, Lorenz WJ (1987) Correction of spatial distortion in MR imaging: a prerequisite for accurate stereotaxy. J Comput Assist Tomogr 11: 499–505
102. Steinberg GK, Fabrikant JI, Marks MP, *et al* (1990) Stereotactic heavy-charged particle Bragg peak radiation for intracranial arteriovenous malformations. N Engl J Med 323: 96–101
103. Steiner L, Leksell L, Greitz T, Forster DMC, Backlund EO (1972) Stereotaxic radiosurgery for cerebral arteriovenous malformations. Report of a case. Acta Chir Scand 138: 459–464
104. Steiner L, Leksell L, Forster DMC, *et al* (1974) Stereotactic radiosurgery in intracranial arteriovenous malformations. Acta Neurochir (Wien) [Suppl] 21: 195–209
105. Steiner L, Greitz T, Leksell L, *et al* (1977) Radiosurgery in intracranial arteriovenous malformations. II. A follow-up study. Proceedings of the 6th

International Congress of Neurological Surgeons. Excerpta Medica, Amsterdam
106. Steiner L, Greitz T, Backlund EO, *et al* (1979) Radiosurgery in arteriovenous malformations of the brain. In: Szikla G (ed) Stereotactic cerebral irradiation. Elsevier/North-Holland, Amsterdam, pp 257–269
107. Steiner L, Forster D, Leksell L, Meyerson BA, Boéthius J (1980) Gamma thalamotomy in intractable pain. Acta Neurochir (Wien) 52: 173–184
108. Steiner L (1984) Radiosurgery in arteriovenous malformations in the brain. In: Wilson CB, Stein BM (eds) Intracranial arteriovenous malformations, current neurosurgical practice. Williams & Wilkins, Baltimore
109. Steiner L (1985) Radiosurgery in cerebral arteriovenous malformations. In: Fein JM, Flamm ES (eds) Cerebrovascular surgery, vol 4. Springer, New York
110. Steiner L, Lindquist C (1987) Radiosurgery in cerebral arteriovenous malformation. In: Tasker RR (ed) Neurosurgery: State of the art reviews, vol 2. Hanley and Belfus, Inc, Philadelphia, pp 329–335
111. Steiner L, Lindquist C, Steiner M (1989) Radiosurgery with focused Gamma beam irradiation in children. In: Edwards SB, Hoffman HJ (eds) Current neurosurgical practice. Cerebral vascular disease in children and adolescents. Williams & Wilkins, Baltimore, pp 367–388
112. Steiner L, Lindquist C, Adler J, *et al* (1991) Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg, accepted for publication
113. Steiner L, Lindquist Ch, Steiner M (1991) Meningiomas and gamma knife radiosurgery. In: Ossama Al-Mefty (ed) Meningiomas. Raven Press, New York, pp 263–272
114. Sturm V, Kober B, Hover KH, *et al* (1987) Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. Int J Radiat Oncol Biol Phys 13: 279–282
115. Taylor BW Jr, Marcus RB Jr, Friedman WA, Ballinger WE Jr, Million RR (1988) The meningioma controversy: postoperative radiation therapy. Int J Radiat Oncol Biol Phys 15: 299–304
116. Tobias CA, Anger HO, Lawrence JH (1952) Radiologic use of high energy deuterons and alpha particles. Am J Roentgenol Radium, Ther Nucl Med 67: 1–27
117. Thomas E, Forbus W (1959) Irradiation injury to the aorta and the lung. Arch Path 67: 256–263
118. Tobias CA, Roberts JE, Lawrence JH, Low-Beer BVA, Anger HO, Born JL, McCombs R, Huggins C (1956) Irradiation hypophysectomy and related studies using 340 MeV protons and 190 MeV deuterons. Peaceful uses of atomic energy. Proc Int Conf in Geneva 1955, United Nations, 10: 95–106
119. Valentino V, Dallore G (1990) Radiosurgery of intracranial meningiomas. Radiosurgery Update, Harvard Medical School. Directors: Eben A, Crowell RM, Loeffler Y, Chapman P
120. van der Kogel AJ (1986) Radiation-induced damage in the central nervous system: an interpretation of target cell responses. Br J Cancer 53 [Suppl VII]: 207–217

121. Wegmann H-J (1969) Das Schicksal operierter Patienten mit arteriovenösem Aneurysma des Gehirns. Juris Druck and Verlag, Zürich
122. Windholz F (1937) Zur Kenntnis der Blutgefäßveränderungen in röntgenbestrahlten Geweben. Strahlentherapie 59: 662–670
123. Wolbach SB (1909) The pathologic history of chronic x-ray dermatitis and early x-ray carcinoma. J Med Res 21: 415–449

Functional Imaging of Blood Brain Barrier Permeability by Single Photon Emission Computerised Tomography and Positron Emission Tomography

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With 2 partly coloured Figures

Contents

A variety of insults, affecting the Central Nervous System (CNS) can alter the structure and function of brain endothelial cells, resulting in a disturbance of Blood-Brain Barrier (BBB) permeability. Alteration of permeability promotes the accumulation of osmotically active substances in the brain and development of an "open barrier" oedema[1]. This event may be the single most important factor in the outcome of patients with

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a variety of clinical disorders. On the other hand the entry into the brain ECS of substances which are normally excluded may directly affect, independently from the presence of oedema, the function and perhaps the structure of nervous cells[2]. Therefore, while the alteration of BBB permeability may be the consequence of a particular disease, it is also the cause of additional damage to the CNS.

The concept of the BBB has evolved. The continuous layer of endothelial cells is not a structure strictly devoted to impeding the passage of polar solutes and allowing the passage of lipophilic substances. In fact the same cells are able to restrict the indiscriminate passage of lipophilic molecules[3]. In addition they possess some metabolic properties resembling those of certain specialized epithelial cells in the body[4].

The BBB seems to have a much more active role than previously thought in the regulation of the "milieu" of the brain and in the evolution of a pathological process.

Thus a purely descriptive approach to BBB permeability appears to suffer from certain limitations in both the experimental and the clinical situation. The introduction of Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) has broadened the spectrum of methodologies to evaluate permeability. This is partly because tracers of different sizes and properties can be used, but more particulary because PET offers the unique opportunity of a quantitative evaluation of permeability. Pathophysiological aspects of the BBB and the theoretical and methodological principles of permeability measurement will be reviewed and analyzed as will the results of permeability studies in various pathological situations.

The Blood Brain Barrier

The idea that the Central Nervous System is separated from the blood by a barrier arose at the beginning of the present century. Its anatomical site, however, remained controversial for the next half century. Studies of Reese, Karnovsky and Brightman identified most of the properties of the BBB within the endothelium of cerebral capillaries[5, 6].

In contrast to capillaries elsewhere in the body, the endothelial cells in the brain are joined together by complex and continuous tight junctions, so that intercellular gaps are absent. In addition they are not fenestrated, and pinocytotic vesicles or channels are also absent. This unique structure impedes the passage of substances through a transendothelial or interendothelial pathway. Therein lies the anatomical basis for the barrier to the passage of large molecules such as proteins and many other polar solutes. The BBB is normally permeable to highly lipid-soluble substances and to those substances that are transported by specific carriers across the BBB. The entry of certain lipophilic compounds, however, may be regulated by

a membrane glycoprotein which is expressed by human capillary endothelial cells[3]. A saturable and stereospecific carrier facilitates the passage of hexoses across the BBB[7]. A similar carrier transports amino acids bidirectionally across the endothelial cells[8]. An asymmetrical distribution of transport mechanisms has also been described: at the abluminal site small neutral amino acids are transported actively from brain to blood[8]. A Na, K-ATPase, also localized on the albuminal membrane, contributes to both the efflux of K^+ from and influx of Na^+ to the brain, and to the formation of brain interstitial fluid[4, 8].

While the primary function of brain endothelial cells is to form a barrier, they also contribute, through specific properties, to the regulation of substrate availability for nerve cells and to the composition of interstitial fluid in the brain.

Mechanisms of Blood Brain Barrier Opening

An increase in permeability and an alteration in properties the barrier could be related to the disruption of the anatomical and physiological features mentioned above.

The tight junctions can be opened both experimentally and clinically by intracarotid infusion of hyperosmolar solutions. Both small and large molecules cross the barrier for a period of minutes to hours depending upon the intensity of the insult. The size of molecules is essential in the evaluation of the opening: smaller molecules are able to cross the barrier for longer periods of time as compared with larger ones[9]. This suggests that pores of a discrete size more than formation of large channels underlie the increase in permeability. There is experimental evidence that barrier openings, seen in chronic hypertension and meningitis are due to a separation of the tight junctions and junctional abnormalities have been found in tumour capillaries[1, 10].

In the choroid plexus or in areas of the brain that lack a BBB the capillary walls exhibit fenestration. The capillaries of a brain tumour are often fenestrated, thereby allowing an increase in capillary permeability in the pathological tissue[11]. Formation of fenestration implies the fusion of the luminal and abluminal membrane; a process unlikely to occur in response to acute stimuli, but probable in response to a long-term inductive influence.

Transvascular transport is another possible mechanism to increase permeability. Vesicles would form at the luminal side, float freely in the cytoplasm and then fuse with the abluminal wall, releasing their content[12]. Recent observations that intracytoplasmatic vesicles are in fact attached to one side of the cell, has raised doubts about this concept[13]. However, vesicles, rarely seen in normal brain capillaries, have been noticed following

ischaemia, acute and chronic hypertension, seizures, experimental tumours and meningitis[1].

Finally, frank disruption of the endothelial cell wall has been seen in severe injury such as radiation necrosis[14] and the late stage of ischaemic infarction[15].

The opening of the BBB clearly seems to be a more complex phenomenon than a simple on-off mechanism. Different anatomical alterations may have an influence on the size of molecules able to cross the endothelial cell. There is also the suggestion that the type of insult, whether acute or acting within a longer time frame, might induce alterations in permeability through particular anatomical changes. On the other hand specific properties of the BBB may be altered without a significant change in permeability. In experimental ischaemia, for example, glucose transport is altered, but permeability to small molecules remains intact[16].

Imaging and Quantification

The clinical evaluation of BBB permeability in man has relied principally on imaging methods: the uptake of iodinated contrast agents in Computed Tomography (CT), or of Gadolinium-EDTA in Magnetic Resonance Imaging (MRI). Both tracers do not normally cross the BBB, but remain confined to the intravascular compartment. CT and MRI have both been able to image in vivo the spatial distribution of a barrier incompedence in a wide variety of diseases affecting the CNS. A discussion of the well-recognized advantages of the use of contrast media in brain imaging is not an objective of this paper. Certain points should, however, be analyzed. In CT and MRI images it is difficult to differentiate between the uptake due to BBB breakdown and the apparent uptake due to increased vascularization. The two phenomena may also coexist, as they often do, complicating further the evaluation of permeability. On the other hand, as previously discussed, BBB permeability alteration is far from being an all or none phenomenon. The intensity of the alteration varies between lesions: different degrees of alteration may coexist in the context of each individual lesion. The use of tracers with different physical and biological characteristics evaluated can detect various degrees of permeability. However, only by using a quantitative approach can the passage of a substance from blood to brain, thus – the true permeability – be evaluated. Experimentally, BBB permeability has been quantified by measuring the distribution of radiotracers in blood and in brain, and by applying kinetic models of transport[17, 18]. The availability of instrumentation able to measure accurately the concentration of a radiotracer in a living brain has allowed the application of experimental models to human pathophysiology. The result is not an image which indicates the effects of a phenomenon, but rather an image which represents the phenomenon itself.

SPECT

Almost 40 years have passed since the introduction of planar brain scintigraphy which, prior to the CT era, was the only method of evaluating BBB permeability in vivo. More recently the introduction of SPECT has allowed a 3-dimensional representation of tracer uptake with more accurate definition and better contrast. However, the difficult and often inaccurate procedures necessary to obtain quantitative data have limited the use of SPECT in BBB studies to pure imaging of the permeability alteration. A variety of tracers available for SPECT has extended the use of the method. Font *et al.* have used Co-57-bleomycin to image brain tumours[19]. The uptake of the radiotracer was similar to that of Tc-99 m-pertechnetate: no uptake in low grade glioma, clear accumulation in high grade glioma. The suggestion that barrier permeability is dependent upon the degree of malignancy is conspicuous. The interest of the study clearly lies in the use of a labelled chemotherapeutic drug in the evaluation of permeability. The analysis by SPECT of drug accumulation in a tumour is a useful perspective. More recently Thallium has offered another stimulating prospect[20,21]. Thallium uptake by brain tumours seems to be the expression of both BBB permeability alteration and biological malignancy of the tumour. SPECT systems are widely available and their utility in clinical practice cannot be underestimated. The copious literature on cerebral perfusion by SPECT, which has closely followed and even preceded PET studies is a clear demonstration. SPECT still has a defined role in the evaluation of BBB permeability, enhanced by the development of new radiotracers such as labelled drugs or labelled monoclonal antibodies[22].

PET

Positron Emission Tomography allows the in vivo quantification of substances labelled with positron-emitting isotopes in a noninvasive manner. The study of a physiological phenomenon, however, requires the application of simple mathematical models to describe the kinetics of the test substance[23]. BBB permeability has been measured successfully in vivo by combining PET technology with theoretical and physiological information obtained by animal studies.

Theory

In the absence of a specific transport mechanism the amount of a substance which crosses the BBB is a function of the permeability (P), the capillary surface area (S) and the difference of concentration across the BBB.

In vivo P cannot be measured "per se": available techniques measure either an extraction faction (E) or a transfer (K). E is dimensionless, being

defined as the fractional amount of a test substance in the blood which has crossed the capillaries during a single passage through the brain. On the other hand, K is a unidirectional (blood to brain) transfer constant which has the dimensions of a clearance (ml/g/min) measured during multiple passages of the test substance through the brain capillaries[17, 24].

It can be shown that if a substance has a low permeability, so that extraction by the brain during a single passage through the capillaries is very low, then its measured K numerically approaches the value of the permeability × surface area product (PS). A variation in K would be an expression of variations in PS, independently from blood flow. At the other end of the spectrum if a substance is highly permeable, its passage from blood to brain is limited by blood flow only and the magnitude of measured K approaches the value of blood flow. For substances with moderate to high permeability, variations in K, might be dependent upon variations in both PS and blood flow[24].

In PET studies of the BBB, because of the use of tracers with very low permeability, the measurement of Ki has been the most reliable way to derive the value of PS[25].

The Methods

Two major factors predominate when the permeability of a compound across the barrier is measured: the kinetics of the movement across the barrier and the differentiation between the amount of compound that has actually crossed the BBB and the amount that remains within the intravascular compartment.

A PET scanner can accurately measure the activity in a Region of Interest (ROI) but it cannot differentiate the compartments (blood or brain tissue), in which the activity is actually distributed. A simple solution would be to measure independently cerebral blood volume (CBV) to estimate the intravascular compartment. Mathematical models for the exchange kinetics, which mirror physiological events, can be applied to separate the activity within the brain from that in the vascular compartment and thus measure simultaneously both K 1 and Vp: a value which closely approximates CBV.

The simplest model is a bicompartmental one: a direct blood to brain (K 1) and the inverse (K 2) constant define the passage of a substance through the BBB from an intravascular compartment to the brain.

Hawkins *et al.* assuming a bicompartmental model of tracer distribution, and using an iterative procedure, were able to calculate, in patients with brain tumours, K 1, K 2 and Vp[26]. The concept of a reverse constant K 2 is of particular value when permeability is increased and long term measurements are performed[27].

If a tracer, once having crossed the BBB, distributes to ECS the equilibration time between the tracer in the plasma and in the ECS, is a function

of K 1 and of the size of ECS (K 2 = K 1/ECS). We calculated that the equilibration time for EDTA in the normal brain is about 550 minutes[27]. Indeed an increased K 1 allows for a much smaller equilibration time constant: equilibrium is reached earlier and a back flux of the substance could take place during experimental time. Neglecting K 2 would yield to an underestimation of K 1.

Multiple Time Graphical Analysis (MTGA) is another model which allows the simultaneous measurement of K 1, K 2 and Vp[28, 29]. The method does not require assumptions about the configuration of the tracer distribution compartment. The technique is also non-iterative and the graphical solution allows one to verify or disprove the unidirectionality of the transport and to correct for K 2 when necessary.

The Tracers

[68 Ga]-EDTA and [82 Rb] are the two most frequently used tracers in the PET evaluation of the BBB[25]. They have different physical and biological characteristics, but they can both be produced by a generator, thus avoiding the need for an on line cyclotron. Their half life is different (68 Ga = 68 min, 82 Rb = 75 sec) so is their molecular size and permeability in the normal condition (K1-Rb > K1-68GaEDTA). While the distribution space of the GaEDTA is the extracellular space, with a negligible amount taken up by brain cells, Rb, an analogue of potassium, distributes to both extra and intracellular compartments[25].

On the basis of these differences various techniques are employed to measure their K 1. Studies with Rb are of short duration and can be easily repeated. The K 1 measured in physiological conditions is a reliable estimation of PS, but when permeability is increased, as in a malignant brain tumour, a parallel measurement of cerebral blood flow is required to obtain an absolute value of PS[30].

Because of its low permeability, studies with 68GaEDTA require longer, thus increasing the possibility of movement artefacts. However K 1 is an accurate measure of PS in situations of altered permeability when a reliable calculation of K 2 can also be performed[26, 27].

Obviously the theory and the methods briefly summarized above can be applied to study the BBB permeability of any substance that can be marked with a positron emitter. The delivery of cytotoxic drugs for a tumour, already measured in experimental conditions may soon be measured in the context of brain tumours in man.

Blood Brain Barrier Evaluation in Brain Tumours

Several facts have stimulated great interest in the quantitative evaluation of BBB permeability in brain tumours.

The alteration of the BBB is probably the factor which has had the greatest influence on the preoperative diagnosis of brain tumours by CT and MRI. Oedema surrounding brain tumours is the most common form of open barrier oedema[1]. Much effort has recently been devoted to "manipulating" the BBB to increase delivery of drugs to tumours, based on the disappointing clinical results of chemotherapy for cerebral malignancies[31, 32].

It is not surprising then that most of the PET studies on BBB have dealt with the alteration of permeability in brain tumours. Figures 1 and 2 show the two ends of the spectrum: no alteration of the BBB in a grade I astrocytoma, definite changes in permeability in a glioblastoma. The two figures are parametric images: they represent a pixel by pixel distribution of a calculated value, either K 1 or Vp.

Table 1 summarizes the values of K 1, K 2, Vp in normal brain and in gliomas, obtained by using 68GaEDTA as a tracer and applying the MTGA[27].

Low grade gliomas do not show significant changes in either permeability or vascular volume as compared with normal brain – results which have been confirmed by various groups[33, 34]. On the other hand the absence of contrast uptake on CT by low grade gliomas is well recognized.

High grade gliomas always exhibit an increase in both permeability and vascular volume. Numerically the PS is increased by a factor of 10 as compared with normal brain and it is striking that various groups using

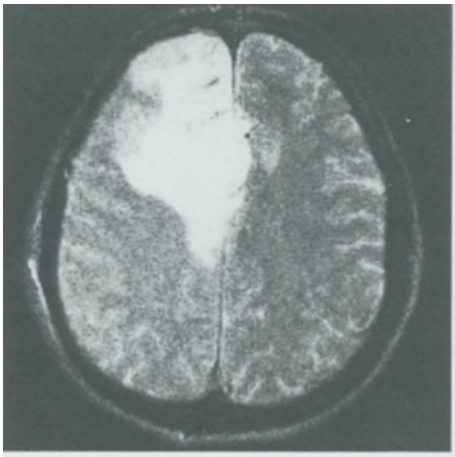
Table 1. *K 1 and Vp from ROI Placed over the Area of Uptake in Patients with an Intracranial Tumour and Control Values from Normal Volunteers*

		K 1	Vp
Astrocytoma I–II	(n = 5)	3.5 + 0.6	3.7 + 0.4
Glioblastoma	(n = 8)	45.3 + 16.3	9.1 + 2.8
Normal	(n = 4)	3.2 + 1.2	4.2 + 0.7

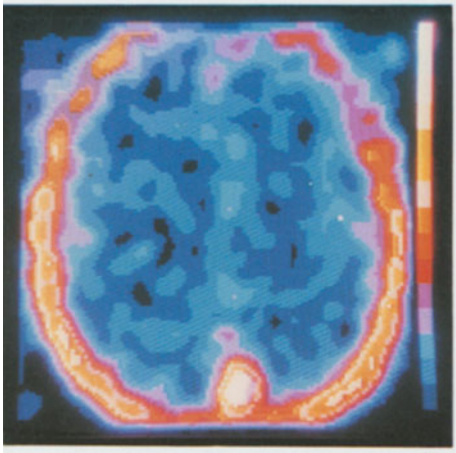
Values are mean + SD ($K1 \times 10^{-4} ml \cdot g^{-1} \cdot min^{-1}$ and $Vp \times 10^{-2} \cdot ml \cdot g^{-1}$)

Fig. 1. Patient with a low grade (I–II) astrocytoma. While the CT was normal the tumour is well shown by MRI (a). The parametric images of both Vp (b) and K 1 (c) do not show any difference in value between pathological and normal brain. There is no alteration of the BBB

Fig. 2. Patient with a glioblastoma. Post-contrast CT scan shows a mass lesion with irregular contrast enhancement (a). Parametric image of Vp indicates an increase in the vascular space in the tumour context (b). Parametric image of K 1 clearly demonstrates the alteration of permeability within the tumour (c)



a



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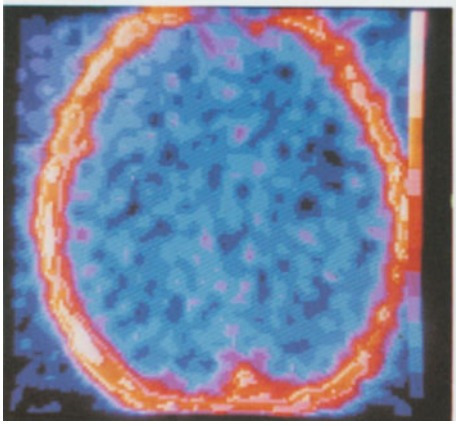

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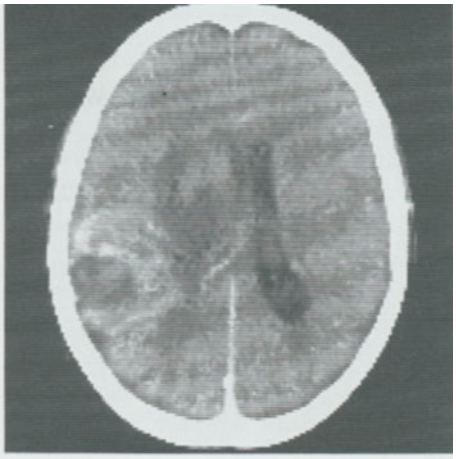
Fig. 1



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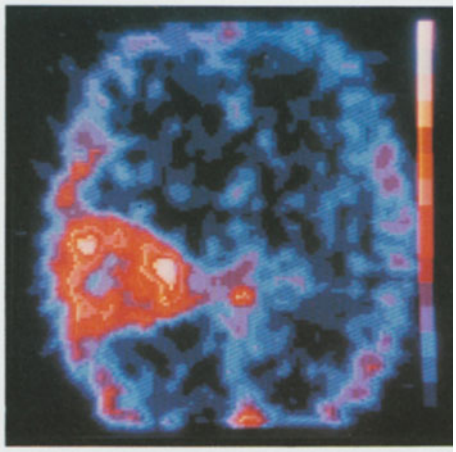

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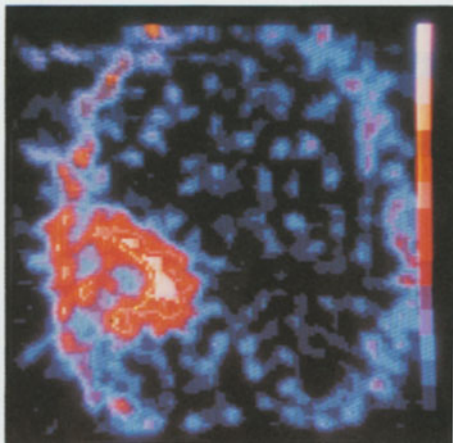

c

Fig. 2

68GaEDTA have measured values of the same magnitude[26,27,33]. Rubidium studies have shown a similar increase in permeability in malignant gliomas, but a numerical comparison cannot be made, due to the afore-mentioned characteristics of the tracers[30,35].

There is no suggestion however that this difference in BBB permeability can be used in clinical practice since other PET methodologies better express the biological malignancy of a tumour[36]. Rather is it of fundamental value for a better understanding of the pathophysiology of the barrier and for the insight it offers into the structure of tumours.

The alteration of permeability is not homogeneous in the context of a tumour. The parametric image (Fig. 2) clearly shows the different values that coexist within a glioblastoma. Indeed this variation in permeability from one area of the tumour to another is partly explained by the histopathological structure of malignant gliomas. Areas of necrosis, of increased cellularity and of increased vascularization coexist in a glioblastoma. The increase in vascular space seems to suggest a straightforward relationship: in areas where the vascularization is increased there is more surface available for the exchange across the BBB, thus permeability increases. However, a close spatial coincidence between regions of increased permeability and regions of increased vascular volume is not always evident. On the other hand the capillary structure and permeability may vary from region to region within a particular tumour. Experimental work with gliomas induced in rats gives rise to some concern about the methodology substantiates the presence of a variable capillary permeability in the presence of a tumour[10].

The non-homogeneous alteration of permeability also gives rise to some concern about the methodology. Different values of K 1 cause different concentrations in the ECS of the substance which has crossed the barrier. Diffusion of the substance within the ECS could then take place, affecting the calculation of the transfer constants.

Once the dynamics of the passage across the BBB have been evaluated, the destiny of the tracer and the kinetics of its distribution within the brain is probably the next challenge for BBB studies using PET[37].

Is Permeability Really Increased?

As previously discussed, measurement of the unidirectional transfer constant K provides a good approximation to the PS product. Thus K 1 changes are a reflection of variations of P and/or S. It could, at least in theory, be possible that increases in K are solely due to an increased capillary surface available for the exchanges without a significant change in permeability. It is a provocative hypothesis. That neovascularization occurs in brain tumours is well known, and the PET studies have shown an increase in the vascular volume in malignant gliomas[26,27,38]. The total vascular surface

(TVS) available for the exchange was calculated in malignant gliomas after surgery and compared to the K 1 previously measured by PET[39]. Although the number of patients was small, all tumours with an increase in K showed an increase in TVS as well. The increase in TVS was insufficient to account entirely for the measured increase in K. It appears evident that the permeability "per se" is indeed altered, but to a lesser degree than what one might be expected. The enlargement of the surface available for the exchange across the BBB contributes to the increase in the PS product.

Blood Brain Barrier Alteration in Oedema

Because of the Barrier's extremely low permeability to proteins the colloid oncotic pressure in the interstitial fluid of the brain is much smaller than in the plasma. When the BBB is open the colloid oncotic pressure of the interstitial fluid rises. This causes water to move from blood to brain and produce brain oedema. Once the barrier is open hydrostatic pressure becomes an additional driving force favouring the movement of solutes and water into the brain. The occurrence of extensive oedema around tumours is a common finding. It is the most frequent clinical form of vasogenic or "open-barrier" oedema[1]. Experimentally, the alteration of the BBB is confined to the tumour itself, but little or no alteration of permeability is found in the surrounding brain[10]. Nor do post-contrast CT images show an uptake in the low density area around tumours. However, permeability in oedematous brain surrounding tumours has been quantified in man only by PET.

In Table 2 the values of K 1 and Vp are calculated from the tumour area, in an ROI in the oedematous brain, and in the contralateral normal brain[40].

There is no increase in permeability in oedematous areas surrounding high-grade gliomas or metastases. The altered barrier within the context of the tumour is the source of the oedema fluid which subsequently spreads through the ECS to the surrounding brain. That bulk flow of open-barrier oedema occurs is substantiated by studies in patients with brain injury and tumours[41, 42]. On the other hand the enlargement of the ECS which occurs

Table 2. *Values (mean + SD) of K1 ($\times 10^{-4}$ ml·g^{-1}·min^{-1}) Measured Within the Tumour, the Oedematous Brain and the Normal Contralateral Brain*

	Tumour	Oedema	Normal
Glioblastoma n = 8	45.3 + 16.3	3.6 + 1.4	3.4 + 1.5
Meningioma n = 4	n.c.	2.3 + 0.7	2.4 + 0.8

n.c. = not calculable.

in both tumours and areas of "open-barrier" oedema, decreases the resistance to the flow of fluids and favours the movement of solutes and water[43]. By a similar mechanism a drug which has entered a tumour via an open barrier might diffuse in the oedematous area. This "sink" action of oedematous brain surrounding tumours is also believed to decrease the exposure of tumours to cytotoxic drugs[37].

The PS product in oedematous areas around meningiomas shows no alterations as compared with normal brain. A different mechanism might be expected to operate since meningiomas are purely extracerebral tumours. If venous compression were the mechanism for oedema production, then one would expect that venous engorgement would produce an alteration of the BBB. A stimulating hypothesis is that fluids might be produced at the tumour-brain interface and subsequently spread within the tissue. Alternatively, compression of the interstitial space and obstructed flow of interstitial fluid may be the reason for the "intact barrier" oedema occurring around meningiomas[1].

Mechanism of Action of Corticosteroids

Corticosteroids reduce the permeability of the BBB to macromolecules in normal animals[44]. They can also reduce the "open barrier" oedema associated with intracerebral neoplasm[45]. In patients with brain tumours, PET studies with rubidium have measured a temporal decrease in K 1 of about 20% in 24 hours following treatment with dexamethasone[46]. Dexamethasone might act through an inhibition of the mediators of increased permeability, however it is ineffective when the barrier is totally destroyed as in the cortical freeze injury. This suggests the hypothesis that permeability decreases because the capillary surface is decreased. In support of this Leenders *et al.*, in fact, using PET, found a decrease in CBF and CBV in tumour tissue following dexamethasone treatment, thus implying a decrease in the number of perfused capillaries[38]. The antioedema action of dexamethasone seems in any event directed towards reducing the formation of the oedema fluid at the site of its production: the altered barrier within the tumour.

Multiple Sclerosis

A disturbance of BBB in some multiple sclerosis plaques was demonstrated post-mortem almost 30 years ago. Areas of contrast medium extravasation have frequently been reported in patients with multiple sclerosis soon after clinical exacerbation[47]. In experimental allergic encephalomyelitis, the experimental counterpart of multiple sclerosis, alteration of barrier permeability seems to occur before cellular infiltration[48].

Brooks *et al.* measured BBB permeability to Rubidium-82 by PET and did not find any change in patients with multiple sclerosis[35]. However their patients were in remission at the time of the study. In another PET study, using Ga 68-EDTA as a tracer, the absence of change in permeability during "remission" was confirmed, despite the CT evidence of low density areas[49]. In patients with "exacerbation" of the disease, instead, areas of accumulation of the radiotracer were visualized. The mean K 1 value, measured in the areas with BBB abnormality was 3 times higher than normal tissue. In these pathological areas Vp had not increased in parallel and there was no suggestion of diffuse BBB abnormality[49].

These data seem to indicate a correlation between BBB alteration and clinical activity of multiple sclerosis. However, the alteration of permeability when present, is strictly focal and of moderate degree.

Dementia of Alzheimer Type

The presence of abundant serum albumin in the ECS of patients with senile dementia of Alzheimer type (SDAT) has suggested the possibility of BBB involvement in the disease[50]. The cerebral vessels containing amyloid could represent the anatomical site of the alteration of permeability. However, quantitative PET measurement of the PS product has failed to demonstrate of BBB breakdown in patients with SDAT[51]. A different type of BBB involvement has now been suggested; a dramatic decrease of the glucose transporter at the BBB site has been described, and this correlates with the decrease in glucose metabolism.

Conclusion

The PET evaluation of BBB permeability has provided data on the pathophysiology of the barrier in vivo and has opened new perspectives.

It is a fact that permeability at the BBB site is necessary for any substance or drug to gain access to the brain. The continuing development of radiochemistry will allow greater insight into the pathophysiology of permeability.

On the other hand, very little work has been carried out in areas such as cerebral ischaemia, in which the temporal profile of the permeability alteration and the barrier properties of the newly formed capillaries are of particular interest.

Therapeutic measures to reduce BBB damage and to act on oedema caused by an "open barrier" will require testing with techniques similar to those available by PET.

References

1. Betz AL, Iannotti F, Hoff JT (1989) Brain oedema: a classification based on blood-brain barrier integrity. Cerebrovasc Brain Metab Rev 1: 133–154
2. Suzuki M, Iwasaki Y, Yamamoto T, Konno H, Kudo H (1988) Sequelae of the osmotic blood-brain barrier opening in rat. J Neurosurg 69: 421–428
3. Cordon-Cardo C, O'Brien JP, Casals D, Rittman-Grauer L, Biedler JL, Melamed MR, Bertino JR (1989) Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites. Proc Natl Acad Sci USA 86: 695–698
4. Betz AL, Goldstein GW (1986) Specialized properties and solute transport in brain capillaries. Ann Rev Physiol 48: 241–250
5. Reese T, Karnovsky M (1967) Fine structural localization of a blood-brain barrier to exogenous peroxidase. J Cell Biol 34: 207–217
6. Brightman MW, Reese TS (1969) Junctions between intimately apposed cell membranes in the vertebrate brain. J Cell Biol 40: 648–677
7. Pardridge WM (1983) Brain metabolism: a perspective from the blood-brain barrier. Physiol Rev 63: 1481–1535
8. Goldstein GW, Betz AL (1986) The blood-brain barrier. Sci Am 255 (3): 74–83
9. Robinson PJ, Rapoport SI (1987) Size selectivity of blood-brain barrier permeability at various time after osmotic opening. Am J Physiol 253: R 459–466
10. Nir I, Levanon D, Iosilevsky G (1989) Permeability of blood vessels in experimental gliomas: Uptake of 99 mTc-glucoheptonate and alteration in blood-brain barrier as determined by cytochemistry and electron microscopy. Neurosurgery 25: 523–532
11. Long DM (1970) Capillary ultrastructure and the blood-brain barrier in malignant brain tumours. J Neurosurg 32: 127–144
12. Simionescu N (1983) Cellular aspects of transcapillary exchange. Physiol Rev 63: 1536–1578
13. Bundgaard M (1980) Transport pathways in capillaries – in search of pores. Annu Rev Physiol 42: 325–336
14. Miquel J, Haymaker W (1965) Astroglial reactions to ionizing radiation: with emphasis on glycogen accumulation. Prog Brain Res 15: 89–114
15. Petito CK (1979) Early and late mechanisms of increased vascular permeability following experimental cerebral infarction. J Neuropathol Exp Neurol 38: 222–234
16. Betz AL, Iannotti F, Hoff JT (1983) Ischaemia reduces blood-to-brain glucose transport in the gerbil. J Cereb Blood Flow Metab 3: 200–206
17. Blasberg RG, Fenstermacher JD, Patlak CS (1983) The transport of aminoisobutyric acid across brain capillary and cellular membranes. J Cereb Blood Flow Metab 3: 8–32
18. Blasberg RG, Kobayashi T, Horowitz M, Rice JM, Groothuis D, Molnar P, Fenstermacher JD (1983) Regional blood-to tissue transport in ethylnitrosurea-induced brain tumours. Ann Neurol 14: 202–215
19. Front D, Israel O, Kohn S, Nir I (1984) The blood-tissue barrier of human brain tumours: correlation of scintigraphic and ultrastructural findings: concise communication. J Nucl Med 25: 461–465

20. Black KL, Hawkins RA, Kim KT, Beker DP (1989) Thallium-201 (SPECT): a quantitative technique to distinguish low-grade from malignant brain tumours. J Neurosurg 71: 342–346
21. Kim KT, Black KL, Marciano D, Mazziotta JC, Guze BH, Grafton S, Hawkins RA, Becker DP (1990) Thallium-201 SPECT imaging of brain tumours: methods and results. J Nucl Med 31: 965–969
22. Gruber ML, Hochberg FH (1990) Systematic evaluation of primary brain tumours. Editorial. J Nucl Med 31: 969–971
23. Phelps ME, Mazziotta JC, Huang SC (1982) Study of cerebral function with positron computed tomography. J Cereb Blood Flow Metab 2: 113–162
24. Fenstermacher JD, Blasberg RG, Patlak CS (1981) Methods for quantifying the transport of drugs across brain barrier systems. Pharmacol Ther 14: 217–248
25. Webb S, Ott RJ, Cherry SR (1989) Quantitation of blood-brain barrier permeability by positron emission tomography. Phys Med Biol 34: 1767–1771
26. Hawkins RA, Phelps ME, Huang SC, Wapenski JA, Grimm PD, Parker RG, Juillard G, Greenberg P (1984) A kinetic evaluation of blood-brain barrier permeability in human brain tumours with 68-GaEDTA and positron computed tomography. J Cereb Blood Flow Metab 4: 507–515
27. Iannotti F, Fieschi C, Alfano B, Picozzi P, Mansi L, Pozzilli C, Punzo A, Del Vecchio G, Lenzi GL, Salvatore M, Conforti P (1987) Simplified, noninvasive PET measurement of blood-brain barrier permeability. J Comput Assist Tomogr 11: 390–397
28. Gjedde A (1981) High and low affinity transport of D-glucose from blood to brain. J Neurochem 36: 1463–1471
29. Patlak CS, Blasberg RG (1985) Graphical evaluation of blood to brain barrier transfer constants from multiple time uptake data. Generalizations. J Cereb Blood Flow Metab 5: 584–590
30. Dhawan V, Jarden JO, Moeller JR, Strother SC, Rottemberg DA (1989) Positron emission tomographic measurement of blood-to-brain and blood-to-tumour transport of 82 Rb. II: Clinical data and validation of technique. Phys Med Biol 34: 1785–1794
31. Neuwelt EAS, Dahlborg SA (1989) Blood-brain barrier disruption in the treatment of brain tumours. Clinical implications. In: Implications of the blood-brain barrier and its manipulation, vol 2. Plenum Press, New York, pp 195–261
32. Fishman RA (1987) Editorial: is there a therapeutic role for osmotic breaching of the blood-brain barrier? Ann Neurol 22: 298–299
33. Herholtz K, Wienard K, Pawlik G, Seldon L, Beil C, Heiss WD (1985) Functional imaging of reversible and irreversible 68 Ga-EDTA uptake in brain tumours. Acta Physiol Scand 72 [Suppl]: 127
34. Ilsen HW, Sato M, Pawlik G, Herholtz K, Wienard K, Heiss WD (1984) 68 Ga-EDTA positron emission tomography in the diagnosis of brain tumours. Neuroradiology 26: 393–398
35. Brooks DJ, Beany RP, Lammertsma AA, Leenders KL, Horlock PL, Kensett MJ, Marshall J, Thomas DGT, Jones T (1984) Quantitative measurement of

blood-brain barrier permeability using rubidium-82 and positron emission tomography. J Cereb Blood Flow Metab 4: 535–845
36. Di Chiro G, DeLaPaz RL, Brooks RA (1982) Glucose utilization of cerebral gliomas measured by (18 F)fluoro-deoxyglucose and positron emission tomography. Neurology 32: 1323–1329
37. Robinson PJ, Rapoport SI (1990) Model for drug uptake by brain tumours: effects of osmotic treatment and of diffusion in brain. J Cereb Blood Flow Metab 10: 153–161
38. Leenders KL, Beaney RP, Brooks DJ, Lammertsma AA, Heather JD, McKenzie CG (1985) Dexamethasone treatment of brain tumour patients: effects on regional cerebral blood flow, blood volume and oxygen utilization. Neurology 35: 1610–1616
39. Iannotti F, Picozzi P, Sampaolo S, Mansi L, Alfano B, Punzo A, Lenzi GL, Salvatore M, Fieschi C, Cervos-Navarro J, Conforti P (1987) The relationship between blood to brain transfer constant (Ki) and vascular surface in human brain tumours. J Cereb Blood Flow Metab 7 (1): S 335
40. Iannotti F, Conforti P, Picozzi P, Alfano B, Pozzilli C, Lenzi GL, Salvatore M, Fieschi C (1989) An evaluation by PET of oedema surrounding brain tumours. J Cereb Blood Flow Metab 9 (1): S 390
41. Reulen HJ, Graber S, Huber P, Ito U (1988) Factors affecting the extension of peritumoural oedema. A CT study. Acta Neurochir (Wien) 95: 19–24
42. Reulen HJ, Graham R, Spatz M, Klatzo I (1978) Role of pressure gradients and bulk flow in dynamics of vasogenic oedema. J Neurosurg 46: 24–31
43. Iannotti F, Schielke GP, Albanese V, Rotondo M, Hoff JT (1986) Brain tissue pressure in focal cerebral ischaemia with and without reperfusion. In: Miller JD, Teasdale GM, Rowan JO (eds) Intracranial pressure VI. Springer, Berlin Heidelberg New York, pp 566–569
44. Hedley-Whyte ET, Hsu DW (1986) Effect of dexamethasone on blood-brain barrier in the normal mouse. Ann Neurol 19: 373–377
45. Bodsch W, Rommel T, Ophoff BG, Menzel J (1987) Factors responsible for the retention of fluid in human tumour oedema and the effect of dexamethasone. J Neurosurg 67: 250–257
46. Jarden JO, Dhawan V, Moeller JR, Strother SC, Rottemberg DA (1989) The time course of steroid action on blood-to-brain and blood-to-tumour transport of 82 Rubidium: a positron emission tomographic study. Ann Neurol 25: 239–245
47. Hershey LA, Gado MH, Trotter JL (1979) Computerized tomography in the diagnostic evaluation of multiple sclerosis. Ann Neurol 5: 32–39
48. Juhler M (1988) Pathophysiological aspects of acute experimental allergic encephalomyelitis. Acta Neurol Scand 78 [Suppl] 119: 1–21
49. Pozzilli C, Bernardi S, Mansi L, Picozzi P, Iannotti F, Alfano B, Bozzao L, Lenzi GL, Salvatore M, Conforti P, Fieschi C (1988) Quantitative assessment of blood-brain barrier permeability in multiple sclerosis using 68 Ga-EDTA and positron emission tomography. J Neurol Neurosurg Psychiatry 51: 1058–1062
50. Alafuzoff I, Adolfsson R, Grundke-Iqbal I, Winblad B (1987) Blood-brain barrier in Alzheimer dementia and in non-demented elderly. An immunocytochemical study. Acta Neuropathol (Berl) 73: 160–166

51. Schlageter NL, Carson RE, Rapoport SI (1987) Examination of blood-brain barrier permeability in dementia of the Alzheimer type with 68 Ga-EDTA and positron emission tomography. J Cereb Blood Flow Metab 7: 1–8

B. Technical Standards

Economic Aspects of Neurosurgery

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Contents

Critics of modern medicine who suspect that some of its activities do more harm than good, and that even avowed benefits may not be worth the cost, usually focus on various types of high technology medicine[1]. Surgery is both the oldest and the most widely practised example of a potentially hazardous and often expensive technological intervention offered to patients to improve their prospects of a good outcome. Within surgery some procedures and specialties are supposed more often than others to be of limited benefit or unusually costly. Examples include surgery for major congenital malformations in infancy and for advanced cancer, transplantation of heart, liver or lung, and the specialties of plastic surgery and neurosurgery. Debate about the ethics and economics of high technology medicine is now on the agenda in all westernised countries. This is

because it is increasingly realized that rationing of health care is inevitable in even the most affluent societies. As a result, equity in the distribution of health care resources is recognized as an important principle of medical ethics[2]. Two other principles, non-maleficence (not doing harm to patients) and respecting patient autonomy, indicate that the use of some technologies is sometimes inappropriate even when resources are not an issue. We consider here the contribution that economic principles can make to this debate, dealing first with surgery in general and then with neurosurgery, for which some recent studies provide practical examples.

Economics of Surgery in General

Economics is about balancing costs and benefits of alternative strategies. In most health care situations it is easier to measure costs than benefits, and costs to the health service are more readily estimated than those borne by the patient and his family. Clinicians are usually more accepting of cost-effectiveness than of cost-benefit analysis, although they are sometimes confused about the difference between them[3, 4]. Cost-effectiveness is concerned with technical efficiency – the least costly means of achieving a specified beneficial end, whether diagnostic or therapeutic. Common measures of efficiency in surgery are the time waiting for a consultation, interval until admission, and time in hospital before and after operation. Other measures are the numbers of patients seen per clinic, operated on per week or admitted per year. These performance indicators are likely to attract the attention of managers, but they deal only with throughput. They give no indication of whether the activities performed were appropriate, defined as those that are both necessary and effective.

Cost-benefit analysis is about allocative efficiency, about whether resources are better used in trying to achieve one end rather than another. Because it is about choosing ends rather than means, it questions whether the balance of work in a unit is appropriate. Would it, for example, be better to treat fewer malignant brain tumours in order to be able to deal with more patients with benign conditions that do not threaten life, but where the treatment could improve the quality of life? This approach requires monetary evaluation of benefits, few of which involve readily ascertainable financial gains, such as improved earning capacity. To ascribe values to intangibles such as the relief of pain or the resolution of anxiety and uncertainty, requires judgment rather than calculation. Clinicians may disagree about these values, which reflect an assessment of quality of life. But the attempt to do this has the advantage of making it clear how much weight is attached to value judgments, as compared with more readily ascertainable benefits and burdens.

The measure most commonly used in cost-benefit analysis is the number

of years of quality adjusted life that are gained as a result of medical intervention[5, 6]. This requires comparing the outcome of treatment with that expected either with no treatment or with alternative methods of treatment. Hence, benefit is defined in terms of "product of care"[7]. This is the difference between the expected number of unacceptable or bad outcomes without treatment, and the observed number following treatment. Such benefit must be qualified by life expectancy, years of life saved by intervention being defined as "(product of care) × (life expectancy)". The concept of quality adjusted life years (QALY) refers to the value placed on each life year, given the spectrum of moderate and severe disabilities following treatment for a particular condition.

Cost of Surgery to the Health Service

The decisions of surgeons result in the deployment of substantial revenue resources, including not only the time of surgeons, anaesthetists, nurses and technicians in operating theatres, but the use of beds and investigative facilities. Major surgery often entails a commitment to costly postoperative intensive care, while certain procedures use expensive items such as artificial joints, heart valves or vascular prostheses. Elective surgery is therefore very susceptible to limitations in the supply of consumables or of staff. The ready availability of data about numbers of operations makes it easy for managers to estimate the financial implications of surgery, and this makes surgical patients particularly vulnerable whenever there is a need to contain costs in the short term. Occasionally management may declare in advance how many operations of a particular type can be performed (i.e. will be funded). More often resources are reduced and surgeons are left to assign priorities to different types of procedure and to choose between patients. Choices about what use to make of the resources available determine the service that a surgical unit as a whole provides. However, most cost-related reports about the efficiency, effectiveness and benefits of surgery focus on certain procedures, not on a surgical service as a whole.

Most surgical costing is based on estimating the cost per day in a normal surgical bed, and in an intensive care bed (commonly about five times greater). Costs per hour in the operating theatre can also be calculated, with perhaps a higher rate for night or emergency use; also for each major investigation. By aggregating these it is possible to calculate an average cost per procedure. Even ascertaining average costs of this kind is a complex and difficult process, particularly in the UK where billing for medical care has not been part of normal administrative practice in hospitals. The change to some form of internal market in the NHS is revealing how difficult it is to discover real costs. Even in the US it is accepted that costs and charges

are not the same. Yet another problem is the wide range of costs incurred by different patients with the same condition, according to severity of illness and stage of management (see later). Costs are usually much higher in the first few days because of investigations, surgery and postoperative intensive care. The economic benefits of reducing length of stay by sending convalescent patients home sooner are easily exaggerated – if based on average costs per day.

Focusing only on the costs incurred within the surgical unit during an episode of treatment ignores other hospital costs before and after this. There may have been investigations as an out-patient or undertaken by another specialty (e.g. cardiology or nephrology). Again transplantation involves substantial ongoing costs of drugs and surveillance, making it appropriate to quote "first year costs" for survivors. Less complex surgery may appear to be an inexpensive item in the hospital budget by reason of early discharge or even day surgery. However, nurses and doctors in the community are involved in removing stitches and giving support and advice which would otherwise have been done in hospital. This needs to be taken account of, together with ambulance transport. Patients with disabilities requiring remedial services incur considerable post-hospital costs – whether this is provided at home or by attendance at a rehabilitation unit.

Patient and Family

Financial costs are relatively easily calculated, in lost earnings to the patient and care-givers, together with the added expense of travelling for treatment or to visit. More important, however, are the personal burdens of treatment[8,9]. The patient has to accept the immediate risk of perioperative mortality as well as the possibility of failure to be cured or even to have his condition improved, and of developing complications. Some surgical procedures have inevitable consequences for quality of life even when the procedure has been "successful" and uncomplicated. The surgeon has therefore a duty to present to the patient the benefits and burdens of the surgery proposed, and those of alternatives treatments. He may also discuss the relative merits of surgery now, compared with postponing it, and of different surgical procedures.

Benefits of Surgery

These may be of several kinds and only occasionally is an immediate threat to life averted. There may be reduction of anxiety, uncertainty or lack of wellbeing associated with a feared diagnosis or future threat to life. More often there is relief of present symptoms; if this is reflected in reduced dependency and the resumption of abandoned activities these are further benefits. Some of these improvements may be reflected in financial benefits

both for patients and others, and also in a reduced demand on health services. It is less easy to know how much benefit to ascribe to the presumed reduction in the probability of a bad outcome several years in the future, be that of death or of progressive disability.

It is not enough to claim as a benefit that the patient has a good outcome after surgery. It has also to be shown that this is a significantly better outcome than would have been predicted either with no treatment or with an alternative (perhaps less costly) treatment. The equation needs to consider how many patients benefit, how much they benefit, and for how long they benefit, before it is possible to decide whether a particular surgical intervention is "worthwhile".

There are therefore two crucial steps in assessing how worthwhile surgery has been, the valid assessment of outcome and the reliable prediction of what that outcome would have been without surgery. Pitfalls in the assessment of outcome include attempting this too soon after surgery, particularly if the objective is other than to remove an immediate threat to life. Another is casual assessment by the surgeon involved, ascribing adjectives such as excellent or good which have not been clearly defined. There is much to be said for assessment by a third person or by the patient himself, using structured interviews or questionnaires and scoring systems. For some symptoms these may make use of devices such as the analogue scale – a line on which the patient indicates the severity of symptoms on a scale of 1 to 10. Generic questionnaires such as the Nottingham Health Profile, or the scale of wellbeing can be used to supplement data that are specific to the condition treated. There is a long way to go with outcomes research before we can be confident that we are measuring what patients rather than doctors want out of surgery[10, 11, 12].

Good information about the effectiveness of surgery is available only for a limited number of procedures. Some operations once thought effective have been shown by more formal technology assessment to have been either not effective at all, or to be useful in only a limited subset of patients. False claims for success are usually found to depend on one or more of three errors[13]. The first is to have overestimated the risk of a bad outcome without surgery. The second is to have underestimated the number of patients whose improvement was limited in extent or duration, or who suffered complications. The last is not to have had sufficiently rigorous assessment in terms of sample size, unbiased observers or statistical analysis.

Features of Neurosurgery

In Europe there are some seven times fewer neurosurgeons per capita than in the US, and they are mostly confined to large regional units. These serve many general hospitals in a defined geographical area, and most patients

come by referral from other specialists. Considerable variation in the work patterns of neurosurgical units partly reflect the differing interests of individual neurosurgeons, but also those of other specialists that overlap with neurosurgery. These patterns depend both on the willingness of other specialists to refer certain types of case and of neurosurgeons to accept them; for only some of these are there declared transfer policies. Analysis of this varying interaction between different specialists suggests that certain conditions or procedures can be identified as absolutely limited to one specialty (e.g. intracranial surgery to neurosurgery), whereas others are relative[14]. The brain is obviously close to the territories of the ophthalmic, ENT and facio-maxillary surgeons, whilst orthopaedic surgeons share interest in the spine and peripheral nerves. In some places paediatric surgeons take a major role in the treatment of hydrocephalus and spina bifida.

It is, however, in trauma that the greatest variations in practice are found. In Britain neurosurgeons take little to do with injuries to the spine or peripheral nerves. Responsibility for head injuries varies greatly between and within countries. There are neurosurgical units in Britain that accept 30% or more of all head injuries admitted to general hospitals in their region, while others take only 1%; the national average is about 5%[15]. Fewer head injuries may soon be transferred because the recent siting of CT scanners in most district hospitals is likely to increase the confidence of other surgeons to deal with more cases locally, calling on the help of anaesthetists for the severely injured. Apart from professional wishes there are likely to be demands from financial managers to refer fewer cases to specialist units, if it is felt that they can be managed less expensively locally. The role of neurologists in sharing patient care with neurosurgeons also varies widely. In some places neurologists deal with the preoperative investigation and postoperative recovery of most elective surgical cases, and screen off from neurosurgeons most cases that appear not to need surgery. In some countries neurologists take a major responsibility for the care of the less severe head injuries.

These different arrangements have considerable influence on the scale of provision of facilities for neurosurgery, and on the cost-effectiveness with which services for various conditions is delivered. Where cases are largely investigated by other specialties and returned to them soon after operation, the expenditure per case within the NSU may be modest, and cost per QALY may appear very favourable compared with other specialties. A more valid estimate of the cost of treating some cases would require calculation of the cost to other units of the preliminary investigation and subsequent aftercare of cases operated on by neurosurgeons. For some conditions the cost of negative investigation should perhaps also be added – for example, the many CT scans done in milder head injuries in order to reveal the small number who have acute haematomas. On the

other hand, there are some NSUs which have great difficulty in discharging severely disabled survivors. They may remain for months in the NSU, which is an inappropriate environment for rehabilitation, and which provides much more costly care than is needed.

Whatever the referral style, most NSUs have a greater proportion of high risk cases than most surgical specialties. This is reflected in a higher perioperative mortality rate than for other surgeons (6 times, 3 times and almost twice the rates for orthopaedic, general and cardiothoracic surgery respectively, in one large health authority). Many NSU admissions are emergencies or urgent transfers from other hospitals, with few on waiting lists for elective admission. This makes it unwise to maintain high bed occupancy and yet this is all too prevalent and indeed may be encouraged by uninformed managers. A greater proportion of beds in a NSU are likely to be of the expensive intensive care or high dependency kind. However, the concentration of neurosurgeons in large regional NSUs does avoid the duplication of expensive equipment nationwide, which is commonplace in U.S.A. It also ensures a high volume throughput, which is likely to give better results as the skills not only of surgeons but of other staff are improved. Large units also follow for sub-specialisation, which improves the quality of care, and is also essential for adequate training, and for conducting clinical research.

Specific Neurosurgical Examples

A number of studies have examined certain neurosurgical investigations or diseases, but only the Wessex study has addressed a neurosurgical service as a whole.

(a) Investigations and Early Diagnosis

Neurosurgery has benefited enormously from the revolution in imaging since 1974, but the cost of such investigations forms only a small part of the total cost of patient management. As long ago as 1978, Bartlett and colleagues provided a powerful economic argument in favour of much more widespread introduction of CT scanning than in fact happened[16]. More recently the benefits of magnetic resonance have been denied to many patients because of the inflexibility of capital funding programmes within the NHS. One example of the financial advantages of costly technical diagnostic advances comes from the study of spinal myelography in the Mersey Regional Neuroscience Unit where in 1986 this investigation alone cost at least £486,000[17]. Replacing myelography with MRI not only improves diagnostic accuracy but it avoids the immediate discomfort and long term complications associated with injecting contrast media. Moreover patients need not be admitted to hospital, and overall there could be

considerable cost-saving – but the calculations have not yet been made. Recent advances in the surgical management of the rheumatoid neck have been greatly facilitated by the increased safety and precision of surgery that has been informed by magnetic resonance images. But no one yet knows the cost/benefit ratio compared with conventional management.

This is because it is not enough simply to declare that a given investigative tool, whether new or established, is better than seemingly less expensive alternatives – with the implication that it should therefore be available (i.e. provided by health authority). Several problems arise in determining the cost-effectiveness of different investigative procedures[18, 19]. Should every patient with headache, or dizzy attacks, poor memory or a single fit have a scan? Can large numbers of negative results be justified by the reassurance for both doctor and patient that a sinister condition such as brain or spinal tumour can be excluded? And what of the discovery in a patient with tension headaches of an abnormality on the scan that is probably of no significance? These are perhaps more of a problem for neurologists than for neurosurgeons, but as specialized facilities are usually shared between them in regional centres in Britain these questions are relevant.

Before claiming the value of a positive diagnostic finding in saving the cost consequences of delayed or missed diagnosis, it is essential to estimate how many negative tests were carried out for each positive result. In practice this can be quite difficult to do, except in the context of special studies targetting the discovery of one particular condition. Whether an investigation is regarded as worthwhile should therefore depend on the probability of discovering a lesion that is treatable, together with the likelihood that the outcome of treatment would be significantly worse if detection were delayed until the development of other clinical features. The difficulty in calculating the cost of discovering each case of a given treatable condition (e.g. extradural haematoma or small acoustic neuroma) is that many patients reach the neurosurgeon only after investigation by more than one other service – and it is difficult to find out the aggregate of negative investigations that has led to the disclosure of one positive case.

There is abundant evidence that many diagnostic tests are overused and that their cost-effective use requires guidelines or policies that identify the subset of patients for whom their use is appropriate. Good examples of such protocols are those for the investigation of transient ischaemic attacks and minor strokes[20] and for the early detection of acoustic neuromas[21, 22]. Guidelines for the investigation and management of acute head injuries have led to changes in practice and to improved outcome, as described below.

As CT scanners become more widely available it is inevitable that many more patients will be investigated in non-specialist settings. Many will have

a much lower likelihood of useful findings that those who previously found their way through the narrow door of a regional unit. Not only may many of these investigations be considered unnecessary, but the lower level of expertise in general radiology departments is likely to result in more false positive and false negative findings, with the clinical, personal and economic consequences that these bring. If the investigations already done in the other hospitals are repeated by the regional centre in a high proportion of cases (to secure better images), then that also has to go into the equation. The economic advantages of investigation in a general hospital are the reduced number of referrals to the regional unit, each of which incurs transport cost and inconvenience, and often also personal expense for the patient and his family. Whilst neurologists and neurosurgeons might consider many of the investigations carried out in general hospitals unnecessary by their standards, it may well be more cost-effective to resolve the uncertainty of the general clinician by instant imaging on site. The alternative is to spend time attending the regional centre for a specialist consultation, to say nothing of the wait for an appointment, as well as the cost involved at the regional centre – which may soon have to be paid by the referring general hospital.

(b) New Therapeutic Drugs and Technologies

Until recently neurosurgery has been much less dependent on drugs than several other specialties. There is no equivalent to the expensive postoperative regimes that transplant surgery requires. Nor are there drug-based medical alternatives to surgery, such as those for coronary heart disease or renal failure, to balance against the costs of surgical intervention. Even cancer chemotherapy has a limited role in the management of tumours of the nervous system. For most conditions that a neurosurgeon sees the alternative to surgery is no treatment (zero cost), albeit termed medical, expectant or conservative management.

However, a decade of intensive developmental research in the pharmaceutical industry is bringing to the market several drugs that claim to control certain aspects of the chemical cascade associated with trauma, ischaemia and oedema in the brain and spinal cord. Theoretically these might be expected to benefit a wide range of acute conditions. Multi-centre trials are being completed for some and are in progress for others, and if favourable findings become available there may be pressure to use these drugs – perhaps on a considerably wider basis than the trials addressed. These drugs, some of which are certainly expensive, are likely to be only part of a package of treatment, and the marginal benefits and cost truly ascribed to them may not be easy to define. A good example is the calcium antagonist nimodipine, which has been shown in well-conducted trials to

reduce bad outcomes after subarachnoid haemorrhage[23]. The apparent additional expense of this drug needs to be seen in the context of the overall cost-benefit of patient management, rather than the immediate burden to the neurosurgical budget. Each bad outcome averted by nimodipine costa about £ 3,900, but each severe disability not averted costs at least £ 474,000 in long term care. One of the fallacious arguments targetted at high technology medicine is reflected in the design and timescale of hospital budgets, which are incapable of revealing the long term cost-benefit of neurosurgical intervention. These budgets take no account of savings in indirect costs (for lost production because of disability, or due to premature excess mortality), let alone the ongoing costs of disability to the health service, community and family.

When it comes to equipment with high capital cost it is necessary to consider not only what benefit is expected to accrue each time it is used, but also how often it is likely to be needed. If a laser knife or a cavitron is used only once every two or three months, does that justify its purchase? Another aspect of volume throughput is its effect on the development of skills in the use of particular equipment. These two factors favour subspecialisation, with only some units developing certain complex and expensive services, avoiding wasteful duplication and under-utilisation of expensive equipment. The recent arrangement in the NHS that such services can be bought from one health authority by another should facilitate economic appraisal of proposals to set up such services. For example, specialized centres for the investigation and treatment of cases of intractable epilepsy, some of whom benefit from surgery, have been shown to cost less and bring more benefit over a series of cases than traditional "low tech" management[24]. But it is unlikely that every NSU would have enough cases to justify setting up such a service. Another example is radiosurgery, which the Society of British Neurological Surgeons agreed with the Department of Health should be established in only one centre, and be supported by supraregional funding.

(c) Management of Acute Head Injuries

This presents a particularly interesting challenge to economic appraisal, for several reasons. The condition is a common one which can use resources in several other specialties. These include accident/emergency, general and orthopaedic surgery, radiology, intensive care, paediatrics and, for disabled survivors, rehabilitation. There is a range of organisational options that involve neurosurgical units to varying degrees, and there are wide variations in practice in different places; these apply both between and within countries. Moreover CT scanning has probably done more to alter the management of this condition than of any other, providing an effective and

non-invasive method of detecting acute intracranial haematomas. There is evidence that well-organized services that ensure the appropriate use of scanning and timely neurosurgical intervention can improve outcome from this complication, which is the main cause of potentially avoidable mortality and morbidity[25, 26].

The economic and logistic problem is that this complication affects only a tiny minority of the large number of less severe injuries that present to accident departments, and only a small proportion of those admitted to general hospitals. Questions that arise are, which patients should have skull X-ray in accident departments, which should be admitted, and which should be referred to regional NSUs for scanning? In UK until recently scanners for emergency use have mostly been sited in these units. Radiologists have argued that it is a waste of resources to X-ray large numbers of mildly injured patients, because skull fractures do not require treatment. Neurosurgeons, however, point to the greatly increased risk of a haematoma developing in patients with a fracture. They claim that X-ray is a useful triage tool – for admission for further observation, and for referral for scanning or neurosurgical opinion[27]. Excluding a skull fracture (by X-ray) can substantially reduce the number of patients admitted, and even overnight admission costs are many times the price of the skull X-ray[28].

Ten years ago the proportion of patients admitted to general hospitals who were referred to NSUs varied from 1% to 50% in Britain, where the national average was 5%[15]. Guidelines that recommended the transfer of more patients to NSUs for scanning and treatment led to twice as many transfers per year in one unit, where head injuries came to account for 20% of the admissions and bed days[29, 30]. In that unit a third of all scans and half of all emergency scans were for head injured patients, who accounted for 50% of intensive care bed days. There are, however, still wide variations between neurosurgical units (from 210 to 60 head injury admissions per million population). Moreover it is difficult to calculate the cost of the improved outcomes for operated intracranial haematomas, because these have resulted from changing policies in many hospitals that affected admission, X-ray investigation and transfer.

As more general hospitals get scanners and intensive care units it is important to discover the comparative benefits of management there or in an NSU[31]. Whilst there is no serious disagreement that intracranial surgery should be done only in NSUs, it is more difficult to identify the benefits of an NSU for head injured patients in coma before or after surgery (or not requiring surgery). Some benefits would be expected to derive from the availability of medical and nursing staff skilled in dealing with brain damaged patients in the ITU, and of neuroradiologists to interpret repeat scans in patients with continuing problems. In one health authority the day costs for general surgery were only 60% of those in the neurosurgical

unit (excluding intensive care, which was priced at six times the NSU day cost). Costing of individual head injury patients in the NSU in that authority ranged from £135 to £8302, with the average range £214–£2220 (1984/85 prices – × 1.497 for 1989/90). This points up the difficulty of dealing with average costs for conditions as heterogeneous as head injury. Adoption of an "aggressive" intensive care programme for head injuries in Lund, Sweden, increased the costs per treated patient by about 46%[37]. Mortality decreased but unfortunately several changes were made at the same time, making it difficult to know how much benefit came from each[38]. It did appear that the cost per surviving patient remained unaffected and that a larger proportion of the economic expenditure was spent on patients who ultimately recovered well.

(d) Use of Intensive Care

Neurosurgeons make considerable demands on the costly services of intensive care units, whether these are within a neurosurgical department or shared with other users in hospital. The day costs in intensive care units are about five times those in normal wards, largely because of the high nursing levels. It is therefore particularly important to use intensive care only when it is appropriate. Policies for the routine use for postoperative cases should be considered carefully – which patients should go and for how long? This is not only because of cost, but because an intensive care unit involves both medical risks and personal disadvantages for patients, and these may outweigh the supposed advantages.

Apart from patients who may not need intensive care, there are those who are so badly brain damaged that they cannot benefit from further intensive care. Every NSU faces the dilemma of patients who have survived a severe brain insult, by virtue of life-saving technologies which may have included surgery, who are not brain dead but who are very unlikely to make any kind of useful recovery. The question of when to make a decision to limit treatment has important ethical and economic implications[32]. Increasingly the public is indicating to doctors that they regard survival with certain degrees of brain damage as a fate worse than death (e.g. in the vegetative state). Once it is declared that if survival is likely to be achieved, it will leave the patient with very severe permanent brain damage, many families regard extending life as inappropriate and undignified. Questioned about the degree of certainty of a poor outcome that would lead them to withdraw or withhold treatment, a group of neurosurgeons from several countries indicated that they would want treatment for themselves to be abandoned much sooner than they normally did for their own patients[33].

From an economic viewpoint, failing to make a decision to withdraw treatment from a hopeless patients is in effect a decision to deny treatment

to another patient who could benefit – because resources for intensive care are almost always and everywhere limited. Both ethics and economics therefore require that a decision to limit treatment be made sooner rather than later, once the prognosis is clear. In one NSU half the deaths were found to have followed a written decision to limit treatment[34]. Quite often this decision had been made soon after the patient had arrived at the NSU, usually after CT scanning had confirmed the clinical impression of irrecoverability based on the degree of brain damage and the patient's age.

(e) The Wessex Study of Cost-benefit in a NSU

The opportunity for a comprehensive cost-benefit analysis of regional neurosurgical care arose when the Wessex Regional Neurological Unit was costed in considerable detail during the year 1983–84 by the regional authority[35]. As a separate exercise the neurosurgeons defined the "product of care" and the cost for each major neurosurgical diagnostic group – subarachnoid haemorrhage, head injury, intracranial tumours, spinal disorders (non-metastatic), central nervous system metastases and miscellaneous. The Wessex Neurological Centre provided a neurosurgical service for a population of 2.7 million in 1984, when there were 1,185 admissions of 1,026 patients. Of the 978 patients with available case records, 919 (94%) were followed up. The cost of in-patient care in the NSU for patients discharged during 1984 were calculated, and their outcomes assessed six months or more after discharge, and compared with natural history and life expectancy.

Patients were graded using the Glasgow Outcome Scale. This was modified where necessary, for example to take account of visual or endocrine symptoms in patients with pituitary tumours, and pain or problems of mobility and power in those with spinal problems. Patients with degenerative spinal disorders whose condition remained the same after operation were graded as 3 (severe disability), even when the realistic aim of surgery was to prevent further deterioration rather than to facilitate improvement. The expected outcome without neurosurgical intervention varies from the well-defined (for example, subarachnoid haemorrhage) and the reasonably obvious (for example, malignant brain tumours) to the more uncertain.

For each diagnostic category, the likely outcome after six months and after 10–20 years without neurosurgical intervention, was estimated from published data or from a postal questionnaire completed by a panel of 18 Consultant Neurosurgeons from throughout the United Kingdom. A Delphi exercise was then completed in which the results of the first assessment by the panel were fed back to them to clarify any misunderstandings, and to give pause for further reflection on difficult problems. The spectrum of severity of the disorder was defined as that to be expected on presentation

Table 1

Diagnosis	No of patients	Total length of stay (days)	Total cost (£)	Bad outcomes averted	Cost per bad outcome averted (£)	Mean (range) of cost per aLY (£)[a]	Mean (range) of cost per QALY (£)[a]
Subarachnoid haemorrhage	178	2237	326602	45	7258	279 (173-∞)	310 (192-∞)
Head injury	161	1317	192282	35	5494	137 (37-∞)	151 (41-∞)
Intracranial tumours:							
Malignant	116	1876	273896	4	68474	61138 (788–332008)	68694 (788–400010)
Benign	82	1489	217394	39	5574	199 (135–394)	243 (148–588)
Spinal disorders (non-metastatic)	159	2286	333756	64	5215	193 (57–343)	261 (76–476)
CNS metastases	66	610	89060	8	11133	11133	
Miscellaneous	216	2376	346896	48	7227	241 (34–3260)	307 (34–4180)
Total (range)	978[b]	12191	1779886	243	7325	293 (34-∞)[c]	351 (34-∞)

[a] Ranges refer to different diagnoses within major diagnostic group; aLY = acceptable life years saved; QALY = quality adjusted life year.

[b] 48 Case records were not available and hence 127 occupied bed days (12318-12191) are unaccounted for. Outcomes were known in 919 patients.

[c] Overall mean life expectancy = Overall mean life expectancy = 25 years.

Reproduced from Pickard[7] *et al* (1990) Br Med J 301: 629–635.

at a typical British neurosurgical unit. The population for subarachnoid haemorrhage was particularly well-defined because of the concurrent prospective double-blind, randomized trial. The possibility that the Expert Panel might have been too pessimistic has been examined by comparing its assessments with published studies, and by reporting the range of panel members' opinions. The order of magnitude of the cost per QALY and the conclusions to be drawn were not affected by variations in the views of the Expert Panel for those diagnostic groups with reasonable numbers of patients. Wide fluctuations were, however, found in small diagnostic groups with a broad spectrum of severity at presentation (vide infra).

Costings

The overall cost of neurosurgery in the Wessex unit for the year 1983–84 was £ 1,795,000. Independently recorded bed occupancy data provided the total occupied bed days for the year, giving an average cost per occupied bed day of £ 146 (1984/85 prices). The mean length of stay for patients in

Table 2. *Cost of Avoiding One Death or Long Term Disability (1983 – 4 prices)*

General	Cost (£)	Neurosurgery
Preoperative chest X-ray	1000000	
Cervical cancer screening	54000 – 285000	
Breast cancer screening	39000 – 80000	
	68000	Malignant brain tumours
Open spina bifida	22000	
Sudden infant death*	16000	
Whole body scan	11000	Metastatic tumours in central nervous system
Open heart surgery	10000	
Kidney transplant	8000	
	7000	Subarachnoid haemorrhage
	5500	Head injury; benign intranial tumours
	5000	Spinal disorders
Hip replacement	2000	
Operation for perforated peptic ulcer	1500	
Routine estimation of haemoglobin concentrations	200	
Blood pressure screening	100	

* Surveillance by health visitor.

Reproduced from Pickard[7] *et al* (1990) Br Med J 301: 629–635.

each diagnostic category was calculated from examining individual case notes. No attempt was made retrospectively to define nurse dependency, the cost of investigation, or of operating theatre by diagnostic group, nor was any estimate made of the use of or cost of intensive care.

Costs of Averting Death or Severe Disability

For each diagnostic category, the total cost was calculated from the length of stay multiplied by £ 146. The cost of averting a death or severe disability was derived by dividing the total cost by the difference between observed and expected outcomes. Table 1 summarizes the data within the six diag-

Table 3. *Cost per QALY (1983–4 prices)*

General	Cost (£)	Neurosurgery*
	69000	Malignant brain tumours
Haemodialysis in hospital	14000	
Coronary artery bypass graft for moderate angina and one diseased vessel	12000	
	11000	Metastatic tumours in central nervous system
Heart transplantation	5000	
Cervical cancer screening	2500–15000	
Breast cancer screening	3000	
Renal transplantation	3000	
Coronary artery bypass graft for disease in main vessels	1040	
Thrombolytic treatment for acute myocardial infarction	600–3000	
Hip replacement	750	
Inserting pacemaker for artrio-ventricular heart block	700	
	350	All neurosurgery
	310	Subarachnoid haemorrhage
	300	Miscellaneous
	260	Spinal disorders
	240	Benign intracranial tumours
	150	Head injury

* Neurosurgical QALY refers to deaths and severe disabilities averted and has been modified to take account of proportion of patients left moderately disabled.

Reproduced from Pickard[7] *et al* (1990) Br Med J 301: 629–635.

Table 4. *Cost of Averting Severe Disability (SD) and Persistent Vegetative State (PVS) Excluding Death*

Diagnosis	No of patients	Bad outcomes		Expected minus observed	Cost of neurosurgical intervention (£)	Cost per SD or PVS averted (£)	Standard life expectancy	Corrected life expectancy	Projected working life	Cost per patient of long term care (excluding loss of earnings (£)[a]	Total cost of long term care averted (£M)
		Observed (at 6 months)	SD or PVS expected								
Subarachnoid haemorrhage	178	3	15	12	326602	27217	31	26	15	474500	5·7
Acute head injury	145	8	13·3[b]	5·3	158118	29834	43	38	33	693500	3·67
Chronic subdural haematoma	16		4·5[b]	4·5	34164	7592	11	6		109500	0·49
Cerebral abscess	11		1[b]	1	38398	38398	31	26	18	474500	0·47
Total	350			22·8	557282						10·33

[a] Cost of care in an institution or at home is £50–£70 a day plus social security payments – assume £18250 a year at £50 a day.

[b] Expected severe morbidity at 6 months according to expert panel.

Reproduced from Pickard *et al* (1990) Br Med J 301: 629–635.

nostic groups (full details available in the original publication). There was a wide variation in estimated costs (and confidence intervals) of averting death or severe disability: for example £41/QALY for extradural haematoma, £25,039 for cerebral metastases, and £68,694 for malignant brain tumours. Given popular misconceptions about the high cost of neurosurgery, it is instructive to compare the cost per bad outcome averted and per QALY for neurosurgery with those for medicine in general (Tables 2 and 3). Neurosurgery in general appears to be good value for money.

Costs of Averting Severe Disability Alone (Table 4)

This analysis assumed the unacceptable and naive view that death is cheap and that patients with neurosurgical conditions left untreated will succumb. Even with these cynical abstractions, it remained cost-effective to avert severe disability for four conditions that can lead to severe disabilities – subarachnoid haemorrhage, acute head injury, chronic subdural haematoma and cerebral abscess. Total cost of neurosurgical intervention in these four groups was £0.56 million compared to £10.33 million for long term care if they were untreated.

Future Directions

High technology activities such as intensive care, cancer therapy and transplant, cardiac and neurosurgery have often been criticized in recent years as being disproportionately expensive. The implication is that more mundane medical and surgical activities may be more worthwhile in cost-benefit terms. There are, however, few facts on which to base comparisons and studies such as those referred to above are an important step in the right direction. The Wessex study shows that the cost benefit of some neurosurgical treatments compares well with that of other specialties. This should serve to educate public and administrative opinion and to correct potentially damaging assumptions based on misconceptions. However, it is too simplistic to claim that neurosurgery as a whole is therefore a worthwhile activity. Indeed an important lesson from this study for neurosurgeons is that some conditions are much more worthwhile treating than others, in economic terms. Whilst this may seem to be self-evident, the scale of the difference was not previously recognized. Managers may make macro-allocation decisions about resources between specialties, but clinicians need to consider how they use the resources provided for their specialty, by deciding on the balance of their work as between different conditions and different patients.

There is evidence that health authorities in the affluent west, both in Europe and in North America, are starting to make explicit choices about what clinical services they can afford for their populations. The state of

Oregon has led the way in attempting to contain health care costs while establishing a programme by which everyone is eligible for at least some basic health care[36]. At a second attempt, the Oregon Health Services Commission has completed the ranking of over 700 conditions and treatments, taking great care to solicit public opinion for priority setting. In Britain by contrast one regional health authority, without taking any public consensus, advised that five treatments be curtailed because there was no overriding clinical need (varicose veins, non-malignant lumps and bumps, wisdom teeth, tattoo removal and in vitro fertilisation). On a BBC television programme this year 11 health authorities provided lists of conditions which were on a "not to be funded" list.

It is clear that these decisions were not made as a result of studies of the kind described here, information gathering for which is extraordinarily expensive in terms of both professional time and money. This might be considered better employed in patient care, but it is in the interests of neurosurgeons to take an active interest and to participate in accumulating accurate information about their activities and their costs, in order to be able to defend their activities. Some such questions could helpfully be examined at national and international levels, with scope in the European context for comparing the cost of managing specific diseases under different systems of neurosurgical provision.

Unless neurosurgeons do this and produce reliable data about the clinical effectiveness and and costs of their interventions, then decisions about priorities are likely to be made by others even though no good data are available. The danger is that the quest for cost-effectiveness may suppress traditional values of caring and humanity, which have hitherto been characteristic of European health services. These values do not, however, justify embarking on expensive and elaborate programmes of treatment for patients who are very unlikely to benefit, as already explained. Treatment choices should be made on the relative prospects of benefit, and every effort made to resist a two-tiered health system in which rationing is more rigid for vulnerable groups of patients or those less able to pay.

Both managers and clinicians have an interest in acquiring good information about cost-effectiveness and cost-benefit, and they should share the finances needed to acquire such information. There is some prospect of this developing in Britain, with the developing emphasis on clinical audit and on resource management, under new health service legislation. It will, however, take time to accumulate adequate information, but the time scale might be shortened if there was more national and international sharing of information. Clinicians who consider that they have a good product to offer should not be shy of inviting economists to collaborate with them. When the Department of Health in Britain commissioned health economists to study the cost-effectiveness of heart transplantation, it was suspected

that they expected this to show that it was so expensive that the programme could be limited. In the event the economists showed that heart transplantation greatly improved quality of life; also that two year survival rates compared very favourably with much surgery that was done without question in other specialties. The consequence of that study was the immediate allocation of additional funds to expand the heart transplant programme.

References

1. Jennett B (1986) High technology medicine – benefits and burdens. Oxford University Press, Oxford and New York
2. Jennett B (1987) Are ethics and economics incompatible? Proc Roy Coll Phys Edinb 17: 190–195
3. Jennett B (1984) Economic appraisal. Br Med J 289: 1781–1782
4. Mooney GH, Ludbrook A (1984) The NHS: efficiency need not be a dirty word. Br Med J 288: 1817–1818
5. Williams A (1985) Economics of coronary artery bypass grafting. Br Med J 291: 326–329
6. Smith A (1987) Qualms about QALYs. Lancet i: 1134–1136
7. Pickard JD, Bailey S, Sanderson H, *et al* (1990) Steps towards cost-benefit analysis of regional neurosurgical care. Br Med J 301: 629–635
8. Jennett B (1985) Benefits and burdens of surgery. Br J Surg 72: 939–941
9. Jennett B (1988) Balancing benefits and burdens in surgery. Br Med Bull 44: 499–513
10. Greenfield S (1989) The state of outcome research: are we on target? N Engl J Med 320: 1142–1143
11. Carlson H, Pellettieri L (1989) Doctors' versus patients' evaluation of results after neurosurgery. J Neurol Neurosurg Psychiatry 52: 153–155
12. Meyer CHA, Hitchcock ER (1991) Keeping the score: neurosurgical audit of clinical outcome (abstract). J Neurol Neurosurg Psychiatry (in press)
13. Jennett B (1989) Surgery to prevent stroke: high hopes and deep disappointment. Int J Tech Assess in Health Care 5: 443–457
14. Jennett B (1979) How many specialists? Lancet 1: 594–597
15. Jennett B, Murray A, Carlin J, *et al* (1979) Head injuries in three Scottish neurosurgical units. Scottish head injury management study. Br Med J 2: 955–958
16. Bartlett JR, Neil-Dwyer G, Banham JMM, *et al* (1978) Evaluation of the cost effectiveness of diagnostic equipment: the brain scanner case. Br Med J ii: 815–820
17. Sandercock PAG, Roberts MA, Blumhardt LD (1989) A prospective audit of the use and costs of myelography in a regional neuroscience unit. J Neurol Neurosurg Psychiatry 523: 1078–1084
18. Jennett B (1986) Diagnostic investigations – towards more appropriate use: I. A clinicians' viewpoint. Health Bull 44: 8–12
19. Ludbrook A, Mooney G (1986) Diagnostic investigations – towards more appropriate use: II. The economic perspective. Health Bull 44: 13–19

20. Hankey GJ, Warlow CP (1990) Symptomatic carotid ischaemic events: safest and most cost effective way of selecting patients for angiography, before carotid endarterectomy. Br Med J 300: 1485–1490
21. Moffat DA, Hardy DG (1989) Early diagnosis and surgical management of acoustic neuroma: is it cost effective? J Roy Soc Med 82: 329–332
22. Swan IRC, Gatehouse S (1991) Clinical and financial audit of diagnostic protocols for lesions of the cerebellopontine angle. Br Med J 302: 701–707
23. Pickard JD, Murray GD, Illingworth R, *et al* (1989) Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. Br Med J 298: 636–642
24. Silfvenius H (1988) Economic cost of epilepsy – treatment benefits. Acta Neurol Scand 78 [Suppl 117]: 136–144
25. Teasdale G, Galbraith S, Murray L, *et al* (1982) Management of traumatic intracranial haematoma. Br Med J 285: 1695–1697
26. Jennett B (1991) Epidemiology of severe head injury: socio-economic consequences of avoidable mortality and morbidity. In: Scriabine A, Teasdale GM, Tettenborn D, Young W (eds) Nimodipine. Pharmacological and clinical results in cerebral ischaemia. Springer, Berlin Heidelberg New York
27. Teasdale G, Murray G, Anderson E, *et al* (1990) Risks of acute traumatic intracranial haematoma in children and adults: implications for managing head injuries. Br Med J 300: 363–367
28. Mendelow AD, Campbell DA, Jeffrey RR (1982) Admission after mild head injury: benefits and costs. Br Med J 285: 1530–1532
29. Group of Neurosurgeons (1984) Guidelines for initial management after head injury in adults. Br Med J 288: 983–985
30. Bryden JS, Jennett B (1983) Neurosurgical resources and transfer policies for head injuries. Br Med J 286: 1791–1793
31. Jennett B, Macpherson P (1990) Implications of scanning recently head injured patients in general hospitals. Clin Radiol 42: 88–90
32. Jennett B (1990) Decisions to limit the use of technologies that save or sustain life. Proc Roy Coll Phys Edinb 20: 407–415
33. Barlow P, Teasdale G (1986) Prediction of outcome and the management of head injuries: the attitudes of neurosurgeons. Neurosurgery 19: 989–991
34. Barlow P, Jennett B (1991) Decisions to limit treatment in a neurosurgical unit: an aspect of audit of mortality. Scot Med J 36: 109–111
35. Rees M (1985) The costs of the cardiothoracic and neurological units in the Southampton General Hospital; Report of the Regional Services Project Steering Committee. Winchester: Wessex Regional Health Authority
36. Dixon J, Welch HG (1991) Priority setting: lessons from Oregon. Lancet 337: 891–894
37. Sundbarg G, Norlund A, Nordstrom CH, Messeter K (1989) Severe traumatic brain lesions in Sweden. Part 3: Economic aspects of aggressive neurosurgical intensive care. Brain Injury 3: 283–293
38. Jennett B (1989) Severe head injuries – Swedish style. Brain Injury 3: 215–217

Current Concepts of Measurement of Cerebrospinal Fluid Absorption and Biomechanics of Hydrocephalus

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With 20 Figures

Contents

New investigate methods have extended the scientific and clinical knowledge of the circulation of the cerebrospinal fluid (CSF). Methods of measurement of resistance to CSF outflow have improved during the last 15 years (Børgesen *et al.* 1978; Ekstedt 1978; Shapiro *et al.* 1984; Kosteljanetz 1987; Gjerris *et al.* 1989 a). A thorough knowledge of the dynamic equilibrium between CSF production and absorption is essential for the understanding of the changes in the intracranial space during pathological conditions. CSF dynamics comprehend all factors concerning formation, flow rate, direction, and absorption of CSF.

Treatment of hydrocephalus by shunting is afflicted with an over-all complication rate close to 50% (see later). Shunting based on clinical and radiological findings alone leads to improvement in around 50% of the cases. Therefore, shunting must be based on parameters with acceptable diagnostic specificity and sensitivity, i.e. R_{out} measurements.

Production, Formation, Volumes and Absorption of the Cerebrospinal Fluid

Production

The main *production site* of CSF (70–80%) is the choroid plexus in the lateral ventricles, and the roof of the third and fourth ventricles, where both a filtration across the endothelial capillary wall and a secretion by the choroidal epithelium occur (Milhorat 1972; Pollay 1975; Davson *et al.* 1987). CSF production is influenced by enzyme inhibitors, by the autonomic nervous system, by changes in CSF osmolality, by low cerebral perfusion pressure and by the choroidal blood flow. The remaining 20 per cent of the CSF production arises as a bulk flow of the interstitial fluid (the extrachoroidal source) in the white matter of the brain (Davson *et al.* 1987; Cserr 1989).

Formation

The CSF *formation rate* (FR) is in man between 0.30–0.40 ml/min or 500 ml per day. The CSF is actively secreted as an ultrafiltrate in the choroidal epithelium and subsequently carried by diffusion into the ventricles. An ATPase Na^+/K^+ pump mechanism takes part in the secretory process and can be enzymatically blocked. FR can be measured by the indicator dilution technique by ventriculo-cisternal or ventriculo-spinal isotope perfusion (Pappenheimer *et al.* 1962; Welch 1975), or by the computerized infusion test (Czosnyka *et al.* 1989). FR varies remarkably in different species. Pollay

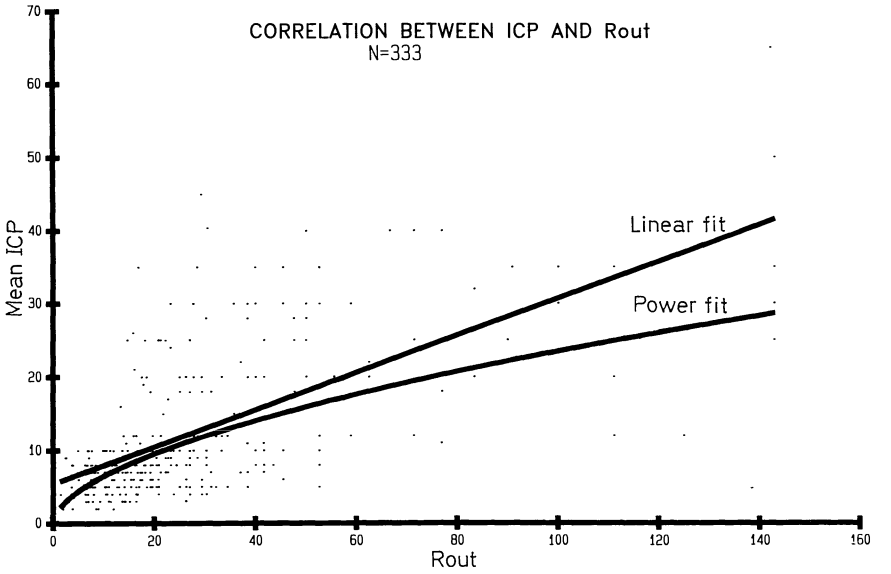

Fig. 1. The best curve-fit correlating mean ICP to R_{out} is a polynomial. The fit indicates that with increasing ICP the FR of CSF tends to decrease

et al. (1983) have shown that a fall in perfusion pressure results in a significant decrease in both plexus blood flow and CSF production. It has been assumed, that FR is unaffected by rising ICP. Børgesen and Gjerris (1987) found in clinical studies in patients with high ICP, that FR tends to decrease with long-standing increase in ICP (Fig. 1). Changes in FR are less important in affecting CSF dynamics, as a reduction of FR by one third only decreases ICP less than few mmHg.

Transportation

The driving forces to convey the CSF out of the ventricular system are the pressure gradients between the different parts of the ventricular system, the subarachnoid space and the venous sinuses. These pressure gradients are created by the continuous CSF-secretion and may be enhanced by the pulsations of the brain (Pollay 1985). The pressure differentials and the resistance elements within the CSF circulation are schematically illustrated in Fig. 2. Major resistance sites are the foramen of Monro, the aqueduct of Sylvius, the foramina of Luschka and Magendie and the arachnoid villi. All CSF produced in the lateral and third ventricles passes through the aqueduct of Sylvius. The physical size of the aqueduct influences the flow accoring to the Hagen-Poiseulle's law:

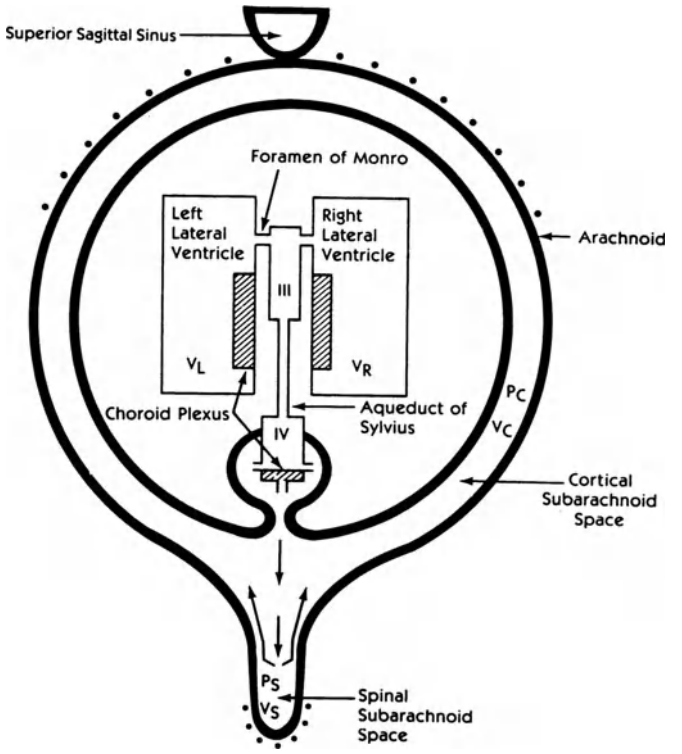

Fig. 2. The pressure differentials within the CSF space are shown in a computer simulation of a mathematical model of ventricular volume regulation (Rekate *et al.* 1988, with permission)

$$\text{Flow} = \frac{\text{PI} * (P_1 - P_0) * r^4}{8 * L * u^{-1}} \quad (1)$$

where PI is the initial pressure, r the diameter of the aqueduct, L the length of the aqueduct and u the viscosity constant. The flow is related to length and diameter of the aqueduct. With a normal diameter of the aqueduct of 0.25 mm, a length of 10 mm and a normal viscosity of CSF, the flow may be 60 times normal FR without creating increased intraventricular pressure.

Composition and Volumes

CSF composition parallels an ultrafiltrate of plasma. Active secretion is involved in the concentration of the single solute (protein, transmitter etc), which differs very much in the various parts of the CSF space (Wood 1980; Wood 1983; Gjerris 1988; Gjerris *et al.* 1988).

CSF volumes are connected closely to FR, to absorption and R_{out} of CSF, to changes in ICP and BP and to the proportions of the brain. Teasdale

et al. (1989) found, that the cranial CSF volumes in normal subjects estimated by MRI range from 57 to 286 ml. The total CSF volume increases with age, mainly the sulcal volume. The ventricular CSF volume fluctuates between 6.8 to 30 ml and is correlated to total CSF volume (Teasdale *et al.* 1989).

During development of acute hydrocephalus the volume of the ventricular system will enlarge. As the size of the ventricles increases, the ICP decreases (Børgesen and Gjerris 1987). This apparently paradoxical phenomenon and the correlation between ventricular size and ICP in hydrocephalus have been evaluated by Penn and Bacus (1984) and Hakim and Hakim (1984), who have set up a working hypothesis of the components and forces operating during the hydrocephalic development both with a closed and an open skull. Early and Finck (1976) and Portnoy (1989) have explained this hydrocephalic phenomenon by the law of La Place. When the law is applied to a thin walled sphere, the equation is

$$F = \pi * R^2 * P \tag{2}$$

where F is the force on the ventricular side, P the transmural pressure and R the radius of the sphere. When the ventricles increase in size the force on the wall of the ventricles decreases, or the disruptive force (F) is equal to the product of transmural pressure (P) and the area of the equatorial circle (πR^2) (Early and Finck 1976).

Absorption and Sagittal Sinus Pressure

The CSF is absorbed through the villi valves penetrating the sinuses. An unknown part of CSF, probably 15% in man, is assimilated in the spinal villi. In animals a part of CSF is absorbed along the olfactory nerves into the nasal mucosa, to the extracellular dura or to the lymph system (Cserr 1989). The arachnoid villi contain the pressure-sensitive regulation of CSF outflow. CSF absorption depends on the transvillus pressure gradient (Sahar *et al.* 1969; Gjerris *et al.* 1989 a; Rekate *et al.* 1989). The flow is proportional to the pressure gradient between the subarachnoid space and the dural sinuses:

$$\text{Flow} = \frac{\text{ICP} - P_{SS}}{R_{out}} \tag{3}$$

where ICP is the pressure in the subarachnoid space, P_{SS} is sinus pressure and R_{out} is the resistance to CSF outflow. The normal pressure gradient is about 3–4 mmHg. The eq. (3) indicates a linear relationship between CSF absorption and ICP (bulk flow). The absorption begins at a CSF pressure as low as 5 mmHg. The CSF has been proposed to be absorbed either through the villi valves (valve mechanism) or by vacuoles in the endothelium (vacuolar mechanism). Alternative absorptive pathways may be the capillaries of the

brain, the choroid plexus or the subarachnoid space (brain parenchyma) (Pollay 1985).

Correlation Between ICP and CSF Formation/Absorption

The balance between CSF formation and absorption in holding ICP constant is given by the Davson equation

$$ICP = FR * R_{out} + P_{SS} = ER * R_{out} + P_{SS} \quad (4)$$

where R_{out} is the resistence to CSF outflow, P_{SS} the pressure in the sagittal sinus and ER the elimination rate of CSF. Based on an average volume of 150 ml the turnover of CSF is 14% per hour. In a material of 333 patients with disturbances of CSF circulation Børgesen and Gjerris (1987) found, that the relation between formation rate and ICP could be described by

$$ICP = 3.0 + 0.3 * R_{out} \quad (5)$$

This indicates that the normal FR of CSF was 0.3 ml/min. However, the best fit of the scatter plot as illustrated in Fig. 1 depicts a slightly curved correlation demonstrating that FR of CSF decreases with increasing ICP. ICP is normally maintained by the resistance of CSF outflow, as given by the Davson equation. An increased amount of CSF (hydrocephalus) presupposes a reverse volume change in one of the other intracranial volumes, the so-called Monro-Kellie doctrine. The sum of the intracranial volumes (CSF, cerebral blood volume, interstitial fluid, neurons and glia) is constant. The CSF volume of the craniospinal axis itself is no longer believed to be constant, and volume changes are related to ICP changes (Teasdale *et al.* 1989). Distention of meninges, compression of vascular structures and venting of CSF constitute the three mechanisms which serve to protect the brain from elevations of ICP. The compliance factors (meningeal distention and partial venous compression) are effective only on the lower part of the pressure volume curve.

Man has a low outflow resistance compared to animals. CSF outflow can sustain efflux rates of at least 2.0 ml per minute. We have during investigations in hydrocephalic patients even found up to 5.0 ml per minute. The correlation between an expanding volume and the resulting pressure is known as the pressure-volume (PV) relationship.

Vasopressin and ICP

The brain water permeability is regulated by centrally released vasopressin and a central neuroendocrine regulation controls the brain ion homeostasis and volume (Raichle 1981). Sørensen *et al.* (1984) investigated CSF vasopressin in patients with pseudotumour cerebri, intracranial tumour, hydrocephalus and controls and found an increased level in patients with increased

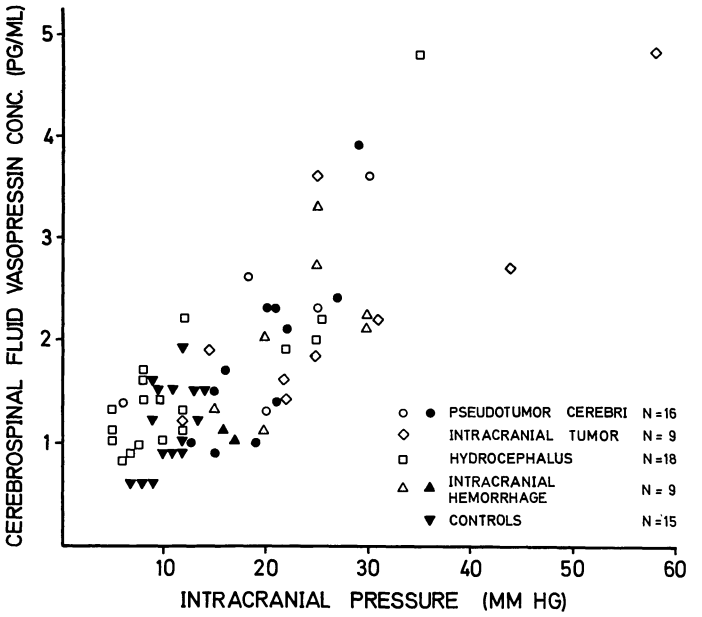

Fig. 3. Relationship between intracranial pressure and cerebrospinal fluid vasopressin concentration in 67 patients with normal or increased intracranial pressure ($r = 0.79$; $p < 0.001$). Open triangles indicate epidural or intraventricular ICP measurement; filled triangles indicate ICP measured by lumbar puncture (Sørensen *et al.* 1984, with permission)

ICP. The linear correlation between ICP and the concentration of CSF vasopressin is shown in Fig. 3. Dóczi and Bodosi (1989) showed a linear correlation between ICP, R_{out}, and CSF vasopressin. It is suggested that vasopressin has some effect on CSF absorption (Sørensen 1986; Dóczi and Bodosi 1989; Sørensen and Gyring 1990).

Measurement of Resistance to CSF Outflow

The absorption and resistance of CSF outflow (R_{out}) can be measured by isotope dilution procedures (Pappenheimer *et al.* 1962), by bolus- and infusion methods or by perfusion techniques (Børgesen 1984; Kosteljanetz 1987; Marmarou and Tabaddor 1987; Gjerris *et al.* 1989 a; Pollay 1985; Price 1989). Measurement of R_{out} has proved (see later) to be valuable in diseases associated with disturbances in the CSF-dynamics, but the invasive procedure connected with intrathecal infusion or perfusion has limited their general use. In clinical practice three different methods are in use for measurement of resistant to CSF outflow:

I. Infusion methods.
II. Bolus injections methods.
III. Isotope dilution methods.

I. Infusion Methods

All these procedures monitor the ICP during infusion of mocked CSF or Ringer lactate and are based on identical principles of a) injecting, infusing or perfusing intrathecally at either a constant rate or a constant pressure and b) plotting the flow (= ml/min) against ICP levels. The slope of the regression line is an expression of *conductance to CSF outflow* (C_{out}), and the reciprocal value is *resistance to CSF outflow* ($R_{out} = 1/C_{out}$) (Fig. 4). The calculation of R_{out} implies a constant CSF production and constant CSF and cerebral blood volumes, irrespective of the increases in ICP during the study. All the mathematical estimations and methods used for measurement of R_{out} should be evaluated critically (Portnoy and Croissant 1976; Gyring *et al.* 1986; Marmarou and Tabaddor 1987; Børgesen *et al.* 1989; Fridén and Ekstedt 1989). Three different techniques are in use:

A. Constant pressure servo-controlled infusion technique.

B. Constant infusion and constant pressure technique.

C. Constant rate infusion technique.

All the methods imply a risk of CSF leakage, which will give a too low estimation of the R_{out}-values. In the closed set up of some of the infusion methods spontaneous ICP fluctuations are inevitable, which renders interpretation of the pressure rises difficult. In the open system of the lumboventricular perfusion it is possible to avoid these vascular reactions.

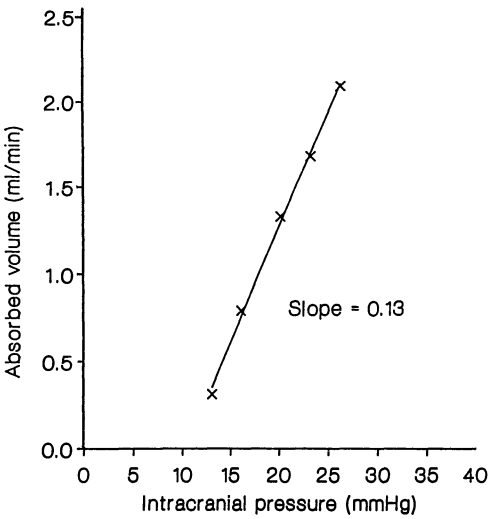

Fig. 4. R_{out} values and linear regression line, method of least squares (Albeck *et al.* 1991, with permission)

A) The Constant Pressure Servo-controlled Infusion Method

This method was developed by Davson *et al.* (1970) and modified by Ekstedt (1977). The set up gives the possibility of calculating R_{out}, P_{SS} and the volume/pressure relationship, but not FR. Ekstedt and Fridén (1989) concluded from their vast experience of CSF outflow measurements in humans in 2256 investigations over 17 years, that the infusion methods give the best estimate of R_{out}. The time consumed for the constant pressure servo-controlled infusion method is a clinical disadvantage.

B) The Constant Infusion and Constant Pressure Method

The only parameter obtainable by the *lumbo-ventricular perfusion test* is R_{out}. It was originally developed to obtain a practical, not too time-consuming, clinical usable test with reliable and reproducible results (Børgesen *et al.* 1978; Børgesen 1984; Børgesen 1984; Børgesen *et al.* 1989). With later modifications (Gjerris *et al.* 1985; Børgesen *et al.* 1991) we have used the following three routes:

The lumbo-ventricular perfusion.

The ventricular infusion.

The lumbar infusion.

The advantages are the possibility of various CSF-analysis (Sørensen *et al.* 1984; Gjerris *et al.* 1988) and long-term ICP monitoring (Børgesen 1984). The disadvantages are the risk of complications, especially the infection risks, and the ventricular drain inserted through a frontal burrhole.

The lumbo-ventricular perfusion

After the obtained 24 hours baseline ICP R_{out} is measured with the patient in a lateral lying position. The lumbar cannula (Fig. 5) is connected to an

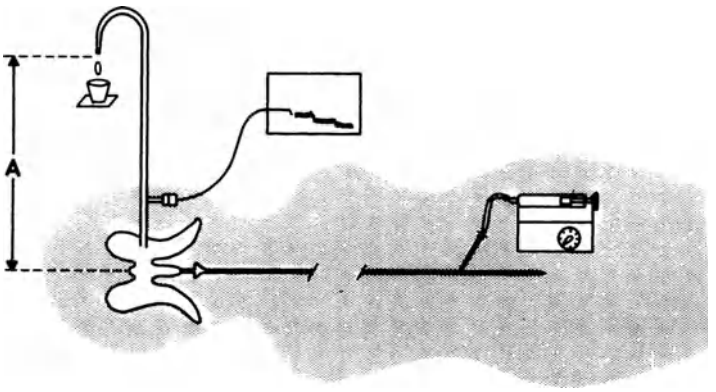

Fig. 5. The set up for a constant infusion and constant pressure (lumbo-ventricular perfusion) method (Børgesen *et al.* 1978, with permission)

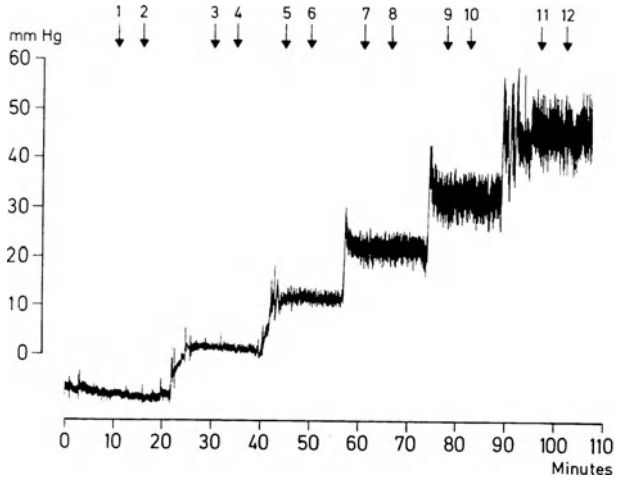

Fig. 6. Measurement of absorption at different pressure levels by elevation of the outflow tube in periods of 3–5 minutes (Børgesen *et al.* 1978, with permission)

infusion pump through which an infusion of Ringer lactate (V_{in}) starts at a rate of 0.5–2.0 ml/min and may – if necessary increase to over 4 ml/min. The cannula in the right lateral ventricle is connected to the pressure monitoring system. The surplus volume (V_{out}) is sampled from the outflow tube in periods of 3–5 mins and measured at 6–7 different pressure levels (Fig. 6). The outlet of the outflow tube is elevated in steps to increase ICP. During the elevation of the outflow tube care must be taken not to allow reflux into the ventricles, either by slowly rising the outflow catheter-tip or by a short increase in the infusion rate. A minimum of at least 2 minutes is required to obtain a steady state ICP and CSF-volume at all new pressure levels.

The procedure is finished within 1–2 hours. A constant FR of 0.4 ml/min is presumed, and CSF-absorption (V_{abs}) is calculated from the formula

$$V_{abs} = V_{in} + 0.4 - V_{out} \quad (6)$$

Corresponding values of ICP and V_{abs} are plotted, and the linear regression line is calculated by the method of least squares (Fig. 4).

The ventricular infusion

After monitoring of a baseline ICP for 24 hours a ventricular infusion (Gjerris *et al.* 1982) is performed. Five to eight ICP levels are measured.

The lumbar infusion

The lumbar puncture cannula is connected with two tubes to the infusion pump and pressure monitoring system. After monitoring of a baseline lum-

bar pressure ("ICP") for 30 minutes a lumbar infusion (Gjerris *et al.* 1985) is performed. Five to eight pressure levels are measured.

C) The Constant Rate Infusion Test

ICP is monitored during constant infusion of saline and from the pressure rise the resistance to outflow can be calculated. The test is often called the Katzman test (Katzman and Hussey 1970). We have used the following two techniques:

Standard infusion technique.

Computerizied infusion technique.

The computerized analysis of the ICP signal also gives the possibility of calculating the pressure in the sagittal sinus and the FR of CSF.

The standard infusion test

Standard lumbar infusion at constant rate is easy. The method is time-consuming, requiring several hours to gain an ICP equilibrium. The interpretations of the pressure increases and eventually plateaus are difficult and unreliable due to the often spontaneously occurring B-waves or to restlessness of the patient (Ekstedt 1978; Børgesen 1984).

The computerized infusion test

Czosnyka *et al.* (1989) have constructed a soft ware programme for a standard PC, which makes it possible to measure R_{out} together with other CSF values in a very short time with an uncomplicated set up. Lumbar infusion with constant infusion rate and monitoring of the lumbar pressure is performed. The analogue pressure signal from the pressure amplifier is converted and processed by spectral analysis, allowing filtration of normal fluctuations and artifacts. From the non-linear regression curve of ICP during infusion the programme computes the static measurement of R_{out}, FR, and pressure volume index (PVI) (from the pulse wave/ICP relation). If a steady state is not obtained or if infusion rate is changed during the test, the programme can compute R_{out} from the non-linear ICP/time regression curve.

We have compared R_{out} measured by this programme with a conventionally measured R_{out} in 15 patients representing a broad spectre from normalcy, normal pressure hydrocephalus, syringomyelia and pseudotumour cerebri. R_{out} values measured by the computerized infusion test correlated well with the R_{out} values measured by lumbo-ventricular perfusion (correlation coefficient = 0.97, regression coefficient 0.93) (Fig. 7). In none of these 15 cases did R_{out} differ unacceptably in the two tests.

The computerized infusion test is simple, quick, less invasive than a perfusion test and is finished in 30–40 minutes, including the lumbar puncture

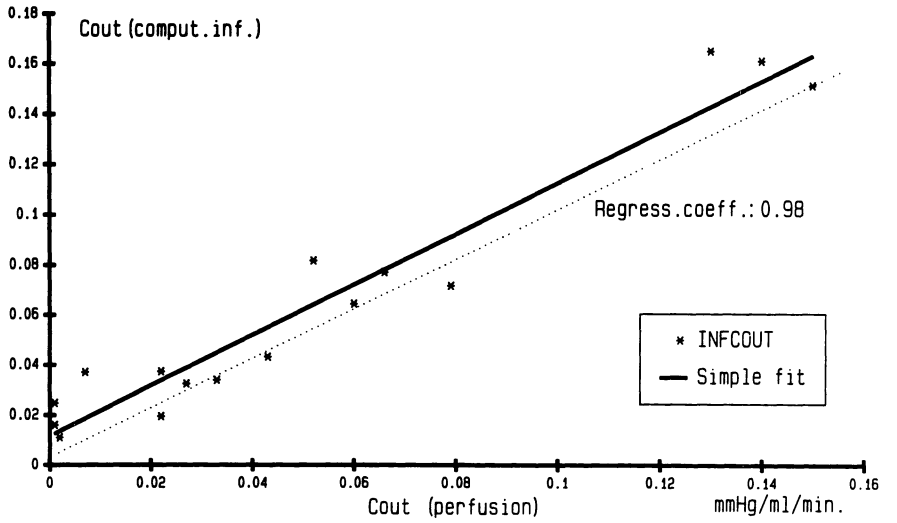

Fig. 7. R_{out} measured by the computerized infusion test compared to R_{out} measured by lumbo-ventricular perfusion. Conductance to CSF outflow ($= 1/R_{out}$)

and the calculations. It is also faster than the steady state servo-controlled infusion test. Furthermore information on FR and on cranio-spinal elasticity may be obtained (Børgesen *et al.* 1991).

II. Bolus Injection Tests

The bolus technique (Marmarou *et al.* 1978) is fast and simple, but based on complicated mathematical computations (eq. 7). Marmarou *et al.* (1975) have introduced the pressure-volume index (PVI) by measuring the response of CSF pressure to a bolus injection and calculating both compliance and resistance to CSF flow. PVI is given by the slope of the volume-log-pressure curve. R_{out} measured by this method is

$$R_{out} = \frac{t_2 P_o}{PVI \log_{10} \frac{P_2}{P_p} (P_p - P_o)/(P_2 - P_o)} \tag{7}$$

where P_p is the peak pressure, P_o the opening pressure, P_2 the instantaneous pressure at time t_2 on the recovery slope, and t_2 is the elapsed time from the instant of injection to the point at which P_2 is determined (Marmarou *et al.* 1978; Shapiro *et al.* 1980; Kosteljanetz 1987; Teasdale *et al.* 1989).

A rapid intrathecal injection of small volume – the bolus – results in instant increase in ICP followed by a decline in pressure. The peak pressure should be greater than the baseline ICP, and the rate of injection should exceed the CSF formation rate (Kosteljanetz 1989). In the bolus injection

test other sources of error are the definition of peak pressure, induced undesirable ICP changes and the absence of ICP fall after obtained peak pressure (Kosteljanetz 1987). The rise in ICP depends on the compliance of the craniospinal space, and the decrease in ICP on both compliance and R_{out}.

A comparison between the bolus injection method and other methods of estimation of R_{out} has been done in both animal experiments and in human research (Børgesen *et al.* 1979; Sullivan *et al.* 1979; Kosteljanetz 1985; Ekstedt and Fridén 1989). Animal experiments showed a good correlation between bolus- and infusion methods. Sullivan *et al.* (1979) found in both animal experiments and human investigations that the bolus method underestimated the R_{out} value. In a bolus study by the lumbar route Børgesen *et al.* (1979) found no concordance between R_{out} measured by either the bolus or by the lumbo-ventricular perfusion. Kosteljanetz *et al.* (1990) did not find the bolus method valuable in the differentiation between brain atrophy and normal pressure hydrocephalus.

All authors agree that values obtained by the bolus method are lower than values obtained by perfusion-infusion methods. Even when the bolus injection is short, it takes a few seconds, as does the pressure rise in ICP. In the meantime some CSF will be absorbed, why an indeterminable part of the bolus does not contribute to the pressure rise (Børgesen 1984). The bolus method seems to be better in patients with increased baseline ICP.

III. The Radio Isotope Dilution Method

Radio-isotope introduced intrathecally either by an suboccipital/lumbar route or into the ventricular system may depict production, transport, and resorption of CSF. The tracer is followed by a gamma camera both in space and time over one, six, 24, and up to 72 hours. Abnormalities in the scintigraphy are described a) morphologically in ventricular dilation and irregular or asymmetrical cisterns, or b) dynamically in permanent or transitory intraventricular stasis, in prolonged pericerebral transit time, in a half time greater than 12 hours and in a transependymal efflux. The method has been widely used to illustrate the CSF compartments, the CSF circulation and to select patients for CSF-shunting (Lying-Tunell 1978; Palma *et al.* 1978). One of the problems of the radio isotope dilution method is the wash-out time of the isotope, which depends of the size of the CSF space, especially of the ventricles. The larger the volume of the ventricles the slower the wash-out time. The pattern of distribution of CSF flow as illustrated by radioactive tracer, is not only an expression of the degree of obstruction to CSF-outflow, but also of the CSF volume.

The originally indicator dilution method introduced by Pappenheimer *et al.* (1962) was for many years the gold standard for estimation of CSF absorption (Va), using the formula

$$V_a = \frac{V_i C_i - V_o C_o}{C_o} \quad (8)$$

where V_i is the inflow perfusion rate, V_o the outflow rate, C_i the concentration of the indicator in the inflow fluid and C_o is the concentration of the outflow fluid. The disadvantages are the invasiveness and the very long time needed to steady state of the indicator concentration is secured. Using this method, Lorenzo *et al.* (1970) described two types of abnormal resorption: one with a linear flow/pressure relation, and one with a breaking point at a certain ICP level. These findings have not been confirmed by other investigators. We have never observed these patterns using the lumbar-ventricular perfusion (Børgesen 1984; Gjerris *et al.* 1989 b).

Normal R_{out} Values

The values from different animal species are shown in Fig. 20. In man nearly all normal values of R_{out} have been obtained from patients (Table 1) investigated on suspicion of an abnormal CSF circulation or a cerebral disease (Børgesen 1984). Ekstedt (1978) re-evaluated the R_{out} values in 58 patients after all investigations had shown no neurological or systemic vascular disorders of the brain and found a mean R_{out} of 6.6 mm Hg × min × ml^{-1}.

Albeck *et al.* (1991) found in eight healthy young volunteers by the lumbar infusion method a mean R_{out} of 9.1 mmHg × min × ml^{-1} and a mean ICP of 11.1 mmHg (SD = 2.4) and confirmed the previous estimated normal values (Sprung *et al.* 1977; Ekstedt 1978; Sklar *et al.* 1979; Børgesen and Gjerris 1982; Tans and Poortvliet 1983; Gjerris *et al.* 1989 b).

Reproducibility and Reliability of Measurement of R_{out}

Børgesen (1984) described a variation of less than 5% during repeated C_{out} measurement, and the same was found, when there only was a short interval between the two R_{out} measurements (Gjerris *et al.* 1986). In pseudotumour cerebri Sklar *et al.* (1979) found an unchanged C_{out}, despite several months

Table 1

Normal R_{out} values in different materials (mmHg × min × ml^{-1})

Ekstedt (1978)	patients	< 8.33
Sklar *et al.* (1978)	patients	< 10.00
Børgesen and Gjerris (1982)	patients	< 12.05
Tans and Poortvliet (1989)	patients	< 13.00
Albeck *et al.* (1991)	normal subjects	< 9.10

between the investigations. Schmidt *et al.* (1989) showed, that the results from both the ventricular or lumbar infusion test and the lumbo-ventricular perfusion test are reproduceable and reliable. More than one examination were performed in 96 patients with normal pressure hydrocephalus (NPH) and pseudotumour cerebri. A good correlation was found in 80 NPH-patients and in 16 patients with pseudotumour cerebri in both tests. After insertion of the ventricular catheter Schmidt *et al.* (1989) also demonstrated that more than six hours had to elapse before measurement of R_{out}. They emphasized that one measurement of R_{out} is sufficient and gives reliable information in patients with disturbances of CSF circulation.

Hydrocephalus

The term hydrocephalus stands in modern medicine for an increased volume of CSF in a dilated ventricular system. The modern concept of pathophysiology of hydrocephalus dates back to the 16th century, where Stensen (Steno) in an autopsy of a hydrocephalic calf as the first in history gave a pathophysiological explanation of hydrocephalus (Gjerris and Snorrason 1992).

Many aetiologies and classifications have been described and used in hydrocephalus, depending on different clinical or pathological findings and on various investigations.

Classification of Hydrocephalus

Hydrocephalus may be classified by CSF-dynamics and ICP-characteristics in high and normal pressure hydrocephalus (Table 2).

By atrophic hydrocephalus (brain atrophy) we understand a condition with normal ICP and nonresistant dilation of the ventricular system without any changes in CSF-dynamics. It is most often seen in Alzheimers and Binswangers diseases or in other degenerative CNS-disorders.

Table 2

Classification of hydrocephalus after CSF dynamics and ICP

Type of hydrocephalus	CSF production	CSF circulation	CSF absorption	ICP
Obstructive	normal(?)	↓↓	??	↑↑ or normal
Malresorptive	normal	normal	↓↓	↑↑ or normal
Atrophic	normal	normal	normal	normal
Hypersecretoric	↑↑	normal	normal	normal

Thus hydrocephalus may be caused by 1) increased CSF-production, by 2) obstruction of CSF-circulation, by 3) impaired CSF-absorption and/or by 4) obstruction of the venous outflow system.

Increased CSF-secretion is only described in a few cases of plexus papilloma in children, even in cases, where the ventricular system is not blocked by the tumour itself (Welch 1975; Sahar *et al.* 1980). The increased CSF-secretion does not mean that there is a hypersecretion, but only that the volume of the choroid plexus of the papilloma is so enormous that FR exceeds the absorption rate.

The CSF-circulation can be restricted either in the ventricular system, i.e. tumours, congenital brain defects, or in the subarachnoid space, i.e. subarachnoid haemorrhage and conditions with increased CSF viscosity (Børgesen *et al.* 1977; Gjerris *et al.* 1987).

Impairment of CSF-absorption is described in conditions where abnormal number of cells in CSF or increased CSF protein block the arachnoid villi (Hansen *et al.* 1987).

Obstruction of the venous drainage of the brain can result in raised ICP. The knowledge of the intracranial intravenous pressure in disorders leading to hydrocephalus or increased ICP is scarce. Impaired cerebral venous drainage due to venous hypertension or thrombosis of the sinuses are generally not important factors in the pathogenesis of hydrocephalus (Fishman 1980). Sinus thrombosis usually leads to intracranial hypertension and a clinical picture parallel to pseudotumour cerebri. Experimental attempts to produce hydrocephalus by occlusion of the sagittal sinus have not been successful (McComb 1983).

Pathophysiology of Hydrocephalus

Many elements are involved, but two factors are essential. The first is R_{out} and the second is the cranio-spinal compliance.

The Role of R_{out}

Abrupt obstruction of the CSF pathways causes a immediate increase in R_{out} and ICP. The elevated R_{out} leads to dilation of the ventricular system, more rapid the more complete the obstruction. A pressure gradient from the inside of the ventricular system to the surface of the brain is builded up (Børgesen 1984; Hakim and Hakim 1984; Black *et al.* 1989). ICP is probably very quickly balanced again, why the transmantle pressure differential stays modest and is difficult to demonstrate. Only a few investigators have shown this pressure difference (Fishman 1980; Hoff and Barber 1974; Conner *et al.* 1984). The last authors also demonstrated a diminutive transmantle pressure difference in normal animals, which means that intracranial pressure is transmitted equally throughout the intracranial space in normals. After the

development of hydrocephalus by intracisternal injection of Kaolin, Conner *et al.* (1984) found a significant elevated transmantle pressure (3.4 ± 3.9 cm saline). In kaolin-induced hydrocephalus Sahar *et al.* (1971) and Sahar (1979) found a marked elevated ICP during the first week, which dropped towards the end of the first month of the hydrocephalic process and a reduced production of CSF. Presumably the cerebral venous pressure is elevated during the development of hydrocephalus, which may play a role in the maintenance of hydrocephalus. Constriction of the cortical veins may lead to increased venous pressure. However, the expected change in the interstitial fluid can not be documented on MRI.

In acute experimental and clinical hydrocephalus, especially after subarachnoid haemorrhage the first event is an increase in R_{out} (Brock *et al.* 1975; Steiner *et al.* 1975; Conner *et al.* 1984; Hochwald 1984; Gjerris *et al.* 1987; Black *et al.* 1989). The reserve capacity of the venous and CSF spaces is exhausted resulting in a disappearance on CT of sulci and cisterns (Fig. 8). The R_{out} and development in the CSF-dynamics after SAH are illustrated in Fig. 9 (Gjerris *et al.* 1987). Acute hydrocephalus has been induced in lambs by mechanically increasing the amplitude of the CSF intraventricular pulse pressure (a pulsating balloon) without interfering with CSF-circulation or -absorption (Di Rocco *et al.* 1978).

Cerebral blood flow is low in patients with NPH and increased R_{out} (Vorstrup *et al.* 1987). They found a decreased preoperative regional CBF (SPECT) in nearly all patients, and an increase in CBF after shunting in some of the patients. Powell *et al.* (1989) investigated NPH patients with positron emission tomography (PET) in an attempt to use the metabolic events as a predictive value for shunting. Hydrocephalus causes a suppression of CBF, and metabolism as shown by $CMRO_2$ mirrors the fall in CBF.

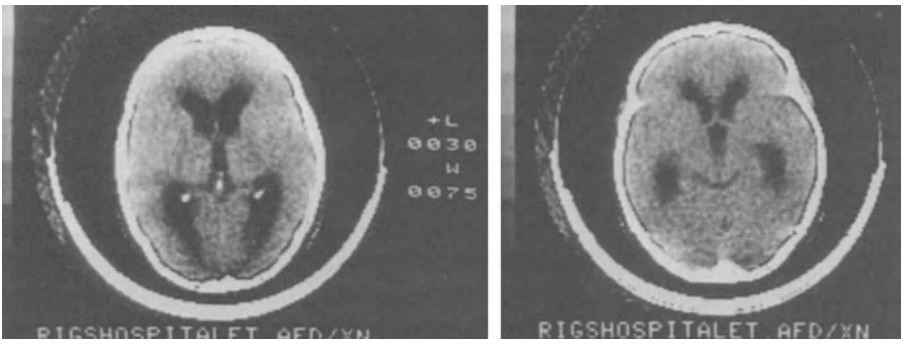

Fig. 8. CT of the brain in hydrocephalus developing two weeks after subarachnoid haemorrhage. Note the periventricular hypodensity especially around the frontal horns, indicating transependymal CSF flow (see text)

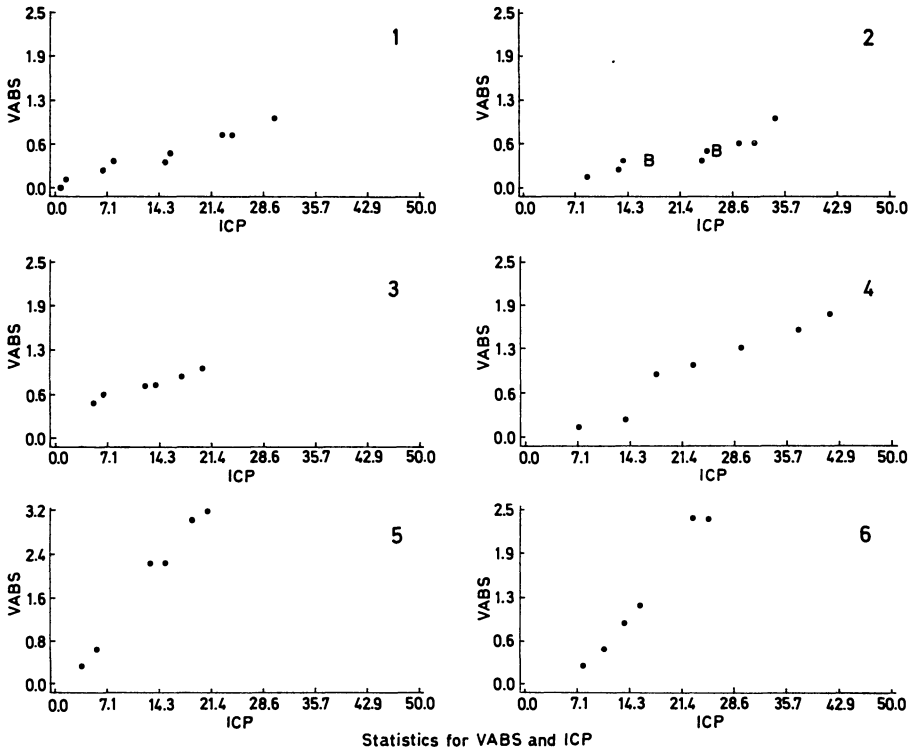

Fig. 9. R_{out} studies in six patients with beginning dilation of the ventricular system or hydrocephalus after SAH. Two patients with HPH and high R_{out} (1, 2); two patients with NPH and an increased R_{out} (3, 4) and two patients with hydrocephalus (brain atrophy) and a normal R_{out} (5, 6) (Gjerris *et al.* 1987, with permission)

They found improvement in CBF and metabolism in some of the patients with hydrocephalus after shunting.

The Role of Brain Compliance

The visco-elastic characteristics of the brain result in a dilation of the ventricular system, when R_{out} and ICP raise. The lateral ventricles are the first to dilate followed in caudal direction by the third ventricle, aqueduct and fourth ventricle, probably caused by the resistance of the deep nuclei (Stensen 1669; Milhorat 1972). On CT a periventricular lucency (oedema) develops in the white matter of the frontal and occipital horns (Fig. 8). In hydrocephalic animals the subependymal layer and ependyma are torn and expanded, but even though the ependymal lining is flattened it may still be functionally intact. The subependymal white matter degenerates and become oedematous with decreased function of the cells. The periventricular oedema is mainly confined to the white matter, often with a sharp demarcation

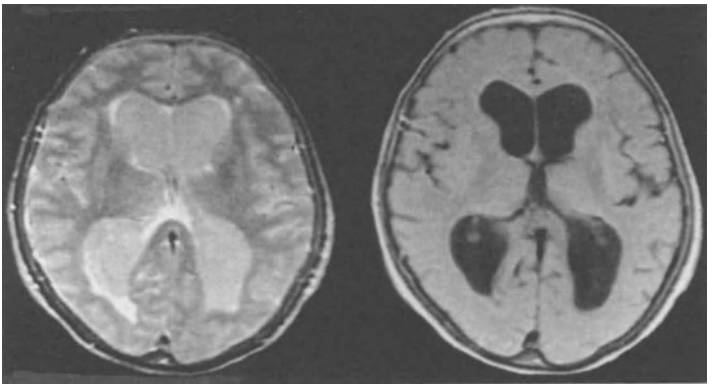

Fig. 10. MRI of periventricular subependymal hyperintensity in acute hydrocephalus after subarachnoid haemorrhage, indicating transependymal CSF flow (see text)

between the oedematous white matter and the intact grey matter, well demonstrated on MRI (Fig. 10). Serial CT scans in acute hydrocephalus show that the periventricular oedema disappears after CSF shunting. The extent of hydrocephalus seems, especially in children dependent on the restraining forces exerted on the brain by dura and skull (Shapiro *et al.* 1989).

CSF-absorption into the blood capillaries is perhaps increased, when CSF penetrates the subependymal area, but no visible changes reflect the increase in fluid uptake by the blood vessels in the periventricular area (Weller and Mitchell 1980). The periventricular oedema has been explained as a transependymal flow of CSF. From a theoretically standpoint it is difficult to explain, how water can be absorbed in the capillaries or the small veins of the subependymal layer. The finding of periventricular lucency correlated to a high R_{out} naturally indicates a low CSF resorption (Børgesen and Gjerris 1982; Børgesen *et al.* 1989). In our opinion the accumulation of fluid in the subependymal layer does not prove a transependymal absorption of CSF, but rather a stasis of the interstitial fluid as proposed by Cserr *et al.* (1977). Reduced turnover of CSF may contribute to a defective removal of brain metabolites, which possibly can alter brain function.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is an entity of progressing dementia, gait disturbances and/or urinary disturbances, hydrocephalus on CT, normal ICP, and elevated R_{out} (Børgesen 1984; Gjerris and Børgesen 1992). NPH is seen following subarachnoid haemorrhage, meningitis, head injury and

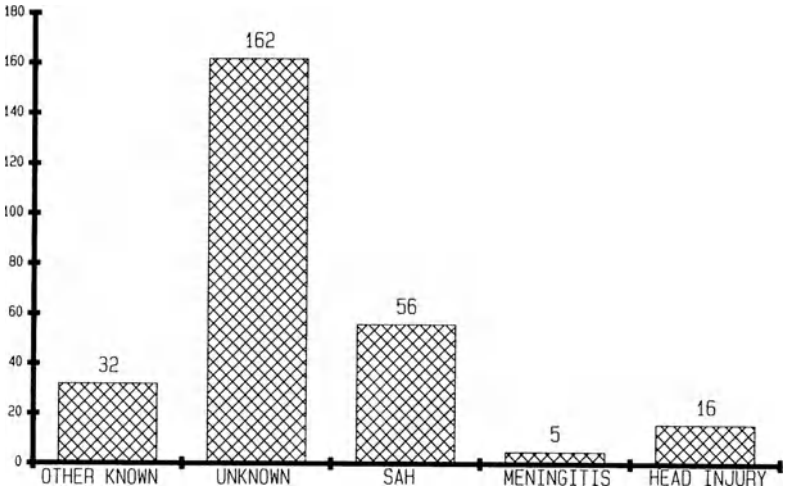

Fig. 11. The aetiology in 240 patients with NPH

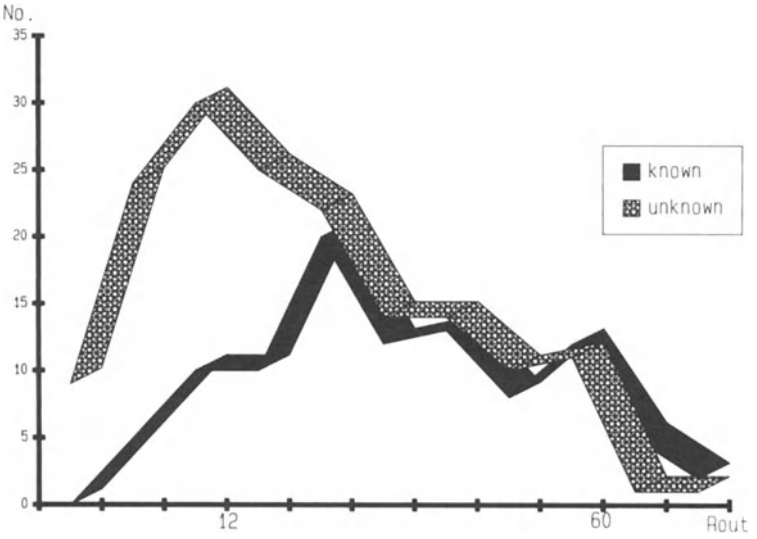

Fig. 12. R_{out} compared to known and unknown aetiology in 333 patients investigated for CSF absorption diseases

intracranial surgery. 60% of the NPH patients have no known aetiology (Fig. 11).

The pathophysiology of NPH has been discussed above and is easier to explain in patients suffering from SAH and meningitis than in patients with an unknown aetiology. The difference in R_{out} between the groups with unknown aetiology compared to known aetiology is shown in Fig. 12 and

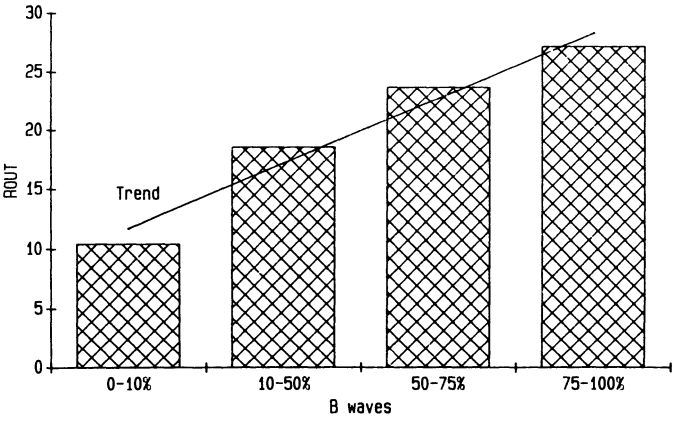

Fig. 13. Plot of correlation of B-waves in percentage of the monitored time against R_{out} in 240 patients with NPH (Gjerris *et al.* 1989, with permission)

is highly significant. Decreased CSF bulk flow – expressed as increased R_{out} has been found by many investigators (Børgesen and Gjerris 1982; Børegesen 1984). In the definition of NPH we have underlined the necessity of a very sharp upper limit of ICP. No patients with a mean ICP of 24 hours monitoring of more than 12 mmHg have been included in our materials (Børgesen 1984; Gjerris *et al.* 1989 b). Nearly all authors have also emphasized the high rate of abnormal B-waves (Fig. 13) in NPH patients (Crockard *et al.* 1977;

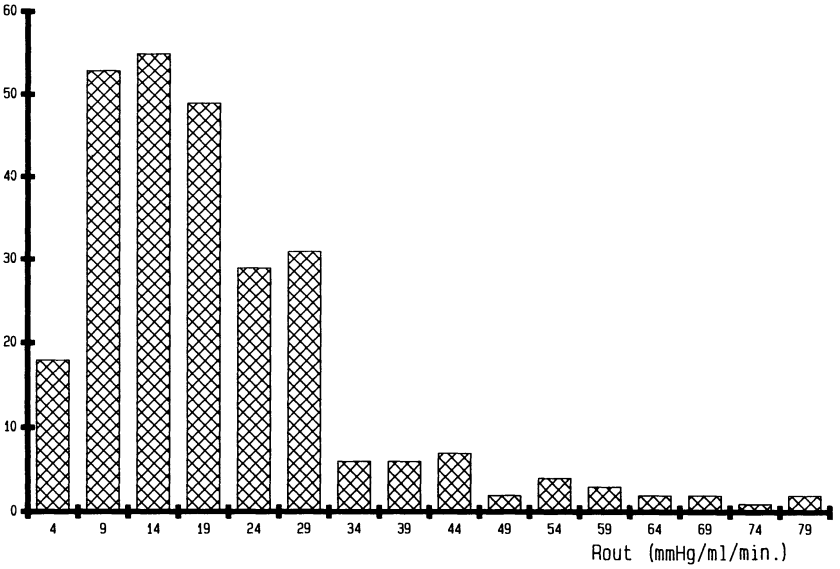

Fig. 14. Distribution of R_{out} in 271 patients with NPH

Børgesen and Gjerris 1982; Gjerris *et al.* 1989 b), probably caused by regular changes in the cerebrovascular volume.

Many investigations have been used as predictors of the effect of CSF shunting, i.e. isotope cisternography, CT, MR, and various intrathecal infusion or perfusion methods and with varying results (Børgesen 1984; Gjerris *et al.* 1989). The outcome for NPH-patients depends on various factors, including age and aetiology (Jeffreys and Wood 1978). The best predictive value is – in our hands – measurement of R_{out} and confirmed by other authors (Costabile *et al.* 1983; Lundar and Nornes 1990). Previously we found the predictive value of R_{out} very high in NPH, especially in patients with a known aetiology (Børgesen 1984). Our latest material comprises 271 consecutive patients with classical NPH and an ICP below 12 mmHg, evaluated by the lumbo-ventricular perfusion method (Gjerris *et al.* 1989 b). The distribution of R_{out} (Fig. 14) shows a considerable variation from normal values to very high values. Patients with a normal R_{out} (below 8.33 mmHg × ml^{-1} × min) were not shunted and nearly all patients with an increased R_{out} had a shunt operation. They were only considered improved, when there was either a) an improvement of one or more degrees in functional grades (Børgesen 1984), b) an improvement in both dementia, gait disturbances and/or urinary incontinence or c) if the family's estimation of the result was good or excellent. More than 80% of the patients with an abnormal R_{out} improved clinically after shunting. No shunted patients with a R_{out} between 8.33 and 12.5 mmHg × ml^{-1} × min improved.

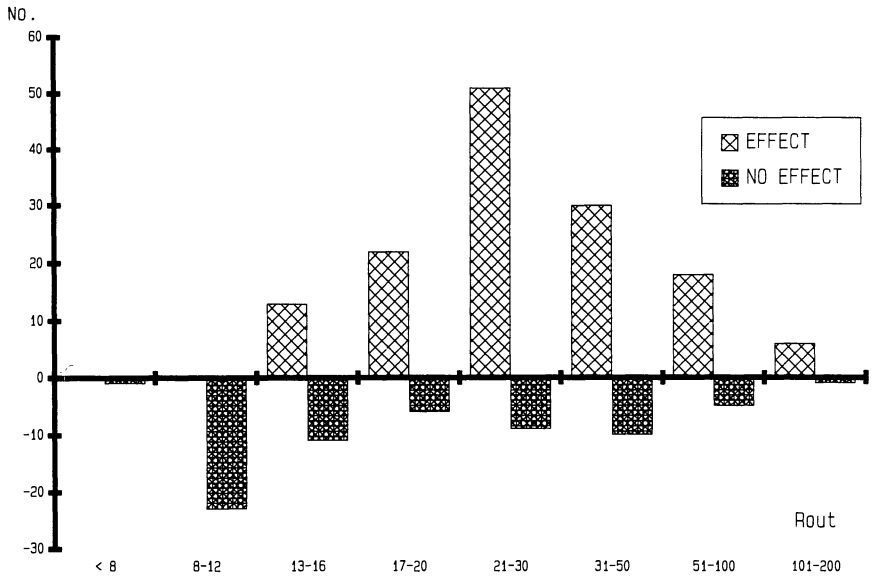

Fig. 15. Effect of shunting correlated to R_{out} in patients with NPH

Comparing the effect of shunting to aetiology, the improvement rate was significantly higher in the group with known aetiology ($p < 0.001$). Our results show that in patients without known aetiology, R_{out} must be even higher than 20 to predict acceptable outcome of shunting (Fig. 15).

From our experiences from clinical examination, CT scan and measurements ICP and R_{out} we propose the decision tree shown in Fig. 16 as a guide for practical, clinical and diagnostic investigations for treatment of the single hydrocephalic patients (Gjerris *et al.* 1989 b). The decision of a shunting procedure in a patient with the NPH syndrome is not easy, especially because of the high complication rate and should be based on R_{out} measurements.

Complications in CSF-Shunting Operations

Treatment of hydrocephalus by CSF-shunting is associated with a high complication rate. The over-all complication rate in shunt operated patients, followed for more than 5 years is close to 50 per cent. In a study of 1311

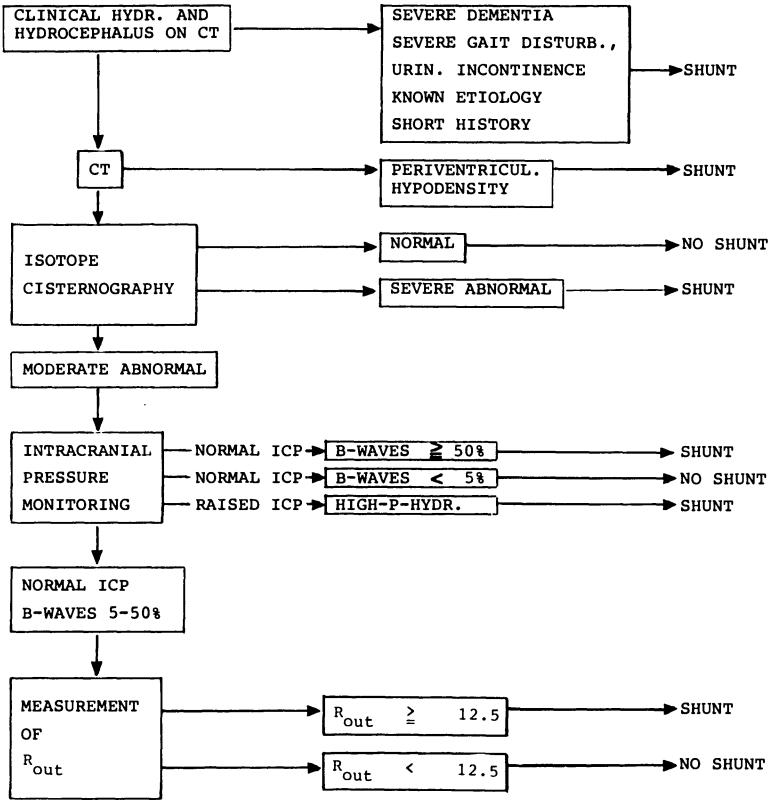

Fig. 16. Flow chart (decision tree) for investigations and treatment for hydrocephalic adults (modified after Gjerris *et al.* 1989 b)

new shunt insertions in 905 patients, the overall complication rate was 45.3%, leading to a total of 1979 operations (Marcussen *et al.*; to be published). Time series analysis of the complication rate and frequency of operations in the years from 1959 to 1990 (Fig. 17) shows that the overall complication rate during the years has not changed substantially. In Fig. 18 the percentage of different shunt complications are shown. In Fig. 19 the total survival

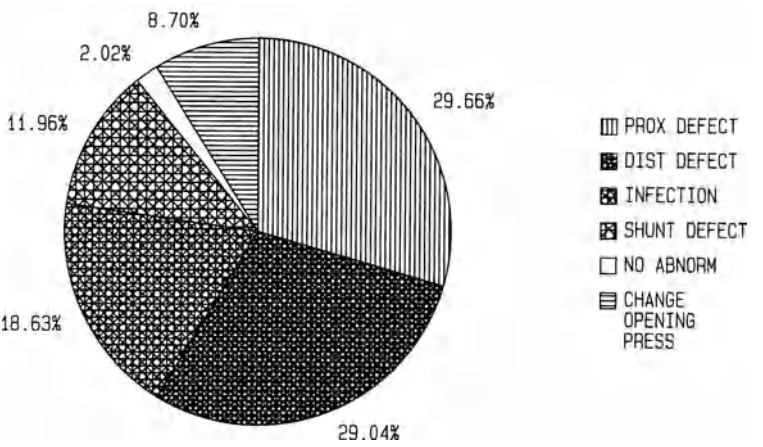

Fig. 17. The complication rate and total number of operations in the period from 1959 to 1990. The complication rate is fairly stable below 50%

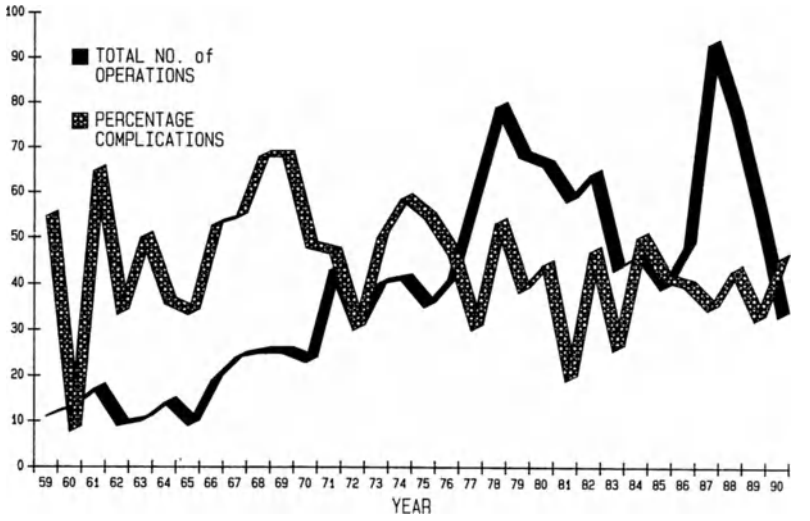

Fig. 18. The distribution of complications in 1954 shunt operations during the years 1959–1989. The figures give the relative frequency of the complications found at the first revision of the shunt (Marcussen *et al.*, to be published)

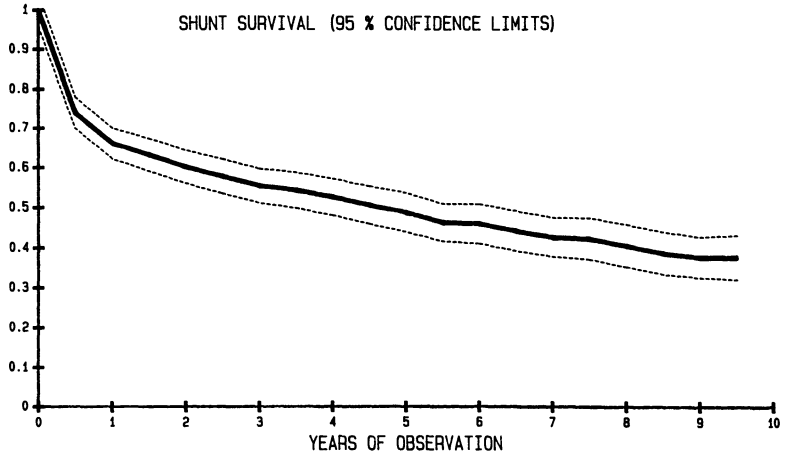

Fig. 19. The survival figure of 1154 shunts inserted in 905 patients during the years 1960–1989 (Marcussen *et al.*, to be published)

curve for all shunts inserted in the period from 1959 to 1989 is shown. Less than 50 per cent of the shunts are still functioning after 10 years.

These complication rates and survival curves are in concordance with the reports from Sainte-Rose (1989), Serlo *et al.* (1990) and Steinbok and Thompson (1976). The figures fortify the demand of precise and strict indications for CSF-shunting. The attitude expressed by some neurosurgeons (Vaneste and van Acker 1990): "Shunt and see" is not justified. Indication for shunting must be based on criteria with a high diagnostic sensitivity and specificity, to promise the highest possible success rate.

Other Diseases with Disturbances of CSF Circulation

Pseudotumour cerebri (benign intracranial hypertension) is characterized by increased ICP (papilloedema), no focal signs except 6th nerve palsy, no space occupying lesion or hydrocephalus on CT and normal composition of CSF (Sørensen *et al.* 1989 a). Pseudotumour cerebri is a diagnosis of exclusion and no single test leads to the correct diagnosis. It is further characterized by increased R_{out} and abnormal water self diffusion in the brain itself (Fig. 16). The effect of treatment by diuretics and if this treatment fails eventual CSF-shunting, either a ventriculo-peritoneal or a lumbo-peritoneal shunt is demonstrated in Fig. 20 by a decrease in ICP and R_{out} (for review, see Sørensen *et al.* 1989 a; Gjerris and Børgesen 1992).

Increased resistance to CSF outflow has been demonstrated in various clinical and experimental pathological conditions in which foreign or abnormal substances (i.e. bacteria, cells, debris, kaolin, protein) are distributed throughout the subarachnoid space and in the arachnoid villi. Functional

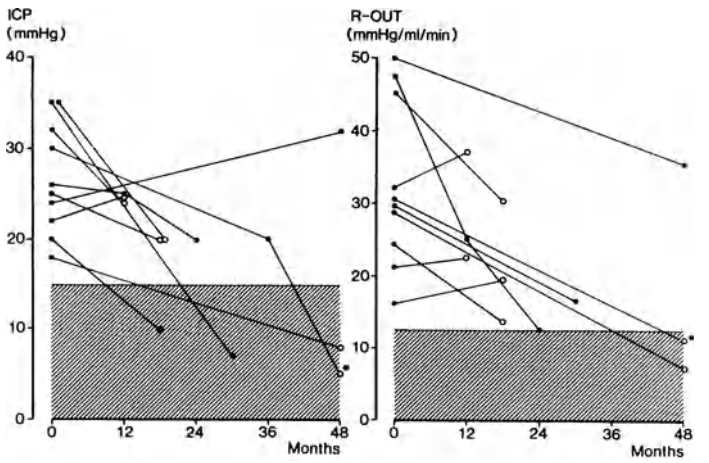

Fig. 20. Course of ICP and R_{out} in patients with pseudotumour cerebri. Closed circles denote clinical symptoms of increased ICP, open circles symptom-free patients (Sørensen *et al.* 1989 a, with permission)

and structural obstruction to CSF outflow, hydrocephalus and increased R_{out} are described after *subarachnoid haemorrhage* (Kosteljanetz 1987; Voldby 1986; Gjerris *et al.* 1987), after *meningitis* (Dacey *et al.* 1980; Gyring *et al.* 1989), in *meningeal carcinomatosis* and *chronic meningo-encephalitis* (Hansen *et al.* 1987), after *head injuries* (Kosteljanetz 1987; Marmarou *et al.* 1989), in *spinal tumours with increased CSF protein* (Børgesen *et al.* 1977), after *surgery of the posterior fossa* (Kaufman and Carmel 1978) and in many other pathological conditions.

References

1. Albeck M, Gjerris F, Børgesen SE, Schmidt JF, Sørensen PS (1991) The resistance to cerebrospinal fluid outflow in healthy volunteers. J Neurosurg 74: 597–600
2. Black PM, Griebel RW, Tzouras A, *et al* (1989) Pressure gradients and accessory absorption pathways in hydrocephalus. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 303–312
3. Brock M, Furuse M, Hasuo M, *et al* (1975) Influence of CSF-resorption pathways on intracranial capacitance. Adv Neurosurg 3: 109–113
4. Børgesen SE (1984) Conductance to outflow of CSF in normal pressure hydrocephalus. Acta Neurochir (Wien) 71: 1–45
5. Børgesen SE, Gjerris F (1982) The predictive value of conductance to outflow of CSF in normal hydrocephalus. Brain 105: 65–86
6. Børgesen SE, Gjerris F (1987) The relationships between intracranial pressure, ventricular size, and resistance to CSF outflow. J Neurosurg 67: 535–539

7. Børgesen SE, Gjerris F, Schmidt J (1989) Measurement of resistance to CSF outflow by subarachnoid perfusion. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 121–129
8. Børgesen SE, Gjerris F, Sørensen SC (1978) The resistance to cerebrospinal fluid absorption in humans. Acta Neurol Scand 57: 88–96
9. Børgesen SE, Sørensen SC, Olesen J, Gjerris F (1977) Spinal tumours associated with increased intracranial pressure. Acta Neurol Scand 56: 263–268
10. Børgesen SE, Gjerris F, Sørensen SC (1979) Cerebrospinal fluid conductance and compliance of the craniospinal space in normal pressure hydrocephalus. A comparison between two methods for measuring conductance to outflow. J Neurosurg 51: 521–526
11. Børgesen SE, Albeck MJ, Gjerris F, Czosnyka M (1991) Computerized infusion test compared to conventional lumbar-ventricular perfusion for measurement of resistance to CSF outflow. Acta Neurochir (Wien) submitted
12. Conner ES, Foley L, Black PM (1984) Experimental normal-pressure hydrocephalus is accompanied by increased transmantle pressure. J Neurosurg 61: 322–327
13. Costabile G, Probst C, Schönholzer AM (1983) Further experiences with the intrathecal infusion test in the management of communicating hydrocephalus. In: Ishii S, Nagai H, Brock M (eds) Intracranial pressure V. Springer, Berlin Heidelberg New York, pp 632–635
14. Crockard HA, Hanlon K, Duda EE, *et al* (1977) Hydrocephalus as a cause of dementia: Evaluation by computerized tomography and intracranial pressure monitoring. J Neurol Neurosurg Psychiatry 40: 736–740
15. Cserr HF (1989) Flow of CSF and brain interstitial fluid (ISF) into deep cervical lymph. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 58–63
16. Cserr HF, Cooper DN, Milhorat H (1977) Flow of cerebral interstitial fluid as indicated by the removal of extracellular markers from rat caudate nucleus. Exp Eye Res 25 [Suppl]: 461–473
17. Czosnyka M, Wollk-Laniewski D, Darwaj P, *et al* (1989) Software for neurosurgery intensive care. In: Hoff JT, Betz Al (eds) Intracranial pressure VII. Springer, Berlin Heidelberg New York, pp 84–87
18. Dacey RG, Welch JE, Winn HR, *et al* (1980) Bacterial meningitis: Changes in CSF outflow resistance. In: Shulman K, Marmarou A, Miller JD, *et al* (eds) Intracranial pressure IV. Springer, Berlin Heidelberg New York, pp 350–353
19. Davson H, Hollingworth G, Segal MB (1970) The mechanism of drainage of the cerebrospinal fluid. Brain 93: 665–678
20. Davson H, Welch K, Segal MB (1987) The physiology and pathophysiology of the cerebrospinal fluid. Churchill Livingstone, Edinburgh, pp 1013
21. Di Rocco C, Pettorossi VE, Mancinelli R, Velardi F (1978) Communicating hydrocephalus induced by mechanically increased amplitude of the intraventricular cerebrospinal fluid pressure: Experimental studies. Exp Neurol 59: 40–52
22. Doczi T, Bodosi M (1989) The central neuroendocrine regulation of brain water and electrolytes, and resorption of cerebrospinal fluid (CSF). In: Gjerris

F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 282–291
23. Early CB, Fink LH (1976) Some fundamental applications of the law of La Place in neurosurgery. Surg Neurol 6: 185–189
24. Ekstedt J (1977) CSF hydrodynamic studies in man. Method of constant pressure CSF infusion. J Neurol Neurosurg Psychiatry 40: 105–119
25. Ekstedt J (1978) CSF hydrodynamic studies in man. J Neurol Neurosurg Psychiatry 41: 345–353
26. Ekstedt J, Fridén H (1989) Estimation of CSF outflow resistance in humans: infusion methods. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 148–165
27. Fishman RA (1980) Cerebrospinal fluid in diseases of the nervous system. WB Saunders Company, Philadelphia, pp 384
28. Friden HG, Ekstedt J (1989) Estimation of CSF outflow resistance: Model validation and resistance calculation by method of CSF volume accounting. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 198–210
29. Gjerris Annette (1988) Baseline studies on transmitter substances on cerebrospinal fluid in depression (Thesis). Acta Neurol Scand 78 [Suppl 346]: 1–35
30. Gjerris Annette, Gjerris F, Sørensen PS, *et al* (1988) Do concentrations of neurotransmitters measured in lumbar cerebrospinal fluid reflect the concentrations at brain level? Acta Neurochir (Wien) 91: 55–59
31. Gjerris F, Børgesen SE (1992) Pathophysiology of the cerebrospinal fluid circulation. In: Crockard A, Hayward R, Hoff JT (eds) Neurosurgery, the scientific basis of clinical practice, 2nd ed. Blackwells Scientific Publications, Oxford
32. Gjerris F, Børgesen SE, Hoppe E, *et al* (1982) The conductance to outflow of CSF in adults with high pressure hydrocephalus. Acta Neurochir (Wien) 64: 59–67
33. Gjerris F, Børgesen SE, Sørensen PS (eds) (1989 a) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 400
34. Gjerris F, Børgesen SE, Schmidt J, Sørensen PS (1989 b) Resistance to cerebrospinal fluid outflow in patients with normal pressure hydrocephalus. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 329–338
35. Gjerris F, Børgesen SE, Sørensen PS, Boesen F, Schmidt K, Harmsen A, Lester J (1987) Resistance to cerebrospinal fluid outflow and intracranial pressure in patients with hydrocephalus after subarachnoid haemorrhage. Acta Neurochir (Wien) 88: 79–86
36. Gjerris F, Børgesen SE, Schmidt K, Sørensen PS, Gyring J (1986) Measurement of conductance to cerebrospinal fluid outflow by the steady-state perfusion method in patients with normal or increased intracranial pressure. In: Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD (eds) Intracranial pressure VI. Springer, Berlin Heidelberg New York, pp 411–416
37. Gjerris F, Snorrason E. Hydrocephalus during historical time (1992) J Hist Neurosci; submitted

38. Gjerris F, Sørensen PS, Vorstrup S, Paulson OB (1985) Conductance to cerebrospinal fluid outflow, intracranial pressure and cerebral blood flow in patients with benign intracranial hypertension. Ann Neurol 17: 158–162
39. Gyring J, Gjerris F, Brøndsted HE, Andersen NEO (1986) CSF outflow resistance: No current model is satisfactory. In: Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD (eds) Intracranial pressure VI. Springer, Berlin Heidelberg New York, pp 111–117
40. Gyring J, Gutschik E, Gjerris F (1989) Resistance to CSF outflow in experimental pneumococcal meningitis. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 80–90
41. Hakim S, Hakim C (1984) A biochemical model of hydrocephalus and its relationship to treatment. In: Shapiro K, Marmarou A, Portnoy H (eds) Hydrocephalus. Raven Press, New York, pp 143–177
42. Hansen K, Gjerris F, Sørensen PS (1987) Absence of hydrocephalus in spite of impaired cerebrospinal fluid absorption and severe intracranial hypertension. Acta Neurochir (Wien) 86: 93–97
43. Hochwald G (1984) Animal models of hydrocephalus. In: Shapiro K, Marmarou A, Portnoy H (eds) Hydrocephalus. Raven Press, New York, pp 199–213
44. Hoff J, Barber R (1974) Transcerebral mantle pressure in normal pressure hydrocephalus. Arch Neurol 31: 101–105
45. Jeffreys RV, Wood MM (1978) Adult non-tumorous dementia and hydrocephalus. Acta Neurochir (Wien) 45: 103–114
46. Katzman R, Hussey F (1970) A simple constant/infusion manometric test for measurement of CSF absorption. Neurology (Minneap) 20: 534–544
47. Kaufman HH, Carmel PW (1978) Aseptic meningitis and hydrocephalus after posterior fossa surgery. Acta Neurochir (Wien) 44: 179–196
48. Kosteljanetz M (1985) Resistance to outflow of cerebrospinal fluid determined by bolus injection technique and constant rate steady infusions in humans. Neurosurg 16: 336–340
49. Kosteljanetz M (1987) Intracranial pressure: cerebrospinal fluid dynamics and pressure-volume relations (Thesis). Acta Neurol Scand 75 [Suppl]: 111
50. Kosteljanetz M (1989) Measurement of resistance to outflow: The bolus injection method. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 134–143
51. Kosteljanetz M, Nehen AM, Kaalund J (1990) Cerebrospinal fluid outflow resistance measurements in the selection of patients for shunt surgery in the normal pressure hydrocephalus syndrome. A controlled trial. Acta Neurochir (Wien) 104: 48–53
52. Lorenzo AV, Page KK, Waters GV (1970) Relationship between cerebrospinal fluid formation, absorption, and pressure in human hydrocephalus. Brain 93: 679–692
53. Lundar T, Nornes H (1990) Determination of ventricular fluid outflow resistance in patients with ventriculomegaly. J Neurol Neurosurg Psychiatry 53: 896–989
54. Lying-Tunell U (1978) Quantitative cisternography. Acta Radiol Diagn 19: 905–917

55. Marmarou A, Shulman K, LaMorgese J (1975) Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. J Neurosurg 43: 523–534
56. Marmarou A, Shulman K, Rosende RM (1978) A non-linear analysis of CSF system and intracranial pressure dynamics. J Neurosurg 48: 332–344
57. Marmarou A, Ward JD, Wachi A, Young HF (1989) Contribution of CSF outflow resistance to ICP rise in head-injured patients. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 356–365
58. Marmarou A, Tabaddor K (1987) Intracranial pressure: Physiology and pathophysiology. In: Cooper PR (ed) Head injury, 2nd ed. Williams & Wilkins, Baltimore, pp 159–176
59. McComb JG (1983) Recent research into the nature of cerebrospinal fluid formation and absorption. J Neurosurg 59: 369–383
60. Milhorat TH (1972) Hydrocephalus and the cerebrospinal fluid. Williams & Wilkins, Baltimore, pp 550
61. Palma A, Kolberg T, Wust R, Entzian W (1978) New aspects of cerebrospinal fluid dynamics in humans investigated by sequential gamma camera cisternography, with data evaluation by digital multichannel analyzer. Acta Neurochir (Wien) 45: 53–88
62. Pappenheimer JR, Heisey SR, Jordan EF, *et al* (1962) Perfusion of the cerebral ventricular system in unanaesthetized goats. Am J Physiol 203: 763–774
63. Penn RD, Bacus JW (1984) The brain as a sponge: A computed tomographic look at Hakims's hypothesis. Neurosurgery 14: 670–674
64. Pollay M (1975) Formation of cerebrospinal fluid. J Neurosurg 42: 665–673
65. Pollay M (1985) The pathophysiology of the cerebrospinal fluid circulation. In: Crockard A, Hayward R, Hoff JT (eds) Neurosurgery, the scientific basis of clinical practice. Blackwells Scientific Publications, Oxford, pp 279–296
66. Pollay M, Stevens FA, Roberts PA (1983) Alteration in choroid-plexus blood flow and cerebrospinal-fluid formation by increased ventricular pressure. In: Wood JH (ed) Neurobiology of cerebrospinal fluid 2. Plenum Press, New York London, pp 687–695
67. Portnoy HD (1989) The physics of hydrocephalus: the Laplacian model. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 315–333
68. Portnoy HD, Croissant PD (1976) A practical method for measuring hydrodynamics in hydrocephalus. Surg Neurol 5: 273–277
69. Powell M, Crockard A, Brookes D (1989) Normal pressure hydrocephalus – ICP and Pet scan studies before and after shunting. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 377–386
70. Price DJ (1989) The clinical value of measurement of CSF outflow resistance. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 390–398
71. Raichle ME (1981) Hypothesis: A central neuroendocrine system regulates brain ion homeostasis and volume. In: Martin JB, Reichlin S, Bick KL (eds) Neurosecretion and brain peptides. Raven Press, New York, pp 329–336

72. Rekate HL, Olivero WM, McCormick J, *et al* (1989) Resistance elements within the cerebrospinal fluid circulation. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cereobrospinal fluid. Munksgaard, Copenhagen, pp 45–52
73. Rekate HL, Williams F, Chisek HJ, *et al* (1988) The application of mathematical modeling to hydrocephalus research. In: Marlin AE (ed) Concepts in paediatric neurosurgery, vol 8. Karger, Basel, pp 1–14
74. Sahar A (1979) Experimental progressive hydrocephalus in the young animal Child's Brain 5: 14–23
75. Sahar A, Feinsod M, Beller AJ (1980) Choroid plexus papilloma: Hydrocephalus and cerebrospinal fluid dynamics. Surg Neurol 13: 476–478
76. Sahar A, Hochwald GM, Ransohoff J (1971) Cerebrospinal fluid turnover in experimental hydrocephalic dogs. Neurology 21: 218–224
77. Sahar A, Hochwald GM, Sadik AR, Ransohoff J (1969) Cerebrospinal fluid absorption. Arch Neurol 21: 638–644
78. Sainte-Rose J, Hoffman HJ, Hirsch JF (1989) Shunt failure. Concepts in paediatric neurosurgery 9: 7–20
79. Schmidt JF, Fedders O, Børgesen SE, Gjerris F (1989) Reproducibility of measurements of resistance to CSF outflow. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 400
80. Serlo W, Fernell E, Heikkinen E, Anderson H, von Wendt L (1990) Functions and complications of shunts in different aetiologies of childhood hydrocephalus. Child's Nerv Syst 6: 92–94
81. Shapiro K (1989) Influences of the skull and dura on the resistance to CSF outflow. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of cerebrospinal fluid. Munksgaard, Copenhagen, pp 215–221
82. Shapiro K, Marmarou A, Portnoy H (eds) (1984) Hydrocephalus. Raven Press, New York, pp 401
83. Shapiro K, Marmarou A, Shulman K (1980) Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. Ann Neurol 7: 508–514
84. Sklar FH, Beyer CW, Ramanathan M, Cooper PR, Clark WK (1979) Cerebrospinal fluid dynamics in patients with pseudotumour cerebri. Neurosurgery 5: 208–216
85. Sklar FH, Beyer CW, Ramanathan M, *et al* (1978) Servo-controlled lumbar infusions: A clinical tool for determination of CSF dynamics as a function of pressure. Neurosurgery 3: 170–175
86. Sprung C, Collmann H, Fuchs EC, *et al* (1977) Pre- and postoperative evaluation of hydrocephalus using the infusion test. Adv Neurosurg 4: 161–175
87. Stensen N (1669) De vitulo hydrocephalo epistola. In: Berryat: Coll. Acad. Part. Etrang., Parisiis, 1769; VII: 188–191, Th. Bartholin T: Acta Med. & Phil. Hafn. 1673; I: 249–262, Th. Bonet: Medicina Septentrional. Genevæ, 1686, liber 1 sect. II cap. VI: 25–28, Le Clerc & Manget: Bibl. Anat., Genevæ, 1685; II-335-38, Maar, Vilh.: Nicolai Stenonis Opera Philosophica. Kbhvn.: V. Tryde, 1950; II: 227–237 og Harriet M. Hansen (ed.): Niels Stensen's

Korrespondance i dansk Oversættelse. (in Danish) Kbhvn.: C. A. Reitzel, 1987; I: 137–146
88. Steiner L, Løfgren J, Zwetnow N (1975) Lethal mechanism in repeated subarachnoid haemorrhage in dogs. Acta Neurol Scand 52: 241–267
89. Steinbok P, Thompson GB (1976) Complications of ventriculo-vascular shunts: Computer analysis of aetiological factors. Surg Neurol 5: 31–35
90. Sullivan HG, Miller JD, Griffith RL, *et al* (1979) Bolus versus steady-state infusion for determination of CSF outflow resistance. Ann Neurol 5: 228–238
91. Sørensen PS (1986) Studies of vasopressin in the human CSF (Thesis). Acta Neurol Scand 74: 81–102
92. Sørensen PS, Gjerris F, Schmidt J (1989 a) Resistance to CSF outflow in benign intracranial hypertension. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of the cerebrospinal fluid. Munksgaard, Copenhagen, pp 343–352
93. Sørensen PS, Gjerris F, Hammer M (1984) Cerebrospinal fluid vasopressin and increased intracranial pressure. Ann Neurol 15: 435–440
94. Sørensen PS, Gyring JA (1990) Intracerebroventricular infusion but not bolus injection of vasopressin increases the cerebrospinal fluid pressure in awake rabbits. Neurol Res 12: 83–88
95. Sørensen PS, Thomsen C, Gjerris F, *et al* (1989 b) Increased brain water content in pseudotumour cerebri measured by magnetic resonance imaging of brain water self diffusion. Neurol Res 11: 160–164
96. Tans TJ, Poortvliet DCJ (1983) Steady-state and bolus infusions in hydrocephalus. In: Ishii S, Nagai H, Brock M (eds) Intracranial pressure V. Springer, Berlin Heidelberg New York, pp 636–640
97. Tans TJ, Poortvliet DCJ (1989) Significance of compliance in adult hydrocephalus. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of the cerebrospinal fluid. Munksgaard, Copenhagen, pp 272–279
98. Teasdale G, Grant R, Condon D, *et al* (1989) Measurement of cranial CSF volumes in normal subjects. In: Gjerris F, Børgesen SE, Sørensen PS (eds) Outflow of the cerebrospinal fluid. Munksgaard, Copenhagen, pp 258–268
99. Thomsen C, Henriksen O, Ring P (1987) In vivo measurement of water self diffusion in the human brain by magnetic resonance imaging. Acta Radiol 28: 355–361
100. Vaneste J, Van Acker R (1990) Normal pressure hydrocephalus: Did publications alter management? J Neurol Neurosurg Psychiatry 53: 564–568
101. Voldby B (1986) Ruptured intracranial aneurysm. A clinical and pathophysiological study (Thesis). Dan Med Bull 33: 53–64
102. Vorstrup S, Christensen J, Gjerris F, Sørensen PS, Thomsen AM, Paulson OP (1987) Cerebral blood flow in patients with normal-pressure hydrocephalus before and after shunting. J Neurosurg 66: 379–387
103. Welch K (1975) The principles of physiology of the cerebrospinal fluid in relation to hydrocephalus including normal pressure hydrocephalus. In: Friedlander WJ (ed) Advances in neurology. Current reviews. Raven Press, New York, pp 345–375

104. Weller RO, Mitchell J (1980) Cerebrospinal fluid oedema and its sequelae in hydrocephalus. Adv Neurol 28: 111–123
105. Wood JH (ed) (1980) Neurobiology of cerebrospinal fluid. Plenum Press, New York London, pp 1101
106. Wood JH (ed) (1983) Neurobiology of cerebrospinal fluid 2. Plenum Press, New York London, pp 961

A Multidisciplinary Approach to the Treatment of Brain Vascular Malformations

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With 3 Figures

Contents

The successful treatment of brain vascular malformations has always been a formidable undertaking. The inadvertent discovery of an arteriovenous malformation (AVM) confronts both patient and physician with a dilemma difficult to resolve. The patient, who feels well, faces the pos-

sibility of a disastrous brain hemorrhage in the future but knows that the treatment to obviate this potential disaster is not without risk. What is the likelihood of hemorrhage? How great is the risk of surgical extirpation? When there are symptoms such as headache, epileptic seizures or progressive neurological deficit the surgeon must consider the risk of surgical intervention with the knowledge that complete, uncomplicated excision of the AVM may still fail to alleviate the symptom for which the operation was done. When a brain vascular malformation presents with hemorrhage, the decision for surgery may very well be easier but its successful accomplishment very difficult. We are learning to stratify the surgical risk according to the features of vascular malformations and balance this against the probability of future hemorrhage[56, 98].

Greater experience with improved diagnostic imaging has also taught us that not all vascular malformations are alike in their natural history and hence different management strategies are appropriate for different lesions. In the past, the clinician in fact chose between surgical excision and no treatment. At present, endovascular therapy (embolization) and radiosurgery have been added to the armamentarium of physicians who care for patients with brain vascular malformations. We have learned that the treatment of AVMs may be staged and that various therapeutic modalities may be combined, for example, surgical excision may be made safer by preoperative embolization which reduces blood flow through the lesion and postoperative or postendovascular radiosurgery may be administered to obliterate AVM remnants.

This account will present the natural history and features of the different types of brain vascular malformations, discuss the expected results and risks of endovascular therapy, radiosurgery, and microsurgical excision and present an approach to decision analysis utilized by the University of Toronto Brain Vascular Malformation Group which is comprised of clinicians representing diagnostic and interventional radiology, radiation oncology, and neurosurgery.

It has been estimated that a patient who is found to have an unruptured, high-flow cerebral arteriovenous malformation has a two to three percent chance of suffering a hemorrhage in the first year and an approximately 30% chance of hemorrhage over the first 10 years[114]. The likelihood of sustaining a significant cerebral neurological deficit from the hemorrhage is approximately 50% and the likelihood of dying approaches 10 percent[114]. Furthermore, the probability of a second hemorrhage in the year after the presenting one is likely as high as six percent with similar probabilities of morbidity and mortality as for the first hemorrhage[114]. Recent evidence[76] suggests that the mode of presentation, that is, hemorrhage, neurological deficit, epileptic seizure, headache or incidental discovery may not influence the propensity to bleed and that the annual incidence of hemorrhage may

be as high as four percent. With these risks in view, an appropriate treatment regimen must be designed from the therapies currently available. In general terms, if the immediate risk of bleeding is high and complete excision is technically feasible, surgical excision would be favoured. If the likelihood of immediate rupture of the lesion is small, endovascular obliteration may be considered as an adjunct to surgical excision or as definitive treatment. Radiosurgery, which has a delayed effect, may be selected if a two year latency period prior to efficacy is acceptable. Some lesions currently defy safe treatment and should be observed, others are in fact normal variants and require no treatment.

Classification of Brain Vascular Malformations

Vascular malformations are traditionally classified into four groups: Capillary telangiectasis, venous angiomas, cavernous hemangiomas, and arteriovenous malformations[91]. This pathological classification has been questioned, as recent radiological and clinical experience with these lesions has significantly improved our understanding of these entities[48, 55, 108, 110, 115]. Venous angiomas in fact represent a variation of normal and are therefore more properly classified as developmental anomalies rather than malformations[46]. Cavernous hemangiomas located within the orbit or liver, for example, are true neoplasms. Intracerebral hemangiomas, which are not, are therefore best identified as cavernomas or cavernous malformations. It is also important from an imaging point of view to attempt to differentiate as much as possible between angiographically occult vascular malformations and thrombosed arteriovenous malformations. All imaging modalities are required to classify these lesions properly so as to allow multidisciplinary treatment planning.

Capillary Telangiectasis

This type of vascular malformation is occasionally identified at autopsy and is most commonly located within the pons or subcortical white matter. So far, all imaging modalities including angiography, CT and MRI have proved incapable of demonstrating cerebral capillary telangiectasis in vivo.

Venous Angioma (Developmental Venous Anomalies)

Venous angiomas most likely represent an extreme variation of the normal venous drainage pattern[34, 46]. At angiography there are normal arterial and capillary phases. The venous phase of the angiogram reveals multiple venules draining in an umbrella-like pattern towards the engorged draining vein which is often positioned perpendicular to the cortex or the ventricle[107, 113]. In deep seated venous angiomas, the corresponding superficial cortical

venous system is poorly developed and hypoplastic. The unenhanced CT scan is normal in the majority of cases, although sometimes a rounded or elongated hyperdense area can be identified. The enhanced CT scan shows a rounded or linear area of enhancement which is not associated with mass effect or surrounding edema[20, 64]. MRI shows enlarged intracerebral draining veins manifested by hypointense appearance on T1 weighted images without mass effect which appear as a hyperintense signal on T2 weighted images[3, 9, 13, 22, 52, 75, 94].

Cavernous Hemangiomas (Cavernomas, Cavernous Malformations)

Angiography of this type of malformation is frequently normal[92], although prolonged injection angiography may occasionally demonstrate a capillary blush within the lesion[70]. CT findings consist of a hyperdense and often partially calcified lesion. Following contrast injection fairly homogeneous enhancement may occur, although it may be difficult to appreciate, if calcification is dense. The lesion is not associated with mass effect or surrounding edema except when recent hemorrhage is present[5, 31, 70, 87, 93].

The MRI appearance of cavernous malformations has been well described[3, 9, 52, 89, 92]. Cavernomas appear as well defined areas of mixed, but predominantly increased signal intensity on T1 and T2 weighted images surrounded by a hypointense rim. The central area of bright signal is caused by the presence of methaemoglobin, the mixed densities by subacute and chronic hemorrhage and the hypointense rim by hemosiderin deposition. Although initially the MR findings were thought to be pathognomonic, further experience has shown that other conditions such as thrombosed arteriovenous malformations and hemorrhagic metastases may show a similar appearance[9, 89]. Multiple cavernomas may be present and are readily identified by means of MRI. MRI is the method of choice in following patients with known intracerebral cavernomas.

Arteriovenous Malformations

The angiographic appearance of arteriovenous malformations is that of abnormally dilated and tortuous feeding arteries and a racemose tangle of increased vascularity with early drainage into tortuous elongated and enlarged veins. The term microarteriovenous malformations has been applied to lesions with a nidus of less than 1 cm, fed by normal sized arteries with rapid shunting into normal sized veins[116]. Occasionally the malformation may appear to be obliterated as a result of a recent adjacent hematoma and angiography may be negative at this stage. Resolution of the hematoma may then allow visualization of the underlying vascular malformation in six to eight weeks' time.

The CT appearance of intracranial arteriovenous malformations, when not associated with recent hemorrhage, is fairly characteristic[12, 36, 42, 85, 106]. The lesion most commonly presents on the unenhanced CT scan as an area of mixed density. Focal areas of hyperdensity are interspersed with areas of decreased density. The margins of the lesion are poorly defined and irregular in outline. After contrast infusion, the lesion will show non-homogeneous enhancement. Feeding arteries and draining veins may be recognized on CT. The lesion may be associated with focal atrophy or localized mass effect, but surrounding edema is extremely uncommon.

A small number of arteriovenous malformations are heavily calcified and contrast enhancement in these lesions is difficult to assess. This type of lesion is often angiographically occult.

Hemorrhagic complications associated with cerebral arteriovenous malformations are readily shown on CT. Bleeding usually occurs into the subarachnoid space, ventricular system or the brain parenchyma. Rarely, blood is released into the subdural space. Hemorrhage may occasionally obscure the malformation on the initial CT scan. Follow-up CT scanning and angiography may therefore be necessary to demonstrate the underlying pathology.

The MRI appearance of intracerebral AVM has been well described[9, 18, 41, 51, 52, 96]. Low intensity signal (flow void) on both T1 and T2 weighted images is noted to involve the nidus as well as the feeding arteries and draining veins. Slow flow within the lesion may result in increased signal on T2 while previous hemorrhage may reveal itself as a bright signal on both T1 and T2. Calcification or embolic material from previous endovascular treatment may be difficult to appreciate on MRI[96] and is often better shown on CT. CT has also proven to be more sensitive than MRI in delineating small calcified arteriovenous malformations[27, 54, 67]. MRI is probably superior to CT and angiography in demonstrating the exact anatomic relationship between the nidus, the feeding and draining vessels and the adjacent structures[68]. Angiography remains mandatory in the treatment planning and post-treatment assessment of intracerebral AVMs (endovascular, surgical, or radiotherapy) and is so far the only reliable method of demonstrating the micro AVM[116].

CT and MRI are equally efficient in demonstrating complications following treatment but MRI is probably more accurate in assessing residual nidus following partial embolization or radiotherapy[62, 63, 96].

Dural Arteriovenous Malformations

Although not strictly brain vascular malformations, these dural AVMs may produce similar complications and are therefore considered in this account. The dural location of the nidus of these malformations is rarely

demonstrated on CT although abnormally prominent venous draining channels may indicate secondary evidence of such lesions. CT may show the complications associated with these lesions such as intracerebral and subarachnoid hemorrhage.

MRI of dural AVMs has so far been limited to the demonstration of the complications of dural AVMs with cortical venous drainage such as hemorrhage, venous congestion, and enlarged draining veins. The actual dural nidus is rarely identified prospectively on MRI.

Angiography remains the only method to demonstrate the nidus, the feeding vessels and the venous drainage pattern of dural arteriovenous malformations. Superselective angiography of the middle meningeal, ascending pharyngeal and occipital branches of the external carotid artery is recommended as part of the pretherapeutic protocol[45]. The venous drainage may be into dural sinuses or into cortical veins. The presence of cortical venous drainage may account for central nervous system symptomatology and indicate a higher incidence of associated intracranial hemorrhage[47]. Dural arteriovenous malformations along the anterior cranial fossa and tentorium are frequently associated with subarachnoid and intracerebral hemorrhage.

Superselective angiography is essential in recognizing the underlying pathology and for proper treatment planning.

Endovascular Therapy

History

Embolization of brain arteriovenous malformations (BAVMs) began with microspheres as the embolic agent using a flow dependent technique. This technique was first reported in 1960 by Luessenhop and Spence[58] and later by Wolpert and Stein[118]. This approach was flawed by frequent neurological complications and long-term follow-up demonstrated the development of collaterals with no significant reduction in nidus size[57]. Similar findings on long-term angiographic controls were found by Serbinenko[95] and Romodanov[90] who used detachable balloons to occlude arterial feeders to the AVM.

In the 1970's, with Kerber's development of soft microcatheters[37], the age of superselective catheterization of intracranial vessels began. With selective catheterization of feeding pedicles, Kerber began using isobutyl 2-cyanoacrylate (IBCA)[4], a liquid adhesive agent, as the embolic material. These microcatheters were equipped with a calibrated-leak balloon at their tip to aid in their flow guidance towards the AVM. The ideal placement of IBCA proved to be difficult. Occlusion of the feeding pedicle alone only promoted collateral flow to the nidus. In addition there was the risk of "gluing" the catheter in place. Attempts were made to adjust the poly-

merization time of the IBCA by adjusting the ratio of IBCA to Lipiodol or using acetic acid[99]. Due to the difficulties in using IBCA other embolic agents came into use including polyvinyl alcohol[49], silk threads, microcoils and a mixture of ivalon, alcohol, and avitene. N-butyl cyanoacrylate (NBCA) replaced IBCA when the latter became unavailable[10]. More recently a new liquid agent, ethylene vinyl alcohol copolymer (EVAL) has been used[105].

Since 1987, selective catheterization of intracranial vessels has been facilitated by the introduction of the variable stiffness microcatheters[16]. These microcatheters have a long, floppy distal segment which takes advantage of flow and a stiffer proximal segment to allow direct control. They can be used in conjunction with a floppy guide to increase proximal stiffness or aid in selective catheterization of proximal intracranial vessels.

Techniques

At present, embolization of brain AVMs is done using the arterial approach with variable stiffness microcatheters. The procedure is done in the radiology department under neuroleptic anesthesia. Intra-operative embolization using a direct catheterization of feeding pedicles is no longer done. Most centres presently use a transfemoral approach with a guiding catheter in the internal carotid or vertebral arteries. The variable stiffness microcatheter is advanced through the guiding catheter into the intracranial circulation. Most centres use full heparinization. When NBCA is the embolic agent some centres use a calibrated leak balloon at the tip of the microcatheter. This facilitates flow guidance and can produce flow arrest during injection of the NBCA to better control the deposition of the embolic material. Other centres do not use a balloon so as to allow the NBCA to flow freely taking advantage of the sump effect. Most centres cover the patients with steroids for three days after embolization to reduce any inflammatory reaction secondary to the embolic material. Most centres use a staged approach to allow the vessels to accommodate hemodynamic changes after embolization. During an embolization procedure, selective catheterization of a number of feeding pedicles is done. The decision to embolize any given pedicle is based on the risks. In our own practice we do not embolize if any healthy branches are visualized on the test injection. Some centres use an Amytal challenge to see if neurological deficits develop[109].

Results

There are two separate fundamental strategies in the embolization of brain AVMs. Most centres do preoperative embolization with particles to facilitate surgery[86, 97]. Like a few other centres, we began with a mixture of

IBCA, pantopaque and tantalum powder. Since 1988 our preference has been to embolize with the liquid adhesive agent, NBCA, to achieve an angiographic cure if possible. If a cure is not possible, partial embolization may be done to facilitate surgery or make the nidus smaller to increase the efficacy of stereotactic radiation.

In any series, the combined results of embolization of the entire group are not instructive. Brain AVMs are diverse and the goals of treatment for each patient varies. For example, in our recent report by Fournier an angiographic cure by embolization alone (NBCA or IBCA) was obtained in 7 of 49 patients (14.2%)[24]. These cures were only obtained in Spetzler Grade I and II malformations. Thus if Fournier only includes Spetzler Grades I and II the angiographic cure rates are much higher. A recent report by Picard *et al.* on embolization of corpus callosum AVMs with liquid adhesives had an angiographic cure rate of close to 50 percent[81]. Thus in certain centres, selected brain AVMs may have a good chance of cure by embolization alone.

Recently, recanalization of brain AVMs treated with liquid adhesives has been a contentious issue[88]. In our series and also in Picard's, recanalization has not occurred when excellent penetration of the nidus has been achieved[24,81]. When only the feeding vessel has been occluded recanalization may occur.

Progressive neurological deficit is another indication for embolization. Fox described three patients with rolandic AVMs and significant limb deficit who had virtual complete recovery after embolization with IBCA[25]. In our series, 9 of 21 patients had better seizure control after embolization with liquid adhesives but no patients had an improved neurological deficit[24].

The commonest indication for treatment of brain AVMs is to reduce the chance of hemorrhage. It has not been established whether partial embolization by liquid adhesives reduces the chance of future hemorrhage. Since matched controls do not exist, a long-term analysis of a large cohort of patients embolized must be compared to patients not treated. In our own experience, the first 15 patients who initially presented with hemorrhage did not have a rebleed following embolization in a follow-up of five years or less[24]. Since the estimated average time to bleeding after discovery of an AVM is approximately 7.7 years, longer follow-up is required to draw reliable conclusions[76]. In fact, in an as yet unpublished review of our most recent experience, the incidence of hemorrhage in patients with partially obliterated AVMs who had not bled prior to treatment, was no different from the expected natural history of untreated patients with AVMs. The incidence of hemorrhage in patients with incompletely obliterated malformations presenting with hemorrhage was 16.5 hemorrhages per hundred patient years of follow-up; slightly higher than the expected natural history. Further experience will be required to resolve this dichotomy.

Complications of embolotherapy must be severely scrutinized especially in view of the overall low angiographic cure rate. Our series of 49 consecutive patients embolized compares favourably to the other major series by Berenstein and Picard using a similar embolic material[6, 24, 82]. Twelve of our 49 patients developed deficits; 8 were transient and 4 were permanent. There were no deaths related to the embolization[24].

Preoperative embolization of brain AVMs by either particles or liquid adhesives has become a standard practice in many centres[2]. In some centres, embolization with liquid adhesives is the only treatment or is done to reduce the size of the nidus before stereotactic radiation[44]. The results and morbidity of embolization in combination with stereotactic radiation have yet to be analyzed. Embolization is an integral part of the analyzed treatment protocol for patients with brain arteriovenous malformations.

Radiosurgery

History

The term radiosurgery was first coined in 1951 by Leksell[53], who, after experimenting with several systems for the delivery of ionizing radiation, developed the device consisting of multiple collimated sources of cobalt-60 radially directed at a central target that has come to be known as the "gamma knife"[59, 103, 104, 111]. A high dose of radiation to a specific target, such as an AVM, may also be delivered by a linear accelerator modified so that the radiation source sweeps through an arc or arcs[8, 15, 83, 117] always centred on the target with the result that a high radiation dose is absorbed by the target and relatively little by the overlying brain. Focused beams of charged particles, that is, protons and helium ions, have also been modified for the delivery of radiation to arteriovenous malformations[38, 39, 62, 63]. Common to all radiosurgery methods is the accurate selection of the target by means of a stereotactic device used in conjunction with the imaging modalities described above that positions the AVM at the centre of multiple collimated beams of photons or charged particles or at the centre of rotation of collimated beams of photons that turn through multiple noncoplanar or complex acrs of rotation.

Techniques

A principle of radiation therapy in general is to deliver a high dose homogeneously across a target volume while minimizing the dose to the surrounding tissues. The radiation may be delivered by single or multiple beams. For a single photon beam, the maximum dose is deposited at a predetermined depth below the skin surface. The beam's energy is further attenuated with increasing depth. Since the dose to overlying normal tissues

may exceed the dose to the AVM, single photon beams are unsuitable. In contrast, for single proton or helium ion beams[38, 39, 62, 63], there is minimal deposition of energy along the beam's path until a predetermined depth is reached. At this point, a large quantity of energy (the Bragg peak) is distributed over a small volume. By focusing the Bragg peak on the AVM, the adjacent normal tissues may be differentially spared.

When photons are delivered using multiple fields, the beams may be coplanar (have a common central axis) or noncoplanar (intersect only at a point). With a conventional coplanar setup of two photon beams with standard beam sizes arranged in a parallel opposed fashion, a homogeneous dose is delivered across the target volume with a reasonably high dose also received by the adjacent tissues. This is desirable when treating neoplasms since microscopic extension of the tumour dictates a high dose to the gross disease plus a dose to a margin of "normal" tissue. For AVMs, methods which enhance the differential sparing of adjacent normal tissues are preferable. These other methods include multiple noncoplanar beams of proton or helium ions and narrow beams of photons intersecting at a stereotactically chosen point. With such beam arrangements, the dose falls off more rapidly outside the target than the dose distribution seen with conventional beam sizes and configurations. Because of this greater sparing of adjacent tissues, treatment can often be delivered in one fraction. For lesions exceeding 3 cm, this advantage diminishes. As a result, many centres, ours included, will not treat lesions larger than 3 cm in diameter.

A gamma knife unit has approximately 201 collimated Cobalt-60 sources spread radially over a segment of a sphere[60, 103]. The dose is varied by varying the length of time the patient is positioned with the AVM at the centre of the sphere. Linear accelerators can deliver photons via several fields intersecting at a point. When using multiple non-coplanar arcs, the treatment couch is stationary while each arc is given[14]. With dynamic rotation, the beam and couch move simultaneously[83]. Similar resultant dose distributions for the gamma knife and the two linear accelerator techniques are achieved, but the setup and treatment times vary considerably. Our modification of the Montreal dynamic rotation reduces the beam on-time to approximately 7 minutes[71]. In comparison, Kjellberg states that the proton beam therapy takes 1 $^1/_2$ to 2 hours per session[38]. Colombo's technique of multiple non-coplanar arcs typically takes 30 to 40 minutes per session[14]. The first AVM to be treated with a gamma knife received 5000 rads (a higher dose than currently used) over 30 minutes[103].

Results

Pathologic changes similar to obliterative endarteritis gradually occur in the vasculature of tissues exposed to therapeutic doses of radiation[72]. On examination of radiated AVMs (be it with photons from a gamma source

or a linear accelerator; protons; or helium ions) such changes are noted[72]. This is evidence that radiation can obliterate AVMs. The degree of radiation effect, and the rapidity of its appearance are dependent not only upon the total dose given, but the number of fractions and the duration of time required to deliver this. With the doses commonly used now, the latency period is of the order of 1 to 2 years. Patients are not protected from hemorrhages during this time.

In evaluating a particular treatment method, all relevant data must be reported to allow adequate analysis of the results. The dose (was it prescribed at the centre or periphery of the AVM), volume (was the entire nidus included) and fractionation (was the total dose delivered in one or more sessions) must be specified. The entire patient population must be accounted for, with the number eligible for follow-up at various post-treatment intervals stated. Angiograms should be performed on all patients to accurately determine the obliteration rate. The endpoints should be clearly defined, such as the meaning of partial obliteration. Unfortunately, not all published series give these details.

Steinberg, Fabrikant *et al.* have reported on 104 patients treated with helium ion radiation through the collaborative program of Lawrence Berkely Laboratory and the Stanford University Medical Center[102]. Fifteen having angiographically occult AVMs precluding angiographic follow-up, were excluded. Of the remaining 89, 3 were lost to follow-up by 4 months and so excluded. But only 71 of the 86 eligible for the analysis had follow-up angiograms. It is unclear why 15 lacked this. Helium ion radiation has been successful with 44 attaining a complete response. However, they state "this series of 86 patients... showed on overall rate of complete obliteration of ... 92% after 3 years"[102]. This percentage is based on 44 complete responses out of 48 patients evaluated angiographically at 3 years. It is however not clear from the article how many patients out of the original 86 were eligible for 3 year follow-up. With this uncertainty about the denominator, it is difficult to know what the true 3 year response rate is. They then subsequently display a 44/71 or 62% complete response rate, encompassing all intervals of follow-up. Even this complete response rate does not use the entire cohort of 86 as the denominator. Obviously the 15 patients without follow-up angiograms may greatly influence this, with the overall complete response rate potentially ranging from 59/86 (80%) to 44/86 (51%). Size seems to be important, with the suggestion that smaller AVMs may have a faster rate of complete obliteration. When examining the effect of dose, the trend is towards an earlier complete response with a higher dose. Seventeen had complications, 7 minor and 10 major. These were in patients treated to a high dose. Subsequent dose reduction has yielded no further complications. Yet, of 86 patients, 60 were clinically "excellent" pretreatment compared to only 50 post-treatment.

Kjellberg reported in 1984 on 444 procedures performed on 439 patients treated with proton beam radiation[39]. Of the 260 eligible for 2 year follow-up, 244 were evaluated. The 2 year "rate of total obliteration in the patients on whom we have follow-up angiograms (57%) was 22%". No explanation for the lack of such follow-up in the remaining 43% is given. One cannot comment accurately on response rates when nearly half of the population was not evaluated. Doing the calculations, it would appear that if 57% of the 244 evaluated patients have angiograms, then 31 patients had a complete response. Therefore the complete response rate would be at least 31/260 or 12%, with this to rise if complete responses are documented in any of the remaining 43% yet to undergo follow-up angiography. Complications occurred in 8 of the first 74 patients. A subsequent dose reduction resulted in only 1 further complication, out of a total of 439 patients or 444 procedures.

Steiner has had the longest experience using the gamma knife[103, 104]. The results of 300 patients treated since 1970 were published in 1984[104]. There are problems with the reporting. Nine patients were retreated "where no results were obtained and the initial treatment was considered technically unsatisfactory"[104]. Of these, two cases were reported simultaneously in each of two categories[104]. Although only 3 were said to be excluded from analysis (1 lost to follow-up; 2 refused angiograms), angiographic follow-up was on only 192 of 300 patients. No explanations were given. Of 248 cases where the field "completely covered the cluster of pathologic vessels"[104], 104 had angiograms beyond 2 years following treatment. Since 90 had a complete response, they stated a 86.5% obliteration rate. The true rate may range from 41% to 94% if none or all of the remaining, unassessed 144 patients did or did not have a complete response. Looking at the entire group undergoing follow-up angiography, there is the suggestion that the entire nidus must be within the target volume to achieve a complete response. Necrosis was seen with doses ranging from 5000 cGy × 2 to 10,000 cGy in 1 treatment.

Lunsford *et al.* have recently reported on 227 patients radiated at the University of Pittsburgh with a gamma knife[60]. Seventy-five patients were eligible for 2 year follow-up but only 46 had follow-up angiograms. There was no explanation regarding the lack of angiographic follow-up in the remaining 29 patients. They stated "complete obliteration was confirmed in 37 patients (80%)"[60], but this percentage was generated using 46 as the denominator. The true complete obliteration rate will clearly depend upon the results of the remaining 29 and may vary from 66/75 (88%) to 37/75 (49%). Immediate post-treatment complications occurred with 8 patients experiencing seizures and 17 developing nausea and vomiting. Of 10 patients (4.4%) developing late complications, all responded symptomatically to oral corticosteroids, but 2 appear to have permanent residual deficits.

Betti has reported on 66 patients treated using multiple non-coplanar arcs on a linear accelerator[8]. Due to a variety of reasons including socioeconomic factors, angiographic follow-up is unavailable for 13 patients. Of the cohort left, 40 were followed for more than 2 years, with 27 showing complete obliteration (67.5%). The volume receiving an adequate dose seemed important, with 25/27 satisfying this criteria showing complete obliteration at 2 years versus 2/13 without the entire lesion receiving an adequate dose. When analyzing by dose, 6/18 treated with less than 3000 cGy had a complete response while 18/21 treated with 3000 to 5000 cGy and 2/4 given more than 5000 cGy had complete obliteration. Sixty-nine percent of small lesions were obliterated with doses less than 2500 cGy. AVM size seemed important. Thirteen of sixteen with lesions less than 12 mm had a complete response compared with 13/28 with lesions measuring 12 to 25 mm, and 1/8 with lesions ranging from 25 to 60 mm. Of 2 patients developing hemiplegia, 1 in retrospect had previous external beam therapy and perhaps should not have been treated.

Colombo has reported on 97 patients[15]. Eighty-two had the entire nidus treated, with all but 2 receiving the radiation in 1 session (2 required 2 sessions). For AVMs up to 15 mm, 4000 cGy at the centre was considered safe. For lesions exceeding 20 mm, a therapeutic dose to the target had to be chosen which allowed delivery of a safe dose to the radiosensitive normal tissues. Thus the minimum target dose ranged from 1500 to 3000 cGy, corresponding to the 60–90% isodose. The maximum dose to radiosensitive structures (visual and motor pathways, cranial nerves, diencephalon, brain stem) varied from 600–1000 cGy. The mean follow-up was 17.1 months (range of 1 to 49 months). Of 56 eligible for 1 year follow-up, 6 refused angiograms. Twenty-six of the 50 evaluated had a complete response. By 2 years, 15 of 20 had complete obliteration. An important observation was made by superimposing the dose distribution onto the follow-up angiogram. Complete obliteration was seen in parts of the AVM receiving doses of 1500 to 2900 cGy. AVM size also appeared important. Complete response at 2 years was 9/10 and 4/5 for lesions less than 15 mm, and between 15 and 25 mm respectively. For larger lesions, 1/9 had complete obliteration. Clinical complications arose in 3, with 6 more showing CT abnormalities. Two have shown regression of the hypodense areas. This is a well-reported series which shows that obliteration can occur with doses of 1500–2900 cGy. These doses help to define the minimum required to obliterate an AVM. One wishes to use the lowest effective dose to reduce normal tissue damage. Again the trend is for smaller lesions to attain a complete response more quickly than larger lesions. In June 1991 Colombo updated his results at the International Stereotactic Radiosurgery Symposium in Pittsburgh. He reported on 146 patients with AVMs, and stated an 80% obliteration rate at 2 years, as well as 7 patients experiencing necrosis.

When attempting to evaluate the complete response rates and the roles of various types of radiosurgery systems relative to each other as well as to surgery and embolization, we are hampered by small numbers of patients or incomplete reporting in many series. From Colombo's work (International Stereotactic Radiosurgery Symposium, 1991) it appears that the 2 year complete response rate with linear accelerator radiosurgery is 80 percent. The gamma knife series have problems with reporting. Since both systems deliver photons, it is reasonable to expect that gamma knife results would be similar provided the same volume was treated (i.e. the entire nidus) and the setup accuracy and doses to the margin of the lesions are comparable. From a technical aspect, Leavitt has recently quoted an unpublished report surveying dosimetry of stereotactic radiosurgery procedures between 9 institutions[50]. The "isocentre-miss distance ranging from 0.7 mm to greater than 3 mm" is really quite impressive. It is likely that such errors are clinically insignificant, especially relative to the error inherent in defining the margin of the AVM[50].

In future, we need to gain more information regarding the minimum dose required to obliterate an AVM, the maximum dose tolerated by normal tissue and the relative radiosensitivities of various parts of normal brain (i.e. brain stem, optic nerve, etc). Use of this knowledge may then improve the complication rate which is approximately 3 to 5% with linear accelerator and gamma knife radiosurgery[60]. Prognostic factors influencing response to radiation need to be elucidated, and may include lesional factors such as flow rate, and treatment factors such as lesion size, extent of nidus treated and dose to the edge of the nidus.

Surgical Treatment

History

The history of the surgical treatment of arteriovenous malformations has been well summarized in the literature[17, 26, 35, 61, 80, 119, 120]. The principles of surgical excision of cerebral arteriovenous malformations were developed by the early pioneers of AVM surgery in the late 1930's and early 1940's[7, 68, 73, 121]. Surgical procedures that did not result in total excision of the lesion including ligation of feeding vessels and partial removal were found to be ineffective and did not protect the patient from later intracranial hemorrhage. With increasing experience together with improved angiographic techniques and a better understanding of the anatomy and physiology of these lesions, these early pioneers were able to advance the technique of surgical treatment and attain remarkable results[40, 69, 74, 84]. The development of microsurgical technique and the use of the operating microscope by Yaşargil in the late 1960's unshered in a new era in the surgical approach to these lesions. He reported excellent results with many arte-

riovenous malformations previously considered inoperable[122]. The current surgical state-of-the-art of AVM surgery has been well described in many subsequent excellent reports[1, 17, 43, 65, 79, 101, 124, 125]

Technical Considerations

Surgery on arteriovenous malformations can be among the simplest (small, superficial lesions in polar locations), or one of the most difficult of all neurosurgical procedures. Many factors must be taken into consideration in planning a strategy for the obliteration of an arteriovenous malformation. Size, location, and hemodynamic characteristics are key determinants for a successful outcome.

In larger, more complex AVMs, we routinely attempt to reduce blood flow through the lesion by preoperative embolization. Endovascular therapy has been helpful in obliterating deep, feeding vessels which may not be easily accessible during the early stages of AVM resection. By reducing the shunt through the lesion preoperative endovascular treatment may decrease the turgor within the vascular malformation and facilitate surgical dissection. Preoperative embolization has also been carried out in the hope it might reduce the incidence of postoperative normal perfusion pressure breakthrough phenomenon. We have not found that preoperative embolization increases the technical difficulty of the AVM resection. Successful placement of the embolic material to fully penetrate the nidus remains the limiting factor in the usefulness of the technique in the preoperative stage.

Our patients are premedicated with anticonvulsants, steroids, and antibiotics. Neurophysiological monitoring is routinely carried out using either scalp or direct cortical recordings. The head is immobilized with pin fixation and positioned well above the heart. The craniotomy must be well planned and large enough to expose all of the surface component of the AVM as well as to permit visualization of the arterial and venous channels in the surrounding normal cortex. Care must be taken in turning the bone flap and in opening the dura as well, so that large, bridging, draining veins are not injured. The exposure is most limited when the lesion is situated in the medial aspect of the temporal lobe, the trigone or the proximal area of the choroid fissure. Following exposure of the AVM, the surgeon should take considerable time to inspect the surface component of the AVM. It may be quite difficult initially even under the operating microscope to differentiate veins from feeding arteries and from normal adjacent vessels. The general principle is to initially open the arachnoid over the sulcus, and using the natural planes of the sulci and fissures, follow a major feeding vessel right up to the AVM so that branches to the malformation can be interrupted immediately adjacent to the lesion, thus sparing normal transit vessels. Whether the dissection is carried out right on the surface of the

AVM or in the gliotic plane between the vessels and brain will depend on the location and morphology of the lesion. The dissection is gradually extended in a circumferential manner, increasing uniformly the depth of the exposure. It is in the deep white matter that one often encounters the thin-walled vessels carrying arterialized blood which often are resistant to cautery. Here, irigating bipolar is indispensable. Following the principle of initially taking feeding vessels and leaving the main draining veins, uncontrollable bleeding should be minimized. If this occurs, the use of hypotension, either systemic or regional will aid in controlling the hemorrhage. The technical difficulties in AVM surgery depend primarily on the size and location of the lesion, including its feeding and draining vessels. The lesions greater than 5 cm are considered giant AVMs and may require special tactics including preoperative embolization and staged procedures.

Confirming that an AVM has been totally excised can be difficult. High quality intraoperative angiography has been used for this purpose. Postoperative MRI scanning is not sufficient to confirm total excision and angiography remains the gold standard. Angiography should be delayed for several weeks as AVM remnants may become visible in the intervening period.

Results

The decision to offer a particular treatment to a patient must always take into consideration alternative treatment modalities and the natural history of the condition without intervention. Increasingly, evidence suggests that the natural history of AVMs, regardless of the mode of presentation, in the long-term is not benign[23, 76]. Operative mortality and morbidity from different surgical series have varied widely[17, 66, 74, 77, 100, 120–125]. The more recent experience of surgeons dealing with large numbers of these lesions and utilizing microneurosurgical techniques has suggested that radical surgery with complete excision can be achieved with mortality of less than 3% and significant long-term morbidity of less than 10 percent[97, 100, 121, 122, 125]. If the AVM is in a readily accessible area and not overly large, one can expect a smooth postoperative course without neurological deficit. In Yaşargil's series, the best results were in occipital and frontal convexity lesions as well as callosal AVMs with a morbidity from 0–2 percent. Temporal, insular, cingulate, and cerebellar lesions also were associated with good outcome. Many AVMs, however, because of their size and location in more inaccessible and critical regions of the brain fall into a high risk category. In these patients one can anticipate a severe neurological deficit in the immediate postoperative phase. However, if there has been complete removal of the AVM with sparing of all transit vessels and meticulous hemostasis, one can anticipate significant recovery of the immediate post-

operative deficits. The degree to which encroachment upon functionally eloquent areas of the cortex will result in important neurological deficit is to some extent unpredictable but has been improved by the development of grading systems that help stratify patients according to risk[56, 78, 98, 121]. At present, except for very large, deep and extensive lesions involving the dominant hemisphere or brain stem, total resection of arteriovenous malformations can be carried out with acceptable operative morbidity and mortality when compared to the natural history of the lesion.

Decision-making

The prime indication for treatment of brain vascular malformations is the prevention of hemorrhage. Various estimates of the risk of hemorrhage in untreated patients are given in the literature[11, 28, 29, 32, 33, 76, 114]. Ondra and co-workers[76] in a report of a population-based study estimated the likelihood of hemorrhage from an arteriovenous malformation at 4% per annum. This means that in 10 years, more than 30% of a cohort of patients will have suffered a first hemorrhage and by 20 years, more than 50% will have bled at least once. It has been estimated that approximately 50% of patients who bleed suffer a significant neurological deficit and nearly 10% die[114]. Furthermore, the probability of a second hemorrhage in the year after the presenting one is likely as high as 6% with similar probabilities of morbidity and mortality as the first hemorrhage. The only current treatment that offers immediate, complete protection against hemorrhage from an arteriovenous malformation is complete excision by means of surgery. What is the true risk of surgery? Fisher, in a formal consideration of the risks and benefits of surgery using clinical decision analysis, produced average etimates derived from a series of publications in the literature of morbidity and mortality of 8.99 and 5.54 percent respectively[21].

Clinical decision analysis[112] is a methodology that structures a clinical problem in a way that probability estimates of various possible outcomes from the application of a particular treatment or treatments may be derived and the optimal course of action for a particular patient may be chosen. Iansek and his colleagues used clinical decision analysis to analyze the case of a 28 year-old man presenting with epileptic seizures from a "moderate-sized right parietal AVM feeding from the anterior and posterior cerebral circulations"[19, 30]. They concluded from their analysis that surgery bears a worse risk than the natural history and provide an epilogue confirming that in fact the patient fared poorly. Fisher, using more sophisticated methods of analysis but essentially the same outcome probabilities, concluded that surgery is preferable to no treatment. For clinical decision analysis to be useful in aiding the clinician, one must specify all treatment options and all probable outcomes[122]. Furthermore, if too many simplifying

assumptions are made, erroneous conclusions may be drawn. For example, if patients may be stratified according to risk[56,78,98], then a decision analysis treatment that ignores this may be misleading, producing recommendations against a particular treatment for a group that might be expected to benefit or supporting therapy for a subgroup that would be placed at risk by a particular treatment. Neither Iansek nor Fisher factor in the characteristics that make AVM surgery safer or more dangerous and neither considers the possibility of endovascular therapy or radiosurgery as unique therapeutic measures or as adjuncts to surgery. As a result, neither analysis can be said to truly apply to the treatment of patients for whom other therapeutic modalities are available. Figure 1 shows a decision tree which, although already quite complex, does not completely specify all possible outcomes. It does, however, serve to illustrate the general approach of our multidisciplinary group. Each patient referred to the group for treatment is "conferenced" and recommendations for treatment are considered. There is often a spectrum of opinion regarding the best course of action. We know from our experience that Spetzler grade I and II are most likely to be completely obliterated by embolization. These are also the AVMs for which surgery is safest and most effective. For lesions less than 3 cm in diameter radiosurgery is also suitable. If the patient has recently bled, is relatively young and a good surgical risk, surgery is likely to be offered. If there has been no hemorrhage within the last six weeks, if there are dominant feeders, good proximal arteries and adequate blood flow, embolization will be offered, with surgery or radiosurgery to follow if the lesion is incompletely obliterated.

For larger lesions, that is, higher Spetzler grade AVMs, embolization is usually undertaken first even though complete obliteration will not likely occur. Partial obliteration will make subsequent surgery safer or permit radiosurgical treatment (Figs. 2 and 3).

If the AVM is less than 3 cm or is reduced to this size by prior embolization or incomplete surgical excision, radiosurgery is recommended. If the AVM is inaccessible to a direct surgical approach, if the patient is elderly or a poor operative risk or has an aversion to an open surgical procedure, radiosurgery may be offered as the primary treatment. Many patients referred to our group for radiosurgery may in fact undergo endovascular therapy or surgery because immediate protection conferred by these latter techniques is preferable to a two year latency as progressive obliteration occurs.

In practice, the discussion and sharing of referred cases has the beneficial effect that each therapeutic modality is utilized only according to its current indications. The interventional radiologists do not feel obliged to push their technique to its limit of safety because surgery or radiosurgery are available as salvage procedures. Similarly, the surgeon with embolization as an adjunct available to him may safely deal with more formidable lesions and

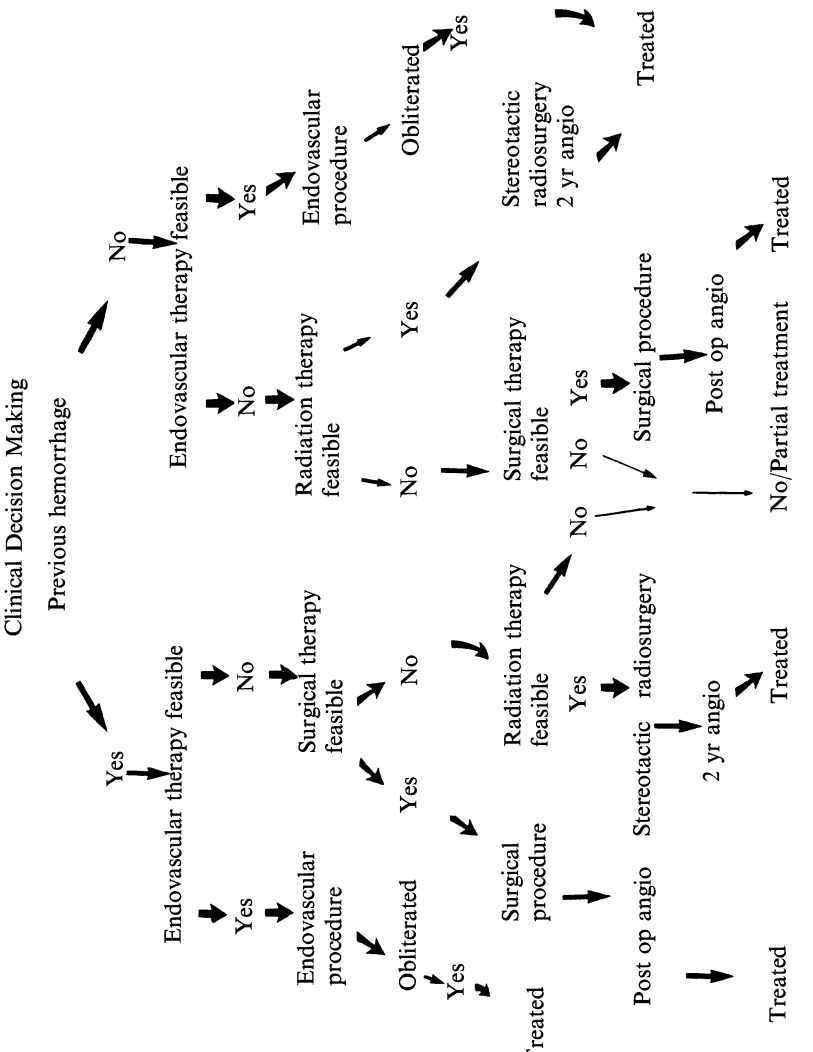
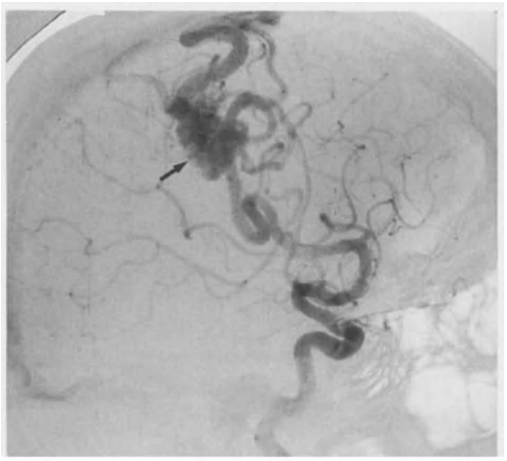
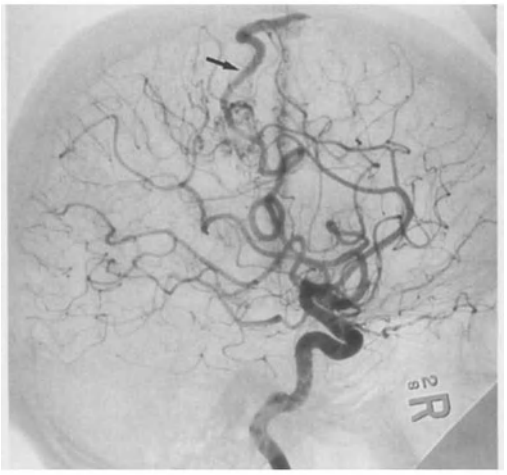


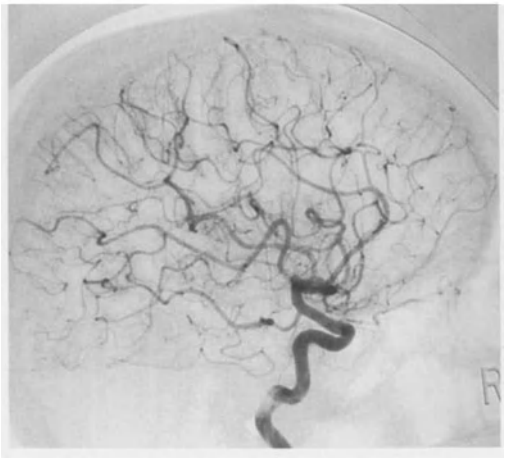
Fig. 1. Summary of decision tree for the multidisciplinary managements of arteriovenous malfunctions



A

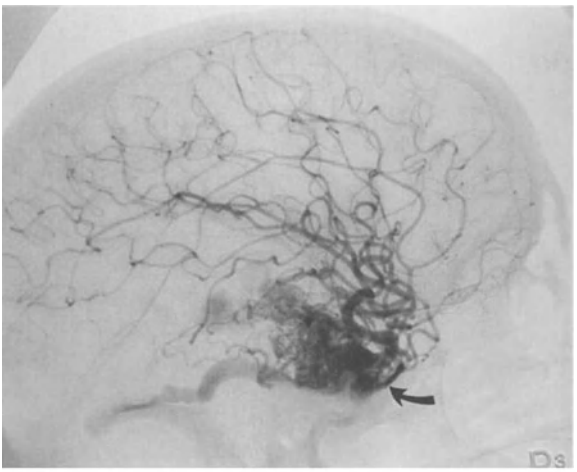


B

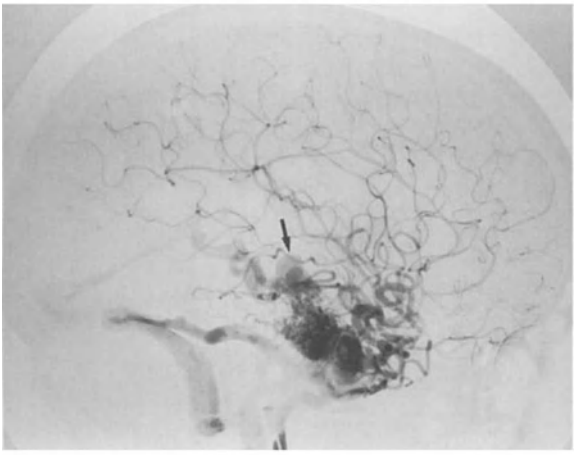


C

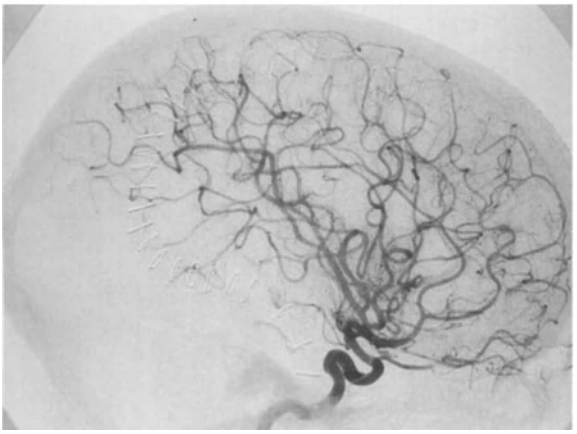
Fig. 2. Embolization followed by stereotactic radiation. A Lateral carotid angiogram shows the parietal AVM (arrow). B Post embolization angiogram shows that most of the nidus has been obliterated but there is still an early vein (arrow). C On the two-year follow-up angiogram after stereotactic radiation the AVM is no longer evident



A



B



C

Fig. 3. Embolization followed by surgery. A Lateral carotid angiogram shows an AVM in the temporal lobe. B Post embolization angiogram shows that the nidus is smaller. Venous ectasias (arrow) in the deep venous drainage are more evident. C Post surgical angiogram shows that there is no residual AVM

may at times opt for an incomplete resection of an AVM in the interest of patient safety, knowing that radiosurgery is available as a salvage procedure for unresected portions of an AVM. Finally, there are patients whose AVMs, by virtue of their size, vascularity and position are not amenable to any current treatment. The resources of a multidisciplinary group permit the accurate documentation, retrieval of information and follow-up that allows study of the natural history of such patients and their recall when new developments permit safe treatment. The structure of the group widens the referral base of patients, enhances the interest and education of its members and results in state-of-the-art care of the patients it serves.

References

1. Amacher AL, Allcock JM, Drake CG (1972) Cerebral angiomas: The sequelae of surgical treatment. J Neurosurg 37: 571–575
2. Andrews BT, Wilson CB (1987) Staged treatment of arteriovenous malformations of the brain. Neurosurgery 21: 314–323
3. Augustyn GT, Scott JA, Olson E, Gilmor RL, Edwards MK (1985) Cerebral venous angiomas: MR imaging. Radiology 156: 391–395
4. Bank W, Kerber C, Cromwell L (1981) Treatment of intracerebral arteriovenous malformations with isobutyl 2-cyanoacrylate: initial clinical experience. Radiology 139: 609–616
5. Bartlett JE, Kishore PRS (1977) Intracranial cavernous angioma. Am J Roentgenol Radium Ther Nucl Med 128: 653–656
6. Berenstein AB, Choi IS, Rupersmith MJ, Kricheff II, Madrid MM (Abstract) Complications of endovascular embolization in 202 patients with cerebral AVMs. AJNR 10: 876
7. Bergstrand H, Olivecrona H, Tonnis W (1936) Gefäßmißbildungen und Gefäßgeschwülste des Gehirns. G Thieme, Leipzig
8. Betti OO, Munari C, Rosler R (1989) Stereotactic radiosurgery with the linear accelerator: treatment of arteriovenous malformations. Neurosurgery 24: 311–321
9. Biondi A, Scialfa G (1988) Morphological and blood flow MR findings in cerebral vascular malformations. J Neuroradiol 15: 253–265
10. Brothers M, Kaufmann J, Fox A, Deveikis J (1989) n-Butyl 2-cyanoacrylate substitute for IBCA in interventional neuroradiology: Histopathological and polymerization time studies. AJNR 10: 777–786
11. Brown RD Jr, Wiebers DO, Forbes G *et al* (1988) The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 68: 352–357
12. Brunelle FOS, Harwood-Nash DCF, Fitz CR, Chuang SH (1983) Intracranial vascular evaluation. Radiology 149: 455–461
13. Cammarata C, Han JS, Haaga JR, Alfidi RJ, Kaufman B (1985) Cerebral venous angiomas imaged by MR. Radiology 155: 639–643
14. Colombo F, Benedetti A, Pozza F, Avanzo RC, Marchetti C, Chierego G, Agostino Z (1985) External stereotactic irradiation by linear accelerator. Neurosurgery 16: 154–159

15. Colombo F, Benedetti A, Pozza F, Marchetti C, Chierigo G (1989) Linear accelerator radiosurgery of cerebral arteriovenous malformations. Neurosurgery 24: 833–840
16. Dion J, Duckwiller G, Lylyk P, Vinuela F, Bentson J (1989) Progressive suppleness pursil catheter: A new tool for superselective angiography and embolization. AJNR 10: 1068–1070
17. Drake CG (1979) Cerebral arteriovenous malformations: considerations for and experience with surgical treatment in 166 cases. Clin Neurosurg 26: 145–208
18. Edelman RR, Wentz KU, Mattle HP, O'Reilly GV, Candia G, Liu C, Zhao B, Kjellberg RN, Davis KR (1989) Intracerebral arteriovenous malformations evaluation and selective MR angiography and venography. Radiology 173: 831–837
19. Elstein AS, Balla JI, Iansek R (1990) Letter to the Editor. Application of decision analysis to unruptured arteriovenous malformations. Neurosurgery 26: 545
20. Fierstein SB, Probram HW, Kieshima G (1979) Angiography and computed tomography in the evaluation of cerebral venous malformations. Neuroradiology 52: 246–250
21. Fisher WS (1989) Decision analysis: A tool of the future: an application to unruptured arteriovenous malformations. Neurosurgery 24: 129–135
22. Fontaine S, De La Sayette V, Gianfelice D, Melanson D, Ethier R (1987) CT, MRI, and angiography of venous angiomas. A comparative study. J Can Assoc Radiol 38: 259–263
23. Forster DMC, Steiner L, Hakanson S (1972) Arteriovenous malformations of the brain. A long-term clinical study. J Neurosurg 37: 562–570
24. Fournier D, TerBrugge K, Willinsky R, Lasjaunias P, Montanera W (1991) Endovascular treatment of intracerebral arteriovenous malformations: Experience in 49 cases. J Neurosurg 75: 228–233
25. Fox AJ, Girvin JP, Vinuela F, Drake C (1985) Rolandic arteriovenous malformations: Improvement in limb function by IBC embolization. AJNR 6: 575–582
26. French LA (1977) Surgical treatment of arteriovenous malformations: A history. Clin Neurosurg 24: 22–33
27. Gomori JM, Grossman RI, Goldberg HI *et al* (1986) Occult cerebral vascular malformations: High-field MR imaging. Radiology 158: 707–713
28. Graf CJ, Perret GE, Torner JC (1983) Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg 58: 331–337
29. Guidetti B, Delitala A (1980) Intracranial arteriovenous malformations. Conservative and surgical treatment. J Neurosurg 53: 149–152
30. Iansek R, Elstein AS, Balla JI (1983) Application of decision analysis to management of cerebral arteriovenous malformation. Lancet 1 (8334): 1132–1135
31. Ito J, Sato I, Tanimura K (1978) Angiographic and computed tomography findings of a convexity cavernous hemangioma. Jpn J Clin Radiol 23: 204–205
32. Itoyama Y, Uemura S, Ushio Y *et al* (1989) Natural course of unoperated intracranial arteriovenous malformations: Study of 50 cases. J Neurosurg 71: 805–809

33. Jane JA, Kassell NF, Torner JC, Winn HR (1985) The natural history of aneurysms and arteriovenous malformations. J Neurosurg 62: 321–323
34. Jimenez JL, Lasjaunias P, TerBrugge K, Flodmark O, Rodesch G (1989) The transcerebral veins: Normal and nonpathologic angiographic aspects. Surg Radiol Anat 11: 63–72
35. Johnson HD (1967) Surgery of cerebral vascular anomalies. In: Walter AE (ed) A history of neurological surgery, Chap X. Hafner, New York, pp 250–269
36. Kendall BE, Claveria LE (1986) The use of computed axial tomography for the diagnosis and management of intracranial angiomas. Neuroradiology 12: 141–160
37. Kerber CW (1976) Balloon catheter with a calibrated leak. Radiology 120: 547–550
38. Kjellberg R, Hanamura T, Davis K, Lyons S, Adams R (1983) Bragg-Peak proton-beam therapy for arteriovenous malformations of the brain. N Engl J Med 309: 269–274
39. Kjellberg R, Davis K, Lyons S, Butler W, Adams R (1984) Bragg-Peak proton-beam therapy for arteriovenous malformations of the brain. Clin Neurosurg 31: 248–290
40. Krayenbuhl HA, Yaşargil MG (1959) L'aneurisme cerebral Documenta Geigy 4: 66–112
41. Kucharczyk W, Lemme-Plaghos L, Uske A *et al* (1985) Intracranial vascular malformations: MR and CT imaging. Radiology 156: 383–389
42. Kumar AJ, Fox AJ, Vinuela F, Rosenbaum AE (1984) Revised old and new CT findings in unruptured larger arteriovenous malformations of the brain. J Comput Assist Tomogr 8: 648–655
43. Kunc Z (1974) Surgery of arteriovenous malformations in the speech and motor sensory regions. J Neurosurg 40: 293–303
44. Lasjaunias P, Manelfe C, TerBrugge K *et al* (1986) Endovascular treatment of cerebral arteriovenous malformations. Neurosurgery 9: 265–275
45. Lasjaunias P, Chiu M, TerBrugge K, Tolia A, Hurth M, Bernstein M (1986) Spontaneous intracranial dural arteriovenous malformations (D AVM): Neurological manifestations. J Neurosurg 64: 724–730
46. Lasjaunias P, Berenstein A (1987) Endovascular treatment of craniofacial lesions. Springer, Berlin Heidelberg New York Tokyo (Surgical neuroangiography, vol 2)
47. Lasjaunias P, Burrows P, Planet C (1986) Developmental venous anomalies (DVA): The so-called venous angioma. Neurosurg Rev 9: 223–244
48. Lasjaunias P, TerBrugge K, Lopez Ibor L, Chiu M, Flodmark O, Chuang S, Goasguen J (1987) The role of dural anomalies in Vein of Galen aneurysms: Report of six cases and review of the literature. AJNR 8: 185–192
49. Latchaw R, Gold L (1979) Polyvinyl foam embolization of vascular and neoplastic lesions of the head, neck, and spine. Neuroradiology 131: 669–679
50. Leavitt DD, Gibbs FA Jr, Heilbrun MP, Moeller JH, Takach GA Jr (1991) Dynamic field shaping to optimize stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 21: 1247–1255

51. Leblanc R, Levesque M, Comair Y, Ethier R (1987) Magnetic resonance imaging of cerebral arteriovenous malformations. Neurosurgery 21: 15–20
52. Lee BCP, Herzberg L, Zimmerman RD, *et al* (1985) MR imaging of cerebral vascular malformations. Am J Neuroradiol 6: 863–870
53. Leksell D (1951) The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102: 316–319
54. Lemme-Plaghos L, Kucharczyk W, Brant-Zawadzki M *et al* (1986) MR imaging of angiographically occult vascular malformation. Am J Neuoradiol 7: 217–222
55. Lobato RD, Perez C, Rivas JJ, Cordobes F (1988) Clinical, radiological, and pathological spectrum of angiographically occult intracranial vascular malformations. J Neurosurg 68: 518–531
56. Luessenhop AJ, Gennarelli TA (1977) Anatomical grading of supratentorial arteriovenous malformations for determining operability. Neurosurgery 1: 30–35
57. Luessenhop AJ, Presper JH (1975) Surgical embolization of cerebral arteriovenous malformations through internal carotid and vertebral arteries: Long-term results. J Neurosurg 42: 443–451
58. Luessenhop AJ, Spence WT (1960) Artificial embolization of cerebral arteries: Report of use in a case of arteriovenous malformation. JAMA 172: 1153–1155
59. Lunsford LD, Flickinger J, Lindner G *et al* (1989) Stereotactic radiosurgery of the brain using the first United States 201 cobalt-60 source gamma knife. Neurosurgery 24: 151–159
60. Lunsford LD, Kondziolka D, Flickinger JC, Bissonette DJ, *et al* (1991) Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 75: 512–524
61. Malis LI (1982) Arteriovenous malformations of the brain. In: Youmans JR (ed) Neurological surgery. Saunders, Philadelphia, pp 1786–1806
62. Marks MP, Delapaz RL, Fabrikant Jl *et al* (1988) Intracranial vascular malformations: Imaging of charged-particle radiosurgery, Part II: Complications. Radiology 168: 457–462
63. Marks MP, Delapaz RL, Fabrikant JI, Frankel KA, Phillips MH, Levy RP, Enzmann (1988) Intracranial vascular malformations: imaging of charged-particle radiosurgery. Radiology 168: 447–455
64. Michels LG, Beaverson JR, Winter J (1977) Computed tomography of cerebral venous angiomas. J Comput Assist Tomogr 1: 149–154
65. Mingrino S (1978) Supratentorial arteriovenous malformations of the brain. Springer, Wien New York (Advances and technical standards in neurosurgery, vol 5, pp 93–123)
66. Morello G, Borghi GP (1973) Cerebral angiomas. A report of 154 personal cases and a comparison between the results of surgical excision and conservative management. Acta Neurochir (Wien) 28: 135–155
67. New PJ, Ojemann RG, Davis KR *et al* (1986) MR and CT of occult vascular malformations of the brain. AJNR 7: 771–779
68. Noorbehesht B, Fabrikant JI, Enzmann (1987) Size determination of supratentorial arteriovenous malformation by MR, CT, and angio. Neuroradiology 29: 512–518

69. Norlen G (1949) Arteriovenous aneurysm of the brain: Report of ten cases of total removal of the lesion. J Neurosurg 6: 475–494
70. Numaguchi Y, Kishikawa T, Fukui M, Sawada K, Kitamuza K, Matsuura K, Russell WJ (1979) Prolonged injection angiography for diagnosis of intracranial cavernous hemangiomas. Radiology 131: 137–138
71. O'Brien PF, Gillies BA, Schwartz M *et al* (1991) Radiosurgery with unflattened 6-MV photon beams. Medical Physics 18(3): 519–521
72. Ogilvy C (1990) Radiation therapy for arteriovenous malformations: a review. Neurosurgery 26: 725–735
73. Olivecrona H, Riives J (1948) Arteriovenous aneurysms of the brain. Arch Neurol Psychiat 59: 567–602
74. Olivecrona H, Ladenheim J (1957) Congenital arteriovenous aneurysms of the carotid and vertebral arterial system. Springer, Berlin Göttingen Heidelberg
75. Olson E, Gilmor RL, Richmond B (1984) Cerebral venous angiomas. Radiology 151: 97–104
76. Ondra SL, Troupp H, George ED, Schwab K (1990) The natural history of symptomatic arteriovenous malformations of the brain: A 24-year follow-up assessment. J Neurosurg 73: 387–391
77. Perret G, Nishioka H (1966) Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section VI: Arteriovenous malformations. An analysis of 545 cases of cranio-cerebral arteriovenous malformations and fistulae reported to the Cooperative Study. J Neurosurg 25: 467–490
78. Pertuiset B, Ancri D, Kinuta Y, Haisa T, Bordi L, Lin C, Maldi M, Arthuis F (1991) Classification of supratentorial arteriovenous malformations. A score system for evaluation of operability and surgical strategy based on an analysis of 66 cases. Acta Neurochir 110: 6–16
79. Pertuiset BD, Ancri D, Sichez JP, Chauvin M, Guilly E, Metzger J, Gardeur D, Bassett JY (1983) Radical surgery in cerebral AVM – tactical procedures based upon hemodynamic factors. Springer, Wien New York (Advances and technical standards in neurosurgery, vol 10, pp 81–143)
80. Pia HW (1975) The indications and contraindications for treatment or assessment. In: Pia AE, Gleave JRW, Grote E, Zierski J (eds) Cerebral angiomas: advances in diagnosis and therapy. Springer, Berlin Heidelberg New York, pp 1–8
81. Picard L, Moret J (1990) Embolization of corpus collosal AVMs using NBCA. 10th Annual Meeting of the Working Group in Interventional Neuroradiology, Val D'Isere, France, January 1990
82. Picard L, Moret J, Lepoire J (1984) Endovascular treatment of intracerebral arteriovenous angiomas. J Neuroradiol 11: 9–28
83. Podgorsak E, Oliver A, Pla M, Lefebvre P, Hazel J (1988) Dynamic stereotactic radiosurgery. Int J Radiation Oncol Biol Phys 14: 115–126
84. Pool JL, Potts DG (1965) Aneurysms and arteriovenous anomalies of the brain. Diagnosis and treatment. Hoeker Medical Division Harper Row, New York
85. Pressman BD, Gilbert GE, Davis DO (1975) Computerized transverse tomography of vascular lesions of the brain: II. Aneurysms. Am J Roentgenol Radium Ther Nucl Med 124: 215–219

86. Purdy P, Samson D, Batjer H, Risser R (1990) Preoperative embolization of cerebral arteriovenous malformations with polyvinyl alcohol particles: experience in 51 adults. AJNR 11: 501–510
87. Ramina R, Ingunza W, Vonofakos D (1980) Cystic cerebral cavernous angioma with dense calcification. J Neurosurg 52: 259–262
88. Rao V, Mandalam K, Gupta A, Kumar S, Joseph S (1989) Dissolution of isobutyl-2-cyanoacrylate on long-term follow-up. AJNR 10: 135–141
89. Rapacki TFX, Brantley MJ, Furlow TW, Geyer CA, Toro VE, George ED (1990) Heterogeneity of cerebral cavernous hemangiomas diagnosed by MR imaging. J Comput Assist Tomogr 14: 18–25
90. Romodanov A, Zozulic Y, Shcheglow V (1979) Balloon catheter occlusion of feeding vessels of arteriovenous malformation. Zentralbl Neurochir 40: 21–25
91. Russell DS, Rubinstein LJ (1977) Pathology of tumours of the nervous system, 4th edn. E Arnold, Edinburgh, pp 126–145
92. Saunders W, Winston K, Siddon R, Svensson G, Kijewski P, Rice R, Hansen J, Barth N (1988) Radiosurgery for arteriovenous malformations of the brain using a standard linear accelerator: Rationale and technique. Int J Radiol Oncol Biol Phys 15: 441–447
93. Savoiardo M, Strada L, Passerini A (1983) Intracranial cavernous hemangiomas: Neuroradiologic review of 36 operated cases. Am J Neuroradiol 4: 945–950
94. Scott JA, Augustyn GT, Gilmor RL, Measley J, Olson EW (1985) Magnetic resonance imaging of a venous angioma. AJNR 6: 284–286
95. Serbinenko FA (1979) Six hundred endovascular neurosurgical procedures in vascular pathology: A ten-years experience. Acta Neurochir [Suppl] 28: 310–311
96. Smith HJ, Strother CM, Kikuchi Y, Duff T, Ramirez L, Merless A, Toutant S (1988) MR imaging in the management of supratentorial intracranial AVMs. AJNR 9: 225–235
97. Spetzler R, Martin N, Carter LP, Flom R, Raudzens P, Wilkinson E (1987) Surgical management of large AVM's by staged embolization and operative excision. J Neurosurg 67: 17–28
98. Spetzler RF, Martin NA (1986) A proposed grading system for arteriovenous malformations. J Neurosurg 65: 476–483
99. Spiegel S, Vinuela F, Goldwasser J, Fox AJ, Pelz D (1986) Adjusting the polymerization time of isobutyl 2-cyanoacrylate. AJNR 7: 109–112
100. Stein BM (1984) Arteriovenous malformations of the cerebral convexities. In: Wilson CB, Stein BM (eds) Intracranial arteriovenous malformations. Williams & Wilkins, Baltimore, pp 156–183
101. Stein BM, Wolpert SM (1980) Arteriovenous malformations of the brain. II. Current concepts and treatment. Arch Neurol 37: 69–75
102. Steinberg G, Fabrikant J, Marks M, Levy R, Frankel K, Phillips M, Shuer L, Silverberg G (1990) Stereotactic heavy-charged-particle Bragg-Peak radiation for intracranial arteriovenous malformations. N Engl J Med 323: 96–101
103. Steiner L (1984) Treatment of arteriovenous malformations by radiosurgery. In: Wilson CB, Stein BM (eds) Intracranial arteriovenous malformations. Williams & Wilkins, Baltimore, pp 295–313

104. Steiner L (1984) Radiosurgery in cerebral arteriovenous malformations. In: Fein JM, Flamm ES (eds) Cerebrovascular surgery, vol 4. Springer, New York, pp 1161–1215
105. Taki W, Yonekawa Y, Iwata H, Uno A, Yamashito K, Ameniya H (1990) A new liquid material for embolization of arteriovenous malformations. AJNR 11: 163–168
106. TerBrugge KG, Scotti G, Ethier R, Melancon D, Tchang S, Milner C (1977) Computed tomography in intracranial arteriovenous malformations. Radiology 122: 703–705
107. Valavanis A, Wellauer J, Yaşargil MG (1983) The radiological diagnosis of cerebral venous angioma: Cerebral angiography and computed tomography. Neuroradiology 24: 193–199
108. Valavanis A, Schubinger D, Wichmann W (1986) Classification of brain arteriovenous malformation nidus by magnetic resonance imaging. Acta Radiol 369: 86–89
109. Wada J, Rasmussen T (1960) Intracarotid injection of sodium amytal for lateralization of cerebral speech dominance. J Neurosurg 17: 266–282
110. Wakai S, Ueda Y, Inoh S, Naggai M (1985) Angiographically occult angiomas. A report of thirteen cases with an analysis of the cases documented in the literature. Neurosurgery 17: 549–556
111. Walton L, Bomford CK, Ramsden D (1987) The Sheffield stereotactic radiosurgery unit: Physical characteristics and principles of operation. Br J Radiol 60: 897–906
112. Weinstein MC, Fineberg HV (eds) (1980) Clinical decision analysis. Saunders, Philadelphia
113. Wendling LR, Moore JS, Kieffer SA, Goldberg HI, Latchow RE (1976) Intracerebral venous angioma. Radiology 119: 141–147
114. Wilkins RH (1985) Natural history of intracranial vascular malformations: a review. Neurosurgery 16: 421–430
115. Willinsky R, Lasjaunias P, TerBrugge K, Pruvost P (1988) Brain arteriovenous malformations: Analysis of angio-architecture in relationship to hemorrhage. J Neuroradiol 15: 225–237
116. Willinsky R, Lasjaunias P, Comoy J, Pruvost P (1988) Cerebral micro arteriovenous malformations (mAVMs). Acta Neurochir (Wien) 91: 37–41
117. Winston K, Lutz W (1988) Linear accelerator as a neurosurgical tool for stereotactic radiosurgery. Neurosurgery 22: 454–464
118. Wolpert S, Barnett F, Prager R (1982) Benefits of embolization without surgery for cerebral arteriovenous malformations. AJNR 138: 99–102
119. Yaşargil MG (1988) AVM of the brain, clinical considerations, general and specific operative techniques, surgical results, non-operative cases, cavernous and venous angiomas, neuroanaesthesia, vol IIIB: Microneurosurgery. Thieme, New York
120. Yaşargil MG (1987) AVM of the brain, history, embryology, pathological considerations, hemodynamics, diagnostic studies, microsurgical anatomy, vol IIIA: Microneurosurgery. Thieme, New York
121. Yaşargil MG (1969) Operations on intracranial arteriovenous malformations. In: Yaşargil MG (ed) Microsurgery applied to neurosurgery. Academic Press, New York, pp 143–148

122. Yaşargil MG (1971) Microneurosurgical approach to the cerebrovascular diseases. In: Present limits of neurosurgery. Proc 4th European Congress of Neurosurgery. Avicenum, Prague
123. Yaşargil MG, Antic J, Laciga R, Jain K, Boon SC (1976) Arteriovenous malformations of vein of Galen. Microsurgical treatment. Surg Neurol 6: 195–200
124. Yaşargil MG, Jain KK, Antic J, Laciga R (1976) Arteriovenous malformations of the splenum of the corpus callosum: microsurgical treatment. Surg Neurol 5: 5–14
125. Yaşargil MG, Jain KK, Antic J, Laciga R, Kletter G (1976) Arteriovenous malformations of the anterior and middle portions of the corpus callosum: microsurgical treatment. Surg Neurol 5: 67–80

Note added in proof

Note that the classification of arteriovenous malformations is still in dispute, a grading system produced by Spetzler and one produced by a Committee of the Federation of Neurosurgical Societies exists but general agreement on classification has not yet been reached.

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