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Preface

This book is the first in a series of topical reviews in neurosurgery. The subjects and authors for this volume owe their place largely to the fact that they first came to mind when I jotted down a list on being asked to edit the series, and I am grateful to the contributors for agreeing to write.

There is always a dilemma whether to choose contributions that are likely to have lasting value rather than ones that describe the latest advances, soon to be out of date. In this series both will be presented. Brian Jennett's chapter is, I hope, an example of the former and is revelant to all that comes thereafter. In contrast, Brian Kendall's chapter on computed tomography will inevitably be the victim of further advances: nevertheless, I believe it gives a valuable survey of the current position.

The value of vascular surgery in neurological disorders is controversial – some would say too controversial to be left to surgeons. I have therefore chosen physicians, Michael Harrison and John Marshall, who have well-known interests in cerebrovascular disease to write chapters on carotid endarterectomy and extracranial-intracranial anastomosis.

David Thomas has marshalled the essential facts about the chemotherapy of gliomas and Norman Guthkelch has contributed a scholarly article on the aetiology of chronic subdural haematoma.

Professor Lindsay Symon enters the lists as a supporter of radical surgery in the treatment of craniopharyngiomas, and my own views about syringomyelia in the final chapter may be considered equally controversial.

To edit these chapters has been a pleasure and an education: I hope the reader's experience will be the same.

J. M. R. E.

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Bryan Jennett

1 Efficacy, Efficiency and Adequacy in Neurosurgery

Several aspects of modern medicine which are increasingly provoking debate in society present a particular challenge to neurosurgeons. One is the suspicion that high technology medicine is apt to indulge in elaborate and expensive investigative and therapeutic procedures without taking due account of the balance between the risks, costs and benefits. Another is the concern expressed about ethical and moral issues associated with extraordinary efforts to prolong life in the face of major organ damage – issues that have a sharpened significance when it is the brain that is damaged. Then there are the political and administrative trends towards greater self-sufficiency in smaller, locally based units of health care which run contrary to the concept of regionalization for tertiary care specialists. Coupled with this is the switch in emphasis from acute medicine to chronic care, which is reflected in reassessment of the allocation of resources, including the numbers of beds and of staff that should be provided in different specialties.

Britain has considerably fewer neurosurgeons than most developed countries, but that does not ensure that neurosurgeons will be protected from pressure to examine and justify both the nature and the scale of their activities. Unless we are prepared to discuss these matters amongst ourselves, there will be no shortage of others willing (even anxious) to do it for us – and then to try to tell us what we should be doing. For these reasons it seems prudent and timely, as well as scientifically interesting, to consider the efficacy and appropriateness of what neurosurgeons do, and the adequacy and efficiency of the service that they provide.

The optimum utilization of existing resources requires both that the acivities carried out are effective, and that these effective procedures are efficiently used. This distinction between effectiveness and efficiency formed the title of Cochrane's classic essay [1]. *Effectiveness* is concerned with whether a particular method of management (investigation or treatment) is effective; that is to say – does it work? *Efficiency* is to do with such factors as the intensity of use of expensive facilities such as beds, operating theatres and CT scanners. *Adequacy* is different again, being concerned with whether enough facilities are provided to ensure that (if optimally used) there is reasonable access for most patients in need.

Efficiency is essentially uncontroversial; it is difficult to imagine the neurosurgeon who would defend inefficient utilization of his resources, although perhaps not enough of us are concerned to discover how efficient

we are, or whether we could improve our performance. Not so with efficacy and adequacy. These provoke profound disagreements between neurosurgeons, as they do among all specialists. A number of specialties, particularly newly emerging ones, have produced 'statements of case' for their activities, based on evidence about the frequency of occurrence of conditions within their field of interest, about what investigations and therapies are currently available and about the manpower and facilities necessary to provide an adequate service. Such statements are usually stronger on dogma than on data, particularly when it comes to efficacy. North American neurosurgeons have done this during the past decade, and it may be salutary to conclude this essay by reference to the views of our cousins across the Atlantic – which include some robust comments about the supposed shortcomings of neurosurgery in Britain.

EFFICIENCY

A fully staffed bed in an acute hospital is one of the most expensive resources over the utilization of which clinicians have direct control; in a specialized unit a bed is even more costly. One measure of efficiency is the number of patients admitted each year to each bed; this depends on duration of stay and on turnover time between one patient and the next. This is a more reliable index than bed occupancy – a ward could remain fully occupied with very little patient throughput. An attractive aspect of these measures is that they can be calculated from the routinely collected statistics on hospital discharges; these are available for all cases in Scotland [2] and for a 10 per cent sample in England and Wales [3]. These have revealed wide discrepancies between the numbers and the utilization of beds in different areas of Britain. One result of this finding has been the development of strict norms for acute hospital bed numbers, on a population basis. The effect of this policy in many places is to reduce acute hospital beds; this is especially so in large cities, which are depopulating – and that is where most British neurosurgical units are situated. As most of the rehousing of people to the outskirts of cities leaves them still in the same neurosurgical catchment area, neurosurgeons may reasonably claim to be spared from most reductions in beds which are based on these population movements. But with the emphasis on devolving health service administration (and financing) to a more local level, there may be no effective authority left to listen to the case for expensive regional services, which are necessarily provided by one health authority for many patients who are the primary responsibility of other authorities.

However, neurosurgeons cannot expect to claim immunity from reduction in their facilities unless they can also show that they are using their resources as efficiently as possible. There are wide variations in the number of neurosurgical beds (per million population) in different regions of

Britain, which partly reflect local policies about the kinds of patients admitted, in particular the proportion of head-injured patients in its catchment area for which a neurosurgical unit accepts responsibility. But they also reflect differences in the level of utilization of the beds that are available, a feature that is common to all specialties. Indeed the discovery that there are such marked differences in the duration of stay for patients with the same condition, between regions and hospitals, and even between wards within the same hospital, has led clinicians in several specialties to review their practices; one result has been a considerable intensification of activity in acute hospital medicine. Reduced stay can be achieved by doing more investigations on an outpatient basis; by careful programming of admissions in order to reduce time spent waiting in hospital for further tests or for operation and by earlier discharge. A review of the utilization of beds in general, orthopaedic and urological surgery in Glasgow showed that 40 per cent of patients in acute surgical beds had no longer any need of the particular facilities which these offered [4]. These patients were still there because of difficulties in moving them to more appropriate (and less expensive) accommodation, not because the surgeons wanted them to stay; many of these patients were elderly.

Because neurosurgeons in Europe largely provide tertiary care for patients who come from other hospitals, the utilization of their beds can be made more efficient by the return of patients to their original hospital once they no longer require the specialized facilities of a neurosurgical unit. Such an arrangement may indeed have to be agreed in advance with the sending hospitals as a condition of the neurosurgical unit's capability to respond rapidly to requests for the urgent transfer of new patients. Another advantage is that relatives often appreciate the return of ill members of their family to a hospital nearer home. Possible disadvantages of such a policy are that some patients may suffer from lack of continuity of care; for example, staff who inherit patients second-hand may show less concern for their rehabilitation than would those who were concerned with the acute stage of their illness. Moreover, the job satisfaction of doctors, nurses and other therapists in the neurosurgical unit may be lessened if many patients are sent away as soon as they begin to recover, and unless follow-up clinics are the rule in the unit the staff may never know the ultimate outcome of their management in the acute stage. Although apparently making for more efficient use of neurosurgical beds and facilities, such a policy inevitably results in more of the patients in the neurosurgical unit being highly dependent on nurses; consequently a higher staffing ratio is required than if patients remained longer.

EFFICACY (EFFECTIVENESS)

This refers to whether methods achieve their objective, which is usually diagnostic or therapeutic. Most often this refers to specific techniques or

procedures. In recent years several disciplines have recognized that unnecessary investigations are frequently employed; and that some treatment methods acclaimed as significantly effective prove on rigorous analysis to be no better than simpler (and usually less expensive) methods for most cases, and to be justified for only a small proportion of patients. If there are too many patients undergoing special investigation or therapy who are either not sufficiently serious to need them, or too seriously affected to benefit, then the yield from their application will be low. It might then be said that the efficacy of a neurosurgical service was less than it might have been had its resources been more appropriately deployed. In this way it might be possible to consider the effectiveness of neurosurgery in a region, or even in a country as a whole, in coping with broad problems such as head injury or subarachnoid haemorrhage.

ASSESSMENT OF EFFICIENCY AND EFFICACY

This depends on the systematic accumulation of data. Information needs to be collected at several different levels in order to discover answers to three separate questions. First, there is 'audit' of the work of a neurosurgical unit – how many patients are dealt with each year, under different diagnostic categories; how have they been investigated and treated; what has the outcome been? Secondly, there is collection of data about patients with one particular condition in order to determine the natural history and to identify factors that influence prognosis. Thirdly, there are trials of intervention, planned to discover the efficacy of one method of management as compared either with an alternative technique or with the natural history of the untreated condition.

Is neurosurgery any better able to refute charges of over-investigation and over-treatment than other acute hospital specialties? Does the neurosurgeon face special difficulties if he wishes to assess the effectiveness of what he does, organizationally or to individual patients? Particularly when it comes to comparing the efficacy of alternative methods of management. I believe that neurosurgeons do face special problems. These relate to accumulating sufficient numbers in a low volume specialty; to practical conditions in dealing with many patients with conditions requiring rapid decision-making in life-threatening situations; and to ethical considerations associated with patients unable to give informed consent because they are confused or unconscious.

The Question of Numbers

Most of the conditions dealt with by neurosurgeons are relatively much less common than, say, cancer of the breast or myocardial infarction – two conditions about which controversy continues in spite of numerous

Table 1.1 Effect of Sample Size on Significance of Change in Frequency of an Event (e.g. Death) in Different Patient Series

Sample size in new series	*Range of variation (from frequency in 1000 series) that would* not *be significantly different (at $P < 0{\cdot}05$)* Frequency of event in 1000 cases (20%)	(50%)
20	5–35	30–70
50	10–30	36–64
100	12–28	40–60
200	14–26	42–58
1000	17–23	46–54

large therapeutic trials. For the neurosurgeon it is difficult to accumulate enough patients of the same kind in a reasonable time for a valid comparative investigation. Studies that span many years may become invalid because of changes in practice other than those under scrutiny. Consider the impact on neurosurgical practice in the past 15–20 years of the operating microscope, of the CT scanner, of developments in neuro-anaesthesia and of the use of corticosteroids. If the period of data collection for a study spanned the introduction of one or more of these innovations, then the results may be difficult to interpret.

Yet the accumulation of sufficient numbers is crucial. The most common reason for reaching false conclusions after the completion of an otherwise well-designed study is that the sample size has been too small. The significance of a difference between two series of patients is governed by a simple mathematical concept, the binomial theorem. Suppose that severe head injury has a death rate of 50 per cent with conventional treatment, and that a new therapy is producing a reduction of mortality, then the number of patients that would have to be treated before improvement could be demonstrated at a given level of statistical significance can be calculated (Table 1.1). If the degree of benefit were less than this, or if a higher confidence limit than $P < 0{\cdot}05$ were demanded, then the numbers required would be greater. If intracranial/extracranial bypass reduces the risk of recurrent stroke by 50 per cent, it is estimated that 1000 cases need to be followed for 5 years, in order to show this effect at $P < 0{\cdot}05$ [5].

To collect enough patients in a reasonably short period of time is difficult in any one centre, even in the large regional clinics in Europe. Almost inevitably therefore such studies depend on collecting from several centres. As soon as more than one place is involved the problem arises of ensuring that methods of assessment and recording are sufficiently standardized to be reliable. This is more difficult than might be expected by clinicians who have never submitted to the discipline and tedium of a well-conducted intercentre study. But the feasibility of setting up collaborative data col-

lection in several centres, and even crossing language barriers, has been demonstrated by the three countries study of severe head injuries [6, 7].

That study was concerned with collection of data about head-injured patients of a certain severity; it did not seek to influence management in any way. It therefore represents the simplest form of collaborative study. At the outset of this study there was no generally accepted classification of the severity of brain damage, and means of assessing this in the early stages after injury had to be devised, as well as ways of monitoring the duration of various levels of brain dysfunction, and of classifying the outcome of survivors months or years after injury. It was necessary to construct a standardized set of definitions which had to be simple and reliable, as indicated by a low rate of interobserver variation [8]; and they had to be accepted as practical by clinicians in different centres. Agreement on a common clinical vocabulary was achieved only after a number of visits by participants to each other's units. Some of the methods evolved for this study, such as the Glasgow Coma Scale [9] and the Glasgow Outcome Scale [10], have now been widely adopted for recording clinical data about patients with recent brain damage, whether traumatic or not. Even so, we consider that when a new centre is added to the head injury data bank an introductory, educational process is necessary in order to be sure that there is uniformity of standards. Once a sizeable series of patients has been collected in a new centre (say 50 patients) it is then possible to analyse the internal consistency of data as an indicator of the quality of the data collection.

The Question of Comparing Patients

Next to inadequate numbers, the most likely reason for reaching false conclusions from clinical studies is that patients have not been sufficiently closely matched. With a condition as diverse as head injury, there is no prospect of having two identical series of patients. Matching means being sufficiently similar to ensure that the expected outcome in two series will correspond, within defined limits. When cases come from more than one centre there may be differences related to local geographical or organizational factors. This may affect the mix of patients in regard to cause, or time of arrival after injury or the frequency of multiple injuries. These is turn may determine the proportion of patients with intracranial haematoma, as distinct from diffuse primary injury. If these differences are indeed marked it may be necessary to limit comparisons between centres to certain subsets of patients in respect of these variables.

Given that patients are reasonably comparable in these ways it is then necessary to ensure similarity in respect of factors influencing outcome, the chief of which are age and severity of injury. Even considering only these two variables it is easy to be misled into believing that cases are comparable when they are not. For example, the mean age of two series of

Table 1.2 Effect of Age Distribution on Expected Mortality in Three Series of Severe Head-injured Patients all with Same Mean Age

Age group	*Mortality** *(%)*	*Proportion of patients* Series I (%)	Series II† (%)	Series III (%)
10–29 yr	35	62.5	50	25
30–49 yr	40	0	25	75
50–69 yr	80	37.5	25	0
Mean age for series		35 yr	35 yr	35 yr
Expected mortality for series		52%	48%	38%

*Estimates from data bank.
†Approximates to 1000 cases in data bank.

patients may be the same even though their age distribution is quite different. This latter discrepancy can make for a higher expected mortality in one series than the other, assuming similar severity of injury (Table 1.2).

The assessment of severity in the early stages after injury allows ample opportunity for error. If the level of brain dysfunction is recorded very soon after injury, especially if before initial resuscitation has been completed, an overestimate of the severity of brain damage is likely. Once the airway is established, blood replaced and systemic arterial pressure restored, the previously flaccid patient with non-reacting pupils may begin to move and the pupils to respond to light. The frequency with which features indicative of severe brain damage were recorded in the first 24 hours after injury was almost twice as great when based on the *worst* rather than the *best* state during this period (Table 1.3). Moreover, children are more likely to show a rapid recovery from an initially severe state than are adults.

When both age and severity of injury are considered together there is even more scope for mistaken similarity, as the contrived example in Table 1.4 indicates. Both these series of patients had an equal number of more

Table 1.3 Signs of Severe Brain Dysfunction in First 24 Hours: Difference in Frequency of Occurrence when Based on 'Best' or 'Worst' State

Severity sign	*Frequency as* best *state (%)*	*Frequency as* worst *state (%)*
Coma sum 3/4	19	49
Non-reacting pupils	23	44
Absent/impaired eye movements	23	34
Abnormal motor response pattern	41	62

Table 1.4 Mortality of Two Series with Different Distribution of Age and Coma Scores

No. of patients	*Age (yr)*	*Coma score (best in 1st day)*	Subset (%)	*Mortality** Whole series
Series A				
100	0–19	3–4	66	80% mortality
100	⩾ 60	5–7	94	
Series B				
100	0–19	5–7	31	63% mortality
100	⩾ 60	3–4	96	

Each series has half its patients in youngest and oldest age groups, and half in each coma score category.
*Estimates from data bank.

and less severely injured patients, and of younger and older patients, but because the younger patients were more severely injured in one series than the other the expected outcome for the two series was quite different.

Once a large enough data bank has been established from which to derive a prognostic model for predicting outcome in individual patients, it is possible to take account of the complex interaction of a number of variables [7, 11, 12]. In this way the outcome distribution in two or more series of patients could be predicted, and this would be a more reliable way of demonstrating similarity than taking account of a number of separate factors. This could be useful in circumventing some of the problems associated with prospective trials of therapy, as is explained below.

The Question of Comparing Therapies

When the outcome of one series of patients is more favourable than that of another the claim is often made that this reflects the superior treatment of the series that did better. Before accepting such an explanation an active search for sources of bias should be conducted. Is it certain that the cases that made a better recovery than expected were not less severe, or younger? Is it certain that the assessment of recovery in survivors was not more generous, or that more of the deaths in those treated by the supposed superior method were not explained away as due to medical or extracranial causes? Even if these factors are taken into account, there is still the possibility of bias leading to the tendency to choose a new or more favoured treatment for those cases that the clinician senses (perhaps without realizing it) have a better prospect for recovery; bias may also result from the total care of patients being more diligent and more active when a new method is under review.

It was to counteract these various sources of bias that the randomized

controlled trial was introduced, and it has an established place in testing the efficacy of new drugs. In conditions associated with a high mortality rate, however, doubts are sometimes expressed about the propriety of using randomized methods, especially those which employ a placebo or no treatment group. For example, the inclusion of a no-treatment group of patients in a recent trial of therapy for herpes simplex encephalitis has been severely criticized. Its consistently high mortality until now, combined with the small number of cases available for testing treatment, made a randomized control trial inappropriate. In any event, the question asked of a new therapy is not whether it has *any* effect (compared with natural history) but whether its benefit is greater than what is already available – 'best conventional treatment'. Randomized control trials also present formidable problems in a condition such as severe head injury, where rapid decisions have to be made about patients in coma who cannot give informed consent, and whose relatives may not yet know that he has had an accident.

Trials of efficacy which involve surgical procedures present other difficulties. What of the experience, special expertise and skills, and the current practice, of the surgeons in different centres contributing to a study? In fact there is a good deal of evidence that factors other than personal surgical skill have a dominating influence on outcome after many types of surgery – doing the right operation on the right patient at the right time is the key to success in most surgery. In any event, if trials are to reveal which treatment should be used, for common conditions at least, they should show what can be achieved in *average* surgical hands. It is therefore proper that the trial should encompass a range of skills and of centres, although there is a natural tendency for such studies to be carried out in larger academically orientated units. A recent book review included these comments: 'This book is written by some of the world's most experienced neurosurgeons . . . with experience in their own area far beyond what can be expected even in a large regional neurosurgical unit. Could the result reported have been obtained by the average neurosurgeons for whom this book was written?' [13]. Various technical aspects of surgical trials have recently been reviewed [14].

Yet another problem with surgical trials is that surgeons often find it difficult to relinquish their role either as decision-makers, or as wielders of the healing knife. With elective procedures they are often encouraged in this both by patients who want surgery done, and by referring physicians who expect action rather than arbitration. Uncritical enthusiasm for the performance of extracranial-intracranial anastomosis as a means of preventing recurrent stroke is threatening the successful completion of the three countries trial set up with such care and at such expense [5]. Such trials always give the clinician an escape clause, allowing him to withdraw any patient whom he (or the referring doctor) declines to have randomized. In some surgical trials so many patients are put in this category that

doubt is cast on conclusions drawn from the selected group of patients who are put into the trial. Sometimes a smokescreen of ethics is put up ('it is unethical to withold this treatment' – even though its efficacy is unproved); at other times there may be concern about the supposed good name of an institution ('patients came to this clinic to be treated, not to be trialled' – even if the treatment given is not effective).

For these and other reasons there has been a reaction against random control trials, and a renewed interest in the use of historical controls [15, 16]. This makes the purist prickle, but that is because he usually thinks of historical controls as the last 100 cases treated prior to the introduction of a new method, or even the last 100 cases reported in the literature. These are indeed often suspect, and probably valid only if a dramatic effect is sought for a condition previously almost always fatal, as with the introduction of penicillin for sepsis.

Data Banks and Prediction as Tools for Therapeutic Trials

It seems likely that the evolution of carefully assembled data banks, with standardized methods of assessing patients before and after treatment, may open up new ways of testing efficacy which could obviate some of these difficulties. They can provide what may be called prospective, historical controls; perhaps a better term would be simultaneous or contemporary, historical controls.

In the three countries data bank study of severe head injuries there was a wide variation in the frequency with which various treatments were used, but the distribution of outcomes was similar in those centres which used certain methods more frequently and those which did not [5]; and a similar finding has been reported for non-traumatic coma, when the outcome for an American series of patients which had been very intensively investigated and treated was no better than for a British series which had been managed more conservatively [17].

In the head injury study some methods of treatment were used more often in patients who were more severely affected. However, a statistical analysis was used which made allowance for severity of brain damage and for the patient's age; this indicated that the use of certain therapies (e.g. steroids) had not apparently had any marked effect on outcome. This was done both by comparing the outcome in two matched 'series' derived randomly from within the data bank of 1000 cases, and also by making predictions about the outcome in a group of patients who had been treated by a certain method, using as a training a series of patients who had *not* been so treated [18].

This prediction technique can also be used to compare the influence of another regimen of treatment in another centre, by making comparisons with cases in the data bank which had had conventional treatment. This was done for the San Francisco General Hospital, where a systematic and

very intensive regimen has been used for treating severely head-injured patients [19]. Over some 2 years all patients were assessed prospectively, according to the data bank system for calculating severity, progress and outcome. Data from these 180 patients were processed in Glasgow, where predictions were then made as to how these San Francisco patients would have fared had they been treated in Glasgow. In the event, the outcomes 6 months after injury in San Francisco were very largely as predicted; this does not preclude the possibility that some of the survivors in San Francisco may not eventually be shown to have recovered more rapidly or more completely than matched cases in Glasgow, nor that there may not be a subset of patients who would benefit from the San Francisco regimen. That too must await further study.

This raises another problem when testing the efficacy of a new method of treating a condition with a high mortality. In a series of such patients there are always some whose condition is so advanced that it is extremely unlikely that any therapy will be effective; and there will be some with a reasonable prospect of recovery with only conventional treatment. A new method of treatment is likely to be effective in improving outcome only in the patients in the middle range of severity. If applied to a series as a whole this benefit may be submerged by the large number of patients whose outcome cannot be affected. A prediction system makes it possible to identify the patients in these different categories, and it would then be practical to conduct a trial on a subset of 'middle severity' patients. This would be likely to show a beneficial effect (if there was one) with fewer patients than if cases of all severities were included.

Neurosurgery is not alone in being slow to adopt formal methods of assessment of treatment. The very small proportion of patients with solid, malignant tumours who are entered into controlled trials in the UK has been described as a disgrace [20]. It is 4 per cent for brain tumours compared with 25 per cent for leukaemia of childhood [21]. It was pointed out that this was particularly difficult to condone because the organization of medicine in Britain should made it easier to collaborate in such trials than in many countries, because of the unified hospital system and the relatively small proportion of patients treated privately. Certainly the relatively large numbers of primary brain tumours treated by the larger British neurosurgical units could make them valuable contributors to the various trials of multi-modality treatment (surgery, radiation and chemotherapy) currently being carried out in various countries. It seems likely that for trials of this kind to recruit sufficient numbers in a reasonable time period requires a catchment population of at least 10 million. For less common tumours there might be a case for referral of the patients to a limited number of centres which would develop special expertise in their management. This was suggested several years ago for craniopharyngioma by Bartlett [22], but his plea has so far fallen on deaf ears.

ADEQUACY

There is a wide variation in the neurosurgical facilities provided for similar catchment populations in different parts of Britain, whereas more uniformity might have been expected considering that all are part of the same central authority. The pattern of work also varies, in particular in the proportion of patients with conditions that in some places are looked after by neurosurgeons but elsewhere by other specialists (Table 1.5). Such differences seldom reflect a planned response to a declared need or demand, but rather the bias of neurosurgeons and other specialists locally – perhaps those of a previous generation who influenced the development of services. Such arrangements do not always result in optimal care, especially when one specialty is unaware of recent technical developments in another, and therefore continues to use outmoded techniques.

Table 1.5 Activities Shared with other Specialists

Head injuries	Primary surgeons/anaesthetists
Spinal injuries Disc disease	Orthopaedic surgeons
Intensive care for coma Lesion making for pain	Anaesthetists
Pituitary/acoustic tumours	Otolaryngologists
Craniofacial orbital tumours/ deformities	Ophthalmologists/Plastic maxillo-facial
Carotid endarterectomy/ extracranial–intracranial anastomosis	Vascular surgeons
Hydrocephalus/spina bifida	Paediatricic surgeons
Tumours	Radiotherapists/oncologists
Diagnosis	Radiologists/neurologists

Head Injury, as an Example

This is probably the commonest condition about which neurosurgeons hold disparate views as to the extent to which they should be involved in providing a service. Whilst 5 per cent of admitted head injuries in Britain as a whole are in neurosurgical wards this proportion varies from 50 to 0·5 per cent in different regions; consequently head injuries account for half of all admissions to some neurosurgical units but for less than a tenth in

others. It is differences in opinion rather than in resources that account for most of these wide variations. Some neurosurgeons maintain that the risk of rapid deterioration after even a mild injury is great enough to justify almost all patients being under neurosurgical supervision from the start [23]. Over 80 per cent of patients admitted to primary surgical wards in Britain after head injuries are fully conscious and develop no complications; over 70 per cent are discharged within 48 hours. To take all these patients into neurosurgical wards would require almost trebling the number of neurosurgical beds in most parts of the country; and it would impose considerable cost and inconvenience on patients and their families [24, 25].

At the other extreme is the view that the hazards of transportation to a regional unit (both the delay and the risk of harmful incidents en route) are so great that almost all head-injured patients should be dealt with by primary surgeons in the hospital to which they have been initially admitted [26, 27]. Most neurosurgeons hold that the most appropriate policy is the selective transfer to neurosurgeons of patients considered in need of special investigation or treatment, but that leaves scope for varying views about selection criteria.

It ought to be possible to compare the results of management by these different methods, if records are regularly kept and analysed. Factors to consider would include the rate of occurrence (per 10^5 population) of clearly defined conditions such as compound depressed fracture, and operation for intracranial haematoma, as an indication that the detection rate is satisfactory. Population-based rates for head injuries of different severities have been published, which provide a basis for comparison [28]. For example, a deliberate effort to transfer more head-injured patients to the regional unit in Glasgow in 1978 resulted in a doubling of the annual number of cases *and* the number of acute intracranial haematomas requiring operation [29]. As there was no evidence that the incidence of head injuries in the community had increased, this strongly suggests that the neurosurgical service in the earlier period was inadequate.

The case mortality and morbidity for patients treated in a particular hospital service indicates whether undue delays or inadequate management are making for sub-optimal results in cases that are recognized. Studies in Glasgow prior to 1977 indicated that about half of all deaths after head injury in the regional neurosurgical unit had one or more avoidable factors contributing to the fatal outcome [30]. Delayed management of intracranial haematoma was the most frequent preventable cause of death and also of disablement in survivors. This was when about 5 per cent of admitted head injuries were being transferred to the regional neurosurgical unit, the same as the average for England and Wales. In Merseyside at the same time only 1·2 per cent of head injuries were going to neurosurgeons, and concern was expressed [31] that some of those who died in primary hospitals might have been saved by neurosurgical intervention.

CONCLUSIONS

Patients with any condition should ideally be distributed among specialties according to their need, not according to the demands or opinions of doctors (whether those sending or receiving the patients). Like all other specialists neurosurgeons need to declare explicitly what conditions they consider to require their facilities, and also which particular patients with each condition they should be consulted about. This will depend on *what is possible,* according to the present state of knowledge and technical development; on *what is provided,* locally and nationally by way of resources; and on *what is offered,* by reason of the bias of interest of neurosurgeons, which again has a local and a national component [32]. There is need to reach agreement not only among the members of one specialty but also between specialties, as to what is appropriate management in different circumstances. Unless this is done there is likely to be both ineffective and inefficient use of regional specialty resources, some patients in need of specialist attention being referred too late for optimal management (or not sent at all), whilst other patients are unnecessarily sent – both those too mildly affected to need special facilities and those too badly affected to benefit. Only when neurosurgeons have defined their objectives will it be possible to approach the question of the relative adequacy of neurosurgical services, whether on the national or local scale.

It might then be possible also to make a valid comparison between Europe and North America. In the USA there is a neurosurgeon per 75 000 population, in Canada one per 140 000 and in Britain one per 400 000 [33]. These are so strikingly different that they cannot all be 'right' in the sense of providing an adequate service by measurable criteria. More neurosurgeons should mean that patients who need their services do more consistently reach them; and hopefully they see them sooner, which might be expected to make for better results from treatment. Thus Drake [34] advances the interesting concept that the majority of American neurosurgeons form 'what might be called the general practice of neurosurgery, which is of great benefit to the community . . . making their skills available earlier in the decision-making process rather than later or not at all'.

However, there is another side to this claim. This is the dilution of experience that must inevitably result when there are more doctors (of any specialty) for a similar disease incidence. In the larger clinics, especially in Europe, sub-specialization is becoming more common and should make for increased expertise and better care for patients with certain conditions: a limited number of centres for a whole country might be justified for less common conditions. In North American the opposite commonly occurs and there are neurosurgeons doing such a limited number of major procedures for even the commoner conditions that it is reasonable to question whether they bring to their patients the expertise of their European

colleagues whose personal experience tends to be much greater. Another aspect of overprovision of doctors is the tendency for them to over-investigate and over-treat the limited number of patients that they do see. Nachemson [35] has pointed out that the laminectomy rate (on a population basis) is as many times greater in the USA and Canada, as in Britain or Sweden, by almost exactly the factor by which North American neurosurgeons outnumber those in Britain and Sweden.

Whilst most North American neurosurgeons agree that they are too numerous, it would be unwise to assume that they envy their European colleagues or their patients. In addition to the general claim that more neurosurgeons means better care, consider these statements. Drake [34] quotes Ransohoff's claim that 'These community neurosurgeons provide the kind of frontline care which is truly not available in other countries, or certainly not at the level it is in the US and which the people of the US expect'. Criticism of the European pattern of neurosurgery is not only implicit; Drake singles out as an example the small proportion of head-injured patients who reach a neurosurgeon in most of Europe, and comments: 'many in North America would be critical of leaving the scourge of CNS trauma to others who are not trained deeply in its pathology, anatomy and physiology, or its modern treatment'.

Clearly there is no level of provision that is ideal; and when socio-economic and cultural settings are as different as they are in Europe and North America then comparisons are full of pitfalls. None the less it might be better to analyse data as a means of discovering what benefits do in fact derive from such very different numbers of neurosurgeons, rather than depending on the resonance of rhetoric.

REFERENCES

1. Cochrane A. L. (1973) *Effectiveness and Efficiency. Random Reflections on Health Services.* Burgess & Son, Berks, for the Nuffield Provincial Hospitals Trust.
2. Scottish Home & Health Department (1976) Scottish Hospital In-Patient Statistics, 1974. Edinburgh, Information Services Division of the Common Service Agency.
3. Department of Health and Social Security (1974) Hospital In-Patient Enquiry for England and Wales. London, HMSO.
4. Strang I. W., Boddy F. A., Jennett B. (1977) Patients in acute surgical wards: a survey in Glasgow. *Br. Med. J.* **1**, 545–8.
5. Barnett H. J., M. Peerless S. J., McCormick C. W. (1980) A progress report on the EC/IC bypass study (Editorial). *Stroke* **11**, 137–40.
6. Jennett B., Teasdale G., Galbraith S. et al. (1977) Severe head injuries in three countries. *J. Neurol. Neurosurg. Psychiatry* **40**, 292–8.
7. Jennett B., Teasdale G., Braakman R. et al. (1979) Prognosis in series of patients with severe head injury. *Neurosurgery* 4, 283.
8. Teasdale G., Knill-Jones R., Sande van der J. (1978) Observer variability in assessing impaired consciousness and coma. *J. Neurol. Neurosurg. Psychiatry* **41**, 603–10.

9. Teasdale G. and Jennett B. (1976) Assessment and prognosis of coma after head injury. *Acta Neurochirurg.* **34**, 45–55.
10. Jennett B. and Bond M. (1975) Assessment of outcome after severe brain damage. *Lancet* **1**, 480.
11. Jennett B., Teasdale G., Braakman R. et al. (1976) Predicting outcome in individual patients after severe head injury. *Lancet* **1**, 1031–4.
12. Titterington D. M., Murray G. D., Parker L. S. et al. (1981) Comparison of discrimination techniques applied to a complex data set of head injured patients. *J. R. Statist. Soc.* **144**, 145–75.
13. Book Review (1979) Microsurgical Approaches to Cerebrospinal Lesions. In: Krayenbuhl H., Maspes P. E., Sweed W. H. (ed.) (1978) *Progress in Neurosurgical Surgery*, Vol. 9. Basle, Karger. *Lancet* **1**, 856.
14. *Lancet* (1980) Blindness in surgical trials. **2**, 1230.
15. *Lancet* (1970) Controlled trials: planned deception. **1**, 534–5.
16. *British Medical Journal* (1979) Emotion and empiricism **1**, 288–9.
17. Bates D., Caronna J. J., Cartlidge N. E. F. et al (1977) Prospective study of non-traumatic coma: methods and results in 310 patients. *Ann. Neurol.* **2**, 211–20.
18. Jennett B., Teasdale G., Fry J. et al. (1980) Treatment for severe head injury. *J. Neurol. Neurosurg. Psychiatry* **43**, 289–95.
19. Jennett B., Pitts L. and Murray L. (1980) Management of severe head injuries. (Letter.) *Lancet* **2**, 370.
20. *Lancet* (1979) UK National Cancer Trials – unstarted business. **2**, 618–19.
21. Tate H. C., Rawlinson J. B. and Freedman L. S. (1979) Randomised comparative studies in the treatment of cancer in the United Kingdom: room for improvement? *Lancet* **2**, 623–5.
22. Bartlett J. R. (1971) Craniopharyngioma – a summary of 85 cases. *J. Neurol. Neurosurg. Psychiatry* **34**, 37–41.
23. Mendelow A. D., Karmi M. Z., Paul K. S. et al. (1979) Extradural haematoma: effect of delayed treatment. *Br. Med. J.* **1**, 1240–2.
24. MacMillan R., Strang I. and Jennett B. (1979) Head injuries in primary surgical wards in Scottish hospitals. *Health Bull.* **37**, 75–81.
25. Jennett B., Murray A., Carlin J. et al. (1979) Head injuries in three Scottish neurosurgical units. *Br. Med. J.* **21**, 955–8.
26. Bartlett J. R. and Neil-Dwyer G. (1979) The role of computerised tomography in the care of the injured. *Injury* **11**, 144–7.
27. Healy T. E. J., Pathakju G. S. and Weston P. A. M. (1980) Intracranial pressure measurements in patients suffering head injury managed in a non-neurosurgical unit. *Injury* **12**, 96–100.
28. Jennett B. and MacMillan R. (1981) Epidemiology of head injury. *Br. Med. J.* **282**, 101–4.
29. Teasdale G., Galbraith S., Murray L. et al. (1981) Traumatic intracranial haematomas: are we doing better? *J. Neurol. Neurosurg. Psychiatr.* (in the press).
30. Jennett B. and Carlin J. (1978) Preventable mortality and morbidity after head injury. *Injury* **10**, 31–9.
31. Jeffreys R. V. and Azzam N. I. (1979) Experiences with head injuries in a regional neurosurgical unit. *Br. J. Surg.* **66**, 562–4.
32. Jennett B. (1979) How many specialists? *Lancet* **1**, 594–7.
33. Miller D. (1980) A European looks at American neurosurgery. *Acta Neurochirurg.* **54**, 3–16.
34. Drake C. G. (1978) Neurosurgery: considerations for strength and quality. The 1978 AANS Presidential Address. *J. Neurosurg.* **49**, 483–401.
35. Nachemson A. (1980) Personal communication.

Brian Kendall

2 Recent Advances in Computed Tomography

The comparative safety of computed tomography (CT) and the reliability and accuracy which can be achieved using machines with high spatial resolution and contrast discrimination have made it an efficient screening test for craniocerebral lesions as well as the common primary and sometimes the only radiological study necessary for the management of neurosurgical diseases. The economic impact of CT is difficult to quantify but it does not require hospitalization and it has also reduced the average length of preoperative stay by decreasing the necessity for invasive neuroradiological studies which are much more expensive per patient than CT. These factors more than balance the high initial cost of providing scanners for neuroscience centres and replacing or updating them as significantly more efficient machines become available.

Radiation Dose

Radiation exposure should be considered in terms of information obtained per unit of absorbed dose [1]. Dose efficiency in the solution of a particular problem should be viewed against the knowledge that radiation changes are cumulative and that diagnostic radiology is the major source of artificial radiation to the general population. Though plain computed tomography is generally accepted as a non-invasive technique as far as immediate ill effects are concerned, for a single section the radiation dose varies from less than 1 rem to as much as 9 rem measured at the skin. In well-designed CT machines the radiation is virtually confined by collimation to the section of tissue being imaged and there is minimal increase in dosage from adjacent sections; in some machines, however, the dose from multiple sections is at least double that of a single one. The biological changes induced by low doses of absorbed radiation are not manifested for several years and are similar to naturally occurring diseases. Nevertheless, it has been suggested on the basis of extrapolation from observations on cancer induction by higher dose levels that the amount of radiation which may be delivered during a five slice CT head scan could possibly carry a risk of carcinogenesis as high as 70 per million [2]. Gonad doses from cranial scanning are generally negligible, but some years ago figures as high as 30 mrad have been reported in infants [3].

The dose within the direct beam from a single conventional X-ray exposure is about 0·2–0·3 rad on the tube side, falling by a large factor on

the emergent side. Clearly, the significance of dose depends on the particular tissues in the direct beam and with cranial irradiation the catarractogenic effect on the lenses of the eyes makes them the most sensitive structures. The lens dose in scanners which do not utilize a full rotation is much reduced when the X-ray beam enters posteriorly; for example, using the EMI 5005 in which the tube passes superiorly, the lens dose is reduced by a factor of 4–8 in the prone position.

The total radiation dose involved in examinations requiring multiple plain films is the summation of the individual exposures; it is reduced by using rare earth intensifying screens and shielding the cornea with lead, but it is generally greater than that for computed tomography. In one series the dose at the cornea in cerebral angiography reached 35·5 rem (mean 12·5 rem) [4].

Spatial resolution is dependent on the size of the volumes of tissue (voxels) in which attenuation values are calculated and which are represented on each picture element (pixel) of the matrix; for example, with pixels 0·75 × 0·75 mm (0·56 mm^2) the voxel size may vary between 4·5 mm^3 and 0·84 mm^3 as slice thickness decreasess from 8 mm to 1·5 mm. Density discrimination is dependent on signal to noise ratio. It is a fundamental physical principle that (density discrimination)^2 × (spatial resolution)^3 is directly proportional to radiation dose for any particular design of scanner. The information from a section can be modified by changing any of the three factors (cf. Image quality), but if either spatial resolution or density discrimination is improved without loss of the other, radiation dose has to be increased in order to keep noise at an acceptable level; the more detailed image achieved with slow scan modes is dependent on delivery of additional radiation and this should be considered before supplementary scans are made merely to obtain images of higher technical quality.

In summary, CT is so safe an investigation that it should be used whenever it can make a significant contribution to management, but like all procedures dependent on radiation, it should be directed to the solution of problems and not merely to illustrate what is already manifest. Radiation is used more efficiently and effectively when the clinical problem has been clearly presented; for example, in some cases modified projections may be indicated and in others, especially follow-up examinations, only a limited number of sections may be required.

Scanning Time

When movement occurs during scanning the computer is presented with incompatible data and responds by producing streaks on the images which are most marked in regions where there are sudden changes in attenuation. Generally, it is evident that they are artefacts and either they can be ignored or, if necessary, the examination repeated, but occasionally they

lead to errors in diagnosis [5]. Head scanning is most seriously affected by postural change and, in the case of orbital scanning, eye movements are also significant. Respiratory and cardiac movement and peristalsis are of relatively greater importance in body scanning, including examination of the spinal cord.

The scan time is a compromise between obtaining many measurements of radiation, on which accurate image reconstruction is dependent, and speed, in order to decrease the possibility of movement artefact. The familiar 'translate-rotate' geometry in the original system had a scanning time of 4½ minutes and computation time of 7 minutes for the pair of adjacent sections from its double detector arrangement. Modification of the mechanics and the use of a fan beam which transmits to a bank of detectors, thus reducing the numbers of angles from which scanning is necessary, have decreased the fast scan time to a minimum of 5·3 seconds (Elscint 905); the stability of the translate-rotate mechanism itself is the main limiting factor.

The original arrangement has been replaced by a purely rotational motion of the tube around the patient's head. In third generation scanners the fan beam is linked to and directed at a bank of detectors, which also rotate; this system (e.g. GE 8800), though liable to circular artefacts from failure of a single detector, has in practice produced excellent results. In fourth generation machines the head lies within a complete circle of stationary, closely packed detectors. Though the most expensive, this type has the greatest stability and there is less blurring due to scanner motion than with any other design. A scan time as low as 2 seconds can be achieved. Two types of mechanical arrangement are possible:

(i) with the tube near the head and the detectors forming a peripheral ring;

(ii) with the detectors in the most efficient location close to the head and the tube rotating peripheral to them. In this type (EMI 7070), the detector ring tilts (nutates) during rotation to carry the detectors on the side of the tube, which are not at that time recording, out of the plane of the incident ray.

The main factor limiting speed with purely rotational mechanisms is the time necessary for each detector to be excited by an incident photon and to return to the resting state. This is short in compressed xenon gas detectors, which have the additional advantages of being thin-walled, which allows close packing, and of being stable, but they are under 70 per cent efficient in responding to incident X-rays and provide low electronic amplification, so that background noise tends to be relatively prominent. Solid state scintillation devices are over 90 per cent efficient with a very high gain. Previously they were bulky and they are less stable than xenon detectors but these defects are being progressively resolved and solid state detectors are presently used in most third and fourth generation scanners.

Image Quality

Given the absence of artefact and consistency of image reproduction, scan quality is assessed by:

1. Maximal spatial resolution, which is about 0·5 mm, compared with 0·2 mm on conventional X-ray film. It depends on matrix size, which is ultimately proportional to the closeness of packing of the detectors, and on collimator size, which determines the X-ray beam width and section depth.

2. Density discrimination, which should always be better than 0·5 per cent (± 5 HU): it is a factor of signal to noise ratio, and values as low as 0·15 per cent can be achieved with acceptable radiation dosage.

Even using small voxels it is likely that several tissues of differing attenuation will be averaged in the attenuation value of the pixel; this is referred to as partial volume effect.

A trade-off may be made between density discimination and spatial resolution which is partly dependent on use of machine soft ware. Thus, density discrimination may be increased by filtering in the high frequency range which contributes most of the noise [6].

High Resolution Sector Scans

Such scans may be obtained on machines with translate-rotate scan systems and are in use on the EMI CT 5005 [7]. In this modification the slow transverse speed (72 seconds) and distance are used as in normal operation but the field of interest is limited and the usual number of attenuation readings, each utilizing about half of the distance transversed for standard resolution, are obtained from the central quadrant. Selected data for the attenuation outside this region are used for calibration. The effective pixel size is thus reduced to one-quarter, the voxel now being $(0{\cdot}375)^2 \times 5$ mm or 0·7 mm^3, and the image is magnified. If, in addition, the beam width is halved, a higher proportion of any attenuation change will be due to the object and less to the background so that resolution will be increased. Since radiation exposure is unaltered there must be loss of signal to noise ratio of $\sqrt{2}$, due to halving the beam width, and there is also a loss of $\sqrt{8}$ due to high resolution construction of half-size pixels. These factors act independently giving effectively a fourfold increase in noise with consequent loss of density discrimination. This modification is of value in examination of regions of high natural contrast. Thus, in the orbit where recognition of minor density differences is of little diagnostic significance, the morphological detail which can be achieved by the high contrast between the soft tissues and the orbital fat is of great value in revealing details of the morphology of the optic nerve and extraocular muscles and frequently shows small vessels (*Fig. 2.1*) and nerves down to 1 mm diameter; equally it allows separation of structures lying very close together, which may be crucial in determining suitability for surgical resection.

These are advantages, however, of high resolution scanning in general. It is achieved directly with the best third and fourth generation machines wihout loss of contrast discrimination. In the orbit such facilities have made other studies redundant for diagnosis unless a vascular lesion is suspected. The small diameter of the orbital apex relative to the thickness of the surrounding bone necessitates use of small collimeters to eliminate partial volume effects in order to show the optic canal, optic nerve and other contents (*Fig. 2.2*). Because of anatomical variation it is difficult to orientate consistently in the axis of the optic nerve so as to include its whole length in a very narrow axial section; a section thickness of about 3 mm is a reasonable compromise for most purposes in examinations of the whole orbit.

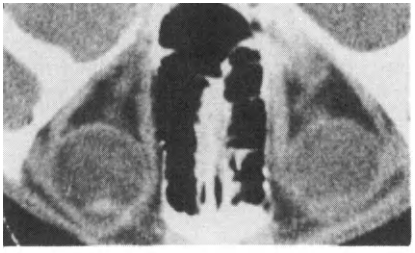
Axial section of the skull base is more easily achieved with CT than with the conventional tomography. CT also has the advantage of less radiation dose and that, at appropriate electronic windows, both soft tissues and bone can be demonstrated, thus revealing the continuity of abnormal processes.

In examination of the ear, high resolution CT with narrow (1·5 mm) collimation clearly shows the structures of the bony labyrinth and the middle ear cleft, as well as the internal auditory and descending facial nerve canals. The individual parts of the ossicles and their ligaments, muscles and tendons, the oval window and the tympanic membrane can all be recognized; even the crura of the stapes, which are under 1 mm in thickness, can be visualized (*Fig. 2.3*), which has not been achieved by any other radiological method [8]. Fractures and dislocations of the ossicles, congenital malformations, tumours and cholesteatomas may be revealed.

The radiation dose at the cornea on axial sections can be as low as 0·75 rem, about the same as a skull series, but greater than is necessary for a carefully controlled hypocycloid polytomography series; lens dose is avoided by using coronal sections, which are technically more satisfactory than more anterior sections being on a plane behind the teeth. Polytomography, which has higher resolution and has been extremely valuable in the examination of this region, inevitably produces low contrast images which are degraded by background blurring in which fine detail may be obscured, due to the rays traversing the overlying structures. At present, polytomography is only superior to CT in showing some very small anatomical features, including the round window and vestibular aqueduct and in the diagnosis of otosclerosis; it has been replaced by high resolution CT where the latter is available.

Scout Film Facility

Several modern scanners can produce a longitudinal image in any desired plane on which the attenuation values can be varied electronically to demonstrate various tissues. This image is achieved by making a low radia-



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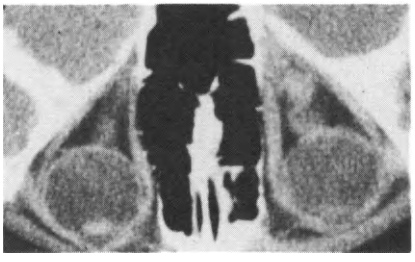

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Fig. 2.1. Angiomatous malformation around left optic nerve: (*a*) just above and (*b*) at the level of the nerve. Tortuous vessels are clearly shown around the whole length of the intraorbital part of the optic nerve, separated by orbital fat from the medial and lateral rectus muscles.

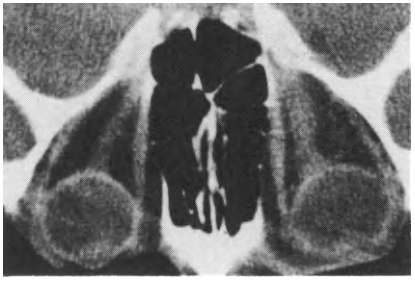


Fig. 2.2. Papilloedema of left eye. The right optic nerve is normal; the left is enlarged due to distension of the sheath.

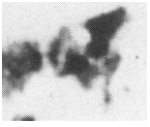


Fig. 2.3. Normal middle ear; high resolution CT. The window has been arranged to show the stapes to best advantage.

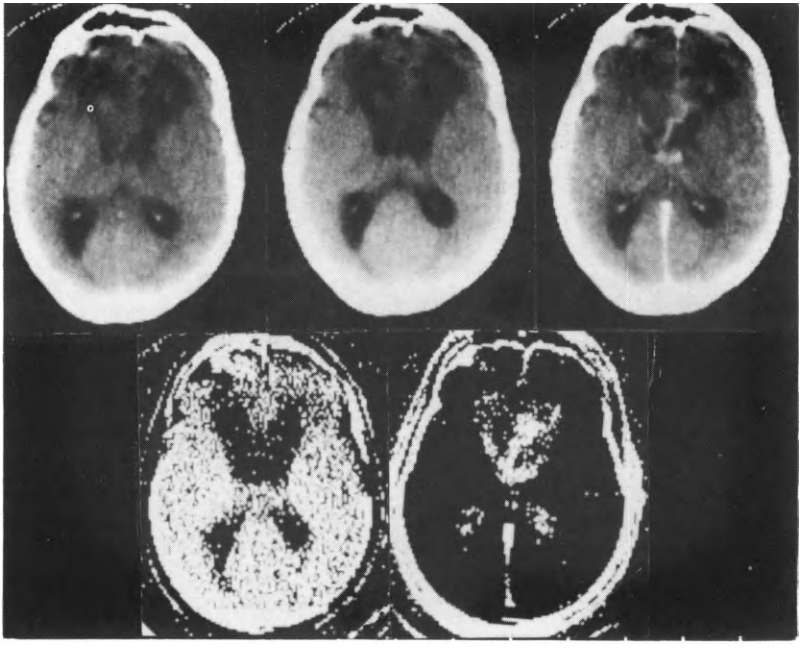


Fig. 2.4. Glioma of corpus callosum and septum pellucidum. *a*, Plain scan. *b*, Same section repeated after repositioning following inhalation of 70 per cent xenon for 20 minutes. *c*, Same section repeated after intravenous bolus injection of 70 ml Conray 420. *d*, Subtraction of (*a*) from (*b*) using a subtraction window (10 Hounsfield units). The xenon has been absorbed into the normal brain tissue, but not into the ventricles or most of the tumour. *e*, Subtraction of (*b*) from (*c*). The iodine enhances the blood shown in the straight sinus, the regions without a blood-brain barrier, including the falx cerebri and choroid plexuses and where the blood-brain barrier is abnormally permeable due to the tumour.

tion dose exposure (100-200 mrad) with a narrowly collimated beam while the detectors and tube remain stationary and the couch and patient are moved through a chosen distance. A cursor line corresponding to the level and axis of the tube and detectors and therefore to the plane of scanning can be incorporated in the image, shown on the display console. Thus the level of a section can be precisely pre-selected as desired and the plane can also be modified by tilting the gantry in scanners which have this additional facility.

The scout film is valuable in both localizing and recording the position of a section and in confirming that the whole of the region of interest has been sectioned. It has replaced the various methods of external marking [9] which were previously necessary both for prospective and retrospective assessment of position. It facilitates the reproduction of particular positions but has its greatest value in situations where the plane and angle of scanning are of critical importance for avoiding partial volume effects, as for example when CT is used for measurement of the diameters of the spinal canal, or the diagnosis of intervertebral disc prolapse and in the assessment of small basal masses.

Arithmetical subtraction of scout films taken before and after intravenous contrast injection will give a selective image of the vascular structures. This forms the basis of one method of digital angiography, a facet of radiology which is rapidly developing practical applications [10].

Reproducing Position for Comparative Studies

Careful standard positioning for CT generally gives images on which comparison with previous studies may be achieved adequate for clinical purposes, such as assessing the progress of a disease over a period of time or the degree of enhancement after contrast medium. Recorded scout images using the scan facility, with superimposition of the cursor line to mark sections of interest, will aid in particular cases.

More exact repositioning is essential if the scanner is to be used for precision techniques such as stereotactic surgery or biopsy, or for measuring changes of tissue attenuation or for exact integration with other radiodiagnostic studies. For sterotactic surgery or biopsy an aluminium base plate, which clamps on to the scanner aperture and to the appropriate mechanical parts of other diagnostic or therapeutic units, is rigidly attached to the patient's head, either directly with screws or pins or, preferably, indirectly using an individually made plastic helmet. The base plate is then a constant and reproducible reference plane and the coordinates may be transformed for use in the other units [11]. This method allows accuracy within 1 mm in each direction, but is rather too complex for routine diagnostic use.

A simpler method of achieving comparable sections has been described [12] in which two television cameras are rigidly fixed to display from

standard angles reference marks on the scanner aperture and the position of the patient's face. Video disc recordings are made during the initial study of positions, which it is necessary to reproduce. These recordings can be projected in positive phase on to a television monitor at the time of any subsequent study, and live images of the head, projected in the negative phase, can be superimposed. The head is moved until all parts of the images are subtracted and is therefore exactly repositioned.

This method has been proved to be sufficiently precise to produce subtractions of plain scans from iodide-enhanced studies (*Fig. 2.4*), as used in the measurement of regional cerebral blood volumes, and from xenon-enhanced sections, which are valuable with rapid scans, for the measurement of regional cerebral blood flow.

Image Reformatting (Fig. 2.5)

Images in coronal, sagittal or other planes may be essential for differential diagnosis and precise localization of intracranial lesions. They are of great value in the elucidation of extra-axial masses showing, for example, the amount of extension of a tumour above and below the tentorial edge or the deformity of the third ventricle caused by anterior or posterior suprasellar or parasellar masses; in the confirmation of subtemporal or high convexity subdural haematoma; and in the diagnosis of expansion of the brain stem and of cerebellar ectopia.

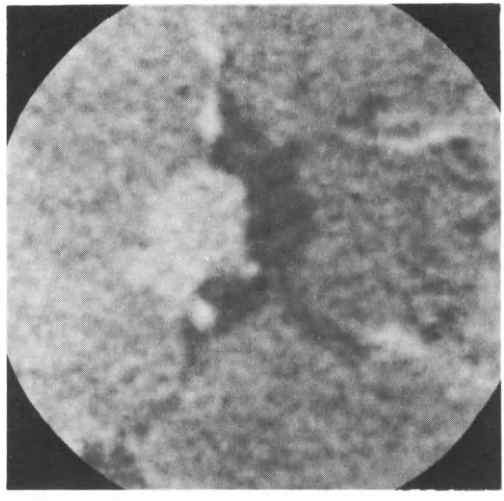
The spatial resolution on reformatted images is dependent on the height of contiguous voxels; good visualization of thin structures which is necessary in the orbit and suprasellar region is only achieved by reformatting thin (1·5–2·0 mm) contiguous sections.

Advantages of Reformatting over Direct Multiplane Imaging

1. A very wide aperture is necessary to accommodate the head in the sagittal position and this is only available on one machine, the Varian. Direct sagittal sections are generally only possible in small babies.
2. To achieve direct coronal sections hyperextension of the cervical spine is necessary. This is uncomfortable and, therefore, tends to induce patient motion. It may cause compression of the cervical spinal cord by spondylosis.
3. Artefacts due to teeth, especially with fillings, may detract from direct coronal images (*see Fig. 2.16d*).
4. On reformatted images an individual pixel may be electronically marked and identified in any plane so that more exact localization is possible than on direct images.

Theoretical Disadvantages of Reformatted Images

1. Narrow interval or thin section overlapping scans increase the time



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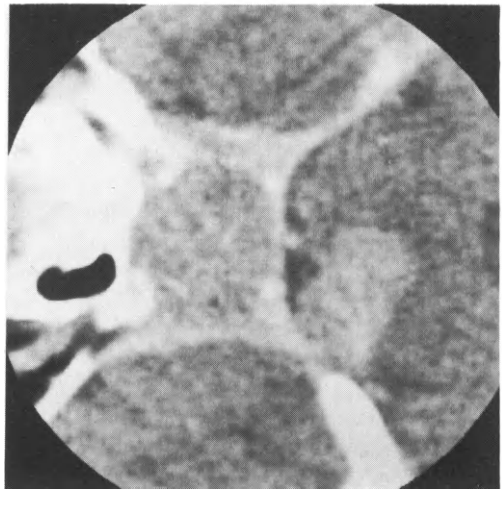

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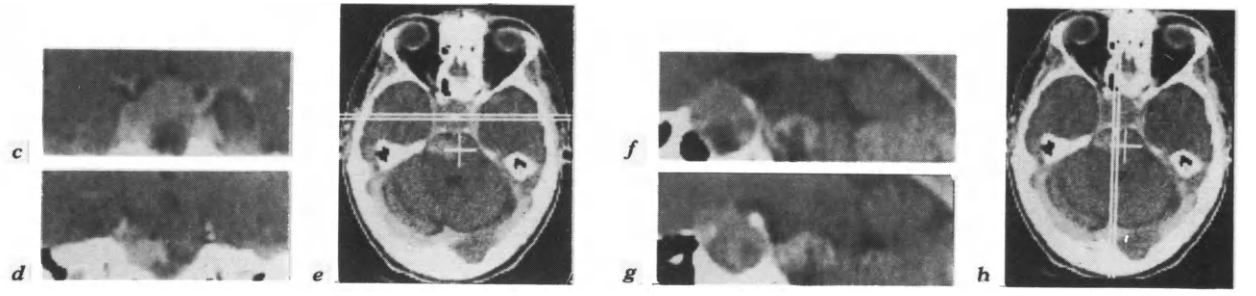

Fig. 2.5. Image reformatting. Pituitary adenoma. Transverse axial sections after intravenous contrast medium. *a*, Through enlarged sella showing the extension of tumour around the right side of the dorsum into the prepontine cistern. *b*, Through the chiasmatic cistern showing a lobulated suprasellar extension. *c, d*, Coronal reformatted sections, 3 pixels in thickness. *c*, Made in plane indicated by double line on section (*e*) shows suprasellar extension up to third ventricle, between supraclinoid segment of carotid arteries. *d*, 2 cm posterior to (*c*) and shows retroclival extension of tumour into cerebello-pontine angle. *f, g*, Sagittal reformatted sections 3 pixels in thickness. *f*, Made in plane indicated on section (*h*) and (*g*), 0·5 cm lateral to it. The relations of the suprasellar and retroclival extensions are well shown. The low density unenhancing anterior half of the intrasellar tumour suggests necrotic or cystic change.

and radiation dose necessary for the original examination, but this is balanced by excluding the necessity for sectioning in more than one plane.

2. Computer processing increases the noise inherent in the original scans and decreases spatial resolution.

3. With some systems using thin reformatted images there is considerable reduction in density discrimination. With most newer soft ware programmes the thickness of the reconstruction can be varied and in this way the defect can be overcome.

In conclusion, the technical difficulties have been mastered and reconstruction programmes are an important routine requirement of a modern scanner.

CT with Contrast Enhancement in Neuroradiology

Contrast enhancement refers to the administration of a substance for the specific purpose of altering X-ray attentuation characteristics. There are a variety of elements with suitable attenuating properties including rare earths and metals, of which the most effective is erbium (atomic number 68), but they are completely impractical for clinical use because of rarity or expense [13].

In clinical practice the substances, which can at present be administered in sufficient total mass to be useful at the effective X-ray energies for CT, are limited to compounds of iodine by intravascular injection, the rare gases xenon and krypton by inhalation and metrizamide, oxygen or air by intrathecal injection.

Intravascular Contrast Media

Those in common use are hypertonic solutions of the sodium or meglumine salts of the monomeric compounds, diatrizoate, metrizoate and iothalamate containing three atoms of iodine. They have similar physical properties and toxicities. Meglumine salts have a theoretical advantage for lesions of the central nervous system in being less neurotoxic than sodium salts, which may be significant when the blood-brain barrier is disrupted and high concentrations or large quantities are used.

The large organic molecules to which iodine is linked are confined within the normal blood-brain barrier, but elsewhere are distributed in both the intra- and extravascular spaces. Intravenously administered contrast medium effuses rapidly, over 50 per cent is in the extravascular space in under 1 minute [14] and equilibrium is achieved in about 10 minutes. Renal clearance is exponential, about 20 per cent being cleared within 5 minutes [15]. The change in attenuation measured by CT is proportional to the total amount of iodine (both intra- and extravascular) contained in the voxel and is equivalent to 26 Hounsfield units mg^{-1} ml^{-1} of iodine concentration at 120 kV [16].

Toxicity

The significant reactions to contrast media are due to idiosyncrasy and are not dose-dependent; they usually occur rapidly after injection and have an incidence of 1 in 14 000 with a death rate of 1 in 40 000 [17]. When the blood-brain barrier is abnormally permeable seizures may be precipitated [18]. For these reasons contrast studies should not be routine, but should be performed for clear clinical and/or radiological indications and with resuscitation facilities available.

Minor transient reactions are much more frequent and their incidence increases with higher dose rates. They usually abate spontaneously and are significant only because of patient discomfort, which may make cooperation difficult, but they may require treatment with hydrocortisone or antihistamines. With extremely high doses, chemotoxic effects could occur. Since enhancement is dose-dependent, a compromise must be made between toxicity and expense on the one hand and degree of enhancement on the other; most workers have found that between 28 and 42 g of iodine, corresponding to 100 or 150 ml containing 280 mg I/ml in adults and proportionally less in children, administered as a bolus injection, produces satisfactory results. Drip infusions and biphasic techniques of administration using the same dose do not produce such intense enhancement and are more complex and time-consuming; though it has been claimed that minor discomforts are less with these techniques, they are no longer recommended. Higher iodide doses may occasionally have diagnostic advantages as, for example, in the detection of extracerebral effusion by rendering small vessels on the surface of the hemisphere more evident.

At the usual time of scanning immediately after the termination of the bolus of contrast medium, the blood iodine level is about 4 mg/ml causing intravascular enhancement of between 80 and 100 Hounsfield units. At this concentration brain vessels down to a diameter of 2 mm can be visualized so that the larger cerebral arteries and veins down to a size corresponding to the major cortical branches can be shown and the larger aneurysms and angiomatous malformations are usually evident.

The visibility of small lesions is increased by high attenuation differences from adjacent structures. If the particular objective is to get maximum demonstration of the vascular system the intravascular iodine concentration at the time of scanning should be as high as possible without administering too large a dose of contrast medium. This is best achieved by utilizing the first circulation during rapid intravenous injection of a bolus of metrizamide, a contrast medium which combines low neurotoxicity with the relatively lower osmolality of an ester. It is hyperosmolality which, by causing vasodilatation and affecting blood flow, is largely responsible for the discomfort experienced with contrast injection and therefore for patient movement. Metrizamide is too expensive for routine use but the recently introduced monoacid dimers are cheaper and also possess the advantages of low osmolality and neurotoxicity between that of the monomeric media and metrizamide.

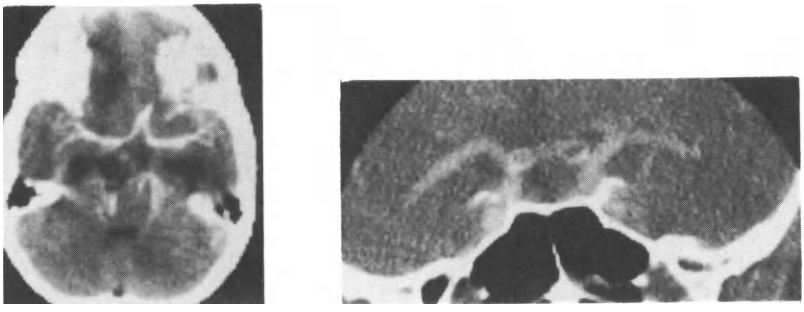

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Fig. 2.6. Scan during rapid bolus injection of sodium iothalamate (420 mg I/ml). *a*, Axial section: the anterior cerebral and the left posterior communicating arteries are displaced to the right and the posterior cerebral is displaced posteriorly by a large left frontoparietal mass causing tentorial herniation. *b*, Semicoronal section: normal. The supraclinoid carotid and the middle cerebral arteries and some branches are well shown. The cavernous sinuses are also evident.

The scan is commenced after a period corresponding to the arm to tongue circulation time (about 10 seconds but measured previously using decholin), plus the estimated cerebral circulation time (7 seconds) from the beginning of the bolus. The whole of the cerebral circulation is maintained opacified throughout the scanning time, which must be short (10 seconds maximum), by making the injection time 7 seconds plus the scanning time. A reasonable injection rate is 1200 mg I/second, equivalent to 4 ml/second with a concentration of 300 mg I/ml. Assuming dilution into 75 ml of blood per second, this will give a concentration of 16 mg I/ml in the cerebral vessels. The enhanced CT sections (*Fig. 2.6*) 'approach the appearances of a specimen injected with Indian ink' [19], and, though CT resolution is insufficient for such sections to replace conventional angiography, they may aid in the diagnosis of aneurysms, vascular malformations and neovascularity; vascular displacements may be recognized and variations in the capillary vascularity, reflected in regional changes in brain density, allow recognition of under perfusion (infarct, haematoma, cyst) or hyperaemia.

Heinz et al. [20] utilized rapid intravenous contrast injection followed by serial 5-second CT scans with inter-scan times of only 1 second, from which the data could be reprocessed to create 12 serial images obtained during the 35 seconds immediately following the contrast injection. The studies provide high resolution cerebral perfusion images, which are normally symmetrical with respect to the two hemispheres. Blood transit time, blood volume and its distribution and abnormal leakage through the blood-brain barrier are recognized by constructing iodine wash-out curves. In ischaemia due to ipsilateral carotid stenosis delayed and diminished perfusion is demonstrated. Infarction is associated with absent perfusion and

several abnormal perfusion patterns are found in brain tumours. The method gives a crude indication of blood flow and it has not yet been correlated with established procedures. However, at its present stage of development it will show markedly diminished flow and could be useful, for example, in immediate preoperative reassessment for significant spasm in some cases of subarachnoid haemorrhage already elucidated by angiography.

The blood-brain barrier prevents passage of iodide contrast medium into the brain substance and normal cerebral enhancement (about 5 Hounsfield units) is due to the cerebral blood volume which constitutes about 5 per cent of the cerebral mass; when the blood-brain barrier is normal, this enhancement has been used to calculate regional cerebral blood volumes [21]. The lack of any similar barrier in the meninges, muscles or in the orbital structures allows interstitial extravasation into these tissues which, therefore, show considerable enhancement (*Fig. 2.4*). The vessels in many tumours and inflammatory processes as well as neocerebral capillaries lack a barrier, which mainly accounts for the enhancement in these lesions. In many pathological processes, including infarcts, damage to the blood-brain barrier occurs which can be diminished by steroids [22]; the associated non-specific enhancement may also be influenced by steroids.

Aneurysms and large angiomas apart, contrast extravasation is generally the main cause of enhancement, and therefore in most cases there is no simple relationship between the vascularity found at angiography or surgery and the degree of enhancement of a lesion. Delayed scans taken 1 or more hours after contrast injection may give some additional information about the nature of a lesion. For example, when there is peripheral enhancement in solid and microcystic tumours, slow diffusion of the contrast medium may take place to totally opacify the mass, whereas similar enhancement occurring around large cystic or necrotic tumours and effusions may progress to dependent layering within the fluid. In regions lacking a blood-brain barrier such as the orbit and tissues adjacent to the skull base and the spine, the total absence of enhancement within a lesion may be significant in suggesting avascularity and, therefore, a cyst, epidermoid or lipoma.

When plain CT shows a focal lesion, the intensity and pattern of enhancement may indicate the likely nature or suggest the probability of a cystic or necrotic element which may be amenable to aspiration. Even when the diagnosis is evident, CT after contrast medium may still be useful, but is obviously contraindicated when it is not going to influence management. Examples of the latter include colloid cysts, extracerebral effusions, and cerebral malformations with typical plain CT appearances, hydrocephalus or atrophies of known aetiology and the follow-up of many lesions during therapy. When plain CT is unequivocally negative, enhancement is indicated in relatively few circumstances; these include clinical probability of an angiomatous malformation or aneurysm unless angio-

graphy is already planned, some recent ischaemic episodes – for example prior to surgical procedures intended to increase blood flow – posterior fossa tumours or basal meningitis.

Xenon Enhancement

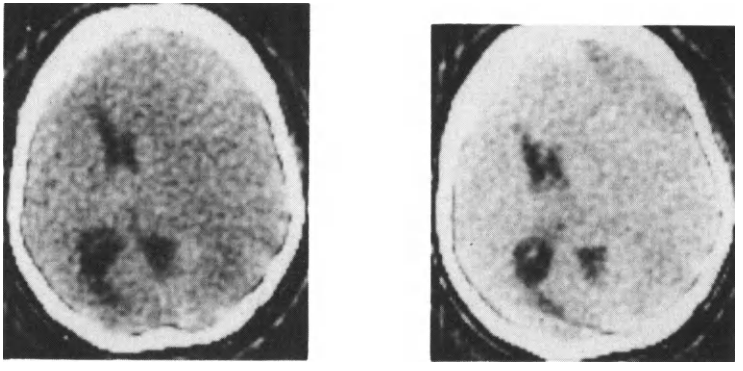
The atoms of xenon (Z54, K-edge 34·6 KeV) and iodine (Z53, K-edge 33 KeV) absorb similar amounts of X-radiation and cause similar attenuation changes on CT scanning, but in other respects they differ radically (*Fig. 2.4*). Xenon is a chemically inert, non-toxic gaseous element, which in concentrations greater than 50 per cent induces anaesthesia. It is usually administered by an anaesthetist through an endotracheal tube in 70 per cent concentration with 30 per cent oxygen, and since it is expensive, a completely closed circuit is usual. Xenon diffuses freely through the blood-brain barrier and it is absorbed into the tissues being 2-3 times more soluble in brain tissue than in water and almost twice as soluble in white as in grey matter.

The distribution of xenon and hence the relative enhancement of tissues on computed tomograms is influenced by three factors:

(i) the concentration of xenon, which is maintained constant;
(ii) the regional blood flow, and
(iii) the nature of the tissues themselves which determines the partition coefficient between the tissues and the blood when equilibrium has been achieved.

Cost apart, xenon is an ideal anaesthetic for computed tomography. The enhancement of the cerebral tissue itself is of value in regions where contrast discrimination is relatively poor for anatomical reasons, these include the spinal cord brain stem. The very low xenon uptake in fluid collections such as subdural effusions, isodense haematomas, cystic and necrotic areas including the central parts of some infarcts allows delineation of the avascular region and definitive diagnosis of some subdural effusions (*Fig. 2.7*) and cysts [21]. It may occasionally be useful in distinguishing between tumour and recent infarction in which uptake is generally lower but may increase with time, but the difference in xenon uptake in various tumours has not proved useful in differential diagnosis.

Using a rapid scanner, curves reflecting the regional cerebral blood flow can be constructed from the change in attenuation values on serial CT sections during the time in which xenon is being washed out of the tissues [24]. Preliminary plain scans are examined and an appropriate level is selected. The patient first breathes 100 per cent pure oxygen for 5 minutes in order to wash nitrogen out of the tissues, followed by a sub-anaesthetic concentration of xenon (30-50 per cent) in oxygen for 10 minutes through a tight-fitting mask from a semi-closed anaesthetic circuit. Scans are next taken at the pre-selected level commencing at 10 seconds, then 30 seconds and at 1 minute intervals for 10 minutes (GE8, 800 scanner). By



a *b*

Fig. 2.7. Isodense subdural effusion. *a*, Plain scan shows displacement of the ventricular system towards the left side with compression of the right lateral ventricle. *b*, During inhalation of 70 per cent xenon there is enhancement of the brain substance but the density of the cerebrospinal fluid and of the fluid in the subdural effusion is unchanged and it is, therefore, relatively less dense than the brain substance and rendered clearly visible.

utilizing the first and/or last scan as a mask, the drop in attenuation can be plotted from subtraction measurements. A problem with the method stems from the relatively small total increase in attenuation (up to 12 Hounsfield units) caused by the low concentration of xenon; consequently the incremental changes during excretion are small. The method is non-invasive and is capable of showing and localizing anatomically relative regional variations in perfusion which could be of value in, for example, the assessment and follow-up of patients with cerebral ischaemia being studied for external to internal carotid anastomosis. Absolute values of regional cerebral blood flow can be obtained by measuring attenuation changes in arterial blood withdrawn at the time of the brain scans or from measurements of simultaneous end-expiratory xenon concentrations [25].

A major advantage of transmission scanning for this type of study is easy availability, which contrasts with ECAT scanning using short-lived oxygen isotopes which though having the advantage of allowing measurements of perfusion, oxygen extraction and utilization will be confined to centres possessing cyclotrons.

Krypton (Z36), being a smaller atom than xenon, causes less enhancement. It is not an anaesthetic but often causes patient agitation and is not generally useful in CT.

Cerebrospinal Fluid Enhancement

When contrast discrimination between soft tissues, including normal neural substance, and cerebrospinal fluid is inadequate, it may be increased by

metrizamide injected into the spinal theca. In the spine (*see below*) at present computed myelography is most frequently used as an adjunct to conventional myelography; sections made at the level of pathology may give a more exact demonstration of the size and position of the spinal cord, of deformity of the theca and of the degree of compression or obstruction (*Fig. 2.8*). For demonstration of morphological changes using CT alone, the dose of metrizamide can be much smaller than for conventional studies, with the advantage of reducing the incidence and severity of the common minor toxic effects such as headache and vomiting.

Computed water soluble cisternography will show minor degrees of brain stem deformity and small extra-axial masses. In the posterior fossa it is used to study acoustic neurinomas and epidermoids (*Fig. 2.9*) unrevealed or incompletely demonstrated by conventional CT. Suprasellar extensions of pituitary tumours and optic chiasm gliomas are well shown with sufficient contrast differential for detailed reconstruction in other planes. Metrizamide cisternography is also useful in distinguishing low density within intrasellar pituitary adenomas from an accompanying partly empty sella (*see Fig. 2.16*). It is not necessary for recognition of typical empty sella in which the pituitary stalk is shown (*Fig. 2.10*).

Fistulas may be accurately outlined provided that leakage is occurring at the time of the study and opacified fluid can be pooled along the track. After a control CT, which establishes the attenuation of any fluid in the region of interest, about 3·5 g of metrizamide is injected in isotonic solution and pooled over the region of the leak. In the usual problem of CSF rhinorrhoea or otorrhoea, preliminary CT will show any fluid collected in sinuses or middle ear clefts, or abnormal air within the skull (*Fig. 2.11*). Imaging, performed in the prone position with coronal sections, will show any opacified fluid within the sella or extending into the sinuses (*Fig. 2.12*) or middle ears. If leakage is not occurring spontaneously it may be possible to induce it to demonstrate the fistula. The patient is positioned so that metrizamide will pool over the suspected site of leakage and 20 ml of 190 mg I/ml concentration is infused by lumbar injection until leakage occurs or until a pressure of 600 mm H_2O is attained [26]. Leaks which are small or into large fluid collections such as pleural effusions or from which pooling cannot be achieved into a track are better confirmed using isotopes.

Intrathecal metrizamide may also be useful in the study of non-enhancing superficial lesions of about CSF attenuation which could be cystic on routine CT. The treatment of arachnoid cysts, especially when they are associated with hydrocephalus, may depend on the presence or absence of communication with the general subarachnoid space. If the cyst opacified simultaneously with the remainder of the subarachnoid space it is considered to be in free communication and may be expected to reduce in size with treatment of the hydrocephalus; if the cyst opacified at a relatively slower rate it is likely to require direct drainage.

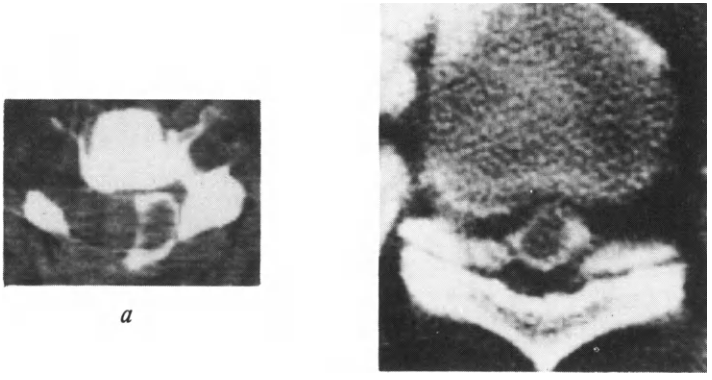


Fig. 2.8. CT with intrathecal metrizamide. *a*, Lower cervical neurofibroma: the tumour has enlarged the left intervertebral foramen and displaced the theca towards the right, compressing the cord. *b*, Thoracic disc protrusion: the protrusion compresses the left side of the theca and slightly deforms the spinal cord.

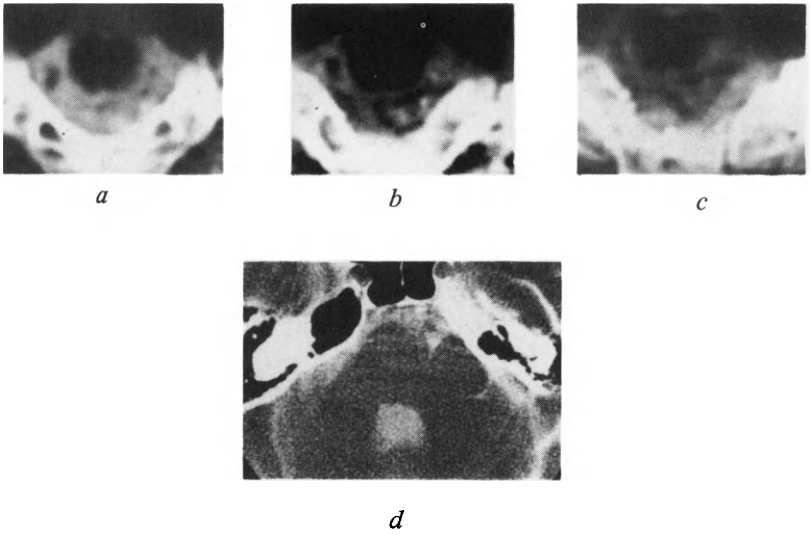


Fig. 2.9. Basal cisterns with intrathecal metrizamide. *a*, *b*, *c*, Epidermoid: adjacent coronal CT sections at level of medulla and lower part of tumour. The cisterns anterior and lateral to the brain stem are enlarged and show multiple filling defects strongly suggesting the nature of the tumour. *d*, Acoustic neurinoma: the tumour causes a smooth, well-defined mass, enlarging the right cerebello-pontine angle cistern. The fourth ventricle is slightly displaced and the right side of the floor is elevated.

Opacification by metrizamide distinguishes arachnoid cysts from epidermoids and other low attenuation masses (*Fig. 2.13*). Similarly, cystic arachnoiditis following surgery may be distinguished from recurrent tumour extending into the subarachnoid space.

a *b*

Fig. 2.10. Empty sella reformatted in (*a*) coronal and (*b*) sagittal plane. Cerebrospinal fluid from the basal cistern fills the enlarged sella turcica. The pituitary stalk (→) traversing the posterior part of the sella distinguishes the condition from a low density tumour.

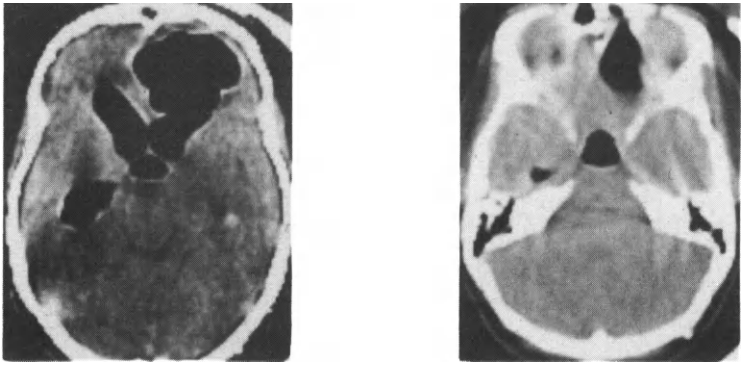


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Fig. 2.11. CSF rhinorrhea. Plain CT (*a*) at the level of the lateral and third ventricles; (*b*) wide window image at the level of the floor of the anterior fossa. There is air in the lateral and third ventricles which are dilated. An aerocoele extends from the frontal horn to expand the frontal lobe to a fracture which passes through the right frontal sinus. In this case the site of CSF rhinorrhea is evident from plain CT alone.

Study of CSF Dynamics

Although RIHSA (molecular weight 69 000) is a much larger molecule than metrizamide (molecular weight 789·1), it has been demonstrated that similar information about CSF dynamics can be obtained using either [27, 28]. RIHSA has certain disadvantages; being radioactive it may give a significant amount of radiation to neural tissue if there is a failure of adequate dilution

a *b* *c*

Fig. 2.12. CSF rhinorrhea through the right nostril. Semi-coronal sections passing through suprasellar cisterns and upper part of sphenoidal sinus after opacification of CSF by metrizamide. Previous surgery for epidermoid erodes the medial part of the right medial fossa including the body of the sphenoid (*a*). Residual or recurrent epidermoid is present within the right side of the sella (*b*) and there is depression of the adjacent part of the floor. A plug of muscle inserted transnasally into the right sphenoid sinus had failed to stop the leak, and there is increased density of the tissue in the upper part of this sinus (*c*) due to seepage of opacified CSF through its superior wall.

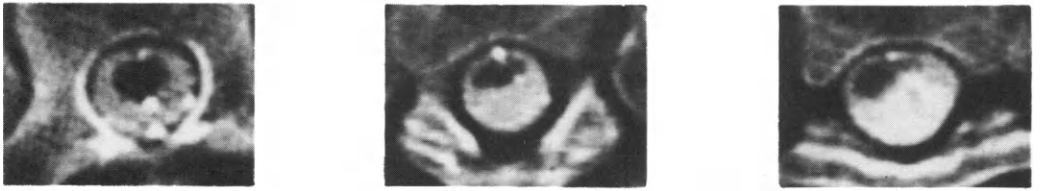

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Fig. 2.13. Arachnoid cyst. Sections through mid-dorsal spine following metrizamide myelogram. *a*, Normal section below cyst. Dense myodil droplets are from an earlier myelogram. *b*, Through lower half of cyst. *c*, At maximum diameter of cyst. The cyst is densely opacified. It displaces the spinal cord anteriorly and to the left and compresses it.

due to the presence of adhesions and it occasionally produces arachnoiditis. Gamma detectors have much lower resolution than CT, and when this is coupled with superimposition of activity in the ventricles and cisterns, there may be difficulty in recognizing the distribution of low concentrations of isotope unless emission tomography is available.

Using a fine (22-26) gauge needle, 5 ml of isotonic metrizamide is injected into the spinal theca. Usually, with lumbar injection, much of the contrast medium is absorbed from the spinal theca and to avoid this the medium is run into the lower posterior fossa with the patient supine; outlining of the fourth ventricle at this stage is advantageous for exclusion of obstruction at its outlets. In clear-cut normal cases filling of the cisterns and fourth ventricle is present on sections taken at approximately 2 hours; by about 5 hours the Sylvian fissures are generally outlined and there may be slight reflux into the third and even lateral ventricles. By 12 hours any contrast medium in the ventricles should be clearing and contrast medium is passing over the cerebral cortex, with some diffusion into the cerebral substance; by 24 hours there is little or no residual metrizamide in the ventricles and it is clearing from the parasagittal subarachnoid space, though some may persist for 36 or even 48 hours especially in the presence of atrophy and in elderly patients. Those cases of communicating hydrocephalus, which are most likely to respond to shunting, tend to have reflux into the ventricles with retention over 24 hours sometimes associated with poor filling of the fissures and sulci and poor cortical staining. Low attenuation may increase or appear in the white matter around the lateral ventricles occasionally followed by increased attenuation due to passage of metrizamide into the same region [29]. The increase in low attenuation suggests additional obstruction to normal CSF flow during the study, which may be related to transient increase in resistance within the arachnoid granulations [30].

Communicating hydrocephalus may also be present with less pronounced abnormalities or with flow dynamics within the range of normal variation and is then less likely to respond to shunt procedures. Cases in which distinction between low pressure hydrocephalus and atrophy, causing enlargement of the ventricular system with relative sparing of high convexity cortical sulci, remains a problem after metrizamide study may require further elucidation by transducer monitoring of intracranial pressure.

Sensory Neural Deafness

Finely collimated high resolution CT after intravenous contrast medium using a fourth generation scanner should detect virtually all small cerebellopontine masses (*Fig. 2.14*). Subtraction of unenhanced from enhanced CT scans has revealed the intracanalicular part of some acoustic neurinomas, and Shaffer et al. [31] have predicted that a scanner with 1 per cent contrast discrimination and 1·5 mm collimation will reliably show small tumours without

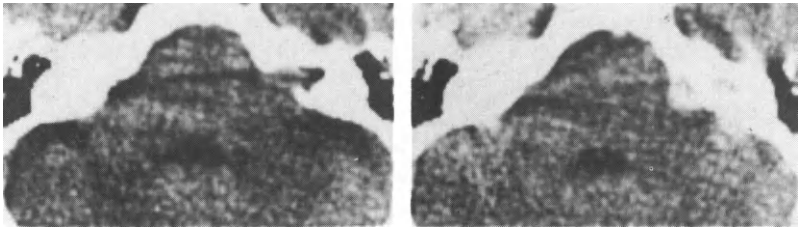

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Fig. 2.14. Acoustic neurinoma. *a*, Plain CT: widened internal auditory meatus. *b*, With intravenous contrast medium: enhanced mass in the right cerebello-pontine angle and within the internal auditory meatus. The tumour is isodense with brain and not clearly identified on the plain scan. Removed at surgery, it was 7·5 mm in diameter.

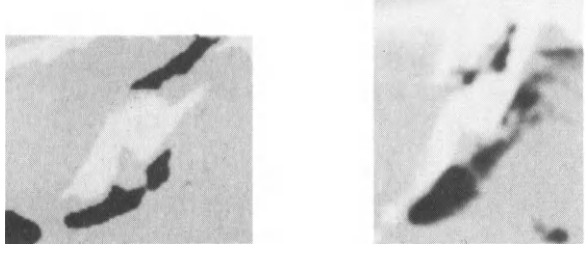

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Fig. 2.15. a, Acoustic neurinoma: the tumour, which projected 0·25 mm from the enlarged meatus, was not revealed by plain scan or with intravenous contrast medium. Air meatogram shows the tumour projecting from the enlarged meatus into the cerebello-pontine angle cistern. The seventh or eighth cranial nerve is visible extending between the tumour and the pons. *b*, Arachnoid cyst of internal auditory canal. The cerebello-pontine angle is well filled with air. No air enters the enlarged meatus which contains a mass of soft tissue attenuation with a minimally convex margin bulging towards the cistern. The seventh or eighth cranial nerve is shown extending from the pons towards the meatus.

the intrathecal contrast medium, which is necessary at present to confirm or exclude them.

Intrathecal Air in Diagnosis of Acoustic Neuroma [32]

The patient's body is placed at a lateral angle of 45° with the head in the lateral decubitus position and 3·5 ml of air are introduced by lumbar puncture and directed into the appropriate cerebello-pontine angle. The full length of the internal auditory meatus is shown in normal cases and the nerves within it are usually visualized. This method may be used to detect the very small acoustic neurinomas which have not been revealed by scanning after intravenous contrast medium (*Fig. 2.15*).

The Pituitary Gland and Suprasellar Region

The normal pituitary gland and pituitary microadenomas have been studied by Syvertsen et al. [33] using a fourth generation scanner (GE 8800). Normal pituitary tissue is homogeneous on CT, nearly isodense with brain, and enhances uniformally to approximately the same attenuation as the adjacent vessels. The height of the gland is between 2 and 5 mm in the male and 2 and 7 mm in the female. Its upper surface is flat or concave inferiorly. It is situated between the cavernous sinuses, containing the cavernous segments of the carotid arteries and having the attenuation of fluid blood which is slightly greater than that of brain; these vessels enhance homogeneously apart from small defects caused by the third, fourth and sixth nerve.

The shallowness of normal pituitary gland and the central umbilication often cause the cerebrospinal fluid in the chiasmatic cistern to be averaged with the central part of the gland on axial sections even if small collimeters are used. In ideal circumstances, the superior and inferior borders of the gland are best studied with coronal and sagittal reformations of thin (1·5 mm) sections or with coronal sections and the anterior, posterior and lateral borders and tumour extensions from them in transverse sections (*Fig. 2.5*).

Unfortunately with many scanners, especially of the second generation, reformatting is inadequate to display the region in sufficient detail and in direct coronal or semicoronal sections artefacts may be troublesome. These factors are much less critical if metrizamide cisternography is used in combination with CT (*Fig. 2.16*), but this should be necessary in only occasional cases if the more efficient machines are used.

A gland with a superiorly convex upper surface or with a height of greater than 9 mm is always abnormal. Most prolactinomas are of lower attenuation with absent or less dense enhancement than normal gland tissue. Other types of pituitary adenoma show more variation in attenuation but are most frequently either isodense with gland or of lower attenuation. Enhancement may be greater than, equal to or less than that of normal brain. Adenomas as small as 3 mm diameter can be recognized; pars intermedia cysts are indistinguishable from non-enhancing adenomas.

About 25 per cent of pituitary adenomas are associated with a partly empty sella and it may be difficult, without re-scanning after metrizamide to distinguish between CSF in the sella and a low density adenoma. The pituitary stalk is often deviated by an adenoma and outlined within an empty sella; when visualized it is a useful distinguishing feature (*Fig. 2.10*).

It should be noted that although failure of a tumour to enhance may indicate a cystic or necrotic component this is not necessarily the case. Calcification occurs in only about 5 per cent of pituitary adenomas and its presence should raise the possibility of craniopharyngioma or meningioma. Curvilinear peripheral calcification in a high attenuation mass

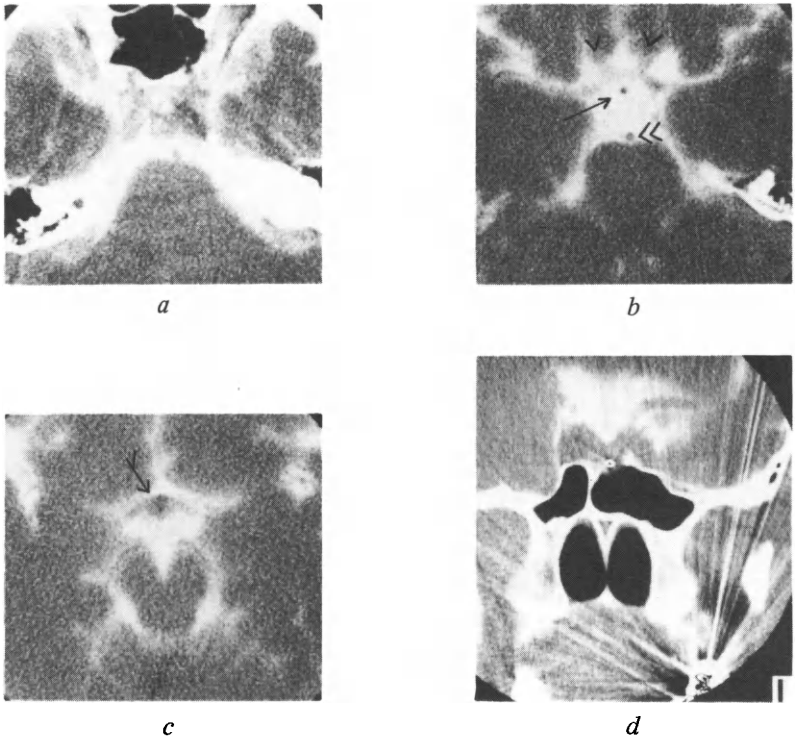


Fig. 2.16. Pituitary adenoma: CT with intrathecal metrizamide. Previously a pituitary adenoma had been treated by yttrium implantation. No radiological evidence of a recurrence. Axial sections (*a*) through the pituitary fossa – contrast medium from the cisterns enters the upper part of the sella; (*b*) through the lower part of the suprasellar cisterns – optic nerves (v) joined by chiasm in U-shaped image, pituitary stalk (→) and basilar artery (⩾); (*c*) just above (*b*) optic chiasm (↠) and tracts forming boomerang-shaped image; (*d*) coronal section. There is a surgical defect in the sellar floor below the metallic implant. The normal inferior convexity of the upper border of the pituitary is accentuated opposite the implant, presumably due to contraction of the gland. Note linear artefacts caused by metallic filling in tooth.

showing almost total enhancement should suggest the possibility of aneurysm. Dynamic scanning showing similar enhancement of the patent lumen and the adjacent arteries may support the diagnosis and there is little doubt that in the near future such lesions, and indeed the disposition of the vessels in the region of the sella and pathology related to it, will be elucidated by digital angiography. A denser periphery with central enhancement may also suggest a partially thrombosed aneurysm.

Plain films of the sella are of importance in differential diagnosis of sellar and parasellar masses and they should be viewed together with the computed tomogram before any further study.

The optic chiasm [34] is usually visible in the chiasmatic cistern. On lower axial sections it is in continuity with the optic nerves as a U-shaped structure; in higher sections it is continuous with the optic tracts and appears boomerang-shaped (*Fig. 2.16*). It is 12-27 mm in transverse diameter and 4-9 mm in anteroposterior diameter. In coronal sections the chiasm is U-shaped at its junction with the hypothalamus and dumb-bell-shaped more anteriorly, where the suprachiasmatic cistern is above it; the vertical thickness measures 3-6 mm. The normal chiasm is smooth in outline, isodense with brain and enhances to a similar degree. Optic chiasm gliomas increase the anteroposterior and vertical measurements, causing rounding of the chiasm. They are often irregular, hyperdense, occasionally calcified and frequently enhance.

Aneurysmal Haemorrhage

CT is of considerable value in the management of patients presenting as apparently primary subarachnoid haemorrhage (SAH). In about 20 per cent of cases an unsuspected abnormality is revealed, such as post-traumatic changes, extension into cerebrospinal fluid of an intracerebral haematoma or haemorrhage from a tumour. Blood is shown in the cisterns in 65 per cent [35] to 100 per cent [36] of cases scanned within the first two days of SAH, falling rapidly in incidence towards the end of the first week. Failure to demonstrate blood obviously does not exclude SAH at any time, but its presence is not only diagnostic; if localized it may be helpful in suggesting the site or at least the side of the source of the haemorrhage. Localization is more exact in the presence of parenchymal haematomas, which are likely to be of aneurysmal origin, only if they extend near the circle of Willis. Intraventricular blood is common in the first few days after the ictus.

Low attenuation of ischaemic origin, caused by restriction of blood flow due to critical narrowing of arteries in spasm, has been shown in up to 21 per cent [37] of carefully studied cases, and acute hydrocephalus is demonstrated in 30-60 per cent [38]. Such features, as well as CT evidence of recurrent or continuing bleeding or of extracerebral effusion occurring before or after surgery, are now essential for the elucidation of patient deterioration.

Contrast enhancement is not necessary if angiography is to be performed, but Ghoshhafra et al. [39] have claimed that it is possible by using contrast enhancement and overlapping CT sections (EMI 1010 and Acta scanners) to detect about three-quarters of the anterior and middle, and over one-third of internal carotid aneurysms responsible for subarachnoid haemorrhage. The smallest aneurysms shown were 5 mm diameter, though aneurysms as large as 15 mm lying close to the skull base or within the haematoma could be obscured.

Angiomatous Malformations

The typical CT appearances of angiomatous malformations (AVMs) are due to the higher than brain attenuation and more marked enhancement of the blood within the enlarged vessels which are shown on section as tubular, oval or circular structures sometimes associated with visible enlargement of feeding arteries or draining veins. There may be low attenuation, due to microcystic changes, in the adjacent brain sometimes accompanied by atrophy with dilatation of the ipsilateral subarachnoid space and ventricle. Mass effect is unusual unless the malformation is very large or there has been a recent haemorrhage. Increased attentuation lesions with CT features of AVMs may not be confirmed by angiography due to thrombosis; enhancement is usual, due to persistence of increased permeability of the blood-brain barrier. An AVM may also fail to fill on an angiogram if it is compressed by clot.

Enhancement may be seen in neocapillaries in the wall of an absorbing spontaneous haematoma or in the brain adjacent to it, but enhancement occurring less than a week after the time of haemorrhage is likely to be within underlying pathology.

Angiomatous malformations may present with unusual CT features. Following absorption of a haemorrhage a low attenuation cyst may remain, with the AVM showing as a dense enhancing nodule in the wall [40]. Cavernous angiomas may cause a well-defined high attenuation enhancing mass and venous angiomas may be suspected from linear enhancement within an enlarged vein, which should direct careful attenuation to the venous phase of angiograms performed to confirm the lesion.

The Spine

The spinal canal and its contents pose exacting problems for computed tomography. Beam hardening, due mainly to thick bone, and the intermittent nature of the bony column interspersed with intervertebral discs and foramina, together with the variable amount of gas and soft tissue overlying it, make discrimination between the small structures within the canal a severe test of both contrast and spatial resolution, especially when there is movement. Short of using general anaesthesia, which is one advantage of xenon (*see below*), even in fully cooperating patients, the tendency to artefacts due to respiratory movements and, to a lesser extent, from cardiac and vascular pulsation can be abolished only by using machines with rapid scanning times. Artefacts in the cervical region due to movement of the larynx during swallowing can usually be voluntarily controlled, though rapid scanning is advantageous for reducing these also.

To display the anatomy clearly and to diminish partial volume effects thin sections in the transverse axial plane perpendicular to the long axis of the spinal canal are optimal. The sections may be made in this axis, but this may involve changing position between individual sections in order to

compensate for the spinal curves in both sagittal and coronal planes which can only be consistently achieved in units possessing both a scout film-cursor line facility and a tilting gantry. The teeth, especially if they contain fillings, may cause artefacts, which can be avoided only by adopting a compromise position to move them out of the plane of section. Alternatively, the sections may be made with an unangled gantry and reformatted in the axial and if necessary coronal and sagittal planes.

Bone and paravertebral tissues are well shown by using wide window settings, especially with high resolution programmes. The shape and size of any part of the spinal canal can be appreciated in the sections perpendicular to its long axis. The size of the pedicles and laminae, and the presence and degree of any stenosis of the canal whether due to a congenitally short anteroposterior diameter or to hypertrophied laminae encroaching on the lateral recesses are better shown by CT than any other method.

A variable amount of low attenuation epidural fat outlines the outer margin of the soft tissue density of the dura; the axillary root pouches can also be seen within it extending through the intervertebral foramina [41]. In sections through them, the margins of intervertebral discs are shown outlined against the epidural fat.

Though cerebrospinal fluid is of lower attenuation than the spinal cord and dura, these structures can be consistently resolved on plain scans, even using rapid high resolution machines, only when the subarachnoid space is more than 2 mm wide [42]. With the CT 5005 high resolution programme, the spinal cord is visible on plain sections in the upper cervical region where the subarachnoid space is widest, in about 50 per cent of patients, decreasing to about 20 per cent at C7 level; it has been shown [43] that special programmes for data filtering and addition of multiple sections taken at the same level give more consistent visualization, at least in the cervical region, though at the expense of an increased dose of radiation.

The grey and white matter of the cord cannot at present be distinguished and the normal cord substance appears homogeneous.

Ideal information for management of a lesion affecting the contents of the spinal canal is a longitudinal image together with selected horizontal sections at known levels. Presently the CT facilities available in many centres are best used for further examination of lesions which have been localized by conventional radiology or isotope study, though there are exceptions.

Spinal CT without intrathecal contrast medium has practical application in several conditions. These include:

Spinal Trauma [44]

Vertical fractures of the bodies and fractures of the vertebral arches, many of which are not evident on conventional films, are well shown. Horizontal fractures, however, are only visualized with coronal or sagittal

reconstruction techniques. The relationships of displaced bone and bullet fragments are usually better appreciated than with conventional radiology and tomography [45]. Soft tissue abnormalities, such as herniated discs and haematomas within the spinal canal, may also be visualized. When they are of high attenuation, haematomas may be specifically recognized [46]. Loss of intraspinal tissue planes may preclude distinction between cord swelling and extrinsic compression; this can be resolved by metrizamide CT.

CT in conjunction with plain films has therefore substantial advantages over conventional tomography, which CT should replace. Metrizamide CT is a useful supplement in both acute and chronic trauma.

Erosion, Destruction and Sclerosis of Bone (Fig. 2.17)

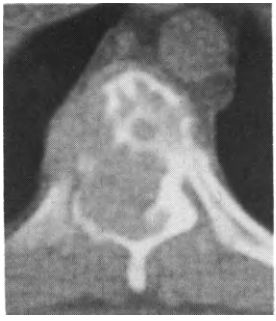
Visualization of a continuous soft tissue swelling encroaching on the epidural fat or extending into the paravertebral region gives a valuable overall view of the extent and relationships of the pathology. However, details of trabecular structure, periosteal bone formation and the degree of disc narrowing, which may be helpful in recognizing the nature of some types of pathology, are generally well appreciated on plain X-rays and conventional tomograms; the studies are complementary.

Spinal Canal Stenosis

Developmental short-pedicle stenosis has been mentioned and can be quantified. The degree of narrowing due to disc bulging or prolapse and osteophytes from the margins of discs or apophyseal joints can be appreciated relative to the original dimensions of the canal (*Fig. 2.18*). Facet hypertrophy, periarticular calcification, subchondral irregularity and erosions indicating osteoarthritis of the apophyseal joints are clearly shown on high resolution CT [47]. Stenosis of the lateral recess by superior articular facet enlargement and of the more central type, caused by inferior facet enlargement, as well as post-traumatic, spondylo-listhetic and post-surgical stenosis are well demonstrated. The precise detail revealed on CT is useful for planning the surgery and judging its effectiveness.

Prolapsed Intervertebral Disc (Fig. 2.19)

A focal protrusion of the disc margin may be shown encroaching into epidural fat, displacing the dura, or into an intervertebral foramen displacing or occluding an axillary root sheath. Partially calcified discs are more easily visualized. If a prolapse corresponding to clinical features is identified, myelography is unnecessary [48]. Also, lateral prolapses, causing a soft tissue mass in the lateral part of the intravertebral foramen or adjacent paraspinal tissues, and L5/S1 discs extending into wide epidural fat and not reaching the dura will not be shown on myelograms.



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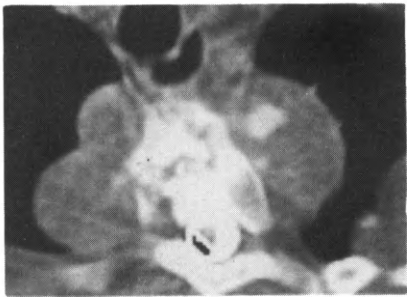


b

Fig. 2.17. a, Myeloma: there is destruction of the right side and posterior half of the body and the right pedicle and also partial destruction of the right lamina of the sixth dorsal vertebra. The tumour causes a small right paravertebral mass and extends into the spinal canal but the theca and its contents are not visible separately from the tumour mass. *b,* Hydatid disease: CT section with intrathecal metrizamide. There are multiple paravertebral hydatid cysts. These are causing partial destruction of the body of the third dorsal vertebra, more extensive on the right side, and of the adjacent parts of the right ribs. There is angular kyphosis at the level of destruction which is causing the asymmetrical appearance of the metrizamide in the theca due to partial volume effect. The low density in the right side of the theca is an artefact due to computer overshoot associated with residual myodil from a previous study.

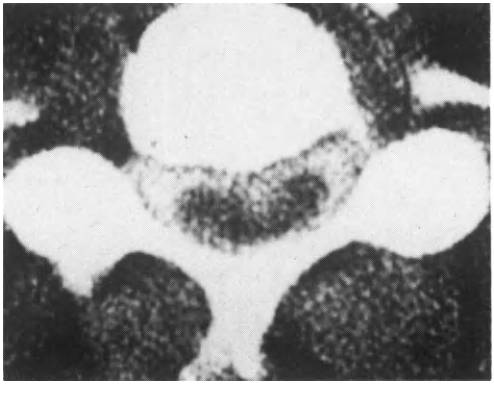


Fig. 2.18. Spinal stenosis: CT with intrathecal metrizamide. The sagittal diameter of the spinal canal is developmentally small. The spinal cord is deformed by a small osteophyte on the posterior border of the 4th cervical body.

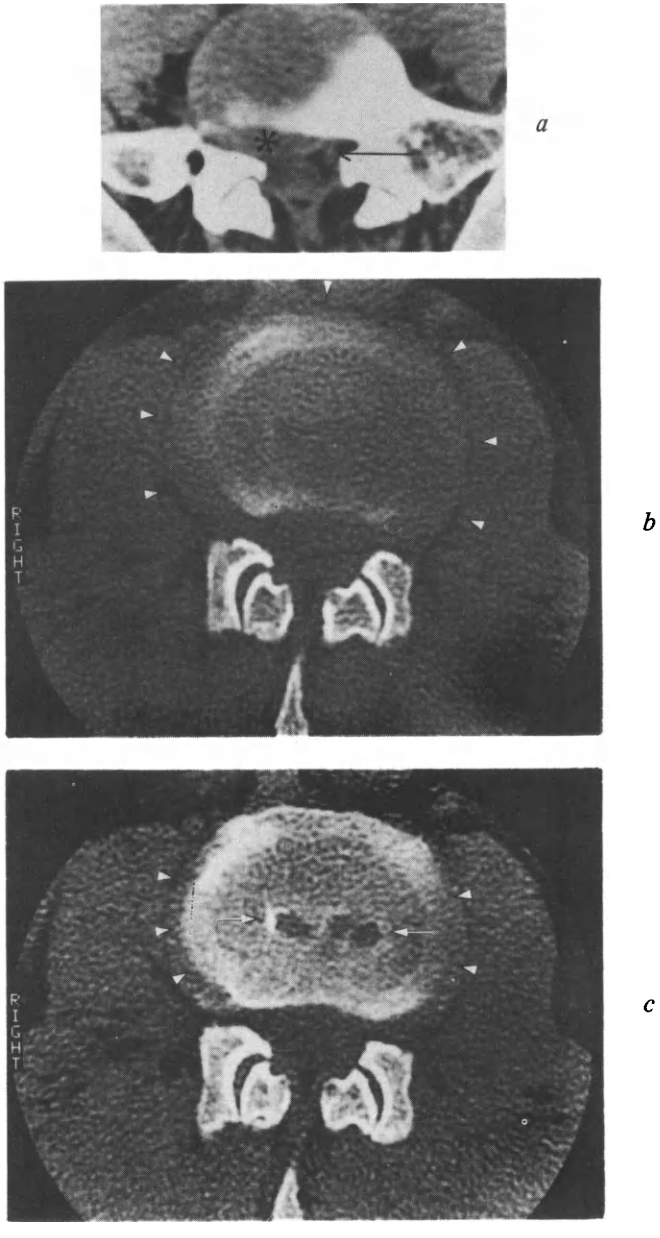


Fig. 2.19. *a*, L5-S1 disc prolapse to right side. The prolapse (*) displaces the epidural fat and occludes the right S1 nerve root sheath. Left S1 nerve root sheath (→). *b*, *c*, L4–5 disc protrusion and osteoarthritis of apophyseal joints: *b*, At level of end plate of vertebral body: (→) Schmorl's nodes: (>) disc margin. *c*, Through disc.

Dysraphism [49]

Any bony deformity (*Fig. 2.20*) is evident and associated congenital tumours such as intra- or extra-thecal lipoma and dermoid may be recognized by low attenuation readings. The size and shape of the spinal cord is also shown in some cases and the small divided cord segments in diastematomyelia can be distinguished from the normal-sized twin cords of the rare condition diplomyelia [50], but details of intrathecal abnormalities including the level of the conus medullaris and the origin and course of the nerve roots will generally require intrathecal metrizamide to elucidate [51].

Lesions which differ markedly in attenuation from the normal intraspinal contents can be recognized, even when the normal structures cannot be resolved. Included among these are high attenuation in meningiomas (*Fig. 2.21*), some of which are calcified, and in haematomas; very low attenuation in lipomas [52] (*Fig. 2.22*); and cerebrospinal fluid attenuation within the spinal cord substance as in syringo- or hydromyelia (*Fig. 2.23*). Using a high resolution system on a CT 5005 scanner. Bonafé et al. [53] demonstrated cavitation in the cervical cord in each case of a series of 32 patients with syringomyelia. The cord was enlarged and rounded (10 cases), flattened in its anteroposterior diameter and lying posteriorly in the spinal canal (13 cases), atrophic and small throughout the cervical region (5 cases) or of normal diameter (4 cases). As the authors point out, in the latter cases the cord appears normal on conventional positive contrast myelography. In these cases associated cerebellar ectopia was identified in only 50 per cent of those in which the cervico-cranial junction was examined. Since surgery is dependent on the condition of the craniocervical junction intrathecal metrizamide is necessary if the tonsils are not shown to be ectopic on plain CT.

The diagnosis of intramedullary tumours by CT has been much less successful. The diminution of the subarachnoid space by cord swelling and the fact that most gliomas of the cord are of similar density to the cord itself renders most of them undetectable. However, regions of low density have been described in some and of high density in others [54]. Enhancement with intravenous contrast medium may reveal haemangioblastomas [55], astrocytomas [56] and large angiomatous malformations [57]. Meningiomas and neurofibromas also enhance with intravenous contrast media. The recognition of intramedullary cysts in association with tumours, which is important in management, is possible with CT in some but not all cases [58] since some cysts are isodense with the cord and low density regions are not necessarily cystic.

Low density has been recorded within the cord in one case of acute demyelination with multiple sclerosis [59]. In several other patients examined the findings have been normal.

Xenon Enhancement

Xenon inhalation considerably increases the attenuation of normal cord

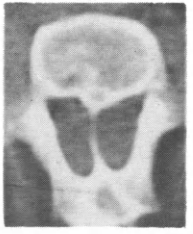
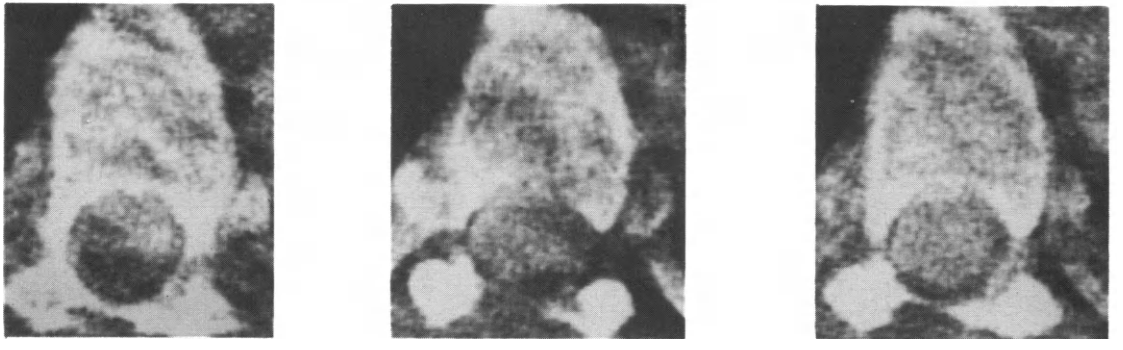
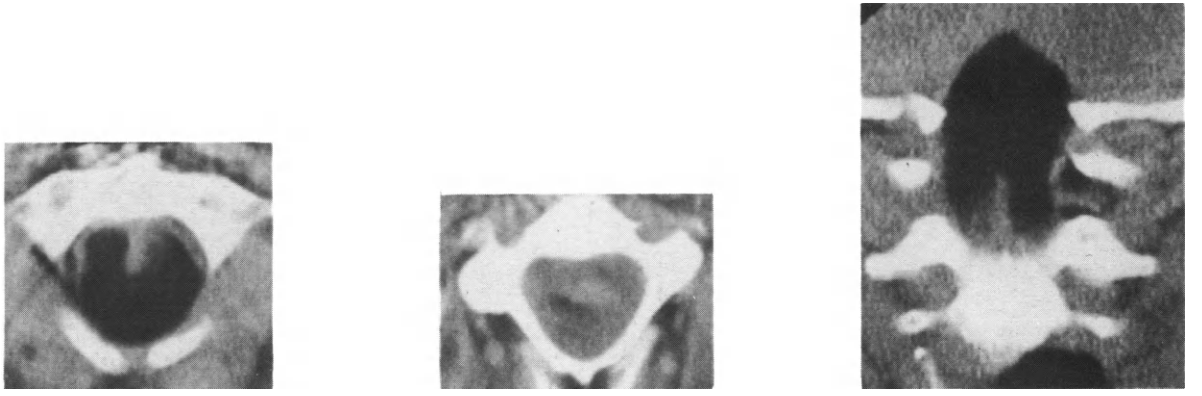


Fig. 2.20. Diastematomyelia:
a central sagittal bony spur completely divides the upper lumbar theca.



a *b* *c*

Fig. 2.21. Meningioma, lower dorsal spine: three adjacent sections. The tumour, which is of high density, lies anteriorly, displacing the theca posteriorly. In the upper section (*a*) the tumour fills half of the spinal canal; in the middle section (*b*), more than three-quarters; and in the lower section (*c*) it almost fills the canal, compressing the theca and its contents to a low density crescent posterior to it.



a *b* *c*

Fig. 2.22. Lipoma, axial sections at level of axis (*a*) and C3 (*b*). Coronal section (*c*). The lipoma is of low density (−30 H). It is partly within the theca, extruding from the posterior aspect of the spinal cord, and partly extradural, extending through the second cervical intervertebral foramina. There is considerable enlargement of the spinal canal.

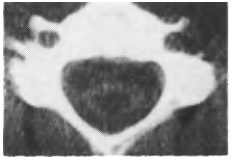


Fig. 2.23. Syringomyelia. The spinal cord is only slightly enlarged. Its substance is of higher density than the surrounding cerebrospinal fluid and the central syrinx.

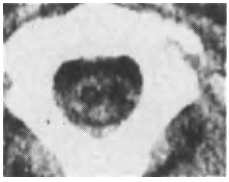


Fig. 2.24. Syringomyelia: scan with xenon inhalation. The xenon enhances the cord substance and increases the difference in density between it and the cerebrospinal fluid. The syrinx, which has a bilocular configuration, is clearly shown.

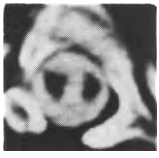
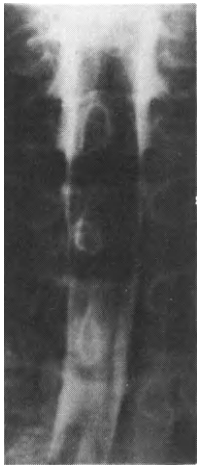


Fig. 2.25. Diastematomyelia in the lower dorsal region. CT scan with intrathecal metrizamide. The spinal canal is enlarged and the cord is divided into two almost equal parts by the subarachnoid space between them. No bony spur was present.



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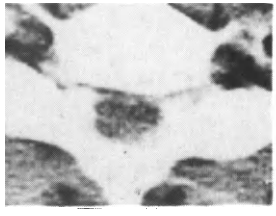

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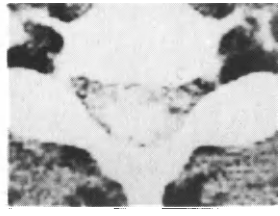


c

Fig. 2.26. Post-traumatic cyst of the dorsal and cervical segments of spinal cord. *a*, Metrizamide myelogram. There is swelling of the lower cervical and dorsal cord. *b*, CT 1 hour after myelogram: expanded cord outlined in opacified subarachnoid space. *c*, Eight hours after intrathecal injection of metrizamide: the syrinx is outlined by the contrast medium and is now denser than the subarachnoid space.

substance. It may be of particular value in the detection of low attenuation avascular lesions including syringo/hydromyelia (*Fig. 2.24*) and cysts associated with tumours [60].

Computed Myelography

On plain scans, it may be difficult and sometimes impossible to show details of the structures within the spinal subarachnoid space. This is particularly so when the space is narrow, whether as a normal variation or due to a pathological process. The anatomy is much more clearly shown after intrathecal injection of a low concentration of metrizamide. The spinal cord and the nerve roots in all regions are then delineated (*Fig. 2.25*), cord atrophy and swelling, small masses and even minor irregularities are outlined.

In syringo- or hydromyelia, the variation in the contour of the cord with posture, consisting of flattening of the uppermost surface has been demonstrated; opacification of those syringo/hydromyelic cavities, which are enlarging the cord, occurs within 6 hours and is generally relatively more intense by 12 hours [61] (*Fig. 2.26*). Intrathecal metrizamide penetrates into cord substance [62]; it is not generally possible to determine whether filling of a syrinx has occurred through the cord substance or directly from the subarachnoid space. The cerebellar tonsils are well shown by coronal scanning or by reformatting.

Since computed myelography involves spinal puncture, it is generally used as an adjunct to conventional metrizamide myelography. The display of a lesion in transverse section often gives a clear indication of its relation to and effects on the spinal contents. An apparently complete obstruction on conventional myelography may allow sufficient metrizamide to extend past it for assessment by CT and an additional puncture may thus be avoided in some cases.

If computed myelography is performed as an elective procedure using a low concentration of metrizamide, longitudinal images obtained with the scout film facility are a valuable supplement to the scan images and in favourable circumstances may replace conventional myelography.

Computed Endomyelography

A well-defined, low attenuation, intramedullary lesion on plain CT suggesting the probability of a cyst or syrinx, may be punctured with a fine needle and a specimen of fluid replaced by a smaller volume of metrizamide. The appearance of the fluid and the contour of the cyst shown on conventional films may indicate the nature of the pathology [63]. Narrow extensions, containing concentrations of metrizamide too low to be visible on conventional films, may be shown on CT.

The method is only very rarely necessary for diagnosis, but it can be useful in two situations. First, to demonstrate extension of a syrinx into

the filum terminale which may be significant if division of the filum for treatment of the syrinx is under consideration and secondly, in long expansions of the cord caused by a tumour combined with a cyst, where the surgeon desires to remove or biopsy the former and drain the latter through a short laminectomy. Endomyelography gives the essential localizing information but CT provides supplementary detail in the transverse axis.

REFERENCES

1. Isherwood I., Pullen B. R. and Ritchings R. T. (1978) Radiation dose in neurological procedures. *Neuroradiology* **16,** 477–81.
2. Gregg E. C. (1977) Radiation risks with diagnostic X-rays. *Radiology* **123,** 447–53.
3. Bhave D. G., Kelsey C. A., Burnstein J. et al. (1977) Scattered radiation doses to infants and children under EMI head scans. *Radiology* **124,** 379–80.
4. Quisling R. G., Seager J. F. and Gabrielston T. O. (1974) Radiation dose to eye lens and gonads during transfemoral cerebral angiography. *Radiology* **112,** 715–17.
5. Kingsley D. P. E. (1977) Computer tomographic artefacts using the CT 1000. In: du Boulay G. and Moseley I. F. (ed.), *Computerised Axial Tomography in Clinical Practice.* Berlin, Springer-Verlag, pp. 36–42.
6. Hounsfield G. N. (1978) Computed tomography – past, present and future. In: Kreel L. (ed.), *Medical Imaging – a Basic Course.* Aylesbury, HM & M, pp. 1–8.
7. Orwell C., du Boulay G. H., Kendall B. E. et al. (1980) High spatial resolution on the EMI 5005 Scanner and 7020 Scanners. Amsterdam, Excerpta Medica, Xtract 8, 2–7.
8. Lloyd G. A. S., du Boulay G. H., Phelps P. D. et al. (1979) The demonstration of the auditory ossicles by high resolution CT. *Neuroradiology* 18, 243–8.
9. Lee S. H. and Villafana T. (1980) Localisation of vertex lesions on cranial computed tomography. *Radiology* **134,** 539–40.
10. Brody W. R., Macouski A., Lehmann L. et al. (1980) Intravenous angiography using scanned projection radiography. *Invest. Radiol.* **15,** 220–3.
11. Greitz T., Bergstrom M., Boethuis J. et al. (1980) Head fixation system for integration of radiodiagnostic and therapeutic procedures. *Neuroradiology* **19,** 1–6.
12. du Boulay G., Fairburn D. and Paden R. S. (1978) Precise re-positioning of the head for serial C.T. examination. *Neuroradiology* **16,** 625–6.
13. Kirschner M., Burmester U., Stringaris J. et al. (1979) Physical experiments on the utility of non-iodine-containing contrast media. In: Gerhardt P. and Van Kaick G. (ed.) *Total Body Computerised Tomography.* Stuttgart, Thieme, pp. 262–3.
14. Newhouse J. H. (1977) Fluid compartment distribution of intravenous iothalamate in the dog. *Invest. Radiol.* **12,** 364–7.
15. Cattell W. R., Fry I. K., Spencer A. G. et al. (1967) Excretion urography: factors determining the excretion of hypaque. *Br. J. Radiol.* **40,** 561–71.
16. Gado M. H., Phelps M. E. and Coleman R. E. (1975) An extravascular component of contrast enhancement in cranial computed tomography. *Radiology* **117,** 589–97.
17. Ansell G. (1970) Adverse reactions to contrast agents. Scope of problem. *Invest. Radiol.* **5,** 374–84.
18. Scott W. R. (1980) Seizures: a reaction to contrast media for computed tomography of the brain. *Radiology* **137,** 359–61.
19. Hacker H. and Becker H. (1977) Time controlled computed tomographic angiography. *J. Comput. Assist. Tomogr.* **1,** 405–9.

20. Heinz E. R., Dubois P., Osbourne D. et al. (1979) Dynamic computed tomography study of the brain. *J. Comput. Assist. Tomogr.* **3**, 640–9.
21. Zilhka E., Ladurner G., Iliff L. D. et al. (1976) Computer subtraction in regional cerebral blood volume measurements using the EMI scanner. *Br. J. Radiol.* **49**, 330–4.
22. Crocker E. G., Zimmerman R. A., Phelps M. E. et al. (1976) Effects of steroids on the extravascular distribution of radiographic contrast materials and technetium pertechnetate in brain tumours as determined by CT. *Radiology* **119**, 471–4.
23. Zilkha E., Kendall B. E., Low L. et al. (1978) Diagnosis of subdural haematoma by computed axial tomography: use of xenon inhalation for contrast enhancement. *J. Neurol. Neurosurg. Psychiatry* **41**, 370–3.
24. Haughton V., Donegan J., Walsh P. et al. (1980) Clinical cerebral blood flow with inhaled xenon and CT. *Am. J. Roentgenol.* **134**, 281–3.
25. Meyer J. S., Hayman L. A., Yamamoto M. et al. (1980) Local cerebral blood flow measured by CT after stable xenon inhalation. *Am. J. Roentgenol.* **135**, 239–51.
26. Spetzler R. F. and Wilson C. B. (1979) Management of CSF rhinorrhoea of the middle and posterior fossa. *J. Neurosurg.* **49**, 393–7.
27. Hindmarsh J. and Greitz T. (1975) Computer cisternography in the diagnosis of communicating hydrocephalus. *Acta Radiol. Diagn. (Stockh.)* **346**, 91–7.
28. Tamaki N., Kanazawa Y., Asada M. et al. (1978) Comparison of cerebrospinal fluid dynamics studied by computed tomography (CT) and radioisotope (RT) cisternography. *Neuroradiology* **16**, 193–8.
29. Hiratsuka H., Fuginora K., Okada K. et al. (1979) Modification of periventricular hypodensity in hydrocephalus with ventricular reflux in metrizamide CT cisternography. *J. Comput. Assist. Tomogr.* **3**, 204–8.
30. Lee B. C. P., Gomez D. G., Potts D. G. et al. (1979) Passage of Amipaque (metrizamide) through the arachnoid granulations. *Neuroradiology* **17**, 185–90.
31. Shaffer K. A., Haughton V. M. and Wilson C. R. (1980) High resolution computed tomography of the temporal bone. *Radiology* **134**, 409–14.
32. Kricheff I., Pinto R., Bergeron R. T. et al. (1980) Air-CT cisternography and canalography for small acoustic neuromas. *Am. J. Neuroradiol.* **1**, 57–64.
33. Syvertsen A., Haughton V. M., Williams A. L. et al. (1979) The computed tomographic appearances of the normal pituitary gland and pituitary microadenomas. *Radiology* **133**, 385–91.
34. Daniels D. L., Haughton V. M., Williams A. L. et al. (1980) Computed tomography of the optic chiasm. *Radiology* **137**, 123–7.
35. Lilliquist B., Linqvist M. and Valdimarsson E. (1977) Computed tomography of subarachnoid haemorrhage. *Neuroradiology* **14**, 21–6.
36. Scotti G., Ethier R., Melançon D. et al. (1977) Computed tomography in the evaluation of intracranial aneurysms and subarachnoid haemorrhage. *Radiology* **123**, 85–90.
37. Yock D. N. and Larson D. A. (1980) Computed tomography of haemorrhage from anterior communicating aneurysms, with angiographic correlation. *Radiology* **134**, 399–407.
38. Weisberg L. A., Nice C. and Katz M. (1978) *Aneurysms in Cerebral Computed Tomography*. Philadelphia, Saunders, pp. 87–94.
39. Ghoshhafra K., Scotti L., Marasco J. et al. (1979) CT detection of intracranial aneurysms in subarachnoid haemorrhage. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **132**, 613–16.
40. Daniels D. L., Haughton V. M., Williams A. L. et al. (1979) Arteriovenous malformation simulating a cyst on computed tomography. *Radiology* **133**, 393–4.
41. Naidich T. P., King D. G., Moran C. J. et al. (1980) Computed tomography of the lumbar thecal sac. *J. Comput. Assist. Tomogr.* **4**, 37–41.

42. Isherwood I., Antoun N. M., Checkley D. et al. (1979) Experience with high resolution scanning of the spine. *J. Comput. Assist. Tomogr.* **3**, 566–7.
43. Ethier R., King D. G., Melançon D. et al. (1979) Development of high resolution computed tomography of the spinal cord. *J. Comput. Assist. Tomogr.* **3**, 433–8.
44. Faerber E. N., Wolpert S. M., Scott R. M. et al. (1979) Spinal fractures. *J. Comput. Assist. Tomogr.* **3**, 657–61.
45. Naidich T. P., Pudlowski R. M., Moran C. J. et al. (1979) Computed tomography of spinal fractures. *Adv. Neurol.* **22**, 207–53.
46. Oberson R. and Azam F. (1978) CAT of the spine and spinal cord. *Neuroradiology* **16**, 369–70.
47. Carrera G. F., Williams A. L. and Haughton V. M. (1980) Computed tomography in sciatica. *Radiology* **137**, 433–7.
48. Williams A. L., Haughton M. and Sylvertsen A. (1980) Computed tomography in the diagnosis of herniated nucleus pulposus. *Radiology* **135**, 95–9.
49. Resjo I. M., Harwood Nash D. C., Fitz C. R. et al. (1978) Computer tomographic metrizamide myelography in spinal dysraphism in infants and children. *J. Comput. Assist. Tomogr.* **2**, 549–58.
50. Arredondo F., Haughton V. M., Hemmy, D. C. et al. (1980) The computed tomographic appearances of the spinal cord in diastematomyelia. *Radiology* **136**, 685–8.
51. Kaplan J. O. and Quencer R. M. (1980). The occult tethered conus in the adult. *Radiology* **137**, 387–91.
52. Dossetor R. S., Kaiser M. and Veiga-Pires J. A. (1979) CT scanning in two cases of lipoma of the spinal cord. *Clin. Radiol.* **30**, 227–31.
53. Bonafé A., Ethier R., Melançon D. et al. (1980) High resolution computed tomography in cervical syringomyelia. *J. Comput. Assist. Tomogr.* **4**, 42–7.
54. Lee B. P. C., Kazam E. and Newman A. D. (1978) Computed tomography of the spine and spinal cord. *Radiology* **128**, 95–102.
55. Baleriaux-Waba D., Retif J. and Noterman J. (1978) CT scanning for the diagnosis of the cerebellar and spinal lesions of Von Hippel–Lindau disease. *Neuroradiology* **14**, 241–4.
56. Handel S., Grossman R. and Sarwar M. (1978) Computed tomography in the diagnosis of spinal cord as astrocytoma. *J. Comput. Assist. Tomogr.* **2**, 226–8.
57. Di Chiro G., Doppman V. L. and Vener L. (1977) Computerised tomography of spinal arteriovenous malformation. *Radiology* **123**, 351–4.
58. Quencer R. M. (1980) Needle aspiration of intra-medullary and intradural extramedullary masses of the spinal canal. *Radiology* **135**, 115–26.
59. Coin C. G. and Hucks-Folliss A. (1979) Cervical computed tomography in multiple sclerosis with spinal cord involvement. *J. Comput. Assist, Tomogr.* **3**, 421–2.
60. Pullicino P., du Boulay G. H. and Kendall B. E. (1979) Xenon enhancement for computed tomography of the spinal cord. *Neuroradiology* **18**, 63–6.
61. Aubin M. L. and Vignaud J. (1980) Contribution of CT to the study of syringomyelia as seen in 40 adult cases of the disease. In: Caillé J. M. and Salamon G. (ed.) *Computerised Tomography*. Berlin, Springer-Verlag, pp. 91–4.
62. Forbes W. St C. and Isherwood I. (1978) Computed tomography in syringomyelia and the associated Arnold Chiari type 1 malformation. *Neuroradiology* **15**, 73–8.
63. Kendall B. E. and Symon L. (1973) Cyst puncture and endomyelography in cystic tumours of the spinal cord. *Br. J. Radiol.* **46**, 198–204.

M. J. G. Harrison

3 Carotid Endarterectomy

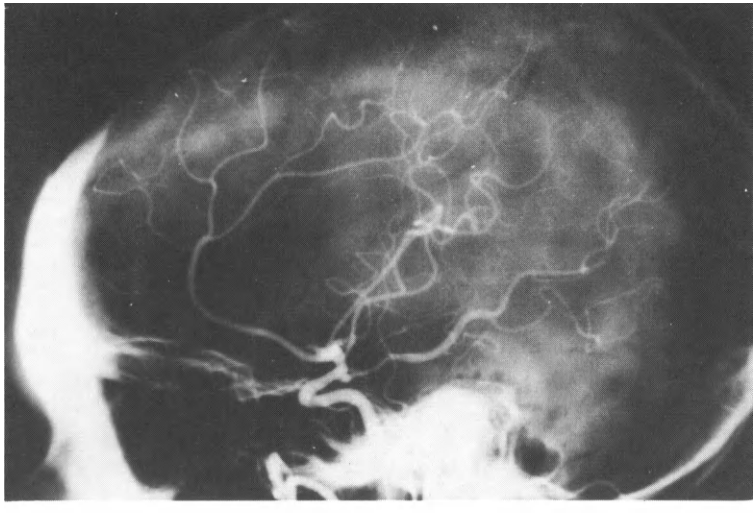
This is an appropriate time to review the role of carotid endarterectomy in the overall management of cerebrovascular disease. The newer extracranial-intracranial bypass procedure (Chapter 4) is being carried out with increasing frequency, and antiplatelet drugs have been shown to be at least partially successful in the prevention of stroke. It is pertinent therefore to re-examine the rationale for carotid endarterectomy, and to reconsider the pros and cons of the procedure in the light of the natural history of stroke disease, and the success of the rival treatments.

RATIONALE

If a large percentage of strokes are due to carotid stenosis, then endarterectomy should logically be an effective preventive measure. It will be necessary to review the evidence that arteriosclerotic disease of the internal carotid artery in the neck can be the cause of cerebral infarction.

Lhermitte et al. [1] studied 122 cases of cerebral infarction in the territory of the middle cerebral artery. In 56 cases the cause of the infarct was occlusion of the internal carotid artery. In 6 of these instances the carotid was obstructed by a cardiac embolus, but in the others the occlusion was due to local thrombosis superimposed on atheromatous stenosis. Forty per cent of the middle cerebral territory infarcts were thus attributable to thrombosis of a previously stenosed carotid artery. Another 40 per cent of the infarcts were due to occlusion of the middle cerebral artery itself. These more distal occlusions were nearly always embolic. The source of the embolic material was shown to have been a stenotic carotid lesion in 6 per cent. Carotid disease was thus the demonstrable cause of 46 per cent of the infarcts in the middle cerebral artery territory.

When one turns to studies of unselected strokes, the role of carotid disease is less striking. Thus carotid occlusion in the neck accounted for 14 of the 80 cases of cerebral infarction in Jorgensen and Torvik's community hospital autopsy survey [2]. Angiographic studies also give a figure of approximately 20 per cent for carotid occlusion [3, 4]. Some 50 per cent of all strokes due to cerebral infarction are believed to be due to cardiac embolism [2, 5], and perhaps 10 per cent are due to embolism from the aorta [6]. The role of carotid stenosis without occlusion is less certain, being seen in many patients without cerebral infarcts [7], but as we have



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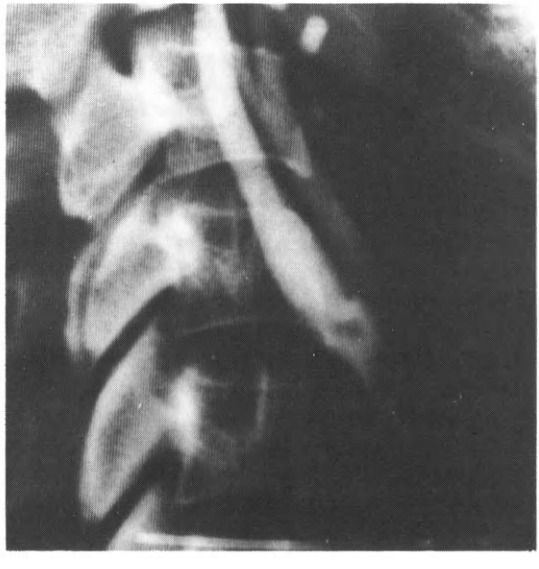

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Fig. 3.1. Example of middle cerebral occlusion due to embolism from the internal carotid artery. *a*, Angiographic demonstration of middle cerebral occlusion. *b*, From neck films of same study: thrombus in the post-stenotic segment of the internal carotid artery.

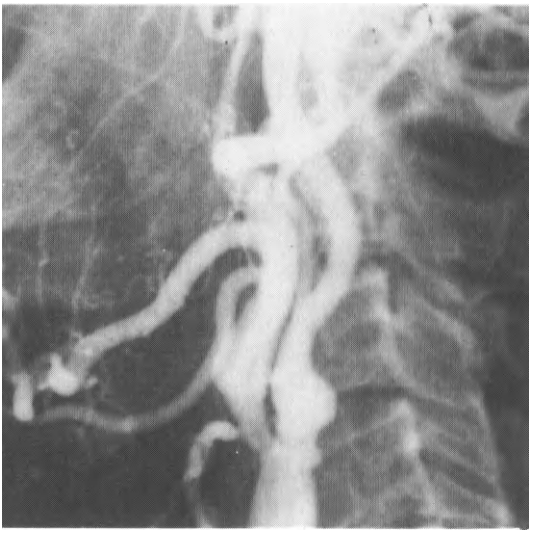

Fig. 3.2. Ulcerative lesion of internal carotid artery at bifurcation. There is also narrowing of the origin of the external carotid artery.

seen in Lhermitte's careful study, embolic occlusion of the middle cerebral artery may occasionally originate in disease at the carotid bifurcation [1] (*Fig. 3.1*).

A further finding of the French study was that the stenosis underlying carotid thrombosis was usually severe [8], commonly 75 per cent or more. This suggests that it is the severely stenosed vessel that is most at risk from thrombosis. There are two possible reasons for this. First, such stenosed lesions are usually ulcerated [9], the ulcerated area being a nidus for thrombus formation. Secondly, stenoses over 65 per cent cause a pressure gradient and at 80 per cent or so cause a reduction in mean flow [10]. This haemodynamic effect would also be expected to favour propagation of local thrombus where the stenosis is tight.

Angiographic evidence of intracranial embolism is twice as frequent in the presence of ulceration of the carotid lesion [11, 12]. Stenotic lesions that have no effect on pressure or flow in the vessel may thus be important to the development of stroke if they are a source of embolism due to the presence of ulceration (*Fig. 3.2*).

The rationale for carotid endarterectomy in the prevention of stroke is thus principally to remove a stenosis that might otherwise thrombose, and to remove an ulcerated lesion that might be the source of embolic occlusion of intracranial vessels such as the middle cerebral artery.

DETECTION OF CAROTID STENOSIS

Clearly the presence of stenotic disease of the internal carotid artery or a source of embolism at the bifurcation needs to be detected before the occurrence of stroke if carotid endarterectomy is to be preventive.

Clinical Features

Although the association of apoplexy with carotid disease was known in the last century [13, 14], detailed clinical studies were only carried out in the 1950s [15, 16]. These showed that some 50 per cent of patients suffering a stroke due to carotid occlusion had had preceding symptoms of transient cerebral ischaemia in the territory of the same vessel. It was thus realized that patients at risk of carotid occlusion could sometimes be detected clinically. Attention then focused on the transient ischaemic attack (TIA) as a marker of the stroke-prone patient.

That TIAs are associated with a high stroke risk is clear from natural history studies. That carried out in Rochester for example [17] revealed that 35 per cent of TIA patients went on to a completed stroke in 5 years, contrasting with a 5 per cent risk in the rest of the community. While the increased risk is striking, it is sometimes forgotten that 65 per cent of such patients will not suffer a major stroke in the next 5 years, that those at risk cannot be separately distinguished [18], and that the major mortality is cardiac [17]. Fifty per cent of the strokes that do occur in TIA patients do so within the first year, 17 per cent in the first month. Any preventive measure, such as endarterectomy, must therefore be considered promptly after the onset of TIAs.

Unfortunately for the early detection of carotid disease, only 10 per cent of stroke victims in the community have such a TIA. This figure rises in the case of patients seen in hospital but is still only 30 per cent [19]. Also, not all TIAs are due to the same mechanism [20]. Many have causes unrelated to atheroma of neck vessels, such as anaemia, polycythaemia, hypoglycaemia, migraine, angioma, aneurysm, subdural haematoma, cerebral tumour etc. Cardiac dysrhythmia, though frequently detected in patients with TIAs [21], is rarely causally related to symptoms of focal cerebral ischaemia [22]. The rare combination of a cardiac dysrhythmia, affecting cardiac output, and a haemodynamically severe carotid stenosis can cause focal symptoms, and indeed this was the situation in the first successful carotid reconstruction [23]. Postoperatively the patient still had cardiac irregularities but with the relief of carotid stenosis these no longer caused retinal and hemisphere symptoms.

The majority of TIA patients have neck vessel disease. The ipsilateral carotid artery shows ulceration, stenosis or occlusion in up to 80 per cent of patients with TIAs in the retina (amaurosis fugax) or hemisphere when these other causes have been eliminated [12]. In a study of over 200 patients with carotid territory TIAs, Harrison and Marshall [24]

found 60 per cent to have atheroma of the carotid though less than 1 in 3 had an operable lesion. Eisenberg found 64 per cent to have a stenotic lesion [25] whilst Wilson and Ross Russell found 30 per cent of patients with amaurosis fugax to have an operable stenosis [26].

Thus no more than half of all strokes can be shown to be due to carotid disease and less than half of these have a preceding TIA. If TIA patients are investigated for the presence of stenosis 50-60 per cent will have such atheromatous lesions but only 1 in 3 may have an operable stenosis. It is against this background that carotid endarterectomy was developed for the treatment of recurrent TIAs and the prevention of stroke.

Asymptomatic Carotid Disease

More recently the possibility of detecting asymptomatic carotid stenosis has been pursued in an attempt to increase the number of patients that could be offered preventive surgical treatment. As angiography is invasive and has associated morbidity and mortality, non-invasive methods have been increasingly investigated [27-30] for use in asymptomatic individuals [31].

Carotid Bruits

The presence of a bruit over the carotid bifurcation has long been known to be associated with the presence of angiographically confirmed vessel wall disease [24]. Experimental study shows that a 40 per cent area reduction causes a bruit but no pressure gradient, a 60 per cent area reduction produces a pansystolic murmur and a reduction in peak systolic flow. A 70 per cent area reduction causes a bruit that extends into diastole and a reduced mean blood flow. There may be no bruit with extreme stenosis and in the presence of occlusion there is no bruit and heart sounds are not conducted up the vessel [32]. The quantitative assessment of bruits in patients also being investigated by angiography has shown that the assessment of the residual lumen compares well [33]. Difficulties arise when the external carotid artery is stenosed and is the source of a bruit, when the internal carotid artery is occluded and when a bruit is conducted into the internal carotid artery from the heart, aorta, innominate or common carotid vessel. Severe stenosis may be missed by carotid phonangiography as may lesions with less than 35 per cent stenosis. Ulcerated lesions causing no flow abnormality will similarly cause no bruit. A bruit may, however, alert the physician to a stenotic lesion of 40-50 per cent that will be causing no pressure drop and therefore be undetected by other flow-dependent non-invasive screening tests.

Doppler Flow Studies

The flow in the supra-orbital artery is influenced by the development of collateral channels if there is a haemodynamically significant stenosis or

occlusion of the internal carotid artery. The direction of flow is monitored by a small directional Doppler instrument at rest and in some versions of the technique, it is monitored also in response to manual compression of the superficial temporal, facial and carotid arteries. A normal result has no significance; any abnormality of flow pattern has a 90 per cent chance of being associated with occlusion or a stenosis of 75 per cent or more. Stenoses that might be clinically important but do not reduce internal carotid artery pressures, and ulcerated non-stenotic lesions, will be missed.

Isotope Scanning

Rapid sequence scintiphotography and rectilinear scanning after $^{99}Tc^{m}$ injection were assessed in TIA patients by Yuson and Toole in 1976 [34]. In patients with an occluded carotid, the rapid sequence scintiphotography proved reliable when positive. There were many false negatives, however (6 of 17). There were fewer abnormalities in patients with stenotic lesions but there were no false positives. When combined with bruit evaluation and ophthalmodynamometry the chances of detecting an abnormality in carotid occlusion were very high. Some abnormality was present in all but 4 patients with stenotic disease but angiography was still necessary to assess suitability for surgery.

Ocular Plethysmography

In one technique the pulse waveform recorded from the two eyes is displayed simultaneously. It represents the change in ocular volume with pulsatile arterial blood flow. A haemodynamically significant stenosis causes a delay of the waveform over the ipsilateral eye. A flow reduction of 40 per cent detected by this method corresponds with a 70 per cent angiographic stenosis [35]. There are difficulties if there is bilateral disease; occlusion cannot always be distinguished from tight stenosis, and stenosis of less than 50 per cent is probably not detectable.

In another technique devised by Gee, ophthalmic artery pressure is measured as ocular pulsations return, after a negative pressure applied to the eye is slowly reduced. McDonald's group [36] have recently compared both techniques and found the Gee method superior for stenosis over 60 per cent.

Oculoplethysmography methods currently represent the most reliable of the non-invasive techniques for the detection of severe stenosis [37].

Ultrasonic Angiography

The use of pulsed ultrasound and B mode scanning promises to overcome many of the difficulties of other non-invasive methods. Thus a plaque

causing 20–30 per cent encroachment on the lumen may be detectable. At present these techniques are still in the stage of development. Calcification of plaques and difficulties in identifying the internal and external carotid artery cause technical problems, but views of the carotid bifurcation in three planes are theoretically possible [37].

Combined Techniques

Haemodynamically significant lesions can be detected by oculoplethysmography, phonangiography and supra-orbital Doppler measurements. Lesions of less than 50 per cent stenosis are difficult to detect though some will be associated with a bruit and may be visualized by ultrasound scanning. Ulcerated lesions with little encroachment on the lumen will be missed by all the non-invasive tests. Occlusion and tight stenosis cannot always be distinguished. If surgery is contemplated, angiography remains obligatory to visualize the atheromatous lesion.

Angiography

For symptomatic (TIA) patients angiography is indicated to detect and define the extent of carotid arterial disease. The highest yields are in patients with both retinal and hemisphere attacks, and in those with a cervical bruit [20, 38]. Patients with brief attacks are more likely to have stenosis than those with symptoms lasting more than 1 hour [39]. Eisenberg found a stenotic lesion of the relevant carotid artery in 64 per cent, occlusion in 17 per cent and ulceration without stenosis in 7 per cent of cases. Over 50 per cent stenosis was present in 34 per cent (*Fig. 3.3*) [25].

In the case of amaurosis fugax the highest yield is in individuals over the age of 50 with hypertension, peripheral vascular disease, associated hemisphere symptoms and a bruit. Normal angiograms are rare in such instances [26].

Overall the yield of operable lesions in the presence of carotid territory TIAs is, however, under 50 per cent [24, 26].

Although thrombus is present in over half the cases subjected to surgery [40], angiographic visualization of thrombi in the lumen of the internal carotid artery above a stenotic lesion is rare [41] (*Fig. 3.4*). Ulceration of the stenotic lesion is detected in approximately half [42], though operative findings [9] suggest this too is a significant underestimate (*Fig. 3.5*).

The complications of angiography include a mortality rate which is, however, less than 0·5 per cent [30], and persisting cerebral complications occur in from 0·5 to 2·5 per cent; patients with severe stenosis and more frequent TIAs appear to be at greater risk [43]. The difference between carotid puncture, brachial and catheter techniques does not seem marked though there are arguments against carotid puncture in this situation.

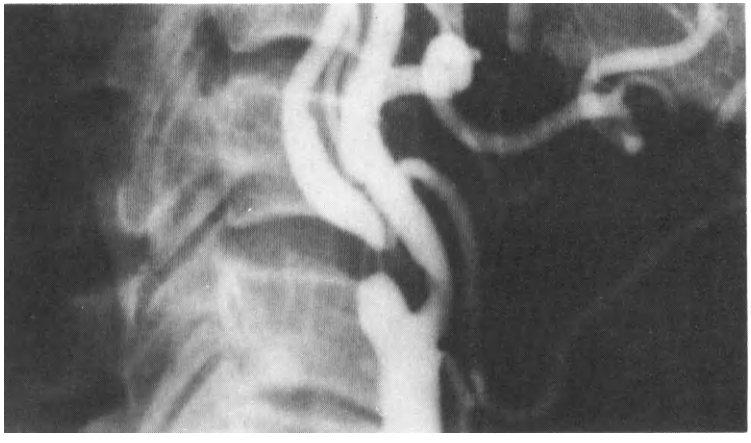

Fig. 3.3. Example of severe stenosis of the internal carotid artery in a patient with transient ischaemic attacks. (Reproduced from Ross Russell R. W. (ed.) (1976) *Cerebral Arterial Disease*, by kind permission of Churchill Livingstone.)

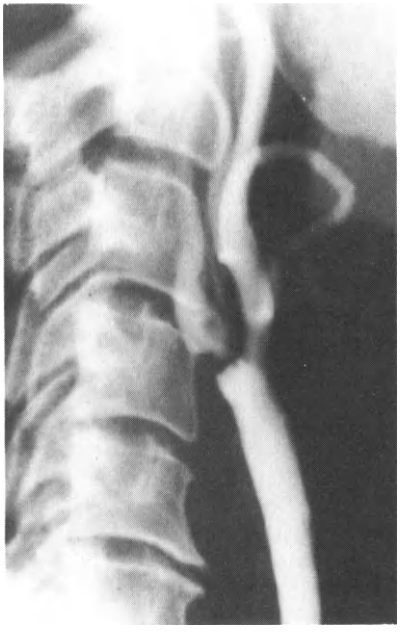

Fig. 3.4. Thrombus visualized in post-stenotic segment of internal carotid artery, in a patient with transient ischaemic attacks.

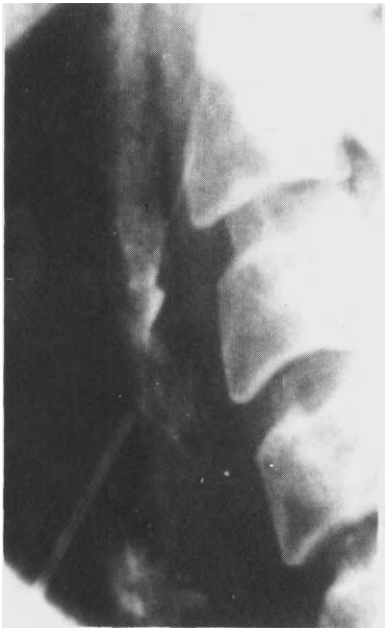

Fig. 3.5. Ulcerated wall lesion shown by retained contrast medium in crater.

Thus, complications attend subintimal injections and up to 25 per cent of cases in one study had a local haematoma [29], which can interfere with subsequent surgery,

Arch angiography is probably attended by a greater risk [30, 31], and often does not give adequate detail of the carotid bifurcation. The patency of the other main cervical vessels and adequacy of the circle of Willis, both factors in the genesis of cerebral infarction [44], may need to be assessed angiographically, however, before surgery can be planned. The risks of angiography must be added to the risks of surgery when judging the advisability of the surgical procedure.

The accuracy of angiography has been assessed at surgery [45] and in post-mortem studies [46]. With stenotic lesions the agreement is high (90 per cent for stenosis over 50 per cent). If ulceration is visible angiographically it is almost always, though not invariably, confirmed at surgery or dissection [47]. Most patients with marked stenosis have ulceration even though it is often not detected angiographically. Most difficulties attend the interpretation of lesions causing less than 50 per cent stenosis [30] and depend on the presence or absence of ulceration in non-stenotic lesions. Here the accuracy can fall to below 50 per cent [42, 46].

Asymptomatic Carotid Disease

The high risk of stroke in patients with TIAs provides a clear rationale for the correction of symptomatic carotid stenosis and prompts investigation by angiography. Clinical examination including auscultation for bruits, and non-invasive investigation of patients with vascular disease in other territories, reveals individuals with asymptomatic lesions of the internal carotid artery. Are these too associated with an increased stroke risk, and therefore to be considered for angiography and endarterectomy?

Angiographic studies show that asymptomatic vessels investigated because of a bruit have less severe stenotic disease than symptomatic cases [12]. Serial angiography, however, suggests that the degree of stenosis is likely to progress in over 50 per cent of carotid arteries affected by local atheroma [47]. The greatest increases in stenosis are seen in patients with a bruit, in hypertensives and in those with most severe stenosis in the first place. These pointers could perhaps be used to select lesions most likely to progress towards a level of stenosis that might then be complicated by occlusion.

The clinical follow-up of asymptomatic carotid atheroma however suggests that the actual risk of stroke is relatively small.

Johnson et al. [48] followed up 103 carotid endarterectomy survivors for up to 4 years to see what had happened to the unoperated but also diseased second side. No strokes had occurred on the unoperated side (3 had occurred on the operated side), only 3 patients had developed TIAs and only 3 had come to further surgery. This benign behaviour of the second side applied equally to cases with contralateral occlusion, and to 22 patients with over 50 per cent stenosis.

Prospective epidemiological studies give a somewhat less benign look to the fate of patients with an asymptomatic carotid bruit. Wolf et al. [49] followed 245 such subjects from the Framingham cohort. Two developed TIAs and 16 had strokes. Six of the strokes were unrelated to neck vessel disease, and more often than not the thrombotic stroke related to a different vascular territory. We must assume therefore that less than 6 strokes occurred in the 245 subjects on the side of their bruit. Though the bruit could be shown to make an independent contribution to stroke risk, the effect seems small.

In patients likely to sustain a period of hypotension, for example during coronary bypass or other major surgery, a haemodynamically significant carotid stenosis could cause hemisphere ischaemia or infarction, even without occlusion. It has been argued that in such patients there is a particular need to detect tight carotid stenosis. As we have seen, non-invasive methods especially in combination can do this with perhaps 90 per cent accuracy [37, 50], though angiography would be needed before endarterectomy was considered. The actual risk of stroke in patients having major surgery or aorto-iliac reconstruction, however, proves to be small. In two studies it was noted that though 15 per cent of surgical patients had

bruits over a carotid artery, none of the small number of postoperative strokes (0·6–1·6 per cent) occurred in those with bruits [51, 52]. Even when non-invasive tests uncovered severe occult stenotic lesions the strokes following cardiac and iliofemoral surgery proved not to have occurred in such individuals [53]. Strokes after aorto-iliac surgery were, however, more common (2 of 7) if the patients had symptomatic carotid disease with TIAs [52].

Moore [54] has some evidence that the stroke risk for asymptomatic patients is much greater with well-marked ulceration (12·5 per cent per year compared with 0·4 per cent per year with little or no ulceration). Therefore, patients with angiographic studies of asymptomatic carotid stenosis that show severe ulceration might be considered special cases.

RISKS OF ENDARTERECTOMY

The operation is attended by a mortality, though in most experienced centres this is below 2 per cent and often below 1 per cent for patients with TIAs or asymptomatic lesions [12, 42, 55, 56]. Most of these deaths within 72 hours of surgery are due to myocardial infarction, less commonly to cerebral infarction. Riles et al. [57] found evidence of myocardial infarction within 72 hours of carotid endarterectomy in 2·3 per cent of 491 patients; 5 died. The incidence in patients with pre-existing heart disease was 4·9 per cent, and in its absence, 0·5 per cent ($P < 0{\cdot}001$). White [58], discussing a series of 200 operations, noted that in addition to 4 postoperative deaths (2 due to myocardial infarction), 13 operations had had to be cancelled due to myocardial infarction or stroke occurring the night before the scheduled procedure.

The operative risk of hemiplegia due to cerebral infarction varies from 0·7 per cent [12, 55] for TIA patients to well over ten times this figure. Most centres with extensive experience report an incidence of 2 per cent or less [42, 59, 60].

The risk of preoperative stroke is up to ten times greater if the patient has had a prior completed stroke [42]. A history of a symptomatic episode over 24 hours, or residual soft neurological signs at the time of surgery, appear just as important causing a similar increase in risk [61]. Goldstone and Moore [62], however, have recently reported successful surgery in 28 patients with a crescendo of TIAs or ingravescent fluctuating stroke associated with a tight 90 per cent stenosis, thus challenging the usual reluctance to tackle unstable cases.

The cerebral risks also relate to the preoperative angiographic findings. The risks of endarterectomy are thought to be increased by contralateral occlusion or stenosis (to be expected in 1 in 3) [63], the presence of combined intracranial and extracranial stenosis (so-called tandem lesions) [61], the presence of visible thrombus, a long lesion or a high bifurcation [56].

Fig. 3.6. Friable material removed at carotid endarterectomy.

The mechanism of the cerebral complications has been debated. Experimentally an endarterectomy site is covered by a carpet of platelets and fibrin, and in the first 48 hours may develop a mural thrombus [64]. This may cause local occlusion requiring re-exploration when it occurs clinically. In Hertzer's study [65], perioperative stroke occurred in 9·9 per cent of 111 operations in the presence of angiographic ulcers, but in only 0·7 per cent of non-ulcerated lesions. This represents further evidence that embolism during manipulation and dissection may well be responsible for many operative deficits. Embolic material is actually present at the time of surgery in as many as two-thirds of cases operated upon shortly after a recent TIA [39] (*Fig. 3.6*).

That flow factors are also relevant is seen in the finding [65] that patients with a low carotid stump pressure after cross-clamping of the carotid artery have an increased risk of persisting stroke after surgery.

Some of the postoperative strokes are haemorrhagic and associated with hypertension [66], and pre-existing hypertension is a further factor in increasing the risk of stroke associated with endarterectomy [67].

Whether or not the use of a shunt reduces the risk of stroke is controversial. Some surgeons have found that the operative risks are lower in patients with a high stump pressure, or if there is a low pressure with the support of a shunt [65]. This argument, and the increased time allowed for careful dissection, leads some to employ shunts routinely [55]. Others

find the operative risk greater with shunts [68], though this latter study referred to the results of less experienced units. Many use a shunt only if there is evidence of a low pressure in the terminal internal carotid artery during clamping. This haemodynamically hazardous situation may be assessed during the operation by stump pressure measurement, cerebral blood flow measurements or by EEG monitoring [69]. Preoperative prediction of the need for a shunt may be possible using supra-orbital Doppler recordings. If frontal artery flow reverses or stops during brief carotid compression, stump pressure proves to be of the order of 25 mmHg. If no change in the direction of flow occurs, stump pressure averages 68 mmHg [70]. There is obviously a theoretical risk in manual carotid compression in such patients though many report no difficulties in practice.

The critical stump pressure for shunt insertion is difficult to judge. Smith et al. [71] noted little difference in stroke risk between patients with stump pressures of over 50 torr and between 25 and 50 torr. Many take 25 as the critical level, others 50. EEG flattening occurs with cerebral blood flow below 14 ml 100 g^{-1} min^{-1} [69], so if cerebral blood flow is used shunt insertion is deemed prudent at 18 ml 100 g^{-1} min^{-1} and perhaps even below 30 [56] (normal level 50-55 ml 100 g^{-1} min^{-1}). Hypercarbia to increase cerebral blood flow is probably unhelpful [72], maintenance of a normal blood pressure being more important.

If both sides are to be operated upon there is little evidence that a long interval between the two procedures is worth while. Timing is usually governed more by any temporary deficit after the first side has been treated [73].

If a coronary bypass procedure is needed in the same patient there is evidence that the operations should be combined, or the cardiac surgery performed first. The cardiac morbidity and mortality attending endarterectomy in patients with unstable ischaemic heart disease is excessive, but is reduced by previous successful coronary bypass surgery [74].

Re-stenosis after endarterectomy affects only a minority (0·6-9·8 per cent). In some this is due to myointimal proliferation [75]. Later atheroma [76] causes symptomatic re-stenosis. Factors in the development of re-stenosis appear to include incomplete removal of a long plaque at the limit of the endarterectomy, hyperlipidaemia and hypertension.

RESULTS OF ENDARTERECTOMY

Since the long term patency is so good, what of the clinical outcome? Does carotid endarterectomy prevent subsequent TIAs and stroke?

There has only been one controlled trial which was carried out on a multicentre basis 10 years ago [77]. A total of 316 patients was allocated to surgical or non-surgical treatment. All had had TIAs in carotid or vertebrobasilar territories. Overall TIAs continued in 36 per cent of surgically treated cases and 47 per cent of medically managed patients. Most of the

attacks, however, were not in the territory of the endarterectomized vessel. TIAs were much less frequent when the surgery had been for a carotid stenosis on the side of carotid territory TIAs. For example, of 44 patients having isolated carotid TIAs, who had unilateral or bilateral carotid endarterectomy, only 2 continued to have TIAs. Of 39 similar patients treated medically, 12 had further carotid TIAs.

New strokes developed in 4 per cent of surgical survivors and 12·4 per cent of medically treated patients. The surgical mortality and morbidity were sufficiently high, however, to cancel out the long term benefit. Also the study is difficult to evaluate as the non-surgical group had diverse medical treatments.

The risks of surgery have declined dramatically since this study was carried out. For example, Moore's group have reported a combined death and stroke risk of 10 per cent for endarterectomies carried out before 1970, contrasting with a figure of 0·9 per cent between 1971 and 1979 [78].

A new trial needs to be done in centres with currently low operative risks. In the meanwhile the joint study [77] has to be 'buttressed' by uncontrolled observations to obtain a workable consensus on the value of surgery.

To reiterate the natural history of symptomatic patients (TIA). Some 5-6 per cent per annum will have a stroke throughout the years of follow-up with a higher rate, perhaps 12-15 per cent in the first year after presentation [17]. The combined risk at 5 years is about 30-35 per cent. Long term follow-up in a number of surgical survivors reveals a stroke risk of about 10 per cent in 5 years [79], or even less [55]. To this, of course, must be added the surgical and angiographic risk.

Clearly where the stroke and death risk attending endarterectomy are high [80], there will be no net gain from the procedure. It will therefore be a parochial decision, based on the success of the local vascular surgeon, whether to refer symptomatic cases of carotid stenosis. Hass has calculated that a stroke complication rate of over 2·9 per cent will negate the long term benefits of surgery [81]. Many of the best centres can report a combined angiographic and surgical risk of this order [67, 68]. West's report [78] calculated that after a combined short term stroke and death risk of 3 per cent. the long term risk of stroke in survivors amounted to 3·3 per cent per annum, probably half the rate to be expected from natural history studies. Stanford et al. [42] reported an initial mortality and stroke risk of 2·5 per cent and a long term stroke risk at an average follow-up of 20 months of 4·7 per cent, approximately one-third of the expected rate. Thompson with an initial operative mortality and stroke risk in TIAs of about 1·5 per cent found a long term stroke risk of 5-7 per cent during a follow-up of up to 13 years [55].

Operation for non-stenotic ulcerated lesions was reported in a separate small study of 35 patients by Moore and Hall [82]. The only operative

death occurred in a patient having bilateral endarterectomy. Three patients had transient neurological deficit, none an operation-related persisting morbidity. Follow-up from 4 to 39 months revealed that only 1 patient had had a stroke and this on the unoperated side, a striking reduction compared with the follow-up of severely ulcerated lesions by the same unit [54]. Without a randomized trial of sufficient size it is impossible to be sure whether surgery should be offered in this group at present.

Long Term Survival

deWeese [79] reported on the long term outcome of 103 patients 5 years after their endarterectomy. Thirty-five had died—5 of stroke and 25 of ischaemic heart disease. The mortality had been 56 per cent in those with preoperative evidence of coronary artery disease, and in these patients 93 per cent of the deaths were due to myocardial infarction. There is no evidence of improved survival after carotid surgery in the long term due to this cardiac mortality [19, 31]. Of deWeese's survivors, 3 had a major and 4 a minor neurological deficit at the end of 5 years.

SPECIAL CIRCUMSTANCES

Contralateral Carotid Occlusion

Despite the theoretical hazards of surgery for stenosis with a carotid occlusion on the asymptomatic side, several surgeons have reported series without excessive complications [55], though the risks are increased [56]. The follow-up shows no excess of long term strokes related to the occluded side [48]. There is no need to exclude such cases from surgical consideration therefore.

TIAs with Residual Neurological Deficit

The definitions of TIA and completed stroke imply that if symptoms remit within 24 hours there has only been reversible ischaemia, but that if they exceed this arbitrary limit infarction has occurred. This is obviously naïve and many patients with brief attacks have evidence of structural change in the form of persisting EEG, CT scan, and/or rCBF abnormality. If there is evidence that an episode, whatever its precise duration, has been due to embolism from the carotid bifurcation it is reasonable to contemplate endarterectomy to prevent recurrence. This policy would therefore be applicable to TIAs with soft residual signs, to small strokes and even major completed strokes if recovery was good. The risks of surgery are, however, higher in these clinical groups [55, 56, 61]. Also, though carotid stenosis is commonly the cause of TIAs, it is less often the cause of completed strokes, and the risk of repeated strokes is probably less than that

of a first stroke after the onset of TIAs. An active approach to such patients is clearly only permissible in centres with the lowest operative casualty rates.

Asymptomatic Cases

The follow-up studies of asymptomatic carotid lesions detected by auscultation or non-invasive investigation of patients with arterial disease in other territories have already been discussed. It was argued that their stroke risk was low, and therefore unlikely to be improved upon by surgery that carried any mortality or appreciable morbidity. The operative risk, however, is at its lowest with asymptomatic cases, and some argue that surgery should therefore be offered to cases with asymptomatic lesions that are haemodynamically 'tight' [55], or heavily ulcerated [54]. Unless the surgical risk is of 0 per cent mortality and 0–1 per cent stroke morbidity it would seem unwise to recommend endarterectomy in these patients. The only exception may be in patients having coronary artery bypass surgery [74].

Carotid Kinks and Loops

The cause and effect relationship between such angiographic findings and TIAs and strokes is controversial. Their presence in cases of amaurosis fugax for example was no more frequent than in the population at large in Wilson and Ross Russell's study [26]. Operative correction is probably only indicated in symptomatic cases with either atheromatous disease in the loop or flow reduction as judged by non-invasive tests.

Carotid Occlusion and Recent Stroke

The chances of restoring patency are less than 50 per cent and the mortality may be as high as 60 per cent due to haemorrhage and oedema in the infarct. Exploration of a recently occluded carotid artery can however be contemplated if seen within a few hours of the onset of the neurological deficit (probably < 6 hours).

Asymptomatic chronic occlusion of the carotid artery has a small risk of stroke (2 per cent per year [83]), and surgery would not seem to be indicated.

MEDICAL TREATMENT

In view of the evidence linking thrombotic occlusion of the carotid artery to stroke, and thromboembolism to both TIAs and strokes, the prevention of thrombus formation should theoretically be a highly effective way of

preventing TIAs and strokes even in the presence of carotid stenosis and ulceration.

Anticoagulants

The prevention of fibrin formation by anticoagulation has proved to be hazardous and of little value in the aftermath of completed strokes due to infarction. In the case of TIAs, several trials were carried out but were either small or not randomized. Attempts to combine the figures from the few randomized studies, or to use natural history studies as controls, suggest a modest benefit in reduction of TIAs [84] and less certainly a reduction in stroke [85, 86]. In none of the randomized trials was the reduction of strokes by anticoagulants statistically significant. There is some evidence that the risk of stroke in the first few months after a TIA is reduced [87], whilst haemorrhagic complications are unusual before 12 months. Some physicians who still employ anticoagulants have therefore changed to a short term use. There is, however, an increased risk of TIA and stroke on withdrawal of treatment [86].

Antiplatelet Drugs

Since the first step in mural thrombus formation is considered to be the adherence of platelets to sub-endothelial structures, and the propagation of a platelet aggregate, drugs that inhibit platelet adherence and aggregation have been sought. Dipyridamole, which inhibits the development of a platelet mass on injured arterial vessels in the rabbit [88], has not, when administered alone, been found to affect patients with TIAs [89]. Combined with anticoagulants, dipyridamole does improve the suppression of embolism from prosthetic heart valves [90]. Its more widespread use in cerebrovascular disease is at present without scientific justification.

Aspirin inhibits platelet aggregation by such materials as collagen through an irreversible inhibition of synthesis of thromboxanes by platelet cyclo-oxygenase. Small doses are sufficient to cause this effect for the lifetime of the exposed platelets. Aspirin also inhibits the synthesis in the vessel wall of a different prostaglandin, prostacyclin. Whilst thromboxanes are vasoconstrictive and promote platelet aggregation, prostacyclin is a powerful vasodilator and inhibits platelet aggregation. The net effect of aspirin ingestion, especially in small doses, is probably to inhibit *in vitro* platelet aggregation since the inhibition of prostacyclin synthesis is short lived. The prolongation of bleeding time by aspirin also suggests this.

Anecdotal evidence suggested that aspirin could inhibit thromboembolism to the retina at least [91], and the large Canadian trial has looked at this compound in TIAs of all sorts [92]. Aspirin in a dose of 1300 mg/day produced a 48 per cent reduction in stroke and/or death rate in males with TIAs. No effect was discernible in females and the result for all patients

was only just significant at $P < 0{\cdot}05$. The study had not been stratified to test for a male/female difference, and so this and other detailed findings of the study are to be reinvestigated in a UK trial which will also include a 300 mg/day 'arm'. We do not yet know whether aspirin is equally successful in patients with severe carotid stenosis, ulceration without stenosis and in those with normal angiograms. It is also possible that the effect of aspirin is influenced by haematocrit [93] and so it may be less effective in patients with a high normal haematocrit. Such patients also have a low cerebral blood flow related to their higher viscosity [94], and a higher risk of stroke [95]. A combination of aspirin and venesection might be required in such individuals.

Sulphinpyrazone, despite its ability to lengthen the platelet half-life, was ineffective in the Canadian trial [92], although a pilot study had been promising in cases of amaurosis fugax [96]. It seems quite possible that the small emboli involved in amaurosis fugax are more sensitive to antiplatelet medication than larger thromboemboli involved in some patients' cerebral TIAs. Antiplatelet drugs would also not be expected to affect embolization of cholesterol debris from ruptured atheromatous plaques.

Even this limited discussion reveals that one might expect different therapeutic efficacy of aspirin in patients with emboli of different size and structure. We do not yet know how clinically to identify the nature of the embolic material in different patients except perhaps in the retina [97]. It thus remains to be seen how often aspirin will be indicated and whether it is successful in preventing stroke in those same patients in whom carotid endarterectomy is currently considered indicated. Combinations of antiplatelet drugs such as dipyridamole and aspirin are also under trial, and may be found to have yet another spectrum of activity.

BYPASS PROCEDURES

The extracranial–intracranial bypass procedure is discussed in Chapter 4. Its success in revascularizing the middle cerebral artery territory with little morbidity and mortality is already accepted. How often this is relevant to the prevention of stroke is debatable. The operation is still under evaluation therefore, but might be considered most logical in those patients who have TIAs above an occluded carotid artery, or with intracranial stenosis of the carotid or middle cerebral artery. Barnett [98] has, however, shown that some cases of carotid occlusion continue to have TIAs due to embolization from the stump and respond to re-exploration of the bifurcation.

Other bypass procedures have been carried out extracranially in the presence of severe stenotic or occlusive disease of neck vessels [99]. They are difficult to evaluate, however, as they have never been subjected to

trials and many patients remain asymptomatic despite occlusion of major cervical arteries.

CONCLUSIONS

1. Though only 20 per cent of all strokes relate to carotid occlusion, some 45 per cent of strokes in the middle cerebral territory can be attributed to disease of the internal carotid artery, usually thrombotic occlusion of a severe atheromatous stenosis.

2. Fifty per cent of patients whose strokes are due to carotid occlusion have had previous TIAs, presumably at a time when the carotid artery was stenosed rather than occluded. Thirty per cent of hospital strokes, and 10 per cent of community strokes, give a history of TIAs.

3. TIA patients have an increased risk of stroke which amounts to approximately 30 per cent in 5 years.

4. Angiographic study of patients with carotid artery TIAs reveals the presence of atheromatous disease of the internal carotid artery in 50-65 per cent, including an operable stenosis in a third or more.

5. Carotid endarterectomy carries a risk of approximately 1 per cent mortality and 2 per cent neurological morbidity in the best units, but in less experienced hands the combined risk can reach 20 per cent, and is commonly 6-7 per cent.

6. Successful carotid endarterectomy reduces the long term stroke risk to 10 per cent or less over 5 years.

7. Auscultation of the neck and non-invasive tests of carotid blood flow detect a large number of patients with asymptomatic carotid disease. Their stroke risk, however, is small, and it is unlikely that the benefit of endarterectomy outweighs the risk except in a few centres with a zero mortality for such cases.

8. An adequate randomized trial has never been carried out to prove whether anticoagulants cause a significant reduction in stroke risk. Such a trial is now unlikely to be started. In view of the uncertainty and risks, the popularity of anticoagulants is on the wane except for cardiac embolism.

9. Aspirin is currently under evaluation, but appears to reduce the stroke risk in males with TIAs, perhaps by as much as 50 per cent. The particular circumstances in which aspirin does and does not have this preventive effect, and the optimal dosage, are as yet unknown.

10. The correct indications for the extracranial-intracranial bypass procedure are as yet unknown, but may well prove to be limited.

Policy

It therefore seems appropriate at the present time to recommend carotid endarterectomy for patients at risk of stroke as identified by the occur-

rence of a TIA, and in whom stenosis of the ipsilateral carotid artery has been delineated by angiography. This advice only applies if the centre concerned has an acceptably low mortality and morbidity for the procedure. Patient selection needs to consider adverse risk factors of which the most important is probably evidence of a previous cerebral infarct.

For patients with ulcerated atheroma without stenosis, and for those with high surgical risk factors, aspirin would appear preferable, this policy to be modified by the results of the new series of medical trials. Asymptomatic carotid stenosis might be considered for carotid surgery in exceptional centres. Elsewhere medical rather than surgical treatment would again be preferred until adequate controlled trials are carried out.

REFERENCES

1. Lhermitte F., Gautier J. C., Derouesné C. et al. (1968) Ischaemic accidents in the middle cerebral artery territory. *Arch. Neurol.* 19, 248–56.
2. Jorgensen L. and Torvik A. (1966) Ischaemic cerebrovascular disease in an autopsy series. Part 1. *J. Neurol. Sci.* 3, 490–509.
3. Bull J. W. D., Marshall J. and Shaw D. A. (1960) Cerebral angiography in the diagnosis of the acute stroke. *Lancet* 1, 562–5.
4. Harrison M. J. G. and Marshall J. (1975) The results of carotid angiography in cerebral infarction in normotensive and hypotensive subjects. *J. Neurol. Sci.* 24, 243–50.
5. Blackwood W., Hallpike J. F., Kocen R. S. et al. (1969) Atheromatous disease of the carotid arterial system and embolism from the heart in cerebral infarction: a morbid anatomical study. *Brain* 92, 897–910.
6. Hutchinson E. C. and Acheson E. J. (1975) *Strokes.* Philadelphia, Saunders, p. 43.
7. Mitchell J. R. A. and Schwartz C. J. (1965) *Arterial Disease.* Oxford, Blackwell Scientific.
8. Castaigne P., Lhermitte F., Gautier J. C. et al. (1970) Internal carotid artery occlusion. *Brain* 93, 231–58.
9. Blaisdell W. F., Clauss R. H., Galbraith J. G. et al. (1969) Joint study of extracranial arterial occlusion. IV. A review of surgical considerations. *JAMA* 209, 1889–95.
10. deWeese, J. A., May, A. G., Lipchik E. O. et al. (1970) Anatomic and hemodynamic correlations in carotid artery stenosis. *Stroke* 1, 149–57.
11. Kishore P. R. S., Chase N. E. and Kricheff I. I. (1971) Carotid stenosis and intracranial emboli. *Radiology* 100, 351–6.
12. Houser O. W., Sundt T. M., Holman C. B. et al. (1974) Atheromatous disease of the carotid artery: correlation of angiographic clinical and surgical findings. *J. Neurosurg.* 41, 321–31.
13. Chevers N. (1845) Remarks on the effect of obliteration of the carotid arteries upon the cerebral circulation. *London Medical Gazette* 31 Oct., pp. 1140–51.
14. Kussmaul A. and Tenner A. (1859). *On the Nature and Origin of Epileptiform Convulsions caused by Profuse Bleeding, and Also Those of True Epilepsy.* London, The New Sydenham Society.
15. Fisher C. M. (1951) Occlusion of the internal carotid artery. *AMA Arch. Neurol. Psychiatry* 65, 346–77.
16. Hurwitz L. J., Groch S. N., Wright I. S. et al. (1959) Carotid artery occlusive syndrome. *AMA Arch. Neurol.* I, 491–501.
17. Whisnant J. P., Matsumoto N. and Elveback L. R. (1973) Transient cerebral ischaemic attacks in a community. *Proc. Mayo Clin.* 48, 194–8.

18. Marshall J. (1964) The natural history of transient ischaemic cerebrovascular attacks. *Q. J. Med.* **33**, 309–24.
19. Whisnant J. P. (1976) A population study of stroke and TIA: Rochester, Minnesota. In: Gillingham F. J., Mawdsley C. and Williams A. E. (ed.) *Stroke*. Edinburgh, Churchill Livingstone, pp. 21–39.
20. Harrison M. J. G. (1974) Transient ischaemic attacks. In: Ledingham J. G. G. (ed.), *Advanced Medicine Symposium 10*, Tunbridge Wells, Pitman Medical, pp. 215–23.
21. Luxan L., Crowlter A., Harrison M. J. G. et al. (1979) A controlled study of 24 hour ambulatory electrocardiographic monitoring in patients with transient neurological symptoms. *J. Neurol. Neurosurg. Psychiatry* **43**, 37–41.
22. Reed R. L., Siekert R. G. and Merideth J. (1973) Rarity of transient focal cerebral ischemia in cardiac dysrhythmia. *JAMA* **223**, 893–5.
23. Eastcott H. H. G., Pickering G. W. and Rob C. (1954) Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet* **2**, 994–6.
24. Harrison M. J. G. and Marshall J. (1975) Indications for angiography and surgery in carotid artery disease. *Br. Med. J.* **1**, 616–17.
25. Eisenberg R. L., Nemzek W. R., Moore W. S. et al. (1977) Relationship of transient ischaemic attacks and angiographically demonstrable lesions of carotid artery. *Stroke* **8**, 483–6.
26. Wilson L. A. and Ross Russell R. W. (1977) Amaurosis fugax and carotid artery disease: indiations for angiography. *Br. Med. J.* **2**, 435–7.
27. Vitek J. J. (1973) Femero-cerebral angiography: analysis of 2000 consecutive examinations, special emphasis on carotid arteries catheterization. *AJR* **118**, 633–47.
28. Miller J. D. R., Grace M. G., Russell D. B. et al. (1977) Complications of cerebral angiography and pneumography. *Radiology* **124**, 741–4.
29. Olivecrona H. (1977) Complications of cerebral angiography. *Neuroradiology* **14**, 175–81.
30. Hass W. K., Fields W. S., North R. R. et al. (1968) Joint study of extracranial arterial occlusion II: Angiography, techniques, sites and complications. *JAMA* **203**, 961–8.
31. Toole J. F., Yuson C. P., Janeway R. et al. (1978) Transient ischaemic attacks: a prospective study of 225 patients. *Neurology* **28**, 746–53.
32. Boucher-Hayes D. J., Maloney R. D., Reidy N. C. et al. (1978) Hemodynamic studies of the audiofrequency analysis of carotid bruits. *Arch. Surg.* **113**, 920–3.
33. Lees R. S. and Kistler J. P. (1978) Carotid phonangiography. In: Bernstein E. F. (ed.), *Noninvasive Diagnostic Techniques in Vascular Disease*. St Louis, Mosby, pp. 187–94.
34. Yuson C. P. and Toole J. F. (1976) Bruits, ophthalmodynamometry and rectilinear scanning on transient ischemic attacks. *Stroke* **7**, 541–5.
35. Kartchner M. M. and McRae L. P. (1978) Clinical application of oculoplethysmography and carotid phonangiography. In: Bernstein E. F. (ed.), *Noninvasive Diagnostic Techniques in Vascular Disease*. St Louis, Mosby, pp. 201–11.
36. McDonald P. T., Rich N. M., Collins G. L. et al. (1978) Doppler cerebrovascular examinations, oculoplethysmography and ocular pneumoplethysmography. Use in detection of carotid disease: a prospective clinical study. *Arch. Surg.* **113**, 1341–9.
37. Ackerman R. H. (1979) A perspective on noninvasive diagnosis of carotid disease. *Neurology* **29**, 615–22.
38. Lemak N. A. and Fields W. S. (1976) The reliability of clinical predictors and extracranial artery disease. *Stroke* **7**, 377–8.

39. Harrison M. J. G. and Marshall J. (1977) The finding of thrombus at carotid endarterectomy and its relationship to the timing of surgery. *Br. J. Surg.* **64**, 511–12.
40. Harrison M. J. G., Marshall J. and Thomas D. (1978) Relevance of duration of transient ischaemic attacks in carotid territory. *Br. Med. J.* **1**, 1578–9.
41. Roberson C. H., Scott W. R. and Rosenbaum A. E. (1973) Thrombi at the site of carotid stenosis. *Radiology* **109**, 353–6.
42. Stanford J. R., Lubow M. and Vasko J. S. (1978) Prevention of stroke by carotid endarterectomy. *Surgery* 83, 259–63.
43. Fraught E., Trader S. D. and Hanna G. R. (1979) Cerebral complications of angiography for transient ischemia and stroke: prediction of risk. *Neurology* **29**, 4–15.
44. Battacharji S. K., Hutchinson E. C. and McCall A. J. (1967) Stenosis and occlusion of vessels in cerebral infarction. *Br. Med. J.* **3**, 270–4.
45. Gomensoro J. B., Maslenikov V., Azambuja N. et al. (1973) Joint study of extracranial arterial occlusion VIII: clinical radiological correlation of carotid bifurcation lesions in 177 patients with T.C.I.A.s. *JAMA* **224**, 985–91.
46. Croft R. J., Ellam L. D. and Harrison M. J. G. (1979) The accuracy of carotid angiography in determining carotid artery disease. *Lancet* **1**, 977–1000.
47. Javid H., Ostermiller W. F., Hengesh J. W. et al. (1970) Natural history of carotid bifurcation atheroma. *Surgery* 67, 80–6.
48. Johnson N., Burnham S. J., Flanigan D. R. et al. (1978) Carotid endarterectomy: a follow-up study of the contralateral non-operated carotid artery. *Ann. Surg.* **188**, 748–52.
49. Wolf P. A., Kannel W. B., Gordon T. et al. (1979) Asymptomatic carotid bruit and risk of stroke: the Framingham Study. *Stroke* **10**, 96.
50. Ginsberg M. D., Greenwood S. A. and Goldberg H. I. (1979) Non-invasive diagnosis of extracranial cerebrovascular disease: oculoplethysmography-phonangiography and directional Doppler ultrasonography. *Neurology* **29**, 623–31.
51. Evans W. E. (1978) The significance of asymptomatic unilateral carotid bruits in preoperative patients. *Surgery* **83**, 521–2.
52. Carney W. I., Stewart W. B., DePinto D. J., et al. (1977) Carotid bruit as a risk factor in aorto-iliac reconstruction. *Surgery* **81**, 567–70.
53. Berkoff H. and Turnipseed W. (1979) Postsurgical stroke in cardiac and peripheral vascular disease. *Stroke* **10**, 106–7.
54. Moore W. S., Malone J. M., Boren C. et al. (1979) Asymptomatic ulcerative lesions of the carotid artery – natural history and effect of surgical therapy compared. *Stroke* **10**, 96.
55. Thompson J. E. and Talkington C. M. (1976) Carotid endarterectomy. *Ann. Surg.* **184**, 1–15.
56. Sundt T. M., Sandok B. A. and Whisnant J. P. (1975) Carotid endarterectomy: complications and preoperative assessment of risk. *Mayo Clin. Proc.* **50**, 301–6.
57. Riles T. S., Kopelman I. and Imparato A. M. (1979) Myocardial infarction following carotid endarterectomy: a review of 683 operations. *Surgery* **85**, 249–52.
58. White C. W., Allarde R. R. and McDowell M. A. (1976) Anesthetic management for carotid artery surgery. *JAMA* **202**, 1023–7.
59. Javid M. (1966) Can surgery prevent stroke? *Surgery* **59**, 1147–53.
60. Collins G. J., Rich N. M., Anderson C. A. et al. (1978) Stroke associated with carotid endarterectomy. *Am. J. Surg.* **135**, 221–5.
61. Harrison M. J. G. Unpublished observations.
62. Goldstone J. and Moore W. S. (1978) A new look at emergency carotid artery operations for the treatment of cerebrovascular insufficiency. *Stroke* **9**, 599–602.
63. Lhermitte F., Gautier J. C. and Derouesné C. (1966) Anatomopathologie et physiopathologie des stenosis carotidennes. *Rev. Neurologique* **115**, 641–72.

64. Durrenberger R. A. and Sundt T. M. (1978) Carotid endarterectomy. *J. Neurol.* 48, 201–19.
65. Hertzer N. R., Beven E. G., Greenstreet R. L. et al. (1978) Internal carotid back pressure, intraoperative shunting, ulcerated atheroma and the incidence of stroke during carotid endarterectomy. *Surgery* 83, 306–12.
66. Caplan L. R., Skillman J., Ojemann R. et al. (1978) Intracerebral hemorrhage following carotid endarterectomy: a hypertensive complication? *Stroke* 9, 457–60.
67. Fleming J. F. R., Griesdale D. E., Schutz H. et al. (1977) Carotid endarterectomy changing morbidity and mortality. *Stroke* 8, 14.
68. Prioleau W. H., Aiken A. F. and Hairston P. (1977) Carotid endarterectomy: neurologic complications as related to surgical techniques. *Ann. Surg.* 185, 678–83.
69. Sundt T. M., Sharbrough F. W., Trautman J. C. et al. (1975) Monitoring techniques for carotid endarterectomy. *Clin. Neurosurg.* 22, 199–213.
70. Bone G. E., Slaymaker E. E. and Barnes R. W. (1978) Noninvasive assessment of collateral blood flow of the cerebral hemisphere by Doppler ultrasound. *Surg. Gynecol. Obstet.* 145, 873–6.
71. Smith L. L., Jacobsen J. G. and Hinshaw D. B. (1976) Correlation of neurologic complications and pressure measurements during carotid endarterectomy. *Surg. Gynecol. Obstet.* 143, 233–6.
72. Baker W. H., Rodman J. A., Barnes R. W. et al. (1976) An evaluation of hypocarbia and hypercarbia during carotid endarterectomy. *Stroke* 7, 451–4.
73. Satiani B., Liapis C., Pflug B. et al. (1978) Role of staging in bilateral carotid endarterectomy. *Surgery* 84, 784–92.
74. Ennix C. L., Lawrie G. M., Morris G. C. et al. (1979) Improved results of carotid endarterectomy in patients with symptomatic coronary disease: an analysis of 1546 consecutive carotid operations. *Stroke* 10, 122–5.
75. Cossman D. and Callou A. D. (1978) Early re-stenosis after carotid endarterectomy. *Arch. Surg.* 113, 275–8.
76. Kremer J. E., Gee W., Kaupp H. A. et al. (1979) Re-stenosis or occlusion after endarterectomy. *Arch. Surg.* 114, 608–10.
77. Fields W. S., Maslenikov V., Meyer J. S. et al. (1970) Joint study of extracranial arterial occlusion. *JAMA* 21, 1993–2003.
78. West H., Burton R., Roon A. J. et al. (1979) Comparative risk of operation and expectant management for carotid artery disease. *Stroke* 10, 117–21.
79. deWeese J. A., Rob C. G., Satran R. et al. (1973) Results of carotid endarterectomies for transient ischaemic attacks – 5 years later. *Ann. Surg.* 178, 258.
80. Easton J. D. and Sharman D. G. (1977) Stroke and mortality rate in carotid endarterectomy: 228 consecutive operations. *Stroke* 8, 565–8.
81. Hass J. S. (1979) An approach to the maximal acceptable stroke complication rate after surgery for transient cerebral ischemia (T.I.A.). *Stroke* 10, 104.
82. Moore W. S. and Hall A. D. (1970) Importance of emboli from carotid bifurcation in pathogenesis of cerebral ischemic attacks. *Arch. Surg.* 101, 708–11.
83. Furlan A. J. and Whisnant J. P. (1979) Long-term prognosis following carotid artery occlusion. *Stroke* 10, 105.
84. Genton E., Barnett H. J. M., Fields W. S. et al. (1977) Cerebral ischaemia: the role of thrombosis and of anti-thrombotic therapy. *Stroke* 8, 150–175.
85. Frank G. (1971) Comparison of anticoagulation and surgical treatments of T.I.A. *Stroke* 2, 369–77.
86. Olsson J. E., Müller R. and Berneli S. (1976) Long-term anticoagulant therapy for TIAs and minor strokes with minimum residuum. *Stroke* 7, 444–51.
87. Whisnant J. P., Matsumoto N. and Elveback L. R. (1973) The effect of anticoagulant therapy on the prognosis of patients with transient cerebral ischemic attacks in a community: Rochester, Minnesota 1955 through 1969. *Mayo Clin. Proc.* 48, 844–8.

88. Emmons P. R., Harrison M. J. G., Honour A. J. et al. (1965) Effect of a pyrimidopyrimidine derivation on thrombus formation in the rabbit. *Nature (Lond.)* **208**, 255–7.
89. Acheson J., Danta G. and Hutchinson E. C. (1969) Controlled trial of dipyridamole in cerebral vascular disease. *Br. Med. J.* **1**, 614–15.
90. Sullivan J. M., Harken O. E. and Gorlin R. (1968) Pharmacologic control of thrombo-emboli complications of cardiac valve replacement. *N. Engl. J. Med.* **279**, 576–80.
91. Harrison M. J. G., Meadows J. C., Marshall J. et al. (1971) Effect of aspirin in amaurosis fugax. *Lancet* **2**, 743–4.
92. Canadian Cooperative Stroke Study Group (1978) A randomized trial of aspirin and sulphinpyrazine in threatened stroke. *N. Engl. J. Med.* **299**, 53–9.
93. Davies J. A., Essien E., Cazenave J. P. et al. (1979) The influence of red blood cells on the effect of aspirin or sulphinpyrazine on platelet adherence to damaged rabbit aorta. *Br. J. Haematol.* **42**, 283–91.
94. Thomas D. J., Marshall J., Ross Russell R. W. et al. (1977) Effect of haematocrit on cerebral blood flow in man. *Lancet* **2**, 941–3.
95. Tohgi H., Yamanouchi H., Murakami M. et al. (1978) Importance of the hematocrit as a risk factor in cerebral infarction. *Stroke* **9**, 369–74.
96. Evans G. (1973) Effect of platelet suppressive agents on the incidence of amaurosis fugax and transient cerebral ischemia. In: McDowell F. and Bennan R. (ed.), *Cerebral Vascular Diseases 8th Conference.* New York, Grune & Stratton, pp. 297–9.
97. Ross Russell R. W. (1968) The source of retinal emboli. *Lancet* **2**, 789–92.
98. Barnett H. J. M., Peerless S. J. and Kaufman J. C. E. (1978) 'Stump' of internal carotid artery – a source of further cerebral embolic ischaemia. *Stroke* **9**, 448–56.
99. DeBakey M. E., Crawford E. S., Cooley D. A. et al. (1959) Surgical considerations of occlusive disease of innominate, carotid subclavian and vertebral arteries. *Ann. Surg.* **149**, 690–710.

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4 Indications for Extracranial – Intracranial Anastomosis

Advances in treatment are sometimes made in response to an urgent therapeutic need. The introduction of intermittent positive pressure respiration, at first manually operated by teams of volunteers, during the epidemic of poliomyelitis in Denmark in 1950 is an example of this. At other times a technical advance with therapeutic potential is made, but then conditions must be sought in which it may be used with benefit. The successful anastomosis of arteries of 2 mm diameter [1] and its use in the cerebral circulation in man [2] provides such an example. This operation was whimsically described as 'a good operation looking for an indication'. During the past decade indications have progressively emerged and it is the purpose of the present chapter to discuss and define them.

The management of disease of the internal carotid artery at its origin is the subject of a separate chapter in this book, but as the place of extracranial–intracranial anastomosis can only be determined in reference to the carotid system as a whole, besides referring the reader to Chapter 3, a brief recapitulation of the essential features of carotid disease will be given here.

Clinical interest in disease of the carotid artery began with the classic papers of Miller Fisher [3, 4] who found stenosis and occlusion of the carotid artery in the neck to be common among cases of cerebrovascular accident. Although Miller Fisher himself recognized from the outset that reduction of blood flow was unlikely in general to be responsible for the link between the two, the general tendency was to seize upon stenosis and a reduction of blood flow as the causative factor in both transient ischaemic attacks and completed strokes. So much was this so that radiologists developed a habit of reporting stenoses of less than 25 per cent of the lumen as 'not significant'. A stenosis of this degree would certainly not reduce flow; a reduction of the lumen of the artery by 90 per cent is required before there is an appreciable fall in flow [5]. This may nevertheless be significant clinically because it frequently provides a source of emboli to the cerebral vessels as has now been amply documented [6]. Endarterectomy of the origin of the internal carotid artery is carried out in most instances to remove a source of emboli and not to increase blood flow which is not in fact reduced.

Occlusion of the internal carotid artery at its origin presents a different problem because flow is reduced to the point of being absent. Moreover, though occlusion by thrombus commonly starts at the origin of the vessel, because of the absence of branches in the cervical portion of the artery, it

rapidly extends to the level of carotico-cavernous or ophthalmic branches and becomes organized so that re-establishment of flow by surgery in the neck is rarely successful. Here would seem to be a prime case for bypassing the occluded segment.

The problem is, however, not so simple. In patients who are experiencing transient ischaemic attacks (TIAs), occlusion of the carotid artery does not always cause a stroke and is usually followed by cessation of TIAs. This latter phenomenon is one of the arguments for the embolic origin of TIAs, occlusion of the vessel being nature's ligature, cutting off the source of emboli. The absence of a stroke is undoubtedly due to the abundant collateral circulation, primarily via the circle of Willis, but also via external–internal carotid branches such as the facial-ophthalmic.

If these collateral systems are inadequate, occlusion of the internal carotid artery is followed by a stroke, again with cessation of TIAs in most cases. Occlusion of the internal carotid artery with or without a completed stroke does not therefore of itself appear to provide a strong indication for bypass surgery. If a stroke has occurred, the damage has been done; if a stroke has not developed, nature has already provided adequate collaterals.

However, in some instances of internal carotid occlusion, TIAs recur in the territory of the vessel, usually after the lapse of a considerable period of time. Until recently this has been taken as an indication of progressive inadequacy of the collateral circulation, presumably due to advancing atheroma, the TIAs being haemodynamic rather than embolic in origin. Clinical features of the attacks, such as their occurrence with sudden change of posture or in association with cardiac dysrhythmia, points strongly to this conclusion. This situation, namely recurrence of TIAs after a carotid occlusion, would seem to be a clear indication for bypass surgery to supplement the failing collaterals before infarction occurs.

As with most subjects that become the focus of intense study, it is not long before seemingly impregnable conclusions are challenged. Recent observations have indicated that in some instances post-occlusion TIAs may be embolic. Occlusion of the internal carotid usually occurs about 1 cm from its origin leaving a 'stump' (*Fig. 4.1*). In a recent careful clinico-pathological study [7, 8] it has been shown that thrombus may form in the stump, extend back to the common carotid artery and give rise to emboli which pass into the external carotid artery and reach the internal carotid circulation distal to the occlusion via collaterals. New clinical events from this cause occur weeks to years after the initial occlusion.

Similarly, in a well-documented angiographic study of patients experiencing post-occlusion TIAs, in which the vessels distal to the occlusion were filled from the opposite side by cross-circulation, evidence of embolic occlusion of distal cerebral vessels was found [9]. Thus the haemodynamic origin of one type of TIA which seemed eminently suitable for bypass surgery has been challenged.

It has already been mentioned that in cases of stenosis at the origin of

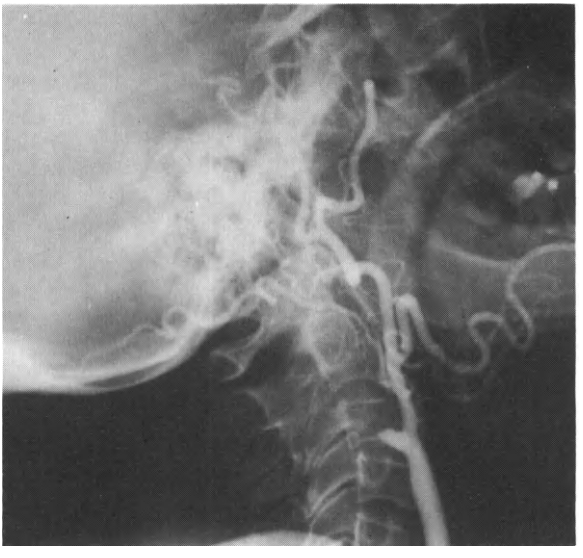


Fig. 4.1. Angiogram showing a typical 'stump' at the origin of an occluded internal carotid artery.

the internal carotid artery, endarterectomy is most frequently carried out to remove a source of emboli rather than to increase blood flow, the latter being unimpaired. On this hypothesis stenosis in the carotid siphon – which cannot be reached in order to carry out endarterectomy – would seem better treated by anticoagulants than by bypass surgery. Again the problem is not so simple as it appears at first sight.

Some TIAs associated with stenosis in the carotid siphon are haemodynamic, the stenosis being severe and the circle of Willis inadequate. But even when the TIAs are believed to be embolic in origin, a case can be made for increasing the blood flow beyond the stenosis by bypass surgery. The fate of emboli and the degree of damage they cause depend upon a number of factors. Prominent among these is of course the balance between coagulation and fibrinolytic mechanisms in the blood, but speed of blood flow is also important. This is one of the reasons why thrombosis is much more common in veins than in arteries. It can be argued, therefore, that even if TIAs associated with stenosis of the carotid siphon are embolic, increasing the blood flow beyond the stenosis might facilitate the disintegration of emboli and so reduce the damage they cause.

The same argument could be applied when the internal carotid artery has been occluded, except that if thrombus in the stump emerges as a common occurrence, providing more pathways by which emboli might

pass from the external to the internal carotid circulation might be deemed inappropriate.

These considerations have been set out at some length to underline the fact that rules of thumb cannot be applied when considering the suitability of a case for bypass surgery. Indeed this applies to the entire spectrum of cerebrovascular disease, but is particularly apposite in relation to bypass surgery. Although general guidelines can be laid down, each case must be considered individually and an attempt made to determine the nature of the pathophysiological disturbance, difficult though this may be in clinical practice. It is against this background and with this reservation, that the following 'indications' for bypass surgery are suggested.

Although the decision to operate will rest largely upon angiographic findings, patients present with a clinical disturbance, hence it seems best to approach the problem from this starting point. Most frequently the clinical disturbance will be a TIA, which is indeed the best starting point as irreversible damage to the brain has not yet been done, whereas with a completed stroke there has already been cerebral damage, albeit mild in some cases.

FIRST PRESENTATION WITH CAROTID TIAs

Stenosis in the Siphon

If a patient presents with TIAs which he is experiencing for the first time in the internal carotid territory, angiography is usually required. Most commonly a stenosis at the origin of the internal carotid will be found in which case endarterectomy is indicated. But if the stenosis is in the siphon, then particular attention should be paid to the circumstances in which the TIAs occur (as indeed should be done with all TIAs) in order to try to decide whether they are embolic or whether they are haemodynamic in origin. If the evidence favours the latter, then anastomosis of the superficial temporal to a branch of the middle cerebral artery is clearly indicated. When the evidence favours the former, it is reasonable to try anticoagulant therapy. If this is going to be efficacious, cessation or at least a dramatic reduction in frequency of TIAs will soon be apparent. Should this not occur, bypass surgery should be undertaken.

Stenosis in the siphon is sometimes associated with stenosis at the origin of the internal carotid artery – often referred to as stenosis in tandem. Previously the double lesion deterred surgeons from performing endarterectomy at the origin, partly because of the increased risk of surgery and partly because there seemed little advantage in dealing with a proximal stenosis whilst leaving a distal lesion untouched. It could of course be argued that removing the proximal stenosis reduced the risk of emboli from that site lodging in the distal lesion but on the whole this argument did not appear to carry great weight.

The advent of extracranial-intracranial anastomosis offers opportunity for a new approach. The distal stenosis can first be bypassed and at a later stage the proximal lesion dealt with by endarterectomy. This does not reduce the risk of embolization during surgery, but does provide a collateral circulation which could be beneficial if the distal stenosis is reducing flow.

Carotid Occlusion

When a patient who presents for the first time with carotid TIAs is found to have occlusion of the appropriate internal carotid artery, this would formerly have been taken as a strong indication for bypass surgery. The fact that the patient presents in this way suggests that the occlusion is of long standing and has been compensated for by collateral circulation which is now proving inadequate. This might, for example, be due to advancing stenosis of the contralateral internal carotid artery or progressive disease in collateral channels. Certainly the condition of the contralateral internal carotid artery has to be taken into account, but in view of the recent observations on the 'stump' of the occluded internal carotid described above, careful examination of the angiograms is indicated. If thrombus appears to be present, then surgical obliteration of the stump is required. If there is no thrombus (and surgical exploration may be required to establish this definitively) superficial temporal-middle cerebral anastomosis is indicated.

Middle Cerebral Occlusion or Stenosis

Stenosis or occlusion of the middle cerebral artery is much less frequent than is disease of the internal carotid in patients presenting for the first time with TIAs. When such a lesion is found the decision is straightforward; anastomosis of the superficial temporal artery to a branch of the middle cerebral should be undertaken. Unfortunately stenosis of the trunk of the middle cerebral artery is relatively uncommon; only 9 out of 59 angiographically identified lesions of the middle cerebral artery were stenotic [10]. Likewise, few trunk occlusions present as TIAs; the great majority (87 per cent) [11] present with a completed stroke. Thus the lesions most suitable for extracranial-intracranial bypass are either uncommonly met with or have already caused considerable cerebral damage.

LATE PRESENTATION WITH CAROTID TIAs

Patients with a past history of TIAs (or even a completed stroke from which there has been substantial recovery), who were found at the time to have an internal carotid occlusion, in whom TIAs recur require careful assessment.

Contralateral Stenosis

Increasing stenosis of the contralateral internal carotid requires that endarterectomy be considered. The risks of this operation are greater when one internal carotid artery is already occluded [12]. Nevertheless, restoring normal blood flow through one internal carotid artery is likely to contribute more to overall cerebral perfusion than will bypass surgery. Measurement of cerebral blood flow by a non-invasive ^{133}Xe clearance technique can be of great help in this situation. If overall cerebral perfusion is considerably reduced, the indication for removing the contralateral stenosis is strong.

Embolism from the Stump

If the contralateral internal carotid artery is normal, but there is a stump remaining at the origin of the occluded internal carotid artery, surgical obliteration of the stump is the treatment of choice. To provide further anastomoses between the external and internal carotid systems beyond those which have developed spontaneously is to provide more pathways for the passage of emboli. The first logical step is to eliminate a possible source of emboli.

Haemodynamic TIAs

Absence of a stump or of thrombus within and a normal contralateral carotid artery, is a strong indication for superficial temporal-middle cerebral anastomosis. TIAs in these circumstances are highly likely to be the result of inadequate collateral circulation. This may have been sufficient originally but collaterals, like main vessels, become diseased, hence the need to supplement them by suitable surgical procedures.

PRESENTATION WITH COMPLETED STROKE IN THE CAROTID TERRITORY

It is always regrettable when a patient presents with a completed stroke particularly if there were preceding TIAs, the significance of which was ignored. One thing is, however, quite clear, namely that surgery is positively contraindicated in the acute stage. A completed stroke means that a degree of infarction has taken place and to increase the blood supply to recently infarcted tissue will aggravate the situation [13], converting white to red infarcts. This is the same situation as was encountered in the early days of carotid endarterectomy which, when carried out in the acute phase of a completed stroke, made matters worse.

The contraindication to surgery in the acute stage of infarction does not, however, apply to the later stages. Once the infarct has healed, obser-

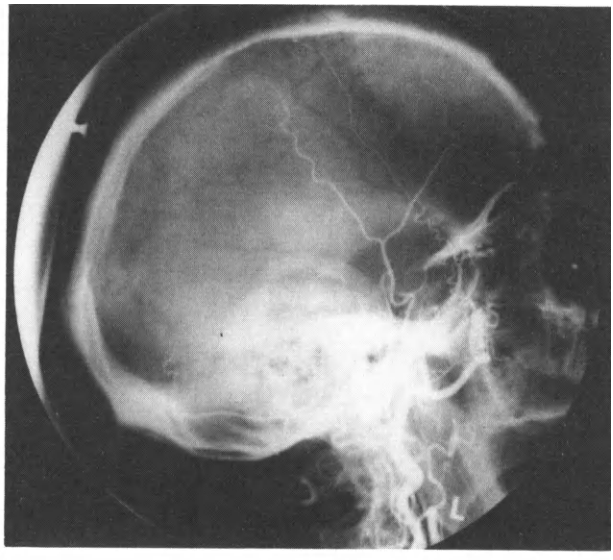
vation of which is greatly facilitated by the CT scan, the situation should be reviewed. Much depends upon the clinical condition of the patient. Patients who are left with severe deficits are not likely to benefit from any increase in blood flow howsoever produced. Patients with milder deficits which do not prevent them from functioning adequately can be considered much as patients who presented with TIAs and the same principles applied.

For example, if they subsequently develop TIAs, the reason for this should be sought in the manner described in the section on TIAs and appropriate action taken.

Whether extracranial-intracranial anastomosis helps patients with mild fixed deficits cannot be decided at the present time as there is insufficient experience on which to base reliable conclusions. The argument for fashioning surgical anastomoses in such cases is that around an infarct there is a zone in which the neurones though suffering a degree of ischaemia are not irreversibly damaged. There is now much experimental animal work showing that evoked potentials and metabolic activity can be restored after considerable periods of ischaemia [14]. Still less do we know the situation in man, in whom despite encouraging reports in the literature [2, 15-23], it is difficult to distinguish between the natural tendency of many stroke patients to improve, the effect of increased cerebral blood flow and that of the inevitable increase in attention to rehabilitation measures during the postoperative phase. Nevertheless the facts that neurones have a potential for recovery from ischaemia of considerable duration and that extracranial-intracranial anastomosis does restore the flow of blood through cerebral arteries (*Fig. 4.2*) provide a sound basis for exploring the possible benefit of bypass surgery in carefully selected cases of completed stroke. More care will, however, have to be given to determining to what extent patients improve and why, before a definitive statement can be made as to the place of this operation.

PRESENTATION WITH DEMENTIA

Longer life expectancy has increased the proportion of the population in the older age groups with a consequent rise in the number of people with dementia, an affliction most commonly encountered in old age. Although such patients are commonly referred to as suffering from 'cerebral arteriosclerosis', in fact the majority have primary degenerative changes in the brain of the type known as Alzheimer's disease. It is the minority who have vascular disease and, though there are arteriosclerotic changes in the cerebral vessels, the striking feature is the presence of multiple small infarcts. For this reason the term 'multi-infarct dementia' has been applied to this group [24] as being more accurately descriptive of the pathological condition. Measurements of cerebral blood flow in mild to moderate cases



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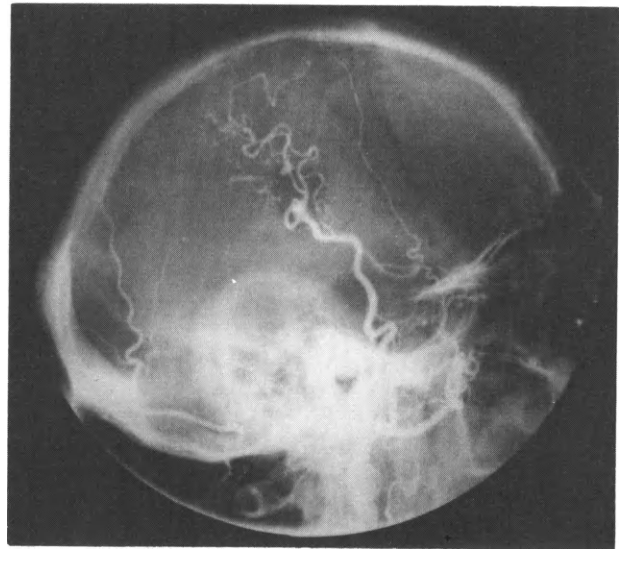

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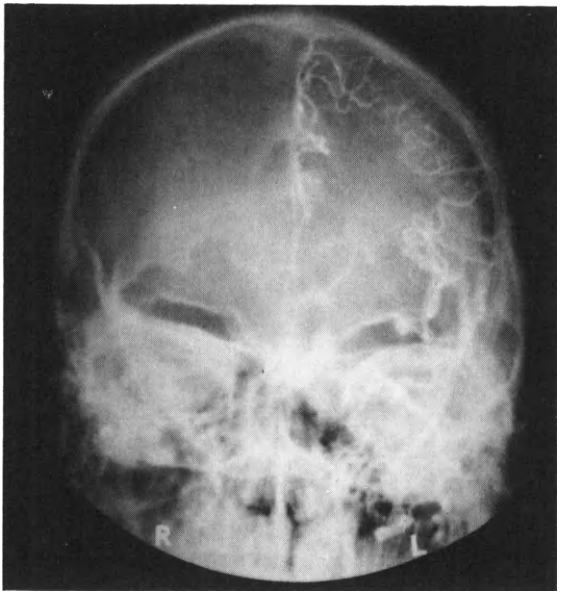
Fig. 4.2. a, Preoperative angiogram showing carotid occlusion with no filling of middle of anterior cerebral arteries. *b*, Postoperative angiogram showing enlarged superficial temporal artery supplying branches of middle cerebral artery via the anastomosis. *c*, Anteroposterior view of (*b*) showing contrast medium in anterior cerebral artery also. (By courtesy of Mr J. S. P. Lumley, FRCS.)



c

of dementia have shown that whereas in the Alzheimer group it is in the low normal range, in multi-infarct dementia it is significantly reduced [25]. This raises the possibility that increasing cerebral blood flow might arrest the progress of the condition. Angiography does not reveal occlusion or stenosis of major vessels as the cause of the reduced cerebral blood flow. Moreover, it has been shown that the reduction is not the result of arterial insufficiency of small vessels [25] because increasing $PaCO_2$ produces a significant increase in cerebral blood flow. This indicates that reduced metabolic demand for, rather than inability to supply, blood is the cause of the low cerebral blood flow.

Nevertheless this still leaves us with the cause of the multiple small infarcts which appear to be related to changes in the walls of small vessels, particularly in relation to hypertension [26]. If thrombotic occlusion at the site of these arterial wall lesions is the final determinant of infarction it can be argued (as was argued above in relation to emboli) that increasing blood flow might retard this process. Because the external carotid circulation from which the collateral flow is derived by anastomosis is not determined by cerebral metabolic demands, it could be that increasing blood flow via this route might be beneficial. In the light of these considerations it cannot be said that multi-infarct dementia is an indication for extracranial-intracranial anastomosis but it is certainly a subject worthy of careful study.

Although dementia associated with vascular disease is in most cases of multi-infarct type there is a small group in which low cerebral blood flow is the primary cause. These are cases in which angiography reveals extensive occlusion or stenosis of the carotico-vertebral system. Endarterectomy of major vessels and bypass procedures are clearly appropriate here, the type of surgery being determined in each case by cerebral blood flow measurements and angiographic findings.

PRESENTATION WITH VERTEBRO-BASILAR SYMPTOMS

Continued technical advance has enabled surgeons to fashion anastomoses between extracranial arteries and branches of the vertebro-basilar system [27, 28]. What place these procedures have in the management of vertebro-basilar ischaemia is difficult to determine. Transient ischaemic attacks in the vertebro-basilar territory are common but the proportion followed by a stroke is less than in the carotid system in some series [29, 30] though not in another series [31]. Some vertebro-basilar TIAs are extremely benign in that they may continue over months or even years, without ever giving rise to residual deficit. In these circumstances surgery would hardly seem justified.

Vertebro-basilar TIAs which are associated with long tract symptoms such as alternating or bilateral weakness or sensory disturbance have a more sinister prognosis and may be followed by brain stem infarction [29]. However, it is far from clear whether these are embolic or haemodynamic in origin. Nor is this a problem which can readily be resolved because measurement of cerebral blood flow through the vertebro-basilar circulation is beset with technical difficulties. For these reasons it is virtually impossible at the present time to indicate what place, if any, there is for extracranial–intracranial anastomosis. Certainly it should at present be restricted to the treatment of TIAs of the more ominous kind and again it would seem wise to place considerable emphasis on the circumstances in which the attacks occur in an endeavour to determine whether or not they are caused by a fall in blood flow.

MIDDLE CEREBRAL ANEURYSMS

This in effect concludes what may be termed the 'medical' indications for extracranial–intracranial anastomosis but to complete the picture mention should be made of the value of the procedure in the management of aneurysms of the middle cerebral artery. When such an aneurysm is of appreciable size it may be difficult for the surgeon to obliterate it without compromising blood flow through the artery. Fashioning a bypass by anastomosing the superficial temporal to a branch of the middle cerebral artery

before operating upon the aneurysm provides an insurance against ischaemia or infarction [32].

REFERENCES

1. Suarez E. L. and Jacobsen J. H. (1961) Results of small artery endarterectomy – microsurgical technique. *Surg. Forum* 12, 256–7.
2. Yasargil M. D., Krayenbuhl H. A. and Jacobsen J. H. (1970) Microneurosurgical arterial reconstruction. *Surgery* 67, 221–33.
3. Fisher C. M. (1951) Occlusion of the internal carotid artery. *Arch. Neurol. Psychiatry* 65, 346–77.
4. Fisher C. M. (1954) Occlusion of the carotid arteries. Further experiences. *Arch. Neurol. Psychiatry* 72, 187–204.
5. Brice J. G., Dowsett D. J. and Lowe R. D. (1964) The effect of constriction on carotid blood-flow and pressure gradient. *Lancet* 1, 84–5.
6. Gunning A. J., Pickering G. W., Robb-Smith A. H. T. et al. (1964) Mural thrombosis of the internal carotid artery and subsequent embolism *Q. J. Med.* 33, 155–95.
7. Barnett H. J. M. (1978) Delayed cerebral ischemic episodes distal to occlusion of major cerebral arteries. *Neurology (Minneapolis)* 28, 769–74.
8. Barnett H. J. M., Peerless S. J. and Kaufmann J. C. E. (1978) 'Stump' of internal carotid artery – a source for further embolic ischemia. *Stroke* 9, 448–56.
9. Einsiedel-Lechtape H. (1979) In: Meyer J. S. (ed.) Proceedings of the 9th International Conference on Cerebral Vascular Disease. *Excerpta Medica Int. Congr. Ser.* 449, 325.
10. Lascelles R. G. and Burrows E. H. (1965) Occlusion of the middle cerebral artery. *Brain* 88, 85–96.
11. Fisher C. M. (1976) The natural history of middle cerebral artery occlusion. In: Austin G. M. (ed.), *Microsurgical Anastomoses for Cerebral Ischemia.* Springfield, Ill., Thomas.
12. Blaisdell W. F., Clauss R. H., Galbraith J. G. et al. (1969) Joint study of extracranial arterial occlusion IV. A review of surgical considerations. *JAMA* 209, 1889–95.
13. Hodge C. J. jun. and Gross C. E. (1978) Cerebral revascularization. *Acta Neurochir.* 44, 115–30.
14. Hossman K. A. and Sato K. (1970) Recovery of neuronal function after prolonged cerebral ischaemia. *Science* 168, 375–6.
15. Reichman O. H., Satovick R. M., Davis D. O. et al. (1972) Collateral circulation to the middle cerebral territory by anastomosis of superficial temporal and cortical arteries. In: Fusek I. and Kunc Z. (ed.) *Present Limits of Neurosurgery.* Prague, Avicenum.
16. Austin G., Laffin D. and Hayward W. (1974) Physiological factors in the selection of patients for superficial temporal into middle cerebral anastomosis. *Surgery* 6, 861–8.
17. Yonekawa Y. and Yasargil M. G. (1976) Extra-intracranial arterial anastomosis. Clinical and technical aspects. Results. In: Krayenbuhl H. et al. (ed.) *Advances in Technical Standards in Neurosurgery 3.* Berlin: Springer. pp. 37–78.
18. Chater N. (1976) Patient selection and results of extra- to intracranial anastomosis in selected cases of cerebrovascular disease. *Clin. Neurosurg.* 23, 287–309.
19. Holbach K. H., Wappenschmidt J. and Bodosi M. (1976) Angiographische Befunde bei extra-intrakraniellen Anastomosen. *Radiologe* 16, 416–23.
20. Sundt T. M. jun., Siekert R. G., Piepgras D. G. et al. (1976) Bypass surgery for vascular disease of the carotid systems. *Mayo Clin. Proc.* 51, 677–92.

21. Bannister C. M. (1977) Superficial temporal–middle cerebral artery anastomosis in patients with reversible ischaemic cerebral episodes. *J. R. Coll. Surg. (Edinb.)* **22**, 136–41.
22. Lumley J. S. P. (1979) Extra-intracranial revascularisation. *Br. J. Surg.* **66**, 317–23.
23. Greenhalgh R. M., Illingworth R. D., McFie J. et al. (1979) Extracranial to intracranial micro-revascularisation for the treatment of completed ischaemic stroke. *Br. Med. J.* **2**, 18–19.
24. Hachinski V. C., Lassen N. A. and Marshall J. (1974) Multi-infarct dementia. A cause of mental deterioration in the elderly. *Lancet* **2**, 207–10.
25. Hachinski V. C., Iliff L. D., Zilkha E. et al. (1975) Cerebral blood flow in dementia. *Arch. Neurol.* **32**, 632–7.
26. Fisher C. M. (1965) Lacunes: small deep infarcts. *Neurology (Minneapolis)* **15**, 774–84.
27. Khodadad G., Singh R. S. and Olinger C. P. (1977) Possible prevention of brain stem stroke by microvascular anastomosis in the vertebral system. *Stroke* **8**, 316–21.
28. Sundt T. M. jun., Whisnant J. P., Piepgras D. G. et al. (1978) Intracranial bypass grafts for vertebral-basilar ischemia. *Mayo Clin. Proc.* **53**, 12–18.
29. Marshall J. (1964) The natural history of transient ischaemic cerebrovascular attacks. *Q. J. Med.* **33**, 309–24.
30. Ziegler D. K. and Hassanein R. S. (1973) Prognosis in patients with transient ischaemic attacks. *Stroke* **4**, 666–73.
31. Cartlidge N. E. F., Whisnant J. P. and Elveback L. R. (1977) Carotid and vertebral-basilar transient cerebral ischemic attacks. A community study: Rochester Minnesota. *Mayo Clin. Proc.* **52**, 117–20.
32. Drake C. G. (1968) Further experience with surgical treatment of aneurysms of the basilar artery. *J. Neurosurg.* **29**, 372–92.

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5 Chemotherapy of Cerebral Glioma: Current Research and its Application to Clinical Practice

The management of malignant tumours of the central nervous system forms a significant fraction of the clinical practice of neurologists and neurosurgeons. In most neurological clinics over half of intracranial tumours diagnosed in adults prove to be malignant gliomas of the cerebral hemispheres, arising from astrocytic glial cells or, less commonly, from oligodendroglial or ependymal cells. In children, most commonly, gliomas arise in the posterior fossa, affecting the cerebellum or brain stem. Treatment of malignant glioma by surgery and radiotherapy is relatively ineffective, and it remains a lethal disease. The cerebral glioma at time of diagnosis generally consists of a tumour 3-5 cm in diameter. At its periphery there is a rim of actively proliferating tumour cells, intermingled with oedematous normal brain, which may still be functionally recoverable. Inside this there is a further actively growing well-vascularized shell of tumour with varying degrees of homogeneity. Within this is an area of tumour poorly vascularized, non-proliferating or only slowly growing, and surrounding an inner core of frankly necrotic and degenerating tumour. Even where selective and macroscopically total removal of the tumour can be performed by radical surgery, without unacceptable neurological damage to the patient, there remains tumour which has infiltrated microscopically into normal brain at the edges of the resection. This continues to grow, causing disability and death due to further diffuse infiltration of normal brain, or by causing fatal raised intracranial pressure with brain herniation. The median survival of patients from time of operation is 5-6 months, with fewer than 10 per cent alive at 2 years [1]. Radiotherapy is commonly used in treatment, either after biopsy operation or more radical resection. This method can be used to kill glial tumour cells selectively in a particular area of brain, but does not stop recurrence of tumour, due to the persistence of viable cells which survive such treatment [2]. Because of the bleak outlook for patients, many forms of chemotherapy for this disease have been tried during the past two decades. No single, highly effective drug has yet emerged. However, with the best agents so far discovered for chemotherapy of glioma, namely nitrosoureas and procarbazine, there is a modest beneficial response which has been clearly shown in carefully designed trials, and there has come a better understanding of the basic concepts important in chemotherapy. The purpose of this chapter is to introduce to those neurologists and neurosurgeons, who may have had

little or no experience with clinical chemotherapy, some of the basic concepts in chemotherapy and to selectively review laboratory and clinical studies which have been performed in cerebral glioma and which indicate directions for progress in the future.

DRUGS FOR CHEMOTHERAPY OF GLIOMA

Chemotherapy of cancer is based on the proposition that the malignant tumour cell is different in some way from the normal cells of the body, so that oncolytic agents may be discovered capable of differentially killing tumour cells more than normal cells. Such an effect is not selective in the same sense that surgical excision of a mass or radiotherapy to an organ is selective. All known oncolytic agents in their effective therapeutic doses have toxic effects on normal body cells, most frequently on proliferating bone-marrow and gut cells. The therapeutic index, that is the ratio of toxic to therapeutic dose, is generally close to 1. The biochemical mechanism by which some agents work is known to some extent, and it is possible to classify chemotherapeutic drugs according to this, as well as by their chemical structure or method of production. A second means of classifying chemotherapeutic drugs, even if their mechanism of action or chemical structures are unknown, is by whether they are cycle-specific or cycle-non-specific, that is whether they act to kill only proliferating cells passing through the cycle of cell division, or whether they can kill both proliferating and resting cells within a tumour.

Drugs Inhibiting Nucleic Acid Function

Bifunctional Alkylating Agents

The nitrogen mustards are the parent substances of this group, which includes chlorambucil, phenyl-alanine mustard, busulphan and cyclophosphamide as well as thio-TEPA and nitrosoureas. These drugs contain chloroethyl groups, and their active products can form bridges between the strands of desoxyribonucleic acid (DNA) in the nucleus, thus preventing their division at mitosis. Thio-TEPA (triethylene thiophosphamide) has been used for intra-arterial chemotherapy of brain tumours [3]. The nitrosoureas, BCNU (1,3-bis-(2-chloroethyl-1-nitrosourea), CCNU (1,(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and methyl-CCNU (MeCCNU), are the most effective agents at present for chemotherapy of malignant glioma [1, 4-6]. Their action, in part, is as alkylating agents. However, they are also carbamoylating agents which inhibit protein and purine synthesis [7] and are cycle non-specific agents.

Antibiotics

These agents are produced from fermentation products of fungi and bacteria and have varying biochemical sites of action, to interfere with normal

DNA or ribonucleic acid (RNA) function in the tumour cell. Bleomycin is radiomimetic and disrupts DNA strands in a way similar to radiotherapy. Purinomycin interferes with transfer of messenger RNA-amino acid complexes and limits protein synthesis. Actinomycin D, adriamycin and mithramycin form complexes with nuclear DNA and inhibit the formation of DNA-dependent RNA. Of these, mithramycin has been used clinically against malignant glioma, and is ineffective [8].

Vinca Alkaloids

Vincristine and vinblastine are extracted from the plant *Vinca rosea.* They act at the mitotic spindle and arrest cell division in metaphase, and are therefore cycle-specific drugs. They inhibit formation of RNA-amino acid complexes. Vincristine has been used effectively alone and in combination chemotherapy of medulloblastoma [9, 10].

Drugs Inhibiting Synthesis of Nucleic Acids or Protein

Most of these drugs are *antimetabolites* which interfere with normal cellular work or metabolism in both normal and tumour cells. They are analogues of vital metabolic precursors with structures so closely similar to the normal biological compound that they compete in essential biochemical pathways and cause blocks, often at a known enzymatic site.

Folic Acid Antagonists

Methotrexate (MTX), one of the most widely used and extensively studied chemotherapeutic drugs, belongs to this group. It is a structural analogue of folic acid and binds with the enzyme dihydro-folic acid reductase, and so blocks the conversion of folic acid to tetrahydro-folic acid. It also inhibits thymidilate synthesis, which may be the major cytotoxic effect on cells treated with MTX. Derivatives of tetrahydro-folic reductase are important co-enzymes in several essential biochemical synthetic pathways. Synthesis of thymidilic acid and purine synthesis, necessary for DNA and RNA synthesis, are reduced. It has systemic toxic effects which can be largely reversed by leucovorin or citovorum factor. It is a cycle-specific drug.

Methotrexate has been employed in the past in several studies of brain tumour chemotherapy, but delivery to brain is difficult. Its main role currently is for treatment of carcinomatous or leukaemic infiltration of the meninges, and in these conditions it is administered by intrathecal injection [11]. Other antifolic agents are more lipid-soluble and may prove easier to deliver to the brain. These include DMP (2,4-diamino-5-(3′,4′ dichlorophenyl)-6-methyl pyrimidine) [12].

Anti-pyrimidines

These drugs are analogues of pyrimidine bases, like thymidine, in nucleic acids. 5-Fluorouracil (5-FU), which enters brain following systemic administration, has been used against glioma alone [13] and in combination [14]. Cytosine arabinoside (ARA-C) has also been used by the intrathecal route for meningeal infiltration with carcinomatous or leukaemic deposits.

Anti-purines

This group includes 6-mercapto purine and 6-azaguanine, analogues of the purine bases. Trials of 8-azaguanine for cerebral tumour were not successful [15], although the enzyme which deactivates the drug is not present in gliomas. DTIC (5-(3,3-dimethyl-1-triazeno) imidazole-4′-carboxamide) is in this group, which has some potential for delivery to cerebral gliomas.

Miscellaneous Chemotherapeutic Drugs

L-Asparaginase

This enzyme causes hydrolysis of L-asparagine to L-aspartic acid, which is an essential amino acid. Since asparagine synthetase is absent in glioma cells this drug theoretically could cause critical inhibition of protein synthesis in the tumour cells.

Epipodophyllotoxin VM 26 (4′-dimethyl-epipodophyllotoxin-D-therylidene-glucoside)

This drug inhibits entry of cells into the mitotic phase of the cell cycle and inhibits thymidine incorporation.

Procarbazine

This is a derivative of the mono-amine oxidase inhibitor drugs. It exerts a complex action on the synthesis of nucleic acids and of proteins, interferes with transfer RNA function, as well as probably having a radiomimetic effect on DNA strands. It is a cycle-non-specific drug and appears to be effective clinically against glioma [16].

Hydroxyurea

This drug acts at the site of the enzyme ribonucleotide reductase, and inhibits protein synthesis.

Corticosteroids

In some forms of cancer glucocorticosteroids are effective chemotherapeutic agents in their own right. In cerebral glioma they are highly effec-

tive in controlling cerebral oedema and, since their introduction, have made a major contribution to the clinical management of patients with glioma of the brain [17]. However, it is not established whether they exert an inhibitory effect on glioma cell proliferation. *In vitro* they may even enhance glioma cell growth [18].

CHEMOSENSITIVITY TESTING

An assumption about chemotherapy is that tumours of one organ, for example glioma, may be sensitive to a drug which is ineffective against tumours of other organs, for example carcinoma of the breast, lung or bowel, while being themselves resistant to drugs effective in those tumours. This assumption has to a large extent been borne out in practice. In the past forty years many thousands of chemicals, most extracted from biological sources but many synthesized by chemists, have been screened against animal tumours, representing haematological malignancies and a panel of solid tumours of different organs, in an attempt to find effective chemotherapeutic agents. A handful of drugs have been synthesized with an anticipated anti-tumour effect, based on rational biochemical predictions. However, most useful agents have been established by taking agents with some activity in the animal screen, and then moving on to clinical trials in man against a panel of various cancers to look for a biological effect. The animal brain tumours employed in this way to screen for activity in new drugs have generally themselves been induced by chemical carcinogens, although virus-induced gliomas and gliomas spontaneously arising in experimental animals are also available [19]. Usually the glioma is passaged from animal to animal, either by intracerebral inoculation or by injection at a more readily accessible site, like the flank. Much of this experimental work has been done not with astrocytoma, which is the most common type of human glioma, but with other histological types, particularly ependymoblastoma and gliosarcoma. Such experimental study models are very artificial analogues of the human tumour, and are relatively insensitive so that they may not reveal the activity of weakly active agents.

Many tens of drugs have been tested in this way and most have been used against human brain tumours in Phase I or Phase II studies (*see below*). Unfortunately, in some cases it has not been possible to obtain a definite answer to drug efficacy, due to variation in selection of patients, dosage of drug or end-point chosen to assess results.

Largely for this reason chemotherapists concerned with the treatment of malignant gliomas have attempted to develop laboratory methods to measure the sensitivity of individual tumours to drugs. By a rational selection of drugs based on some sort of *in vitro* or *in vivo* test it should be possible to maximize the anti-tumour effect and to minimize associated

toxic reactions, by dispensing with drugs to which a class of tumours, for example malignant gliomas, are, in general, resistant.

A second theoretical assumption is that cells from the individual tumours of different patients of identical histological appearance may have differing sensitivities to drugs. In some types of tumours, including malignant glioma, tissue culture methods have been used to assess anti-tumour effect of chemotherapeutic drugs, and have shown that apparently identical tumours exhibit a wide range of chemosensitivity and that this may correlate with the clinical outcome in the patient [20-22]. This offers the potential to screen for chemosensitivity in an individual patient's tumour in an attempt to plan optimum chemotherapy. *In vitro* methods for determination of chemosensitivity generally consist of treatment of cells for a period with graded concentrations of drugs and, after variable periods of exposure and recovery, measurement of residual cell viability. Drug-induced changes in metabolism or cytotoxicity can be measured by isotope uptake or release, or by morphological changes in cells, cell counts or colony formation. Malignant glioma is one human tumour which readily lends itself to *in vitro* chemosensitivity assay. It is possible to initiate cultures from nearly 90 per cent of surgical brain tumour biopsy samples, an unusually high percentage for a human primary tumour. About one-fifth of these cultures will give rise to established cell lines, while remaining cultures die out within 50 passages. Cell cultures from cerebral glioma are not contaminated with stromal fibroblasts, although there may be an appreciable component derived from endothelial cells within the tumour [18]. Easty and Wylie [23] used the microscope to count cells remaining in culture after drug treatment and demonstrated a range of chemosensitivity in human gliomas. Other workers [24-26] have used morphological changes in fixed and stained, drug-treated glioma cells to determine sensitivity to cytotoxic agents, antibiotics and glucocorticoid steroids.

Cloning assays, which rely on the emergence of colonies of cells from stem cells within the tumour, have been used successfully to correlate *in vitro* sensitivity and clinical behaviour in myeloma and ovarian carcinoma [22]. Rosenblum [27] has developed a cloning assay for use in the chemically induced experimental rat glioma, and has recently applied the assay to human glioma [28]. Although the cloning assay may be the best approach on theoretical grounds to the assessment of chemosensitivity of the stem cells of a tumour, not all tumours readily form colonies under a particular set of conditions. The tests are technically complicated and time-consuming to perform and these factors limit their routine use. A micro-cytotoxicity assay, applicable to large numbers of glioma samples, has been developed by Kornblith and Szypko [29]. Cells are treated in micro-titration plates, containing sixty separate wells, which allow numerous variations in dosage and timing of drug exposure to be studied. After recovery the remaining cells are counted and a dose of drug which achieves a 50 per cent reduction in cell count determined. In 24 gliomas tested

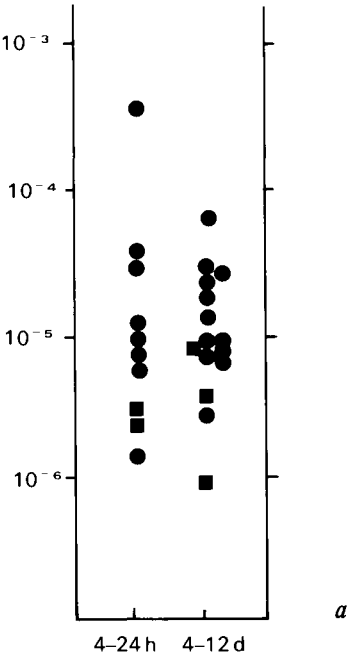
against BCNU they found a fivefold range in chemosensitivity, with three-quarters of the tumours insensitive *in vitro* to BCNU at the concentration approximating to that attained by chemotherapy *in vivo*.

A method which measures glioma chemosensitivity by employing scintillation autofluorography in microtitration plates, and is suitable for routine use in large numbers of tumour samples, has been developed by the author and co-workers [30]. These studies have shown that malignant glioma *in vitro* displays a wide range of chemosensitivity. When treated with CCNU there was a 160-fold range of apparent chemosensitivity in 15 gliomas (*Fig. 5.1a* and *b*). When the frequency distribution of the sensitivity of these tumours is examined, comparing the distribution at short periods of recovery after drug exposure to that late on, it appears that the peak drug concentration fell from within the range 4×10^{-5} M to 1×10^{-5} M to lie in the range 1×10^{-5} M to 7×10^{-6} M (*Fig. 5.1a*). This may represent a latent drug effect, and thus disclose a proportion of tumours which are relatively sensitive, at the right side of the histogram (*Fig. 5.1b*).

Other experimental approaches to chemosensitivity testing of individual tumours have employed transplant of glioma biopsy material to animal hosts, and subsequent treatment of the host with chemosensitivity drugs. In this type of xenograft experiment, special precautions have to be taken in order to obviate destruction of the transplanted tumour by immunologically based transplant reactions. This can be done by using as the host either nude mice, which are congenitally deficient in their lymphocyte function and transplant response, or mice which have been made immunologically deficient by thymectomy and irradiation as neonates. When the glioma is grown in the flank of such hosts direct measurement may be made of its change in size in response to drug administered to the host animal. Studies of this kind have shown a range of sensitivity in human gliomas subjected to irradiation treatment and chemotherapy in animal xenografts [31]. Practical difficulties of the method include a low rate of successful take of the transplant and the need for specially prepared and carefully handled host animals. A more fundamental limitation to the method's potential use for prediction in the individual patient is that the transplanted glioma appears to grow at approximately the same rate as the residual tumour in the human patient's brain. Therefore, information about the tumour's response in the laboratory animal to chemotherapeutic drugs is not available in time to anticipate events in the patient.

PHARMACOLOGY AND DRUG DELIVERY

Delivery of the chemotherapeutic drug to the tumour and maintenance of effective levels during treatment are pharmacological considerations which are vital to the rational planning of chemotherapy and to interpretation of results of empirical clinical studies.



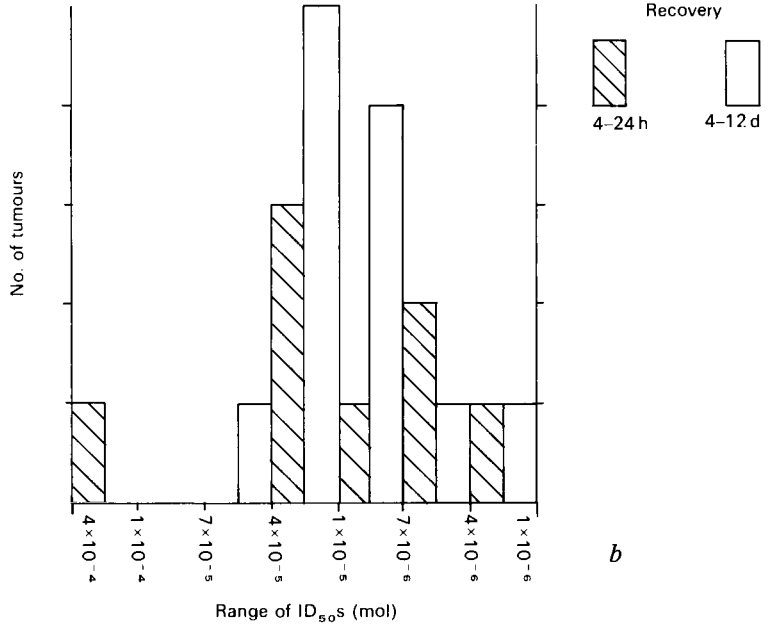


Fig. 5.1. a, Scatter diagram of brain tumour chemosensitivities following *in vitro* treatment with CCNU and either short (4–24 hours) or long (4–12 days) recovery. ● = ID_{50}; ■ = ID_{10}. *b,* Frequency histogram showing distribution of brain tumour chemosensitivities following short (4–24 hours) or long (4–12 days) recovery after treatment with CCNU.

In order to be effective against a malignant glioma cell a chemotherapeutic drug has not only to be delivered to the appropriate site but has to attain adequate concentration for a sufficiently long period of time to kill the malignant cell. Drug delivery in practical terms depends on many properties of the drug, including whether it is aqueous- or lipid-soluble, its molecular weight, degree of binding to plasma proteins and its degradation by metabolism in the body. Many of the environments to which the drug is exposed during delivery are unfavourable. An orally administered drug, like CCNU or procarbazine, passes through the acid pH of the stomach and the enzymes of the small bowel, before crossing the intestinal wall and passing through the hepatic portal circulation to the liver. It is then exposed to degradation by enzymes in the liver. In the blood the drug is also subject to enzymatic degradation as well as to ionization in the aqueous phase, and it may become bound to serum proteins.

Blood enters the brain through 'end arteries' with regional perfusion territories. The intact brain has a very specialized relationship to the circulation. The capillaries of normal brain are composed of endothelial cells with 'tight' junctions between them so that the fenestrations formed by the endothelial cells constitutes a filter with pores 5-7 Ångström units in diameter [32]. The adjacent compartment to the capillary is the extracellular space (ECS), which is in contact both with brain capillaries and with the intracellular space (ICS) of neurones and of glial cells, as well as with the cerebrospinal fluid (CSF) which drains back into the circulation via the arachnoidal villi of the venous sinuses. This effective blood-brain barrier (BBB) at the cerebral capillary is altered to some extent by pathological changes in brain, including the presence of malignant glioma, but in normal brain the passage of a drug across the BBB is proportional to its degree of fat solubility, i.e. its lipophilic nature. Aqueous-soluble, i.e. hydrophilic, molecules with a molecular weight above 180 are excluded by the BBB from entry into the ECS of the brain [33], as are probably also lipophilic molecules of molecular weight above 450.

The ECS is an aqueous medium, and this compartment interchanges water and other molecules with ICS and the CSF. Once in the ECS the chemotherapeutic drug has to pass through the plasma membrane of the glioma cell and the aqueous environment of the cell cytoplasm before reaching its final target, the nucleus or other vital organelle.

In the brain, blood from the venous end of cerebral capillaries, carrying unabsorbed drug or that drug returned from the ECS, drains into the venous sinuses. A further, special, route is provided by the CSF which in turn drains through the arachnoid villi into the dural venous sinuses.

There are several special changes which occur in the circulation of malignant glial tumours which may be very important to rational planning of drug delivery in order to obtain maximum absorption and anti-tumour effect with minimal systemic toxicity. In the central areas of malignant gliomas of the brain, the normal vascular anatomy and physiology is

altered in several ways. The BBB is to some extent broken down, and the capillary endothelium, particularly in malignant glioma, has wide 'gaps' in it [34]. Capillaries in the tumour are also probably spaced further apart, possibly by a factor of two to three times, making it more difficult for nutrients or drugs to reach cells by diffusion. Blood flow through capillaries in malignant tumours, particularly in areas which show necrosis, is probably diminished. However, it is likely that at the infiltrating edge of a malignant glioma, where normal brain is only diffusely involved by tumour, capillary anatomy and physiology remain to a large extent intact.

It has been possible to study the behaviour of isotopically labelled molecules in experimental [35] and human [36] tumours and also to generate theoretical models of the flow between the compartments described above [37]. It appears that the most critical factor limiting drug delivery in brain tumour chemotherapy is permeability at the BBB. The most important characteristic determining permeability of a drug at this barrier is its lipid solubility. This can be quantified by the octanol-water partition coefficient, that is log P (log P = $\log_{10}$ octanol solubility/water solubility [38]). Two nitrosoureas used in glioma chemotherapy have relatively high log P: BCNU, molecular weight 214, log P 1·53 and CCNU, molecular weight 234, log P 2·83. Such lipophilic chemotherapeutic drugs are freely transported from blood to brain, although this transport in practice may be limited by low blood flow in the relatively ischaemic parts of a tumour. This type of drug can attain similar tissue concentrations throughout the tumour and in normal brain. The tissue levels will gradually fall as blood level falls but, because there are no steep concentration gradients, there is no particular tendency for the drug to drain from the tumour into CSF or normal brain. There are some reservations on these theoretical advantages of lipophilic drugs. In use, drugs must be sufficiently soluble in aqueous media, like the blood, to be delivered physiologically to the blood–brain barrier, and excessive lipid solubility may also limit diffusion within the ECS.

Drugs which do not cross the normal BBB may pass into the tumour through abnormal, 'leaky' capillaries. However, the drug which does not cross an intact BBB but only a leaky one into tumour tends to fall rapidly in its concentration within tumour by diffusing down steep concentration gradients into normal brain or CSF. This reduces the period of exposure of the tumour to effective high drug concentrations. It is also probable with this type of drug that the outer shell of tumour which is most nearly normal, and most viable, is relatively under-treated.

Certain hydrophilic drugs of low molecular weight, for example 5FU, may exchange relatively freely between plasma and extracellular water. Binding of a drug to plasma protein is a characteristic that critically affects its behaviour at the BBB or within the ECS. The drug, while it is bound, takes on the size, shape and transport properties of its carrier protein. The release of the drug at the barrier or at the target tumour depends on the

avidity, that is the disassociation constants, of its binding with the carrier protein.

ROUTES OF DRUG ADMINISTRATION

Systemic

The most commonly used chemotherapy for glioma has been systemic administration by oral, intramuscular or intravenous means. These methods are relatively easy and convenient for both patient and chemotherapist. However, when administered by these routes, a drug encounters all the unfavourable factors mentioned above. The behaviour of CCNU, a drug effective in glioma, is an example of what can be achieved in drug delivery by the systemic route. Walker and his colleagues, using isotopically labelled drug, have studied uptake of CCNU, a lipid-soluble agent, following oral administration to patients with malignant glioma of the brain [36]. There is rapid, almost complete absorption with a peak plasma level at 1 hour. The drug is quickly transformed to other active products. These may be bound to macromolecules, through alkylation of nucleic acids and proteins, as well as by carbamoylation of proteins in tissue. In plasma approximately half the drug is protein-bound. The maximum CSF level attained is under half that in plasma. However, tissue levels in glioma biopsied at periods of 1-3 hours after drug administration by mouth show levels similar to those in plasma. There is rapid urinary excretion, and about 70 per cent of the drug's products are excreted by this route in a period of 1 week.

Intra-arterial Route

Intra-arterial injection offers the theoretical advantage of high initial drug concentration achieved with less systemic exposure of the rest of the body to the drug [39]. However, this advantage is not sustained after the first passage through the circulation, although there may be a conceivable advantage for some very rapidly absorbed drugs. This route also avoids the possibility of breakdown of the drug in the hepatic portal or pulmonary circulations. Similarly this route is of no value if enzymatic metabolic steps in the liver are required for activation of a particular drug. A great deal of technical ingenuity has been applied to the catheterization of vessels in the neck in order to perform this sort of drug delivery and the technical problems can be surmounted. At this stage in the development of chemotherapy, however, these methods have not proved superior to less invasive ones.

The Intrathecal Route

It is possible to bypass the BBB by intraventricular or intrathecal lumbar puncture. These routes introduce the technical problems of repeated

cannulation, with the possibility of neural damage and infection as well as technical difficulties with blockage of implanted catheters [11, 15]. There may be also direct toxic effects of the drug on the nervous system, especially if CSF circulation and absorption are disturbed by the tumour's presence. However, this route has found definite acceptance for treatment of leukaemic and carcinomatous infiltration of the meninges. Methotrexate can be administered in this way [11]. It is a water-soluble, ionized drug of 454 mol. wt, which does not cross the BBB. However, when injected directly into the CSF it attains adequate levels in the subarachnoid space and in the Virchow-Robin clefts around pial vessels entering the brain, and in the superficial brain parenchyma. It is effective against leukaemic and carcinomatous infiltration of the meninges.

Intra-tumoral Route

The injection of drugs into the cavity left after surgical resection of cerebral glioma has been attempted, without systemic toxicity and with relatively few serious complications [40]. Changes in residual tumour due to the chemotherapy have been demonstrated, but the clinical effects have so far been disappointing.

CELL KINETICS OF GLIOMA

Frequent mitoses are seen in histological sections of glioma and are generally most frequent in those tumours which, judged by other morphological features including anaplasia, endothelial proliferation and necrosis, appear to be the most malignant. Before methods became available to measure cell proliferation, it was commonly assumed that all cells within a glioma were growing and that the rate of their proliferation was greatest in the most malignant. With the advent of isotopic tracers and their use to follow nucleic acid synthesis in replicating cells [41] it has become evident that the situation is more complex. In a solid tumour, like a glioma, there exist populations of both proliferating and non-proliferating or resting cells. There is some movement between these cell pools, and cells are also constantly dying and being removed. Cell loss is a feature of both normal and neoplastic tissue. Mature normal cells may fail and be replaced, while in a malignant glioma areas of necrosis are frequent, probably due to a failure of vascularization and local nutrition. Tumours increase in size because there is an increase in the proportion of proliferating cells, with possibly some tumour cells proliferating faster than their normal equivalents, and because cell loss exceeds cell removal, so that dead cells contribute to tumour bulk.

Different types of tumours have different lengths of cell cycle and very different proportions of the tumour cell population either growing or

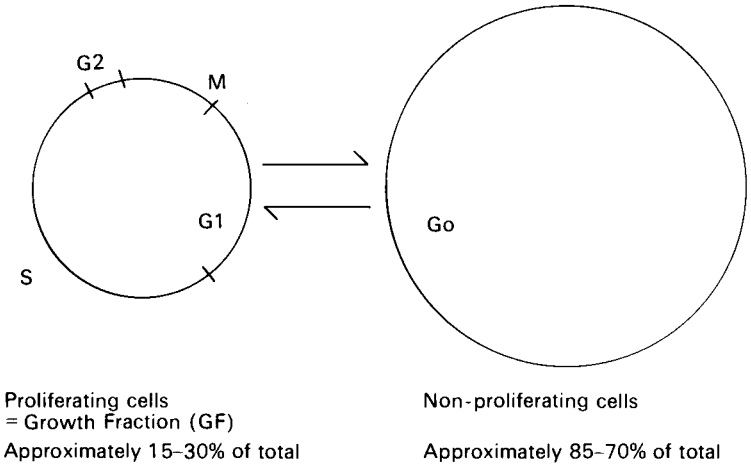


Fig. 5.2. Cell kinetics in human glioma.

resting, i.e. different growth fractions. The normal cells from different tissues of the body also have individual cell kinetic profiles [42]. The cycle-specific drugs kill only proliferating cells in the growth fraction, while the cycle-non-specific drugs affect also resting cells. The cycle-specific drugs may be further sub-divided into those which are phase-specific or non-phase-specific, according to whether or not their action is restricted to a particular part of the cycle or replication and division of a proliferating tumour cell. Knowledge of the cell kinetic properties of any malignant tumour, including glioma, is therefore relevant to the rational choice of chemotherapeutic drugs as well as for deciding timing of drug treatment [43]. Using such information it may also be possible to plan to minimize the toxic effects on normal proliferating body cells [44]. Such relevant knowledge of the biology of cell growth has been obtained from animal and human research. The critical stages of the cell cycle have been determined and a general scheme of cell kinetics applicable to any solid tumour has been demonstrated (*Fig. 5.2*).

The resting, non-proliferating pool of cells is termed G_0. This consists of cells which may re-enter the proliferating pool and sterile cells which may die and eventually be removed (cell loss factor, CLF). It is not known what influences cause a tumour cell to pass into or out of G_0, but possibly reduction of tumour bulk by surgery may encourage resting cells to re-enter the growth cycle. The proliferating cells, undergoing cell division, are in one of four specific phases of the mitotic cycle. These are defined on the basis of desoxyribonucleic acid (DNA) content within the nucleus and are termed M, G_1, S and G_2. The M phase, or mitosis, is visible under the light microscope and consists of distribution of previously replicated

chromosomes containing DNA to two daughter cells and accompanied by physical division of the cell into two. Normally each daughter cell is diploid, that is, it contains a $2N$ complement of DNA, in this post-mitotic gap phase, termed G_1. Tumour cells may have irregular chromosomes and are commonly aneuploid. During G_1 phase, cells are available to move into the non-proliferating G_0 pool, or to proceed to a further cell cycle. Synthesis of enzymes, protein and ribonucleic acid (RNA) occurs and, in those cells which proceed in the cycle, the next phase, termed S phase, begins with the synthesis of DNA. During S phase the genetic material DNA increases from $2N$ to $4N$, as the chromosomes are duplicated. At the completion of S phase there is a short gap, termed G_2, before mitosis starts. In this pre-mitotic phase further protein and RNA synthesis takes place. The ratio of proliferating cells in cell cycle to non-proliferating cells in G_0 is termed the growth fraction (GF). The period of time required for the cycling cell to pass from one mitosis to the next is termed cell cycle time (T_c). If the GF were 100 per cent the theoretical doubling time of the tumour (T_p) would be the same as the cell cycle time (T_c). However T_p is longer than T_c in tumours, like glioma, where the GF is much less than 100 per cent, and where a further factor of cell loss (CLF) operates. The actual observed tumour doubling time (T_d) is therefore considerably longer.

Many values of these parameters, specific to glioma in animals and in man, have been determined in the past decade by Hoshino and co-workers [45-47]. Most of the experimental techniques which have been used in these studies rely on isotopic labelling of precursors of DNA, coupled with histological studies of radioautographically stained sections of tumours. One cell kinetic characteristic, the labelling index (LI), may be determined by administering a dose of the DNA precursor thymidine, labelled with tritium, to the intact host animal or human patient shortly before tumour biopsy. Only cells in the S phase, carrying out DNA synthesis, at the time of the 'flash' labelling will take up the isotope. Subsequently these cells can be identified and counted in an autoradiograph of the tumour section. The LI gives an approximate measure of the proliferative activity in a glioma studied in this way. In grade I, well-differentiated human astrocytoma, LI has been measured at 1-2 per cent, in anaplastic astrocytomas 3-11 per cent and in highly malignant gliomas 8-17 per cent (Table 5.1). However, even if the labelling indices of tumours are the same, their growth fractions, and consequently their doubling times, may differ widely. Other cell kinetic parameters in addition to the LI, therefore have to be determined, using different isotopic labelling techniques or by means of indirect calculations, in order to fully compare different tumours. Newer methods, particularly flow microfluorometric techniques (FMF), are capable of analysing biopsy material with no prior isotope administration to the patient. These techniques are also more rapid and offer the possibility of producing results in the individual patient within days rather than weeks or months generally required by radioautographic methods.

Table 5.1. Cell Kinetic Data for Glioma

	Experimental animal glioma	*Human glioma*
Cell cycle time (T_c)	20 h	2-3 days (52·3-69·1 h)
G1 phase	6-7 h	
S phase	10 h	9 h (average 5-13 range)
G2 phase	2-2·5 h	
M phase	1-2 h	
Growth fraction		15-30 per cent
Cell loss factor (CLF)		80-85 per cent
Labelling index (LI)		1-2 per cent astrocytoma Grade I
		3-11 per cent astrocytoma Grade II-III
		8-17 per cent astrocytoma Grade IV

Data of Hoshino [45-47].

It has proved possible ethically to transfer some of the methods from animal work to study patients with malignant glioma, and to calculate many of the kinetic characteristics of human glioma as well as those of tumour-bearing experimental animals (Table 5.1).

The measured growth fraction (GF) in the non-necrotic areas at the proliferating edge of human malignant gliomas has been in the range 15-40 per cent with an average of 30 per cent. Allowing for the presence of necrotic areas in the tumours, where the GF is virtually zero, a value of nearer 15 per cent may be assumed for the overall average in human malignant glioma. The cell cycle time (T_c) has been found remarkably constant, with an average of 2-3 days, as is the duration of S phase, with a duration of 7-10 hours.

These cell kinetic characteristics of human glioma have theoretical implications for clinical chemotherapy. At the time of diagnosis and surgery a cerebral glioma may commonly be 3-5 cm in diameter, as shown by computerized tomography or other neuroradiological investigations. Approximately 10^9 cells occupy 1 ml volume, so that an approximately spherical tumour of 4 cm diameter may be assumed to contain of the order of $3{\cdot}35 \times 10^{10}$ cells.

Tumour cell kill may be expressed on a logarithmic scale in which a tenfold reduction of cells is a '1 log kill', i.e. 90 per cent reduction = 1 log, 99 per cent reduction = 2 log, 99·9 per cent = 3 log.

Partial surgical resection of a glioma may be expected to reduce tumour bulk by anything from 50 to 90 per cent, i.e. up to 1 log cell kill. If chemotherapy with a cell-cycle-specific drug is then administered in the optimal theoretical way, maintaining therapeutic levels throughout one cell cycle, that is about 2-3 days, at best only those cells in the growth fraction, i.e. 15-30 per cent, could be killed. The number of cells affected would only

be 15-30 per cent of the total number, $3{\cdot}35 \times 10^{10}$, that is approximately 1×10^{10}, reducing the total to $2{\cdot}35 \times 10^{10}$. This would represent much less than a 1 log cell kill, and chemotherapy alone in this way would reduce the tumour diameter in the order of 10 per cent only. If the cell-cycle-specific drug was maintained at effective levels for a shorter period, for example 10-12 hours, only that fraction of the cells within the GF at a phase sensitive to the particular drug would be affected. This would limit even further the theoretical maximum cell kill, so that perhaps only 5-10 per cent of cells in a malignant glioma would be affected.

A subsequent retreatment with cell-cycle-specific drugs, after the proliferating cell population had been reconstituted by cells recruited from G_0, if effective to the same extent, would at most only reduce the number of tumour cells to $0{\cdot}7 \times 10^{10}$. It is therefore unlikely, on cell kinetic grounds, that chemotherapy with cell-cycle-specific drugs will achieve a significant reduction in glioma bulk.

Cell-cycle-non-specific chemotherapeutic drugs, on theoretical cell kinetic grounds, are more likely to be effective because a major proportion of all cells in the tumour may be killed, rather than only those in GF. Drugs like the nitrosoureas, BCNU and CCNU, which are clinically effective in glioma, may exert a 2 to 3 log cell kill following one course of treatment.

It is not known how quickly cell recruitment from G_0 occurs, nor how quickly cell loss (CLF), i.e. removal of dead cells, occurs. However, assuming a cell cycle time of 3 days, GF of 30 per cent and zero CLF, after a course of chemotherapy with a 2 to 3 log cell kill, the tumour will take between 53 to 78 days to repopulate [46]. One reason why cell-cycle-non-specific drugs alone are not curative is that the GF may increase during chemotherapy. Therefore, to obtain a stepwise reduction in tumour mass, the second course should be given within this time. If the GF increases after successful treatment, assuming the most favourable pattern of repopulation with GF approaching 1·0, the minimum times for repopulation following 2 log and 3 log cell kills would be 20 or 30 days respectively [46]. Therefore retreatment with courses in 3-4 week intervals may result in stepwise decrease in tumour size. If cell loss factor (CLF) is appreciable the courses of chemotherapy may be spaced further apart and, as the toxicity of most agents relates to recovery of normal cells, this may be advantageous. Cell kinetic considerations also suggest that cell-cycle-specific agents may have a place after gross surgical or radiotherapy ablation of the tumour, when a small residual tumour mass may contain a high GF, or in combination with cycle-non-specific agents which have effects similar to surgery or radiotherapy, that is, inducing a high GF in residual tumour.

Theoretical cell kinetic considerations are relevant to rational planning of combinations of chemotherapeutic drugs, as well as in selection of dosage and timing of administration, in order to achieve the optimal result. The rationale for combination of chemotherapeutic drugs with differing mechanisms of action, and often rather different limiting toxicity, is to

achieve an additive or even potentiated therapeutic effect, while maintaining toxic side effects at tolerable levels. A method, which on theoretical cell kinetic grounds may be expected to enhance the effect of cell-cycle-specific drugs, is cell synchronization. In the untreated glioma proliferating cells in the growth fraction are very numerous and at any one time they are randomly distributed through the phases of cell cycle in their progress towards cell division. Administration of an agent able to synchronize the dividing cells, so that all pass through the given phases of the cell cycle in step, would confer an advantage when, subsequently, a cell-cycle-specific drug was administered. Such an advantage has been claimed for the combination of VM26 and CCNU [48] and for bleomycin [49].

The effect of drug on tumour is proportional to its dose, but the toxicity on proliferating normal marrow or gut cells tends to be cumulative over time, with repeated doses. There appear to be differences in dose response curves of malignant cells and normal marrow or gut stem cells to a given drug, and these differences are probably in large part due to dissimilar cell kinetic profiles, for example GF and cell cycle time. Generally, intermittent high dose chemotherapy at maximum tolerated dose, repeated as soon as the toxic effects have worn off, offers the optimum effect on tumour with least toxicity [42, 44].

CLINICAL TRIALS IN CEREBRAL GLIOMA

Nearly every drug which has been developed as a chemotherapeutic agent has been administered to some patients with glioma of the brain. Unfortunately the results of many studies have been disappointing and difficult to interpret. In order to make better progress in future it is important to consider basic principles of chemotherapy trials in patients with cancer, and to review some studies in glioma which are sufficiently thorough and well designed to stand up to critical examination.

The sequence of trials which any chemotherapeutic drug passes through before it eventually gains acceptance in routine practice as an effective agent can be divided into three phases. Although not all drugs go through these phases in a clear-cut, precise way it is important to recognize the separate stages involved. Phase I is the first trial of a new drug in man, undertaken with informed consent of the patients. At this point the drug has shown activity in treating animal tumours and the toxic effects in experimental animals have been determined. The purpose of this sort of study is to establish the maximum tolerated dose and the toxic effects in man. The patients who are submitted to this treatment are those in whom all conventional therapy has failed, although they have not necessarily reached a terminal condition. About 20 patients with a variety of tumours, usually not including glioma, are closely studied, primarily to

establish the acceptable dose and means of administration of the drug. It is also hoped that an anti-tumour effect will be seen in the human patients.

Phase II trials consist of the testing of a new drug in a group of patients with a single type of tumour. Generally these patients have recurrent tumours and conventional methods of treatment have been exhausted. Using the pharmacological information from Phase I trials about dose and toxicity, the drug is used to look for any response to therapy which might indicate potential benefit for patients with that specific type of tumour. Several Phase II trials have been conducted with glioma patients, in some cases with response rates of 50 per cent or more and with the remission sustained for 6-9 months [16, 50-54]. It is on the basis of such encouraging results that further prospective randomized controlled trials are planned, or alternatively if the results are discouraging, the drug is abandoned. The Phase III trial consists of such a controlled prospective randomized study in which careful statistical design and analysis is applied to compare the effect of the new drug treatment with what is considered the best currently acceptable conventional methods, which may include some other form of chemotherapy. This establishes objectively whether there is a benefit conferred by chemotherapy with a particular drug, and also indicates whether such benefit, if it exists, is substantial or only marginal.

During these trials human toxicology and pharmacology can be studied in detail, and the optimum dosage and routes of administration established. Often this is a very empirical process, with many compromises accepted in order to achieve a regimen which is acceptable in routine practice. In Phase II and Phase III trials in patients with cerebral glioma particular problems arise when assessing results. These tumours are comparatively rare, and simple statistical randomization of the patients as they are diagnosed, allocating them arbitrarily between new drug treatment and best conventional methods, may not be sufficient to remove bias in results due to aggregation in one group of those with more favourable natural prognosis. The best way to avoid such bias is to stratify the patients before randomization by assessing them according to any known prognostic factors, for example histological grade or age. These factors are taken into account when the input into the different treatment groups is matched. In many previous trials of glioma chemotherapy patients with astrocytoma of intermediate grade and malignant grade have been mingled with those with oligodendroglioma and ependymoma, where it is known that the natural history of these different tumours is significantly different. Exact information about whether certain clinical factors, for example side or site within the brain, which were thought to carry either a favourable or unfavourable prognosis have emerged during the course of chemotherapy trials [55], and some preconceptions have been corrected. In this way a better understanding has been achieved of factors which should be considered in stratifying glioma patients prior to randomization.

Another controversial problem is which parameters should be measured

in the patients in order to assess improvement following chemotherapy. Survival time in patients with malignant glioma treated by conventional methods is short, in the region of 6 months on average. Time to death can generally be easily determined and survival from time of surgery, radiotherapy or chemotherapy accurately determined. However, this measurement does not specify the quality of survival, and can be deceptive, in that chemotherapy patients are more likely to be treated terminally in hospital, possibly prolonging their survival, while those in untreated control groups are often nursed at home. A second method is to measure rate and quality of remissions induced by chemotherapy drugs in patients with residual or recurrent glioma. In order to do this, objective criteria, for example scales for assessing function which can be measured by clinical examination, are required. The Karnofsky scale (Table 5.2 [56]) permits, by repeated serial examination of the patient over a period of months, the response to be estimated in a quantitative way. Neuro-radiological investigations, particularly non-invasive studies like CT or isotope scanning, can be repeated regularly and quantitative scales to report the results of these tests have been developed. One future area for development is the use of biochemical markers of tumour mass to monitor regression or recurrence. Several laboratory assays have been proposed [57, 58] but so far with limited practical advantage.

These sorts of objective measurement of response to treatment have most commonly been applied in Phase II studies, when patients with recurrent glioma are treated at some time, relatively late, after surgery has been performed and radiotherapy completed. In this type of trial these methods of assessment allow objective measurement of tumour regression and may obviate the need for untreated controls, when what is being sought is evidence simply of tumour regression. However, in order to achieve an effect which is tangible by these methods of measurement, a drug requires to exert a cell kill in excess of 1 log, so that the effect of weaker drugs may be overlooked. A further disadvantage is that change in steroid dose during follow-up can also influence parameters of this kind.

With modification these parameters can be used to assess selected patients who are subjected to a prospective randomized trial of adjuvant chemotherapy commenced directly after surgery and radiotherapy. This can be done by measuring the length of the free interval before recurrence takes place. Unfortunately only a proportion of patients with cerebral glioma are entirely free of, or with only minimal, clinical signs and radiological evidence of residual tumour when they commence chemotherapy in this sort of Phase III trial. However, those who meet these criteria can be followed during treatment, and measurements made of the period of time before tumour regression, as determined by sustained change in Karnofsky score and/or in CT or isotope scan during serial examinations, is detected.

Differences in approach to measurement of results, particularly when

Table 5.2. Karnofsky Scale of Patient's Performance

Definition	*(%)*	*Criteria*
Able to carry on normal activity and to work; no special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated, although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment is necessary
	10	Moribund: fatal processes progressing rapidly
	0	Dead

Data of Karnofsky et al. [56].

the available chemotherapeutic drugs are still only modestly active, probably account for some of the conflicting results reported by different groups using the same form of treatment. Other reasons include the problems associated with patient selection, mentioned above, and with differences in the dosage and timing of drugs used in different studies.

RESULTS OF GLIOMA CHEMOTHERAPY

Nitrosoureas

The nitrosoureas, BCNU, CCNU and methyl-CCNU, have been investigated in numerous chemotherapy trials, which have often been performed on a co-operative multicentre basis.

BCNU is administered by intravenous injection, in a dose according to the body surface area of the patient expressed in square metres (m^2). This is calculated from tables relating body weight and height to area. There is often transient nausea and vomiting on the day of treatment, which is readily controlled with prophylactic anti-emetics. A toxic side effect is bone-marrow depression, which occurs late, with peripheral white blood cell and platelet counts falling after 3-4 weeks and recovering at 6-8 weeks, when treatment can be repeated. CCNU and methyl-CCNU have the advantage that they can be administered orally, but have similar side effects.

In Phase I or II trials BCNU [50], CCNU [52] and methyl-CCNU [59], used alone as single agents, have been found to produce objective remissions in a proportion of patients with recurrent glioma. In some trials the rate of remission has been in excess of 50 per cent with a sustained benefit for 6-9 months. BCNU is possibly slightly superior to the other two in rate of remissions induced. In other Phase II studies the combination of BCNU with vincristine [51] and BCNU with procarbazine [60] have not proved more effective against malignant glioma than drug therapy with the nitrosourea alone.

In a Phase III trial by the Brain Tumor Study Group, organized by the National Cancer Institute in the USA, BCNU was found to prolong median survival time in patients with glioma when combined with radiotherapy as an adjuvant therapy, but not when used alone [4]. This Phase III trial by the Brain Tumor Study Group compared four forms of treatment: BCNU alone (80 mg m^{-2} day^{-1} by intravenous injection on 3 successive days every 6-8 weeks), radiotherapy alone (5000 to 6000 rad over 5-7 weeks), the combination of BCNU and radiotherapy in the above doses, and conservative treatment with neither radiotherapy nor chemotherapy following surgery. The use of corticosteroids was carefully controlled to avoid inadvertent bias in the results. A total of 303 patients was entered and randomized. A proportion were later disqualified because of subsequent revision of the histological grading of the tumour, excessive use of steroids, or failure to

administer the drug treatment correctly. Those patients who passed these hurdles constituted the 'Valid Study Group' of 225 patients. Some of these died early, within days or weeks of the commencement of their treatment and so a further restricted group was defined, the 'Adequately Treated Group', of 167 patients. These patients, according to which of the appropriate treatment arms of the trial they were in, had to receive at least 5000 rad of radiotherapy, two or more courses of BCNU, or to have survived 8 weeks or longer from surgery without further treatment. In the Valid Study Group the results were, that the group treated with BCNU alone had a median survival of 18·5 weeks, that with radiotherapy alone 36 weeks, that with combined therapy 34·5 weeks, and that with no additional specific therapy 14 weeks. The Adequately Treated Group showed more meaningful results, with median survival in the group treated with BCNU alone of 25 weeks, that with radiotherapy alone 37·5 weeks, that with combination therapy 40·5 weeks, and that with no additional specific therapy 17 weeks.

This confirmed the increase in survival time achieved by BCNU and radiotherapy, but BCNU alone was less effective than radiotherapy alone. Although combination of BCNU and radiotherapy produced only a small increase in median survival the combination appears to make a more significant effect on longer term survival. At the end of 18 months nearly all those patients who had received either chemotherapy or radiotherapy alone had died, while 18 per cent of those receiving combination therapy survived.

A further Phase III trial by the Brain Tumour Study Group has confirmed the increase in survival time achieved by BCNU and radiotherapy in combination: 349 patients were entered resulting in a Valid Study Group of 263. The effects of BCNU and radiotherapy in the combined doses mentioned above, radiotherapy alone (6000 rad over 6–8 weeks), methyl-CCNU alone (methyl-CCNU 220 mg/m^2 orally at 6–8 week intervals), or methyl-CCNU and radiotherapy in combination in the above doses, were compared [5, 61]. In this series the median survival achieved by methyl-CCNU alone or methyl-CCNU in combination with radiotherapy was 31 weeks, that with radiotherapy alone 36 weeks and that for combination of BCNU and radiotherapy 51 weeks. BCNU in combination with radiotherapy therefore prolonged postoperative survival time in patients with cerebral glioma. A more recent study by the same group confirmed a modest benefit in long term (18 months) survival in those treated with BCNU and radiotherapy rather than radiotherapy alone, but the differences in survival curves were not significant at the 0·05 level [62].

The results of reported trials with CCNU for cerebral glioma are conflicting. In a Phase III study, organized by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group [6] CCNU has been found to prolong median survival time but not to increase the disease free interval before tumour recurrence takes place. However,

Band and co-workers [63] found an increase in the mean time to tumour recurrence. Other groups, using different means of patient selection and assessment as well as different treatment regimens, have been unable to obtain an increase in survival with CCNU [64] or with BCNU, CCNU or methyl-CCNU alone [65].

Procarbazine

Procarbazine has been studied in Phase II trials and is undergoing Phase III trials by the Brain Tumor Study Group.

It is a drug which is administered orally, with bone-marrow depression as a side effect.

Phase II trials [16, 66] show encouraging rates of remission, in the region of 50 per cent, when it has been used to treat recurrent cerebral glioma.

COMBINATION CHEMOTHERAPY

Single agent chemotherapy has shown a modest benefit, and combination chemotherapy with multiple drugs has been investigated in attempts to obtain increased beneficial effects with reduced toxicity. One such combination is procarbazine, CCNU and vincristine. Vincristine is administered by intravenous injection. Its toxic effects spare the bone-marrow, but it can cause peripheral neuropathy. It has been noted that in Phase II trials BCNU and vincristine in combination in the treatment of cerebral glioma were not more effective than BCNU alone [51]. Procarbazine in combination with BCNU was also ineffective in a Phase II trial, in which the drugs were administered simultaneously at reduced dosage. However, there is a suggestion from parallel animal studies that this combination can be made more effective than either drug used alone if an early high dose of BCNU is followed 4–8 days later by a low dose of procarbazine [60].

The rationale for the triple agent combination is that all the drugs have different mechanisms of action and different toxic effects. In a study with this triple drug regimen Shapiro and Young [67] have attained a projected median survival in their patients in excess of 50 weeks.

It is disappointing that these agents which achieve a high response rate in Phase II trials, over 50 per cent in some cases sustained for 6–9 months when used against glioma at the time of recurrence, appear only to produce a marginal increase in median survival when used as adjuvants shortly after completion of surgery and radiotherapy. It is possible that the cells within a tumour which respond to drugs and to radiotherapy are the same 'sensitive' cells and that most of the remaining viable cells are relatively resistant to both modalities of treatment whether used alone or in combination.

FURTHER DIRECTIONS

Malignant gliomas are rapidly proliferating, lethal tumours. The proportion of tumour which can be removed by surgical methods is limited, and the majority of neurosurgeons adopt a policy of partial removal of tumour to produce decompression and to obtain biopsy material for histology. It is possible by carefully planning the exploration with the help of anatomical information that has become available recently from CT scan examinations to maximise the extent of tumour removal and so leave the minimum residual tumour burden to be tackled by other modes of treatment [68]. It has also been suggested that, in those patients in whom the preoperative diagnosis is virtually certain on clinical or radiological grounds, chemotherapy should be started before surgery [69]. If this were done, those cells killed by the first round of chemotherapy would be removed effectively by the surgeon, along with the tissue that is routinely evacuated at the time of craniotomy. This, on theoretical grounds, should create more favourable cell kinetic and pharmacological environments for radiotherapy and subsequent courses of chemotherapy to operate in, as well as avoiding the troublesome cerebral swelling which can be associated with the accumulation of swollen necrotic tumour masses during effective drug therapy. A trial based on this rationale has been commenced by the Brain Tumor Study Group and results are awaited.

A special class of drugs, radiosensitizers such as misonidazole and metronidazole, can, by countering the protective effect of hypoxia on tumour cells, increase the fraction of glioma cells killed by radiotherapy [70]. Some other drugs including nitrosoureas, which are chemotherapeutic agents in their own right, potentiate radiation to tumour cells by preventing repair of otherwise sublethal radiation damage [71].

New schedules for administering currently available drugs in overwhelming doses have been adopted by some chemotherapists. In one such trial [72] the patients have been treated with massive doses of BCNU, after marrow and white blood cells have been removed and stored. The otherwise fatal toxic bone-marrow depression is reversed by subsequent auto-transfusion of marrow and blood. It remains to be established whether this will be more effective against patients' malignant gliomas, and whether late toxicity in other organs, including lung and kidney, will be prohibitive. New methods of drug delivery are being tested, including variations of intra-tumoral and intra-arterial routes, employing liposomes which can carry insoluble drugs directly from site of perfusion to and through tumour cell membrane [73].

New chemotherapy agents are constantly being produced by chemists, using rational synthesis or extraction from biological sources. These drugs are tested in animal and tissue culture screens, and with the development of new animal brain tumour models which more closely resemble the human situation, as well as with the use of panels of cultured human glioma cells, it is hoped that more promising drugs for use in glioma will

be obtained. The nitrosoureas were rationally synthesized with the aim of crossing cell membranes and are amongst the first and most effective chemotherapeutic drugs which have been rationally synthesized [74]. The potential of the nitrosoureas for chemotherapy in glioma is being exploited further by employing chemical modifications of the molecule to create varieties with more anti-tumour effect or with more effective absorption and delivery to brain. It is unlikely that there will be a major advance, in a step-wise fashion, in the management of cerebral glioma by chemotherapy, as there was, for example, in the chemotherapy of bacterial disease with the advent of antibiotics. However, modest advances have been made, and nitrosoureas as adjuvant chemotherapy in the management of patients with glioma of the brain are taking a routine place in treatment. The basic requirements for planning further trials to test new methods have been established and some of the basic scientific principles determining the effectiveness of drugs in glioma chemotherapy have been defined.

REFERENCES

1. Walker M. D. and Gehan E. A. (1976) Clinical studies in malignant gliomas and their treatment with the nitrosoureas. *Cancer Treatment Rep.* **60**, 713-16.
2. Salazar O. M., Rubin P., McDonald J. V. et al. (1976) Patterns of failure in intracranial astrocytomas after irradiation: analysis of dose and field factors. *AJR* **126**, 279.
3. Mark V. H., Kjellberg R. N., Ojemann R. G. et al. (1960) Treatment of malignant tumors with alkylating agents (thiotepa, triethylene thiophosphoramide): its differential concentration and toxicity after arterial infusion. *Neurology* **10**, 772-6.
4. Walker, M. D. and Gehan E. A. (1972) An evaluation of 1-3-bis (2-chloroethyl)-1-nitrosourea (BCNU) and irradiation alone and in combination for the treatment of malignant glioma. *Proc. Am. Assoc. Cancer Res.* **13**, 67.
5. Walker M. D. and Strike T. A. (1976) An evaluation of methyl-CCNU, BCNU and radiotherapy in the treatment of malignant glioma. *Proc. Am. Assoc. Cancer Res.* **17**, 652.
6. EORTC Brain Tumour Group (1976) Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma – first evaluation. *Eur. J. Cancer* **12**, 41-5.
7. Bono V. H. (1976) Review of mechanism of action studies of the nitrosoureas. *Cancer Treatment Rep.* **60**, 699-702.
8. Walker M. D., Alexander E. jun., Hunt W. E. et al. (1976) Evaluation of mithramycin in the treatment of anaplastic gliomas. *J. Neurosurg.* **44**, 655-67.
9. Lassman L. P., Pearce G. W. and Gang J. (1966) Effect of vincristine sulphate on the intracranial gliomata of childhood. *Br. J. Surg.* **53**, 774-7.
10. Crafts D. C., Levin V. A., Edwards M. S. et al. (1978) Chemotherapy of recurrent medulloblastoma with combined procarbazine, CCNU, and vincristine. *J. Neurosurg.* **49**, 589-92.
11. Norrel H and Wilson C. B. (1967) Brain tumour chemotherapy with methotrexate given intrathecally. *JAMA* **201**, 93-5.

12. Stickney D. R., Simmons W. S., DeAngelis R. L. et al. (1973) Pharmacokinetics of pyrimethamine (PRM) and 2,4-diamino-5-(3′,4′-dichlorophenyl)-6-methylpyrimidine (DMP) relevant to meningeal leukemia. *Proc. Am. Assoc. Cancer Res.* **14**, 52.
13. Edland R. W., Javid M. and Ansfield F. J. (1971) Glioblastoma multiforme – an analysis of the results of post operative radiotherapy alone versus radiotherapy and concomitant 5-fluorouracil. *AJR* **111**, 337–42.
14. Levin V. A., Hoffman W. F., Pischer T. L. et al. (1978) BCNU-5-Fluorouracil combination therapy for recurrent malignant brain tumours. *Cancer Treatment Rep.* **62**, 2071–6.
15. Rubin R. C., Larson R. and Rall D. P. (1966) 9-Azaguanine (NSC-749). I. Preclinical toxicity studies and a preliminary report on intrathecal perfusion therapy for patients. *Cancer Chemotherapy Rep.* **50**, 283–6.
16. Kumar A. R. V., Renaudin J., Wilson C. B. et al. (1974) Procarbazine hydrochloride in the treatment of brain tumors. Phase 2 study. *J. Neurosurg.* **40**, 365–71.
17. Gutin P. H. (1975) Corticosteroid therapy in patients with cerebral tumors: benefits, mechanisms, problems, practicalities. *Semin. Oncol.* **2**, 49–56.
18. Guner M., Freshney R. I., Morgan D. et al. (1976) Effects of dexamethasone and betamethasone on *in vitro* cultures from human astrocytoma. *Br. J. Cancer* **35**, 439–47.
19. Bullard D. E. and Bigner D. B. (1980) Animal models and virus induction of tumors. In: Thomas D. G. T. and Graham D. I. (ed.) *Brain Tumours: Scientific Basis, Clinical Investigation and Current Therapy*. London, Butterworth, pp. 51–84.
20. Wheeler T. K., Dendy P. P. and Dawson A. (1974) Assessment of an *in vitro* screening test of cytotoxic agents in the treatment of advanced malignant disease. *Oncology* **30**, 362–76.
21. Holmes H. L. and Little J. M. (1974) Tissue-culture microtest for predicting response of human cancer to chemotherapy. *Lancet* **2**, 985.
22. Salmon S. E., Hamburger A. W., Soehnlen B. et al. (1978) Quantification of differential sensitivity of human tumor stem cells to anticancer drugs. *N. Engl. J. Med.* **298**, 1321–7.
23. Easty D. M. and Wylie J. A. H. (1963) Screening of 12 gliomata against chemotherapeutic agents *in vitro*. *Br. Med. J.* **1**, 1589–92.
24. Gazso L. R. and Afra D. (1969) Study on the effect of actinomycins in tissue cultures from human brain tumours. *Acta Neurochir. (Wien)* **21**, 139–52.
25. Barker M. (1976) Experimental chemotherapy models. In: Fewer D., Wilson C. B., Levin V. A. (ed.), *Brain Tumor Chemotherapy*. Springfield, Ill., Thomas, pp. 75–95.
26. Mealey J. jun., Chen T. T. and Pedlow E. (1970) Brain tumor chemotherapy with mithramycin and vincristine. *Cancer* **26**, 360–7.
27. Rosenblum M. L., Knebel K. D., Wheeler K. T. et al. (1975) Development of an *in vitro* colony formation assay for the evaluation of *in vivo* chemotherapy of a rat brain tumor. *In Vitro* **11**, 264–73.
28. Rosenblum M. L., Vasquez D. A., Hoshino T. et al. (1978) Development of a clonogenic cell assay for human brain tumours. *Cancer* **41**, 2305–14.
29. Kornblith P. L. and Szypko P. E. (1978) Variations in response of human brain tumours to BCNU *in vitro*. *J. Neurosurg.* **48**, 580–6.
30. Thomas D. G. T., Darling J. L., Freshney R. I. et al. (1979) *In vitro* chemosensitivity assay of human glioma by scintillation autofluorography. In: Paoletti P., Walker M. D., Butti G. et al. (ed.) *Multidisciplinary Aspects of Brain Tumor Therapy*. Amsterdam, Elsevier/North Holland, pp. 19–34.
31. Shapiro W. R., Basler M. S., Chernik N. L. et al. (1979) Human brain tumor transplantation into nude mice. *J. Nat. Cancer Inst.* **62**, 447–53.

32. Fenstermacher J. D. and Johnson J. A. (1966) Filtration and reflection coefficients of the rabbit blood brain barrier. *J. Physiol. (Lond.)* **211**, 341-6.
33. Fenstermacher J. D., Fall D. P., Patlak C. S. et al. (1970) Ventriculo-cisternal perfusion as a technique for analysis of brain capillary permeability and extra cellular transport. In: *Capillary Permeability: Proceedings of the Alfred Beuzon Symposium 11.* Copenhagen, Munksgaard, pp. 483-90.
34. Long D. M. (1970) Capillary ultrastructure and the blood brain barrier in human malignant brain tumors. *J. Neurosurg.* **32**, 127-44.
35. Levin V. A. and Kabra P. (1974) Effectiveness of the nitrosoureas as a function of their lipid solubility in the chemotherapy of experimental rat tumors. *Cancer Chemother. Rep.* **58**, 787-92.
36. Walker M. D. and Hilton J. (1976) Nitrosourea pharmacodynamics in relation to the central nervous system. *Cancer Treatment Rep.* **60**, 725-8.
37. Levin V. A. (1975) A pharmacologic basis for brain tumor chemotherapy. *Semin. Oncol.* **2**, 57-61.
38. Hansch C., Smith N., Engle R. et al. (1972) Quantitative structure – activity relationships of antineoplastic drugs: nitrosoureas and triazenoimidazoles. *Cancer Chemotherapy Rep.* **56**, 443-56.
39. Mahaley M. S. jun. and Woodhall B. (1967) Regional chemotherapeutic perfusion and infusion of brain and face tumors. *Ann. Surg.* **166**, 266-77.
40. Garfield J. and Dayan A. D. (1973) Postoperative intracavity chemotherapy of malignant gliomas. A preliminary study using methotrexate. *J. Neurosurg.* **39**, 315-22.
41. Howard A. and Pelc S. R. (1953) Synthesis of deoxyribonucleic acid in normal and irradiated cells and its relation to chromosome breakage. *Heredity* Suppl. 6, 261-73.
42. Bruce W. R. and Van Der Gaag H. (1963) A quantitative assay for the number of murine lymphoma cells capable of proliferation *in vivo. Nature (Lond.)* **199**, 79-80.
43. Skipper H. E., Schabel F. M. jun., Mellett L. B. et al. (1970) Implications of biochemical, cytokinetic, pharmacologic, and toxicologic relationships in the design of optimal therapeutic schedules. *Cancer Chemotherapy Rep.* **54**, 431-50.
44. Skipper H., Schabel F. jun. and Wilcox W. (1964) Experimental evaluation of potential anticancer agents. XIII. On the criteria and kinetics associated with 'curability' of experimental leukemia. *Cancer Chemotherapy Rep.* **35**, 1-111.
45. Hoshino T. and Wilson C. B. (1975) Review of basic concepts of cell kinetics as applied to brain tumours. *J. Neurosurg.* **42**, 123-7.
46. Hoshino T., Wilson C. B., Rosenblum M. L. et al. (1975) Chemotherapeutic implications of growth fraction and cell cycle time in glioblastomas. *J. Neurosurg.* **43**, 127-35.
47. Hoshino T. (1979) Therapeutic implications of brain tumor cell kinetics. In: Evans A. E. (ed.), *Modern Concepts in Brain Tumor Therapy, Laboratory and Clinical Investigations.* London, Castle House, pp. 27-33.
48. Pouillart P., Schwarzenberg L., Ameil J. L. et al. (1975) Combinaisons chimiothérapiques de drogues se potentialisant. III. Application aux tumeurs primitives du système nerveux central. *Nouv. Presse Méd.* **4**, 713-21.
49. Barranco S. C., Luce J. K., Romsdahl M. M. et al. (1973) Bleomycin as a possible synchronizing agent for human tumor cells *in vivo. Cancer Res.* **33**, 882-7.
50. Wilson C. B., Boldrey E. B. and Enot K. J. (1970) BCNU (1,3-bis-2(chloroethyl)-1-nitrosourea) in the treatment of brain tumors. *Cancer Chemotherapy Rep.* **54**, 273-81.
51. Fewer D., Wilson C. B., Boldrey E. B. et al. (1972) The chemotherapy of brain tumors. Clinical experience with carmustine (BCNU) and vincristine. *JAMA* **222**, 549-52.

52. Fewer D., Wilson C. B., Boldrey E. B. et al. (1972) A phase II study of 1-(2-chlorocthyl)-3-cydohexyl-1-nitrosourea (CCNU). *Cancer Chemotherapy Rep.* **56**, 421–7.
53. Gutin P. H., Wilson C. B., Kumar A. R. et al. (1975) Phase II study of procarbazine, CCNU and vincristine combination chemotherapy in the treatment of malignant brain tumors. *Cancer* **35**, 1398–404.
54. Sklansky B. D., Mann-Kaplan R. S., Reynolds A. F. et al. (1974) 4′-Demethyl-epipodophyllotoxin-β-D-thenylidene-glucoside (PTG) in the treatment of malignant intracranial neoplasms. *Cancer* **33**, 460–7.
55. Gehan E. A. and Walker M. D. (1979) Prognostic factors for patients with brain tumors. In: Evans A. E. (ed.) *Modern Concepts in Brain Tumor Therapy, Laboratory and Clinical Investigations.* London, Castle House, pp. 181–7.
56. Karnofsky D. A., Burchenal J. H., Armistead G. C. et al. (1951) Triethylene melamine in the treatment of neoplastic disease. *Arch. Intern. Med.* 87, 477–516.
57. Paoletti P., Vandenheuval F. A., Fumagalli R. et al. (1969) The sterol test for the diagnosis of human brain tumors. *Neurology* **19**, 190–7.
58. Marton L. J., Heby O., Levin V. A. et al. (1976) The relationship of polyamines in cerebrospinal fluid to the presence of central nervous system tumors. *Cancer Res.* **36**, 973–7.
59. Young R. C., Walker M. D., Canellos G. P. et al. (1973) Initial clinical trials with methyl-CCNU 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Me CCNU). *Cancer* **31**, 1164–9.
60. Levin V. A., Crafts D. C., Wilson C. B. et al. (1976) BCNU (NSC-409962) and procarbazine (NSC-77213) treatment for malignant brain tumors. *Cancer Treatment Rep.* **60**, 243–9.
61. Walker M. D. (1979) Brain Tumor Study Group: a survey of current activities. In: Evans E. A. (ed.) *Modern Concepts in Brain Tumor Therapy, Laboratory and Clinical Investigations.* London, Castle House, pp. 199–202.
62. Walker M. D., Green S. B., Byar D. P. et al. (1980) Randomised comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N. Engl. J. Med.* **303**, 1323–9.
63. Band P. R., Weir B. K. A., Urtasun R. C. et al. (1974) Radiotherapy and CCNU in grade III and IV astrocytoma. *ASCO Abstracts* **25**, 161.
64. Reagan T. J., Bisel H. F., Childs D. S. et al. (1976) Controlled study of CCNU and radiation therapy in malignant astrocytoma. *J. Neurosurg.* **39**, 302–5.
65. Brisman R., Houseplan E. M., Chang C. et al. (1976) Adjuvant nitrosourea therapy for glioblastoma. *Arch. Neurol.* **33**, 745–50.
66. Wilson C. B., Gutin P., Boldrey E. B. et al. (1976) Single agent chemotherapy of brain tumors. *Arch. Neurol.* **33**, 739–44.
67. Shapiro W. R. and Young D. F. (1976) CCNU alone and combined with vincristine sulfate (VCR) and procarbazine (PCZ) as chemotherapy for malignant glioma. *Proc. Am. Soc. Clin. Oncol.* **17**, 258.
68. Ransohoff J. and Lieberman A. (1978) Surgical therapy of primary malignant brain tumors. *Clin. Neurosurg.* **25**, 403–11.
69. Walker M. D. and Strike T. (1979) The treatment of malignant glioma in controlled studies. In: Paoletti P., Walker M. D., Butti G. et al. (ed.) *Multidisciplinary Aspects of Brain Tumor Therapy.* Amsterdam, Elsevier/North Holland, pp. 267–74.
70. Urtasun R., Band P., Chapman J. D. et al. (1976) Radiation and high-dose metronidazole in supratentorial glioblastomas. *N. Engl. J. Med.* **294**, 1364.
71. Wheeler K. T., Deen D. F., Wilson C. B. et al. (1977) BCNU-modification of the *in vitro* radiation response in 9 L brain tumor cells of rats. *Int. J. Radiat. Oncol. Biol. Phys. (New York)* **2**, 79–81.

72. Hochberg F. H., Parker L. M., Takvorian T. et al. (1981) High-dose BCNU with autologous bone-marrow rescue for recurrent glioblastoma multiforme. *J. Neurosurg.* 54, 455–60.
73. McKeran R. (1979) Personal communication.
74. Schepartz S. A. (1976) Early history and development of the nitrosoureas. *Cancer Treatment Rep.* **60**, 647–9.

A. Norman Guthkelch

6 The Aetiology and Evolution of Chronic Subdural Haematoma

Although case reports of entities that are recognizable as examples of chronic subdural haematoma (CSH) can be found in the medical literature prior to 1850 [1], modern studies of the aetiology of CSH are usually held to begin with Virchow's well-known review [2]. In this paper Virchow rejected the majority opinion that a CSH represents the results of a free haemorrhage into the subdural space, the periphery of which becomes secondarily organized, and suggested that the underlying condition was a pachymeningitis, the haemorrhages which he observed both within the cavity and within the outer wall of its capsule, being secondary. He may have been misled by the fact that in his era CSH was commonly found at autopsy in demented patients dying in insane asylums and that in such cases a history of injury would often have been lacking. Almost 100 years were to elapse between Virchow's paper and the identification of non-accidental injury [3, 4] as a cause of subdural haematoma, but Virchow himself suggested an analogy between CSH and the 'chronic haematomas of the external ear of backward children'. One may speculate that both conditions were often non-accidentally acquired!

As late as 1911, a standard neurological textbook [5] still referred to CSH as 'pachymeningitis hemorrhagica', noting its association with general paralysis of the insane, chronic chorea, senile dementia and alcoholism, but adding that 'head injuries often pave the way for it'. By this time, however, CSH was no longer just a pathological curiosity: it had become a surgically treatable condition. Trotter [6], on the basis of four consecutive personally observed cases, including one autopsy, stated categorically that CSH was traumatic in origin, noting that he had always been able to elicit a history of injury, that neither at operation nor at autopsy had any of his pathological material shown evidence of actual inflammation and that two out of the four patients made a rapid and complete recovery following surgical drainage of the contained fluid. Since then, the concept of pachymeningitis haemorrhagica interna as a separate disease has been generally abandoned, and the alternative view that the chronic form is only a late stage of an unrecognized acute subdural haematoma has been fully documented [7, 8].

There is, however, some doubt whether the term 'subdural haematoma' is accurate. A number of earlier authors [9] believed that in CSH the haemorrhage had occurred between the layers of the dura mater rather than into the subdural space as usually defined. In its original form the

evidence for this view was unconvincing, but recently Friede and Schachenmayr [10] have suggested from electron-microscopic studies that the inner boundary of what is usually regarded as the subdural space is formed by the cells of the border layer of the dura, which is separated by greatly dilated extracellular spaces from the remainder of the dura and shows no intercellular attachments to it. A subdural haematoma is said by these authors [11] to form by cleavage within the layer of dural border cells, but to avoid confusion the appellation 'subdural haematoma' will be retained in the present review.

THE INITIAL FORMATION OF A SUBDURAL HAEMATOMA

The commonest precipitating cause of a subdural haematoma, as Trotter first suggested [6], is a head injury of concussive type in which the sudden motion of the brain within the skull tears one or more of the cortical bridging veins. However, there are also well-documented examples of the occurrence of a subdural haematoma in circumstances in which there has not been any direct application of violence to the head: it may occur in cases of blast injury [12, 13] as well as accidental [14, 15] or non-accidental [16] whiplash injury. Although symptomatic subdural haematoma is a rather uncommon complication of neurosurgical operations, computerized tomography (CT) of patients who have recently undergone craniotomy reveals a high incidence of subdural collections of fluid, the density of which usually indicates that they contain some proportion of blood, and a few of which develop the ring-enhancement characteristic of membrane formation before ultimately disappearing completely.

The list of factors which predispose to the occurrence of subdural haematoma is considerable. It includes conditions in which the clotting time of the blood is increased, e.g. in haemophilia or as a result of anticoagulant therapy [17]; spontaneous subdural haemorrhage can also occur in acute leukaemia. Intracranial hypotension associated with brain atrophy probably accounts for the relatively high incidence of CSH in old people: the possible additional aetiological factor of repeated trauma, including the non-accidental variety, in senile and alcoholic patients, has already been noted. A further predisposing cause of subdural effusions is the therapeutic conversion of a state of increased intracranial pressure due to hydrocephalus into a low pressure situation. This phenomenon was first noticed as a complication of choroid plexectomy and of cerebrospinal fluid (CSF) drainage into the ureter [18] but is also seen occasionally following the insertion of valved shunt systems [19, 20]. It is particularly apt to occur when the hydrocephalus is of long standing, when the ventricles are very large and when the closing pressure of the shunt is low. Subdural haemorrhage is also encountered from time to time as a consequence of the rupture of an intracranial aneurysm through its overlying arachnoid and into the subdural space [21].

From the clinical point of view, there is some merit in dividing the life history of a subdural haematoma into acute, subacute and chronic phases [22]. This chronology proves to coincide quite well with the CT appearances. A subdural haematoma is usually hyperdense in the first 7 days, isodense in the second and third weeks and hypodense thereafter. Acute subdural haemorrhage is commonly seen as a relatively thin layer of blood or clot overlying one or both hemispheres of the brain occurring after a severe injury with contusion and laceration of the brain substance. The disappointing results of the surgical treatment of this condition suggest that the presence of the haematoma contributes less to the patient's neurological state than does the underlying damage to the brain parenchyma and particularly the oedema which commonly supervenes soon afterwards. In the subacute variety, the patient begins to show clinical deterioration with evidence of increasing intracranial pressure a few days after the injury and neuroradiological diagnostic procedures (CT scan, angiogram, scintillogram etc.) demonstrate the presence of a subdural mass lesion, the composition of which varies between almost pure blood and a faintly yellow fluid, having a protein and cell content which suggests that it is largely composed of CSF. Subacute subdural haematoma probably arises after a relatively large vein has been torn at or near the point at which it crosses from the subarachnoid space to the dura. If over the next few days the intracranial pressure remains sufficiently low to permit further leakage of blood, the effusion may enlarge to the point that it causes symptoms: if there is an accompanying tear of the arachnoid, the effused blood contains an admixture of CSF which, incidentally, prevents it from clotting. The name hygroma (or hydroma) is often applied to a subdural collection of fluid in which the ratio of CSF to blood is high.

The special distinguishing features of a CSH are its complete encapsulation within a membrane and the fact that there is a latent interval amounting to weeks or even months between the presumed initial occurrence of the subdural haemorrhage and the onset of symptoms of cerebral compression. However, though the chronology of the changes in the CT scan can be regarded as setting the dividing line between subacute and chronic lesions at the end of the third week, the distinction may be artificial. There is no *a priori* reason to distinguish between the onset of symptoms of delayed cerebral compression respectively after a few days and after a period of weeks. Histological studies indicate that only a few hours elapse before an effusion of blood into the subdural space begins to provoke a fibroblastic reaction of the inner layer of the dura mater which lies in contact with it, the resulting neomembrane later extending over the inner aspect of the effusion until this is completely encapsulated. During the ensuing days or weeks the layer of fibroblasts thickens and is invaded by vascular channels budding off from the vasculature of the inner layer of the dura. Because of their dilated appearance, these new vessels are sometimes called sinusoids: they are particularly prominent within the

outer layer of the neomembrane. This layer is rather tightly adherent to the inner surface of the dura, while the inner layer is always thinner and less vascular and adheres only lightly to the arachnoid, from which it can be stripped without injuring the latter, although it forms sleeves around any bridging veins which traverse the cavity of the haematoma.

The arachnoid does not seem to play any active role in the encapsulation of a subdural haematoma. Haematomas implanted into the subdural space of cats rapidly become encapsulated if the dura is in direct contact with the clot, but not if a layer of polyethylene film is interposed between these [23]. If, however, the polyethylene is placed between the clot and the arachnoid, membrane formation proceeds normally. The dura appears to be stimulated to its fibroblastic reaction by the presence of fibrin [24]; preformed blood clots introduced into the subdural space do not become encapsulated if they have previously been treated with plasmin to cause fibrinolysis [25]. On the other hand, clots composed of pure fibrin without any blood cells not only become encapsulated, but are also later invaded by red and white blood cells escaping from the new blood vessels in the membrane [23]. The fact that it is the presence of fibrin, or fibrin degradation products, which stimulates the formation of a subdural membrane leads to the important consequence that the fibrin-containing subdural effusions which sometimes complicate bacterial meningitis become encapsulated in exactly the same way as subdural haematomas, the protein content of the fluids in the two conditions being essentially similar [26]. Indeed, unless the effusion is actually purulent, it often assumes the yellow or orange colour of chronic subdural fluid and numbers of red as well as of white blood cells are regularly found within it.

The time required for complete encapsulation of a CSH doubtless varies with the size of the effusion, the age of the patient, and other unidentified factors. In the writer's experience a macroscopically visible membrane is found on both the outer and the inner aspects of a subdural haematoma by the fourteenth day after the accident which caused it, while in small mammals the period is significantly shorter [23].

THE PATHOPHYSIOLOGY OF ENLARGEMENT OF CHRONIC SUBDURAL HAEMATOMAS

Because the subdural space is continuous over the convexities and the bases of the cerebral hemispheres, as well as between one side of the supratentorial compartment and the other, a CSH which is sufficiently large to cause symptoms also usually extends over a large part of the surface of one hemisphere and, as has often been observed, is found to be bilateral in 30-50 per cent of cases. This leads to a rather uniform compression of the brain in which focal neurological signs are minimal or even completely absent and general signs of cerebral malfunction such as headache, mental

confusion, deteriorating consciousness and alterations of vital signs are the only evidence available to the clinician in forming the suspicion of CSH. However, there is one feature of the evolution of CSH which is both more frequent and often more dramatic than when it occurs in patients suffering from cerebral compression due to other mass lesions: namely, a fluctuation in the intensity of the symptoms and signs, particularly conscious level. Sudden episodes of deterioration may be followed by periods of almost complete remission so that a patient who was in a deep stupor one evening may be fully conscious and correctly orientated in time and space the next morning without having received any treatment. Observation of such episodes led to the reasonable hypothesis that a CSH undergoes episodes of sudden enlargement followed either by adjustment of the intracranial dynamics to the new situation or possibly by absorption of some of the haematoma fluid. This conclusion, however, is not logically necessary. An alternative view which has recently been restated, albeit without evidence from pathological studies, is that the presence of CSH causes stretching and narrowing of the cortical bridging veins, thus diminishing venous drainage into the superior sagittal sinus and triggering vasogenic brain oedema [27].

Serial angiography and more recently the use of the CT scan have made it possible to demonstrate actual enlargement of a CSH and to relate this to the patient's clinical state, but even so the source of the extra fluid remains subject to dispute. There are two main possibilities, the first of them being further haemorrhage and the second the entry of more fluid into the cavity through its walls. Trotter was convinced that a CSH enlarged by repeated haemorrhage [6] and Putnam and Cushing noted that surgical drainage of a CSH commonly reveals the presence of fresh erythrocytes [28]. Infants with large CSHs treated by repeated aspiration may at first show falling haemoglobin and haematocrit readings accompanied by the appearance of fresh blood in the aspirated fluid. This does not necessarily imply renewed haemorrhage from a previously injured cortical vein, for histological studies often show erythrocytes actually passing into the haematoma cavity from the outer layer of the neomembrane of a CSH. Direct proof that such new haemorrhage is an important cause of the expansion of a CSH has recently been furnished by Ito and his colleagues [29] who showed that the intravenous injection of ^{51}Cr-tagged red cells into human CSH patients was followed by their appearance in samples of subdural fluid withdrawn 24 hours later, in proportions which indicated the occurrence of new haemorrhage in amounts averaging 10·2 per cent of the total volume of the haematoma with a remarkable maximum figure of 27·2 per cent. High levels of fibrin degradation products have been found in CSH fluid [29, 30], suggesting that the haemorrhage may be facilitated by hyperfibrinolysis. (Since the level of fibrin degradation products was normal both in acute subdural haematoma fluid and in the blood, urine and CSF of CSH patients, these products must have originated within the capsule of the CSH itself [29].)

Gardner suggested many years ago [31] that repeated or continuous haemorrhage is not a sufficient explanation of the secondary expansion of CSH in all cases. Paediatricians and neurosurgeons who have treated infantile subdural haematomas by repeated aspiration are familiar with the fact that they may become symptomatic at a time when their contents comprise yellow or brown fluid containing relatively few fresh blood cells. Also, serial estimations of the protein content of CSH fluid shows that it tends to rise at first but later falls progressively to a level that is much lower than that of plasma and eventually near to that of CSF [8]. Gardner believed that subdural haematomas grew in volume because their proteins broke down into smaller molecules, thus increasing the osmotic pressure of the fluid, so that water was drawn into the haematoma from the CSF in the adjacent subarachnoid space. However, although he claimed to observe expansion of cellophane bags filled with blood and inserted into the subdural space of dogs, a single experiment in which he used the inner membrane of a CSH as a bag which he then filled with blood and suspended in isotonic saline solution was less convincing, the net gain in weight of the blood-filled sac being only 2·9 per cent after 16 hours. Moreover, this was not an accurate model of what happens *in vivo*, for to pass from the subarachnoid space to the interior of a CSH, CSF must cross the outer layer of the arachnoid as well as the inner layer of the subdural membrane [32], which was not demonstrated. In any event, Weir [33] has destroyed the theoretical basis for Gardner's hypothesis by showing that the osmolalities of haematoma fluid and of CSF are equal.

Zollinger and Gross [32], like Gardner, thought that the expansion of a CSH was due to osmotic or oncotic forces, but that the source of the fluid was the capillaries which form in the neomembranes that constitute its walls. Again, Weir has refuted this suggestion by showing that the osmolalities [33] and the oncotic pressures [34] of blood and haematoma fluid are equal, but he notes that modern theories of the dynamics of transcapillary fluid movement are much more complex than the original mixture of hydrostatic and oncotic mechanisms envisaged by Starling, and include consideration of the pore size of the capillaries and the presence of cytoplasmic vesicular transport mechanisms. Thus, as well as from increased hydrostatic pressure in the capillaries of the neomembrane or from decreased intracranial pressure, shifts of fluid into a subdural haematoma could result from an increase in the surface area of its capillary network or an altered balance between the inward and outward transport of the fluid by way of the cytoplasmic vesicles. The activity of the neomembranes in patients with symptomatic CSH has been documented by Sato and his colleagues [35] who have shown that the ultrastructure of the dural layer of subdural membranes taken at operation from patients with clinically symptomatic CSH showed cytoplasmic protrusions described as 'like microvilli or pseudopodia' on both the luminal and the basal surfaces of the capillary endothelial cells. In the area of these protrusions the basement membrane was deficient. In some places there were open gaps

between the adjacent endothelial cells of the capillaries, and the cytoplasm of some of the endothelial cells was abnormally clear, containing large vacuoles. These appearances were strongly correlated with the clinical findings, being almost entirely restricted to those patients who showed evidence of progressive cerebral compression, and would seem to be consistent with increased permeability of the membrane of the CSH with transport of fluid into its cavity.

In summary, the evidence suggests that the outer layer of the capsule of a CSH is well adapted to the passage of blood and fluid. The presence of excessive amounts of fibrinolysin in the haematoma fluid leads to lysis of clots forming on the surface of the membrane after each episode of haemorrhage, thus favouring rebleeding. There are undoubtedly situations in which following traumatic rupture of the ararchnoid, CSF can escape from the subarachnoid into the subdural space: there is no evidence that it also passes through the twin barriers of the intact arachnoid and the inner layer of the neomembrane to expand an encapsulated CSH.

SPONTANEOUS RESOLUTION OF CHRONIC SUBDURAL HAEMATOMA AND THE BALANCE BETWEEN EXPANSION AND REABSORPTION

CSH does not invariably cause death from cerebral compression but may ultimately resolve spontaneously, either with a regimen of bedrest [36, 37] or by the use of corticosteroids and/or intravenous injections of hypertonic solutions of glucose or mannitol [38-40] or even with no treatment at all [41], serial angiography showing reduction in the size of the CSH to the point of complete disappearance.

Encapsulated subdural haematomas induced experimentally in various small mammals also disappear spontaneously [23, 42], while neomembrane formation around large haematomas produced in the subcutaneous tissues of rats is inhibited by daily injections of dexamethasone [43].

Histologically, cessation of expansion and relief of clinical symptoms in CSH patients is correlated with a disappearance of the gaps between the endothelial cells of the capillaries lining the subdural membrane [35] as well as with an overall reduction in the size and number of these. The vascularity of the membrane diminishes and the fibroblasts mature. The contents of the subdural sac are slowly absorbed and the two layers of the membrane come together to leave a single fibrous plaque in which no separation between the inner and outer layers is evident although it may contain a few scattered red blood cells and pigment-containing phagocytes [80]. Such appearances have been found in humans within 6 weeks of the presumed date of appearance of a CSH, and significantly earlier in experimental animals [23]. Ultimately, the neomembranes usually disappear completely, but occasionally their thickness and their layered

appearance suggest that there have been episodes of expansion due to new haemorrhage followed by phases of relative quiescence, occurring over many years, and the writer has seen a particularly striking example of this.

Case Report

An 18-year-old man was referred to the Neurosurgical Service of a general hospital with a 24-hour history of severe headache with vomiting and some mental confusion. He was reported to have been dropped from his mother's arms in infancy, following which he had been noted to have an enlarged head. As a child he had been a poor scholar (IQ 82), requiring special education. He had also been regarded as subject to 'migraine' because of episodes of headaches and vomiting which had occurred at irregular intervals during his childhood. On leaving school at the age of 15 years he obtained employment as an unskilled manual worker and had worked regularly until the day before his hospital admission.

On examination the patient was of normal general physical development apart from an occipitofrontal head circumference of 66 cm. There was bilateral papilloedema and bradycardia with hyper-reflexia and extensor plantar responses. Ventriculography was advised and bilateral front burr-holes were made, but instead of the expected hydrocephalus, these revealed a subdural membrane fully 2 cm in thickness containing an enormous collection of semi-opaque brown fluid in which floated fragments of blood clot measuring up to 5 cm in length. After removal of this effusion the inner layer of the CSH was found to be at a depth of 6 cm from the skull and was so thick that little detail of the underlying cerebral cortex could be seen. The falx cerebri had almost completely atrophied: there were no bridging veins and the subdural spaces over the two cerebral hemispheres communicated freely with one another. Following the replacement of the contents of the CSH with saline and closure of the incisions, the patient's symptoms were relieved although no re-expansion of the brain occurred. He continued working for 3 years, at the end of which time one of the burr-holes became infected and he eventually died of the effects of subdural empyema.

Consideration of such cases as this suggests that the natural history of CSH depends upon a balance between expansion of its contents due to the ingress of blood, extracellular and/or intracellular fluid on the one hand, and contraction due to reabsorption of these same fluids on the other [23, 30]. The particular frequency of subdural haematoma after head injuries occurring in infancy, at which time of life episodes of crying and screaming are of normal everyday occurrence, may well be correlated with the fact that the initial rise of CSF pressure at the beginning of such an episode is followed by a rebound in which the ICP falls sharply below its resting value [44]. This would set up the necessary conditions for haemorrhage or effusion into the subdural space. New haemorrhage would cause a rapid increase in the volume of the CSH in such a situation whereas the process of reabsorption would presumably occur at a more uniform rate and be unaffected by changes of pressure of short duration. Such a series of events would be consistent with the observed course of unrelieved or conservately treated CSH.

Angiography and more recently the CT scan have repeatedly shown that small subdural effusions tend to disappear spontaneously. The larger

ones are more likely to persist, to expand and to become symptomatic: if left untreated they take a long while to clear up. Mathematically, the equation for the surface area of a geometrical figure having the shape of a CSH (which resembles an oblate spheroid) is rather complicated but is derived from the *sum* of functions of the squares of its length (greater diameter) and width (lesser diameter)[23], whereas the volume of such a figure is a function of the *product* of the square of its length multiplied by its width.* Consequently, with increasing size, the volume of a CSH grows more rapidly than its surface area. Assuming that the rate of absorption is proportional to the surface area of the membrane, it would follow that the larger the CSH, the longer it will take to resorb and the process could at any time be interrrupted by episodes of sudden expansion due, for example, to haemorrhage from the surface of the membrane. At this stage, surgical drainage – even if some residual effusion is left behind – would tend to tilt the balance between expansion and resorption in favour of the latter, as well as diminishing the concentration of those anticlotting factors in haematoma fluid which are thought to 'lead to a self-perpetuating cycle of bleeding' [34].

Eventually, maturation of the subdural membranes would tend towards a situation in which expansion due to haemorrhage or the effusion of fluid would cease while resorption continued at a uniform rate, though there is no proof of this and the subject deserves further study. The decrease in the total protein concentration of CSH fluid from the high levels which are found during the first few weeks after its formation to the relatively low ones which occur later is doubtless associated with the hyperfibrinolysis which occurs within a CSH [30] although actual proteolytic enzymes have not yet been detected in CSH fluid.

CONCLUSION

In the past, attitudes to the treatment of CSH have varied from the very radical to the very conservative. Nowadays, our more complete understanding of the evolution of CSH confirms clinical experience [46] in indicating that routine craniotomy and stripping of membranes is unnecessary and obsolete. An entirely non-surgical approach, with the administration of mannitol and/or steroids often leads to complete recovery, but it is difficult to justify the routine use of a method which may require an average of nearly 6 weeks' hospitalization [40] when patients undergoing the surgical alternative are regularly fully ambulant within a few days! Simple evacuation of the haematoma by washing it out through burr holes [47, 48], or, in infants, by tapping the fontanelle [49] usually gives excellent

* It has been pointed out that the volume (V) of a CSH is also given approximately by the expression $V = \frac{1}{2}LWD$ where L = the greater diameter, W = the lesser diameter and D = the depth of the effusion [45].

results. Reaccumulation of fluid can be a problem in infants, though rarely in older patients: it is readily solved by the insertion of a subdural-peritoneal shunt [50]. Whatever the age of the patient, however, consideration of the natural history of subdural haematomas indicates that there is no justification to treat asymptomatic cases solely for the same reason that people are said to climb high mountains – namely, that they are there.

REFERENCES

1. Gurdjian E. S. and Thomas T. M. (1974) Intracranial haemorrhage. In: Feiring E. H. (ed.), *Brock's Injuries of the Brain and Spinal Cord and Their Coverings,* 5th ed. Berlin, Springer-Verlag, pp. 203–82.
2. Virchow R. (1857) Das Hämatom der Dura Mater. *Ver. Phys. Med. Ges. (Würz.)* 7, 134–42.
3. Caffey J. (1946) Multiple fractures in the long bones of infants suffering from chronic subdural hematoma. *AJR* **56**, 163–73.
4. Wooley R. U. jun. and Evans W. A. jun. (1955) Significance of skeletal lesions in infants resembling those of traumatic origin. *JAMA* **158**, 539–43.
5. Oppenheim H. (1911) *Textbook of Nervous Diseases for Physicians and Students,* 5th ed. (Translated by Alexander Bruce.) New York, Stechert.
6. Trotter W. (1914) Chronic subdural hematoma of traumatic origin and its relation to pachymeningitis hemorrhagica interna. *Br. J. Surg.* **2**, 217–91.
7. Munro D. (1934) The diagnosis and treatment of subdural hematoma. Report of 62 cases. *N. Engl. J. Med.* **210**, 1145–60.
8. Munro D. and Merritt H. H. (1936) Surgical pathology of subdural hematomas based on a study of 105 cases. *Arch. Neurol. Psychiatry* **35**, 64–79.
9. Rougerie J. and Caldera R. (1955) L'hématome sousdural chronique du nourrisson. Étude clinique et bases thérapeutiques. *Neurochirurgie* **2**, 38–57.
10. Friede R. L. and Schachenmayr W. (1978) The origin of subdural neomembranes I. Fine structure of the dura-arachnoid interface in man. *Am. J. Pathol.* **92**, 53–68.
11. Friede R. L. and Schachenmayr W. (1978) The origin of subdural neomembranes II. Fine structure of neomembranes. *Am. J. Pathol.* **92**, 69–84.
12. Abbott W. D., Due R. O. and Nosik W. A. (1943) Subdural hematoma and effusion as a result of blast injuries. *JAMA* **121**, 739–41.
13. Murthy J. M. K., Chopra J. S. and Gulati D. R. (1979) Subdural hematoma in an adult following blast injury. Case report. *J. Neurosurg.* **50**, 260–1.
14. German W. J., Flanigan S. and Davey L. M. (1964) Remarks on subdural hematoma and aphasia. *Clin. Neurosurg.* **12**, 344–50.
15. Ommaya A. K., Faas F. and Yarnell P. (1968) Whiplash injury and brain damage. An experimental study. *JAMA* **204**, 285–9.
16. Guthkelch A. N. (1971) Infantile subdural hematoma and its relationship to whiplash injuries. *Br. Med. J.* **2**, 430–1.
17. Wiener L. M. and Nathanson M. (1962) The relationship of subdural hematoma to anticoagulant therapy. *Arch. Neurol.* **6**, 42–6.
18. Anderson F. M. (1952) Subdural hematoma: a complication of operation for hydrocephalus. *Pediatrics* **10**, 11–18.
19. Illingworth R. D. (1970) Subdural hematoma after the treatment of chronic hydrocephalus by ventriculocaval shunt. *J. Neurol. Neurosurg. Psychiatry* **33**, 95–9.
20. Raimondi A. J., Robinson J S. and Kuwanura K. (1977) Complications of ventriculoperitoneal shunting and a critical comparison of the three-piece and one-piece shunt systems. *Child's Brain* **3**, 321–42.

21. Clark E. and Walton J. N. (1953) Subdural haematoma complicating intracranial aneurysm and angioma. *Brain* **76**, 378–404.
22. Echlin R. (1949) Traumatic subdural hematoma – acute, subacute and chronic. *J. Neurosurg.* **6**, 294–303.
23. Apfelbaum R. I., Guthkelch A. N. and Shulman K. (1974) Experimental production of subdural hematomas. *J. Neurosurg.* **40**, 336–46.
24. Putnam I. I. and Putnam T. J. (1927) Experimental study of pachymeningitis hemorrhagica *J. Nerv. Ment. Dis.* **65**, 260–72.
25. Watanabe S., Shimade H. and Ishii S. (1972) Production of clinical form of chronic subdural hematoma in experimental animals. *J. Neurosurg.* **37**, 552–61.
26. Gitlin D. (1955) The pathogenesis of subdural collections of fluid. *Pediatrics* **16**, 345–52.
27. Gutierrez F. A., McLone D. G. and Raimondi A. J. (1979) Physiopathology and a new treatment of chronic subdural hematomas in children. *Child's Brain* **5**, 216–32.
28. Putnam T. J. and Cushing H. (1925) Clinical subdural hematoma. Its pathology in relation to pachymeningitis hemorrhagica interna and its surgical treatment. *Arch. Surg.* **11**, 329–93.
29. Ito H., Yamamoto S., Komai T. et al. (1976) Role of local hyperfibrinolysis in the etiology of chronic subdural hematoma. *J. Neurosurg.* **45**, 26–31.
30. Labadie E. L. and Glover D. (1975) Local alterations of hemostatic-fibrinolytic mechanisms in reforming subdural hematomas. *Neurology* **25**, 669–75.
31. Gardner W. J. (1932) Traumatic subdural hematoma with particular reference to the latent interval. *Arch. Neurol. Psychiatry* **27**, 847–58.
32. Zollinger R. and Gross R. E. (1934) Traumatic subdural hematoma: an explanation of the late onset of pressure symptoms. *JAMA* **103**, 245–9.
33. Weir B. (1971) The osmolality of subdural hematoma fluid. *J. Neurosurg.* **34**, 528–33.
34. Weir B. (1980) Oncotic pressure of subdural fluids. *J. Neurosurg.* **53**, 512–15.
35. Sato S. and Suzuki J. (1975) Ultrastructural observations of the capsule of chronic subdural hematoma in various clinical stages. *J. Neurosurg.* **43**, 569–78.
36. Bender M. D. (1960) Recovery from subdural hematoma without surgery. *J. Mt Sinai Hosp.* **27**, 52–8.
37. Lusins J., Jaffe R. and Bender M. B. (1976) Unoperated subdural hematoma. Long term follow-up study by brain scan and EEG. *J. Neurosurg.* **44**, 601–7.
38. Ambrosetto C. (1962) Post-traumatic subdural hematoma. *Arch. Neurol.* **6**, 287–92.
39. Bender M. B. and Christoff N. (1970) Nonsurgical treatment of subdural hematoma. *Arch. Neurol.* **31**, 73–9.
40. Suzuki J. and Takaku A. (1970) Nonsurgical treatment of chronic subdural hematoma. *J. Neurosurg.* **33**, 548–53.
41. Erkulvrawatr S. and Srinivasan G. (1978) Complete resolution of bilateral subdural hematoma. *South. Med. J.* **71**, 456–8.
42. Goodell C. L. and Mealey J. jun. (1963) Pathogenesis of chronic subdural hematoma. *Arch. Neurol.* **8**, 429–37.
43. Glover D. and Labadie E. L. (1976) Physiopathogenesis of subdural hematomas, Part 2: inhibition of growth of experimental hematomas with dexamethasone. *J. Neurosurg.* **45**, 393–7.
44. Williams B. (1972) Combined cisternal and lumbar pressure recordings in the sitting position using differential manometry. *J. Neurol. Neurosurg. Psychiatry* **35**, 142–3.
45. Sachs J. and Sachs R. jun. (1977) A simple formula for calculating the volume of subdural hematomas. *Neurosurgery* **1**, 60–1.
46. Shulman K. and Ransohoff J. (1961) Subdural hematoma in children. The fate of the child with retained membranes. *J. Neurosurg.* **18**, 175–80.

47. Cameron M. M. (1978) Chronic subdural hematoma: a review of 114 cases. *J. Neurol. Neurosurg. Psychiatry* **41**, 834-9.
48. Svien H. J. and Gelety J. E. (1964) On the surgical management of encapsulated subdural hematoma. *J. Neurosurg.* **21**, 172-7.
49. McLaurin R. L., Isaacs E. and Lewis H. P. (1971) Results of nonoperative treatment in 15 cases of infantile subdural hematoma. *J. Neurosurg.* **34**, 753-9.
50. Moyes P. D., Thompson G. B. and Cluff J. W. (1961) Subdural peritoneal shunts in the treatment of subdural effusions in infants. *J. Neurosurg.* **23**, 584-7.

Lindsay Symon

7 Operative Surgery in Craniopharyngiomas

There can be few tumours in the region of the chiasm which have provoked such contentious debate in their management as craniopharyngioma. Review of the large series published over the past 20 years gives ample evidence of the wanton tendency to recur and of the generally poor prognosis of the tumour [1-8]. Many surgical series have started on the optimistic premise that radical surgery was possible and indicated, only to develop an increasingly qualified pessimism as inevitable recurrences appeared, sometimes up to 20 years later [9]. Since the initial publication of Kramer [10], it has been claimed that minimal surgical intervention with the establishment of the diagnosis, followed by radical radiotherapy, is the treatment of choice [11, 12]. This view has not gained universal acceptance, and several notable protagonists, particularly Matson [1, 3] and Sweet [13], have throughout maintained a steadfastly aggressive attitude to the excision of these tumours, an attitude which the advent of the operating microscope has rendered once more of significant interest.

THE CHOICE OF SURGICAL APPROACH IN CRANIOPHARYNGIOMA

Over the years a variety of routes have been recommended in the approach to craniopharyngioma. The route has varied with the extent of interference planned; thus simple subfrontal exploration to establish the diagnosis and partially remove the tumour if it were accessible beneath the optic nerves, or for tapping of cysts, has in some hands been modified to allow an interhemispheric approach with division of the lamina terminalis [14, 15] or an extended approach with access into the temporal fossa behind the carotid artery. It is now clear, however, that the increased precision of information given by CT scan (*see* Necessary Investigations), makes exploratory surgery in the region of the chiasm less frequent than before. It is therefore likely that the neurosurgeon will have a more accurate idea of probable pathology when the operation is planned, and this in turn justifies planned radical approaches which are more extensive, and which themselves inevitably carry more risk than a simple subfrontal exploration.

This chapter is based upon the developing experience of two surgeons in one clinic between 1954 and 1978. Ninety-four cases were operated upon, 50 by the current author, and 44 by his colleague and predecessor, Professor Valentine Logue. The age and sex incidence of this group of

Table 7.1. Age and Sex Distribution of a Series of 94 Craniopharyngiomas

Age group (yr)	*Male*	*Female*	*Total*
0–10	1	2	3
10–20	4	6	10
20–30	10	7	17
30–40	12	5	17
40–50	14	9	23
50–60	11	2	13
60–70	4	5	9
70	2	–	2
Total	58	36	94

cases is shown in Table 7.1. While the almost uniform approach in the early years was a simple subfrontal exploration, and radical excision was possible only occasionally in tumours that were particularly favourable with a very high placement of the chiasm, it has become increasingly clear that effective removal of the posterosuperior part of craniopharyngiomas could only be achieved by a route which gained access behind the optic nerves. An extended fronto-temporal approach was used by both surgeons for a time, but then, in parallel with developments elsewhere, it became clear that with extensive hormonal support and the excellent outlining of the extent of the tumour by contrast studies and CT scanning, a radical temporal approach carried great promise. It is this operation which has been most used in this clinic in recent years.

Subfrontal Exploration – Unilateral or Bifrontal

Only when the chiasm can be shown on air encephalography to be very high, the tumour well forward so that it scarcely extends into the interpeduncular cistern (*Fig. 7.1*) and has a considerable bulge over the jugum sphenoidale, can subfrontal exploration for attempted radical removal of craniopharyngioma now be justified. The access to the top of a tumour behind the chiasm by this route is poor, and even evacuation of the centre of the tumour leaves the necessity to drag the posterosuperior portion of the capsule forwards and downwards from its attachment to the chiasm, while at the same time rendering this attachment invisible except by extensive traction on the chiasm, turning it more or less inside out. This all too frequently produces a dense bitemporal hemianopia. Total excision of craniopharyngioma by this route is possible only when the anterior portion of the chiasm is at the meridian of the craniopharyngioma so that distortion of the chiasm is minimal as the tumour is gently pulled down from its undersurface. Subfrontal exploration, however, is an operation with

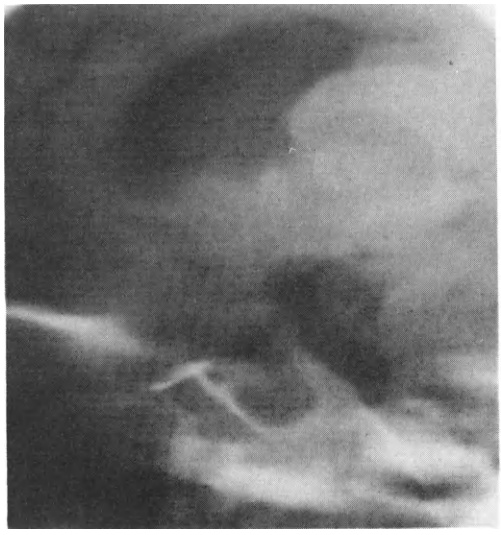


Fig. 7.1. Lateral view of an air encephalogram of a 4-year-old boy, presenting with disturbance but without visual field defect. The intrasellar and suprasellar tumour (whose posterior capsule has partially calcified) is entirely pre-chiasmal.

extremely low morbidity in competent hands, and in the very elderly patient where the greater part of the tumour appears to be cystic, and where minimal intervention is required, it is undoubtedly the most rapid approach and will enable the drainage of a cyst, or the insertion of a catheter into the cyst (in the principle of sump drainage [16]), to be accomplished fairly easily. Where the decision has been made that the size of the tumour or the condition of the patient makes radical intervention impossible, then tissue for biopsy purposes may usually be obtained by this route, although where the space between the chiasm and jugum is small, very little of the presenting face of a craniopharyngioma may be approached subfrontally. Under these circumstances, either an extended subfrontal approach to include the anterior temporal fossa, or more aptly, a small fronto-temporal approach for limited access behind the carotid artery, is probably better even for simple biopsy. Where tube insertion into a large cyst is recommended, then the more lateral approaches have the merit of a more easy direction of the tip of the tube into the cyst cavity than the more frontal approaches, and also give an easier lie of the sump drain or cystopleural shunt tube along the sphenoidal wing, to which the tube may be anchored.

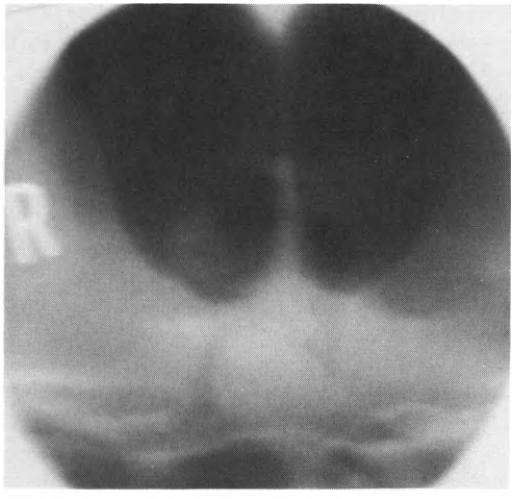
It will be clear, therefore, that the subfrontal approach to craniopharyngiomas is a distinctly limited one, and can be recommended only when rapidity of approach and simplicity of manoeuvre are the main considerations.

A bifrontal approach has occasionally been suggested in the management of craniopharyngiomas, particularly in children. In this operation, a large bifrontal bone flap is turned, both frontal lobes are elevated and the mass of the tumour lateral to and between the two optic nerves is available for dissection. It has even been claimed that preservation of the olfactory tract is possible although it is difficult to see how this can be accomplished. Rather more serious than the almost inevitable bilateral anosmia, however, is a very considerable disturbance of intellectual capacity which extensive bifrontal retraction may evoke, and this approach, as the single subfrontal approach, shares the disadvantage that the posterosuperior portion of the tumour above and behind the chiasm, even with very wide exposure, can only be reached indirectly. In the author's experience, it is not a practicable procedure for radical resection of such tumours and is unsuitable for the management of adult craniopharyngioma.

The Transventricular, Transcallosal and Lamina Terminalis Approaches

Where the tumour mass is in the third ventricle and reaches high towards the foramen of Munro, it may be thought impracticable to consider radical excision by the favoured subtemporal route. In my recent experience, this has occurred in only one case (*Fig. 7.2*), where the extent of the tumour through the foramen of Munro and into the lateral ventricle clearly precluded an attempt to remove it from below. Two choices of approach remain to the surgeon under these circumstances.

The first, the more standard, and employed by myself over a number of years, has been the transventricular approach by a right post-frontal parasagittal craniotomy, through the middle frontal gyrus into the frontal horn, to attack the craniopharyngioma through the foramen of Munro. This manoeuvre suggested first to my knowledge by Dott, in an excellent review of the early radical treatment of craniopharyngiomas [17], is limited in access and although with the microscope and self-retaining retraction extensive dissection of the tumour in the third ventricle is possible and even the removal of the portion within the interpeduncular cistern through the floor of the third ventricle, the access to the anterior portion of the mass behind the chiasm is extremely difficult because the approach is oblique and it is impossible to look round the corner in front of the foramen of Munro. Even division of one pillar of the fornix does not sufficiently improve access and it is probable that this route should be superseded by the approach through the lamina terminalis, advocated by Hoffman et al. [14] and more recently by King [15]. An interhemispheric approach by straightforward right frontal craniotomy, dissecting above the chiasm through the lamina terminalis and into the third ventricle by this method, carries some promise but has the considerable demerit of leaving the posteroinferior portion of the tumour to the last in dissection. It is this portion of the tumour which is liable, in the adult, to have the



a

b

c

Fig. 7.2. Anteroposterior (*a*) and lateral (*b*, *c*) views of an air encephalogram and ventriculogram. The mass of the tumour in the third ventricle extending through the foramen of Munro is visible in (*a*) and (*b*), and the tumour in the floor of the third ventricle extending into the interpeduncular cistern is visible in (*c*).

most extensive vascular attachments – to the choroidal arteries, to the posterior communicating artery and even to the posterior cerebral and the top of the basilar. These vessels, being posteriorly placed, are inaccessible early in the translaminal dissection, and the gamble is therefore taken that the adhesions between the tumour and these vessels will be light and easily broken down. It is probable therefore that this approach should be confined to craniopharyngiomas whose mass is almost entirely within the ventricle and preferably whose mass is very high within the third ventricle. These are, of course, unusual.

The Radical Temporal Approach to Craniopharyngioma

The majority of craniopharyngiomas in adults in the author's personal series have presented in the floor of the third ventricle, occupying the suprasellar and the interpeduncular cisterns, and embraced by the branches of the posterior communicating and choroidal arteries to the thalamus and mamillary bodies. The posteroinferior presenting portion of such tumours lies free in the interpeduncular cistern and gives a considerable quadrant of the mass available for early excision, albeit through an extremely limited access between the branches of the posterior communicating artery, or below the posterior communicating artery itself.

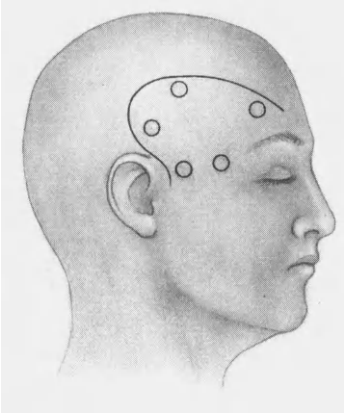


Fig. 7.3. Scalp flap and position of burr holes for radical transtemporal excision of craniopharyngioma.

Where the operations are performed for visual failure, and this type of craniopharyngioma appears likely, the choice of the radical temporal operation is appropriate. With the advent of the operating microscope, this procedure has increasingly become the approach of choice in this clinic. An extended sphenoidal wing approach is used, a moderately sized fronto-temporal flap being turned from the middle of the eyebrow, just below the superior temporal line to above the ear, and turning down in front of the pinna (*Fig. 7.3*). A fronto-temporal bone flap is cut across the sphenoidal wing and broken down into the anterior temporal fossa. The anterior part of the temporal fossa is then rongeured away, together with the outer end of the sphenoidal wing, and the dura opened across the sylvian fissure so that access to the subfrontal and anterior temporal region is assured. Where the diagnosis of craniopharyngioma or of a tumour mass in the interpeduncular cistern with the high probability of craniopharyngioma is certain, the next step is a small resection of the anterior 2 cm of the temporal lobe, with division of the polar temporal veins so that the subfrontal region is laid into continuity with the anterior part of the temporal fossa. Under the operating microscope, the inner end of the sylvian fissure can then be opened, the carotid artery and the optic nerve defined, and dissection pursued behind the carotid artery, along the tentorial edge. Removal of the uncus by secondary suction will give access to the interpeduncular fossa.

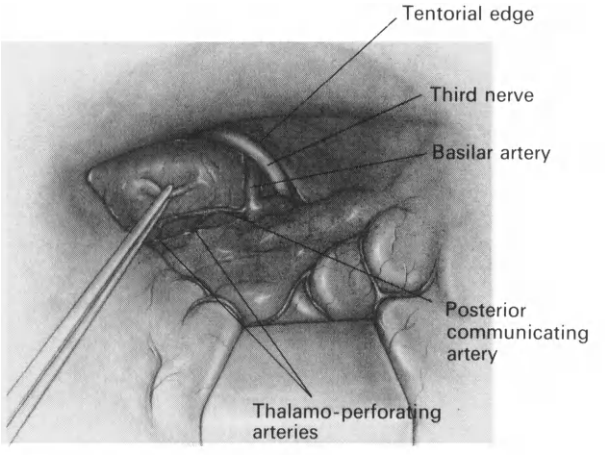
The presenting lower pole of the craniopharyngioma will now be

evident in the interpeduncular cistern, and immediately lateral to it and in their own separate arachnoid, the posterior communicating artery, its thalamo-perforating branches and the third nerve. At this stage it is usually possible to dissect the third nerve clear and preserve it, protected by a pattie against the tentorial edge, and although some degree of third nerve palsy is very frequent in the course of radical excision of craniopharyngioma, it is invariably transient. It will also be possible to define the posterior cerebral artery, and as the lower pole of the craniopharyngioma is approached with the division of arachnoid in the interpeduncular fossa, the top of the basilar artery and its branches may be defined (*Fig. 7.4*).

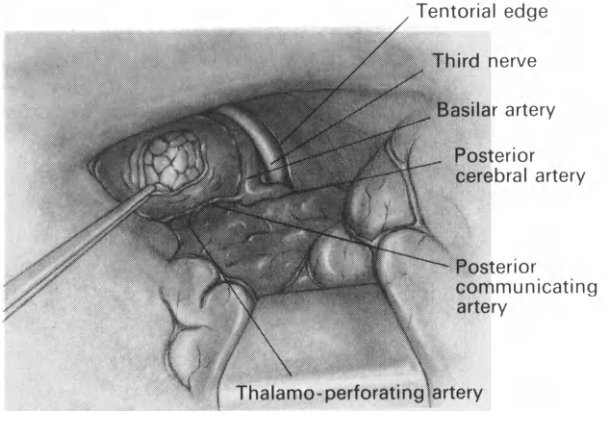
The advantage of the approach is now apparent, in that the lower pole of the craniopharyngioma is free in the interpeduncular fossa, yielding a considerable segment of the mass available for mobilization and for evacuation of the content of the tumour. Access to this portion of the tumour is possible if the tumour extends well down into the interpeduncular cistern, below the posterior communicating artery; but if the tumour is of a lesser size, and visible only as a protrusion through the floor of the third ventricle, it may be necessary to develop the small triangular space between the internal carotid artery and its anterior choroidal branch anteriorly, and the posterior communicating artery and its anterior thalamo-perforating branches below and posteriorly.

In the author's experience, it is unwise to divide either the posterior communicating artery or its thalamo-perforating branches, except in the clear knowledge that this may well be followed by a small infarct in the basal ganglia. The anterior choroidal artery must be preserved, but this being an early branch of the carotid artery, can usually be mobilized forwards, leaving a portion of capsule available for access between it and the anterior thalamo-perforating artery. Whether above or below the posterior communicating artery, the segment of capsule of the craniopharyngioma thus exposed should be entered after careful bipolar coagulation of the intrinsic vessels of the tumour, which may emanate from branches of the posterior communicating artery or from the internal carotid artery itself.

The capsule of the tumour may then be incised. Its common partially cystic, partially solid consistency enables gradual mobilization and break-up of segments of the interior of the tumour, yielding a progressive interior decompression of the mass. In the author's experience, gentle monopolar coagulation on apparently resistant portions of the tumour may assist in break-up of the fragments of soft tissue between portions of calcium, and it may well be that ultrasonic probes, when they have been sufficiently miniaturized, will be of added value in this regard. Blunt hooks, rongeurs and a knife may have to be employed within the cavity of the tumour, but under the dissecting microscope these may be employed satisfactorily, provided great care is taken to steady the portions of the capsule which are liable to be rocked within the third ventricle or against the



a



b

Fig. 7.4. Exposure of the tentorial hiatus by a radical trans-temporal approach. The retractor is on the cut surface of the temporal lobe. In (*a*) forceps hold the arachnoid covering the craniopharyngioma itself; the third nerve, basilar and posterior cerebral arteries, posterior communicating artery and thalamo-perforating vessels are visible. In (*b*) the arachnoid overlying the craniopharyngioma has been opened and the mass itself is visible.

In *Fig. 7.4b* and *Fig. 7.5*, the basilar artery appears parallel to the third nerve; this is the effect of traction on the tumour and foreshortening in the operative film.

major surrounding blood vessels during these manoeuvres. The postero-inferior portion of the capsule may progressively be mobilized, its attachment to the basilar and posterior cerebral arteries being defined and

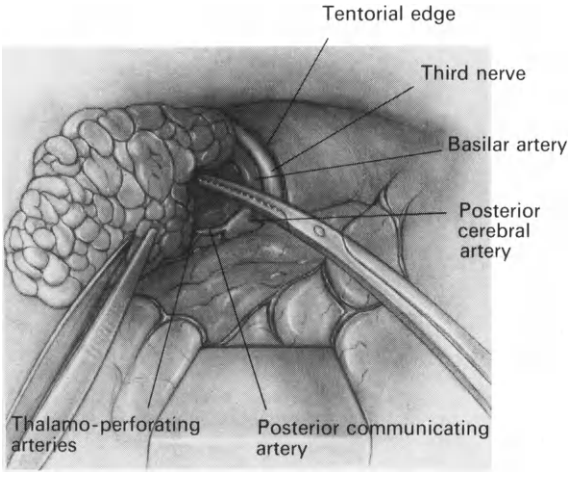


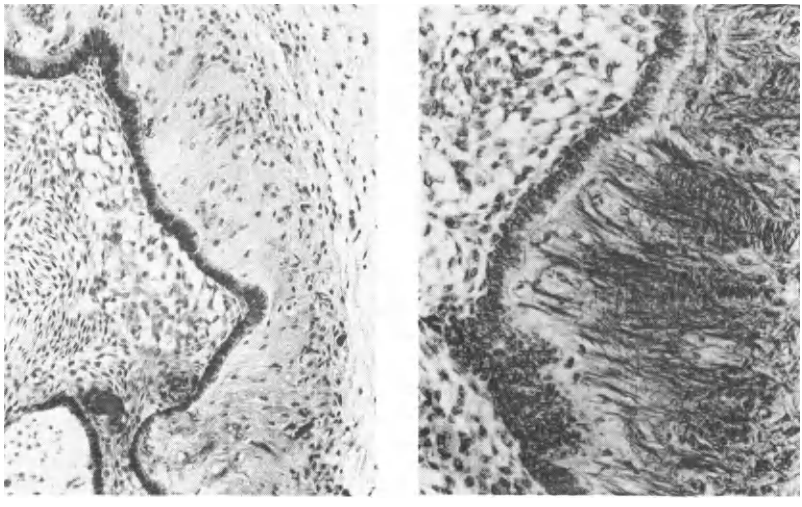
Fig. 7.5. Dissection pursued in the interpeduncular fossa, basilar arteries being displaced backwards by an instrument, the mass itself drawn gently forwards. The retractor is on the stem of the temporal lobe.

divided (*Fig. 7.5*), and the floor of the third ventricle may be transgressed just in front of the mamillary bodies.

From this point forwards, some blind dissection of the top of the tumour is often necessary, although the more effective the internal decompression has been, the more satisfactorily the capsule may be gently dragged down from out of the third ventricle, under direct microscopic vision. The optic tract lying above the posterior communicating artery is almost invariably lightly adherent to the edge of the mass, but it retracts with the remaining portion of the temporal lobe, and, perhaps surprisingly, is not commonly injured in the procedure, unless the mass is extremely large. A transient homonymous field defect may occur, but this invariably recovers provided the integrity of the vascular supply of the tract is preserved and the tract itself is not transgressed.

The nuclear masses on the floor of the third ventricle appear to be substantially separated by the craniopharyngioma. Although dissection of the edge of the craniopharyngioma is apparently through brain, the tumour itself being apparently invasive as has been pointed out by many authors [18–21], careful histological examination reveals that there is a layer of condensed glial reaction to the mass in which dissection may be safely pursued without actual transgression into nuclear masses in the walls of the third ventricle.

This phenomenon, while well known for many years, has been recently put in its proper significance by Sweet [13]. In his experience, which the author confirms, the dense gliosis surrounding a craniopharyngioma is free of nuclear masses from the closely adjacent third ventricular struc-



a *b*

Fig. 7.6. The edge of a craniopharyngioma. *a*, Haematoxylin and eosin × 75: the dark masses in the glia are Rosenthal fibres, which stain predominantly red. *b*, Phosphotungstic acid haematoxylin × 100: the density of glial fibre is evident to the right of the craniopharyngioma edge.

tures, as evidenced by the limited neurological defect produced by excision of what appears to be the floor of the third ventricle from the mamillary bodies forwards to the back of the chiasm, and also by histological examination of the edge of the removed tumour, embedded as it is in dense gliosis. Tongues of epithelial tissue can be seen invading the glial tissue, thought by some to indicate the complete impossibility of total excision. As Sweet has pointed out, however, this intense gliotic reaction, particular in many ways to the craniopharyngioma, is a reaction of glia without inclusion of neural elements and may be used as a plane actually outwith the tumour in which dissection may be pursued. The characteristic presence of Rosenthal fibres with marked eosinophilia [22] contrasts sharply with surrounding reaction of the brain to other suprasellar tumours such as meningioma or epidermoid cyst (*Fig. 7.6*).

Adhesions to the vascular structures on the contralateral side, to the posterior communicating artery, internal carotid or thalamo-perforating arteries are visible as the tumour is folded forwards and downwards out of the third ventricle, and the release of tension in the tumour makes dissection of these vessels feasible, separated as they are by a layer of arachnoid from the wall of the tumour itself. In 19 primary radical excisions, it has not proved necessary to sacrifice contralateral vessels, although in three instances, a branch of the posterior communicating artery (one of the thalamo-perforating vessels) has had to be sacrificed.

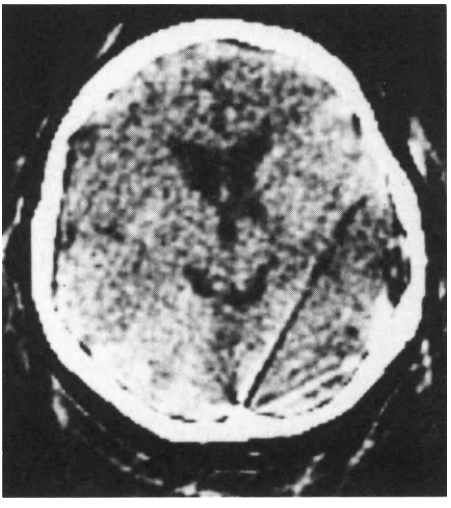


Fig. 7.7. A small infarct in the basal ganglia, without signs, following division of an anterior thalamo-perforating artery.

The effect of this is shown in *Fig. 7.7* – a small infarct in the basal ganglia. This usually has no profound sequelae, but may result in a fluctuating mild hemiparesis for some days postoperatively.

The major difficulty of the radical approach is now at hand. The tumour may be adherent to the diaphragma sellae or the internal carotid artery on one or both sides, and is almost invariably densely adherent to the anterior third ventricle in the region of the posterior part of the optic chiasm. Here, the preservation of a line of the top of the capsule, and the excellent exposure of the ipsilateral optic nerve and optic tract, enable calculation of the line of the chiasm and, under reasonable magnification, sharp dissection of the tumour from the posterior aspect of the chiasm (*Fig. 7.8*).

Adhesions to the carotid complex constitute the usual cause of the abandonment of the radical procedure and conversion to a subtotal excision, since the dissection of hard calcified masses from the suprasellar region, medial to the ipsilateral carotid artery, may be extremely difficult or impossible. Under these circumstances, it may be wise to be content with a subtotal removal in the hope that these more densely calcified portions of the tumour contain less in the way of active proliferative material. It is also worth while noting that in the region of the optic chiasm, the extent of gliosis in the anterior third ventricle may make the dissection and the actual determination of the limit of the tumour itself extremely difficult. High magnification and the excellent lighting provided by the microscope, however, will usually enable some differentiation between

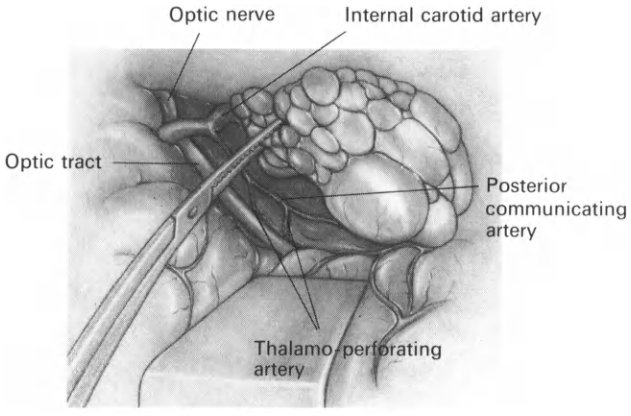


Fig. 7.8. The craniopharyngioma is being drawn downwards and backwards away from the chiasm, and the posterior aspect of the carotid artery. This represents the final phase of dissection, the linear structure above the posterior communicating artery is the artist's representation of the optic tract which is seldom as clearly defined superiorly.

gliosis and proliferative tumour to be made. Of course, where doubt exists, the surgeon should err on the side of leaving potentially viable paraventricular tumour *in situ*.

THE MANAGEMENT OF CYSTIC CRANIOPHARYNGIOMA

Rarely, in the author's experience, a craniopharyngioma may be encountered which is almost completely cystic. Such tumours are in the main unsatisfactory for radical excision by any route, since every movement of dissection of the wall is accompanied by considerable disturbances of the third ventricular structures. Whereas in a solid craniopharyngioma the third ventricle is splinted against the remainder of the craniopharyngioma while the dissection is pursued, no such assurance of absence of disturbance can be achieved where the entire tumour has collapsed, and it seems that lesser operations for such craniopharyngiomatous cysts are probably advisable. Dissection of the filmy walls of such cysts from vascular structures may be impossible. Any solid portion of the tumour having been removed, it is now the author's practice to insert a large gauge (5 mm internal diameter) rubber or Silastic tube with several side holes, anchored to the dura along the sphenoidal wing, its free end lying within the cavity of the cyst. If the cyst wall has been perforated over only a small area for biopsy, the assurance of accurate placement of this catheter may be made with greater confidence. The tube may then be brought out along the sphenoidal wing to a Rickham reservoir in the temporal muscle. Closure of

the primary craniotomy can be followed within some days by aspiration of the cyst through the Rickham reservoir, confirming the placement of the tube in an adequate situation for recurrent aspiration, or the tube may be subsequently connected, in the author's preference, to the pleural cavity. This operation, which was suggested to the author by his colleague in the National Hospital, Mr Lawrence Walsh, has been performed now in three cases, and is in many ways similar to the sump drainage of craniopharyngioma suggested by Miles [16].

Connection to the pleural cavity through a wide-bore tube, aided by recurrent negative pressure during respiration, has enabled the adequate drainage of these cases for periods of up to 5 years without further trouble. The long term results of course are unlikely to be satisfactory since it seems almost inevitable that blockage of the tubing will occur. It has been the experience of many surgeons, however, that the dissection of the often multiple ramifications of a cystic craniopharyngioma with its thin membrane investing nerves and vessels, invading the posterior fossa and sometimes the lateral ventricles, is an impossible task. Under these circumstances, lesser procedures with their manifold disadvantages and undoubted higher recurrence rates, may be the only course open to the surgeon.

NECESSARY INVESTIGATIONS

Endocrine and General Metabolic Investigations

Some degree of embarrassment of pituitary hypothalamic function is common in craniopharyngioma, and ideally should be elucidated in a full preoperative work-up. It must be admitted, however, that the key to endocrine management in the radical excision of craniopharyngiomas is the use of large doses of dexamethasone and control of the inevitable diabetes insipidus by judicious doses of DDAVP. Under these circumstances, many clinics may prefer to place the patient on high steroid dosage preoperatively, and to defer detailed endocrine investigation until the postoperative period when the degree of impairment of pituitary hypothalamic function may be assessed in detail and necessary replacements planned. This pragmatic approach is intellectually unsatisfying and where first class endocrinological facilities are available, then little time is wasted in detailed preoperative work-up, and a comparative analysis of the endocrine defects before and after surgery will provide the operating surgeon in retrospect with valuable information as to the degree of disturbance of the third ventricular wall produced by what, in many instances, must be a very resolute dissection.

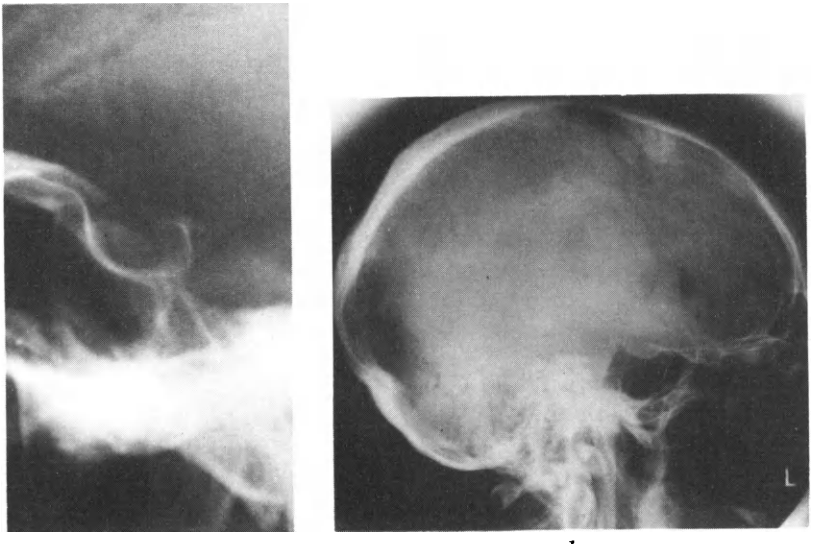
It should be noted here that the differential diagnosis of a suprasellar tumour with impairment of growth, impairment of vision and diabetes

insipidus in the young, is substantially between craniopharyngioma, germinoma or ectopic pineal tumour in the anterior portion of the third ventricle and the curious condition of Gegel's granuloma or histiocytosis of the anterior third ventricle. This differential diagnosis has been much eased by the use of CT scan, but in general it may be stated that over 80 per cent of children with craniopharyngioma show intracranial calcification of the mass, at least in part, that the earliest presenting feature of the histiocytosis of the chiasm is almost always diabetes insipidus and that the diagnosis of germinoma of the anterior third ventricle is, according to Handa, acceptably made on the presence of lymphocytic-like cells in the CSF which in his experience are almost always seen in this condition. It should be pointed out that this seems not invariably true in Western series, but the CT scan appearances of this latter tumour with a tendency to 'sugar ice' the ventricular system and to have homogenous enhancement, of itself uncommon in the craniopharyngioma, may facilitate the differential diagnosis. The occasional case of suprasellar metastasis [23] will occasion the rare error in differential diagnosis: one of the author's series, for example, was confidently preoperatively diagnosed as craniopharyngioma and presented as adenocarcinoma on histological examination.

The Radiological Investigation

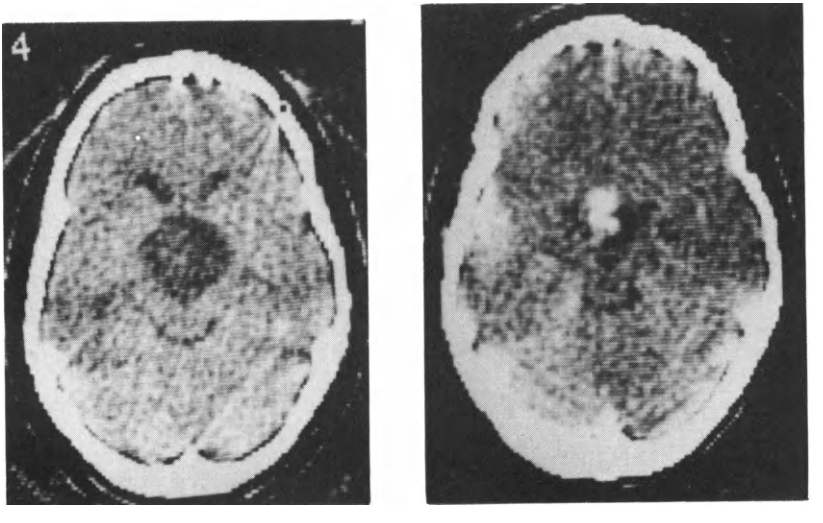
The plain X-ray features of craniopharyngioma have been well and extensively described. The presence of calcification in between 80 and 100 per cent of craniopharyngiomas in children is accepted, with a large proportion of adults, between 25 and 50 per cent, showing detectable calcium on plain X-rays. The characteristic shortening of the dorsum sellae has also been well described (*Fig. 7.9*), but these plain film features, while of diagnostic help, are without significance in the detailed planning of the surgical approach, and further specific studies are necessary in this regard.

Computerized tomography [24] is of considerable value in assessment of the size and probable extent of the craniopharyngioma. The characteristic picture is of a mixed attenuation lesion (*Fig. 7.10*) lying predominantly in the suprasellar region, often with lacunae of density so diminished as to suggest a cystic component, and usually irregularly enhancing on the injection of contrast medium. All these factors are of interest, but it is in the demonstration of the extent and direction of spread of the tumour, its spread subfrontally (as in *Fig. 7.11*) and its spread across the tentorium into the posterior fossa (as in *Fig. 7.12*) that the CT scan provides information which, though accessible by other radiological means, can in no other way be so readily and conveniently obtained. The CT scan will also give valuable information as to ventricular size and, to some extent, the degree of involvement of the third ventricle in the top of the mass, although this is more specifically outlined by air study. Where the intracranial pressure is raised, CT scan and arteriographic studies have largely taken the place of ventriculography.



a *b*

Fig. 7.9. Plain films in two cases of craniopharyngioma. In (*a*) a coned view of the sella reveals a dorsum which could be thought abnormal. In (*b*) the gross flattening of the dorsum and downward pressing of the anterior cliniod with opening out of the sella is more typical. In neither case is the deformity completely diagnostic of craniopharyngioma.



a *b*

Fig. 7.10. Two cases of craniopharyngioma. *a*, A large, partly cystic legion lying predominantly within the third ventricle. *b*, A partially calcified, partially cystic lesion. Both were radically excised.

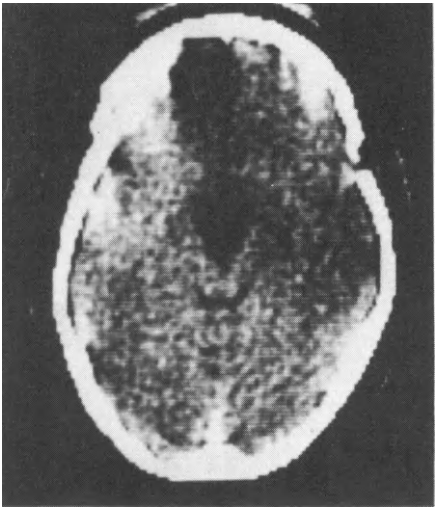


Fig. 7.11. Predominantly cystic craniopharyngioma with an anterior subfrontal cystic extension. Concentration on the quality of the CT scan here will differentiate this from the frontal CT scanning artefact, which may occasionally be a problem.

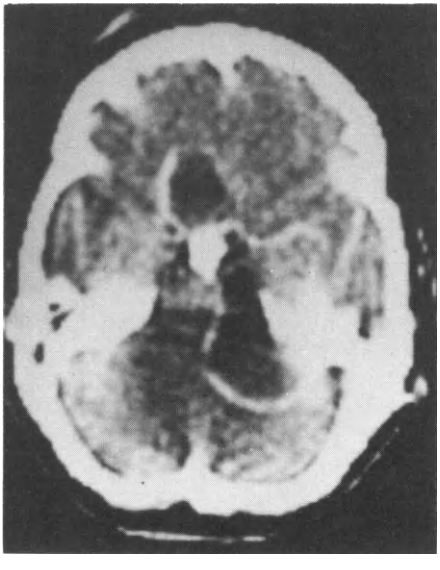


Fig. 7.12. CT scan of a massive craniopharyngioma which has been drained on a number of occasions elsewhere over the years. Left subfrontal central third ventricular and posterior fossa extensions are visible.

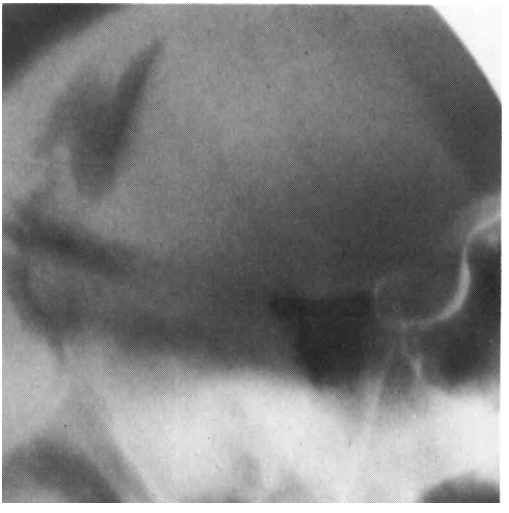
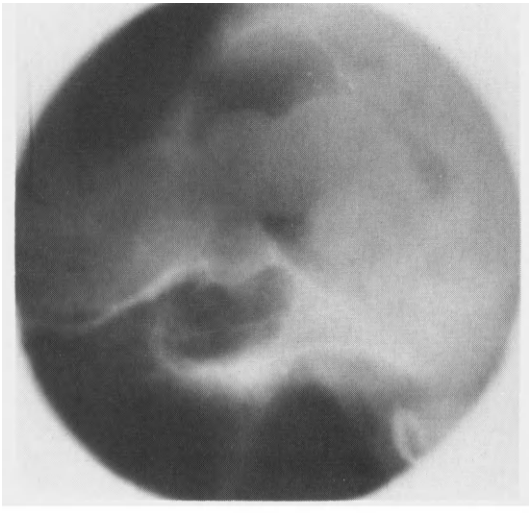


Fig. 7.13. A filling film of an air encephalogram showing the gross displacement of the third ventricle and the lower edge of the mass in the interpeduncular cistern. (The CT scan of this tumour is shown in *Fig. 7.10a*.)

Air Study

Except in the relatively uncommon adult case with papilloedema [25] (less than 8 per cent in the current series of 94 cases), the most specific information as to the extent of the tumour and its involvement with the third ventricular structures is undoubtedly obtained by air encephalography. The examination should concentrate first on demonstration of the posterior border of the mass and its relationship to the brain stem, interpeduncular cistern and posterior part of the floor of the third ventricle. This may be best obtained on filling films with careful tomography (*Fig. 7.13*), while the anterior relationships of the mass, a prediction of the possible situation of the chiasm and of the presence or absence of temporal and subfrontal extensions, are thereafter made on AP and lateral tomographic films with the patient supine (*Figs. 7.14, 7.15*). From the filling of the ventricular system, the anterior end of the third ventricle and the situation of the uppermost portion of the craniopharyngioma may be outlined.

The aim throughout the investigation should be to predict the relationship of the mass to the sella, to the brain stem, and to the floor of the third ventricle. It may also be possible to guess at the probable situation of the chiasm from the deformation of the chiasmatic cistern and recesses of the third ventricle, although visualization of this portion of the third ventricle may be impossible in lateral view because of extensive obliquity and deviation of the front of the third ventricle to one side.



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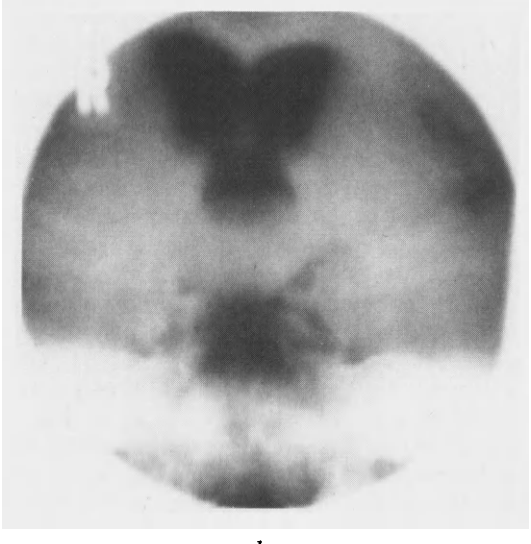

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Fig. 7.14. Air encephalogram of an anteriorly placed, partially intraventricular craniopharyngioma. In (*a*) the anterior placement of the chiasm across the front of the mass can be inferred, and the lower part of the mass seen in the interpeduncular fossa. In (*b*) the extent of stretching of the floor of the third ventricle can be inferred.

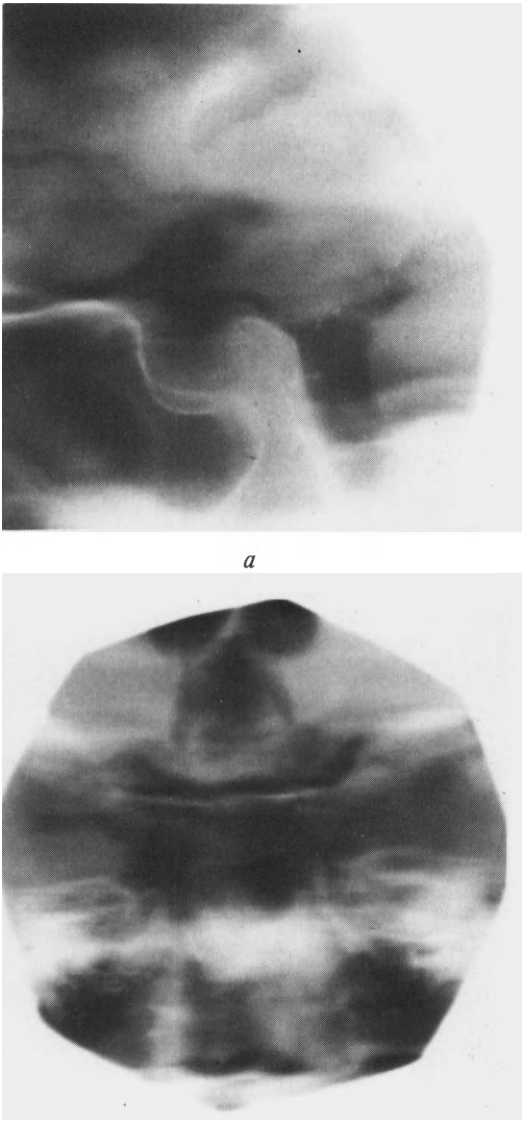


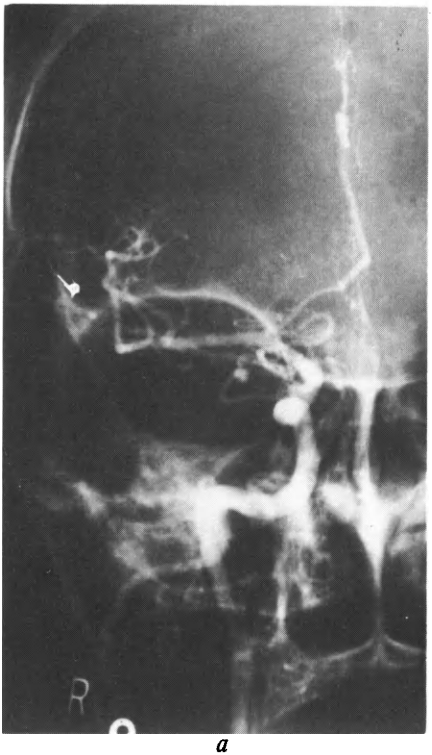
Fig. 7.15. Air encephalogram of craniopharyngioma. In (*a*) the backward extension of the mass in the interpeduncular fossa, displacing the brain stem, can be clearly seen, and the fact that the chiasm is quite anteriorly placed across the front of the mass. In (*b*) the irregular superior extent of the tumour in the third ventricle is visible; it reaches almost to the foramen of Munro but was successfully excised by the temporal approach.

Arteriography

While the air encephalogram will outline the size, shape and situation of the mass, its relationship to major arteries can only be determined with confidence by careful arteriography. Bilateral carotid angiography with magnification studies, and vertebral angiography, is necessary to show the situation of the terminal carotid branches and their relationship to the mass (*Fig. 7.16*). Thus the posterior communicating arteries are commonly displaced downwards and laterally by a predominantly intrinsic craniopharyngioma, which spreads the anterior choroidal artery and thalamo-perforating branches of the posterior communicating artery across its lateral aspect (*Fig. 7.17*). The relative size and situation of these vital perforating vessels are of considerable importance in the choice of route, and in the decision for or against the sacrifice of any one of them should this become necessary in the course of the surgical excision. The relation of the mass to the top of the basilar artery and to the proximal first segments of the posterior cerebral vessels is outlined by vertebral arteriography (*Fig. 7.18*), and the relationship of the thalamo-perforating branches of the posterior cerebral artery and the posterior choroidal arteries to the top of the lesion lying within the third ventricle, is also displayed. In this author's view, such detailed preoperative anatomical analysis of the circulation is essential.

RESULTS

This chapter concerns itself primarily with operative technique, but it would be impossible to describe such radical surgery detached from its results. One might suppose that more radical excision occasions fewer recurrences with a slightly higher initial mortality, and this is indeed borne out by detailed case analysis. Primary radical excision in this series was performed in 19 cases with a mortality rate of 10·5 per cent. Secondary radical excision, that is a radical excision after one or more previous interferences with the tumour, was carried out in 7 cases with a mortality rate of 28·5 per cent. From this group of 26 cases, 20 patients are still alive without recurrence, with a follow-up ranging from over 2 years to over 20 years (76 per cent). Cases operated on in the past 2 years have not been included in the present study. Four patients have survived more than 20 years without recurrence, 2 patients more than 10 years, 7 between 4 and 8 years, and 7 between 2 and 4 years. With a less radical operation, 34 cases were operated on with an operative mortality of 3 per cent. Recurrence, however, has taken place in 15 of these cases (44 per cent) and only 26 of these cases now survive. The percentage of survivors is at this time, therefore, the same as for apparently more radical operation, though presumably more recurrence is to be expected in the less radical group.



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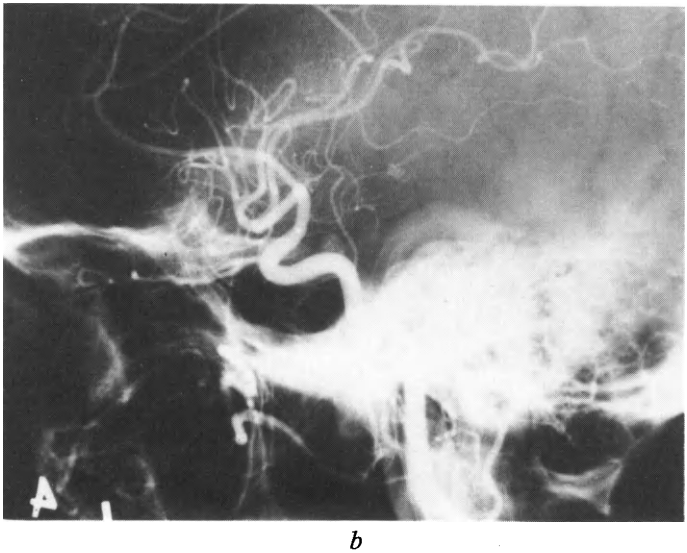
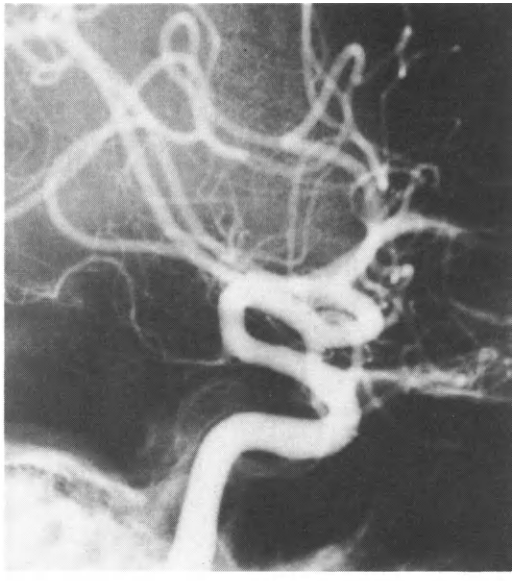


b

Fig. 7.16. Anteroposterior and lateral views of carotid arteriograms in a craniopharyngioma which could on these films have been any suprasellar mass, such as a pituitary tumour. Carotid arteriography alone will not make the differential diagnosis.



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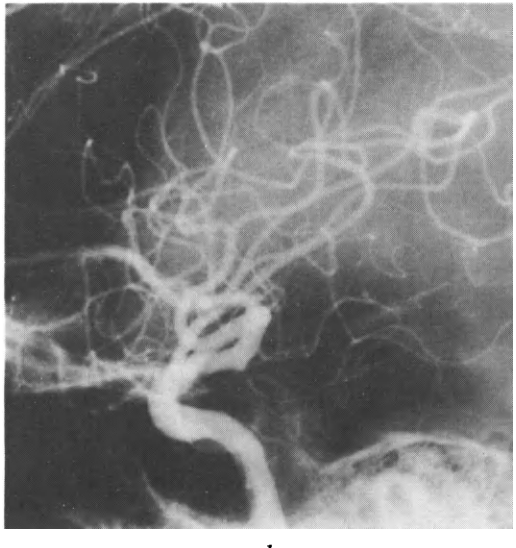

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Fig. 7.17. Right and left lateral carotid arteriogram in a typical posteriorly placed craniopharyngioma. In (*a*) the downward displacement of the posterior communicating artery is visible, and the position of the two thalamo-perforating vessels can just be made out. In (*b*) the vascular displacement is less evident, but the downward bowing of the posterior communicating artery is visible, the artery being small and its branches not so easily seen.

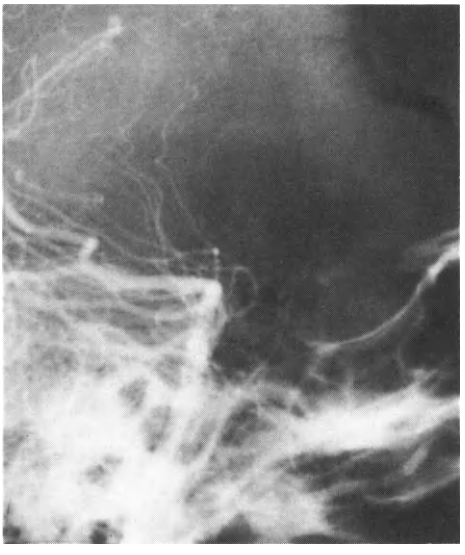
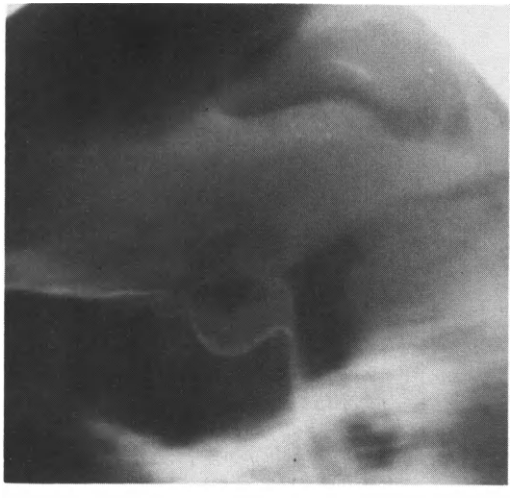


Fig. 7.18. Displacement of posterior choroidal branches of the posterior cerebral artery around a large craniopharyngioma. Calcification of the posterior part of the lesion is just visible. This tumour was successfully excised by a trans-temporal route.

Where a considerable portion of the tumour is known to have been left behind, 22 cases in the current series, the operative mortality of 23 per cent is somewhat higher, although this includes many cases early in the series. Only 10 of these cases now survive, 5 having survived reoperation and 5 requiring no further surgery. This represents 22·7 per cent of the original group. Exploration with biopsy and shunt surgery was performed in 19 cases, but only 9 patients now remain alive. Only 3 of the original 19 cases survived without further surgery, although the mortality of the original operation was only 12 per cent.

CONCLUSION

Throughout this chapter, the use of the term 'complete excision' has been avoided. It seems that the best that can be hoped for in any surgery related to craniopharyngioma is maximal removal of accessible tumour at the time of the primary exposure. If, after 25 years, the tumour has not recurred, then perhaps it has been completely removed. Even at this late date, however, it would be a brave man who would state that recurrence was impossible. Assessment of the extent of radical excision may be either by CT scanning (*Fig. 7.7*) or by postoperative air encephalography, of which the latter is by far the more effective. *Fig. 7.19* shows the pre-



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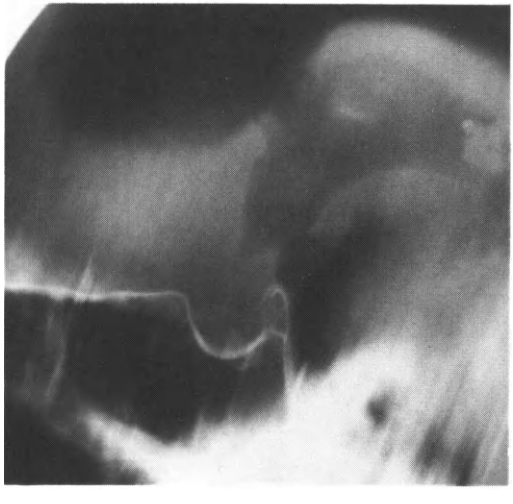

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Fig. 7.19. Lateral air encephalograms, preoperatively (*a*) and postoperatively (*b*) in a case of craniopharyngioma excised radically by the trans-temporal route.

and postoperative appearance following radical excision in a young man. The postoperative air encephalogram shows no evidence of a mass. Even here, however, cellular infiltration in the gliosis behind the chiasm, with perhaps the inclusion of a few nests of epidermoid cells, may mean that recurrence, hopefully long delayed, is still possible. CT scanning is at the present less certain, but if known detectable residua of the tumour remain, their size may be followed confidently over a period of time. The slice thickness and degree of resolution of the current generation of CT scanners mean that small portions of craniopharyngiomas, sufficient to show on a postoperative air encephalogram, will not be evident on CT scan.

The role of radiotherapy remains uncertain. The persuasive reports of Kramer and his associates, and substantial bodies of opinion in this country, still suggest that partial removal followed by radical radiotherapy, is the best form of treatment. Up to date statistics and an accurate follow-up on these patients might prove or disprove this point. Backlund [26] and his associates in Sweden have further given unequivocal CT scan evidence of reduction in size of craniopharyngiomas following stereotactically controlled radiotherapy, but the complete eradication of such tumours by radiotherapeutic means has not been described. From the natural history of these masses, it is clear that only total removal of the tumour will prevent recurrence sooner or later, and to this author it seems that radical surgery with the use of the microscope and appropriate hormonal replacement, undertaken at a fairly early stage in the course of the tumour when excision is possible without too formidable a dissection, represents the best and most hopeful means of cure at the present time.

Acknowledgements

The case analysis referred to here forms part of a study in course of preparation [27].

The operative diagrams were prepared by Miss Angela Christie; photomicrographs for *Fig. 7.6* were kindly prepared by my colleague, Professor Leo Duchen, of the Institute of Neurology.

The evolution of the radical trans-temporal approach in my hands owes much to the stimulus and example of my colleague, Professor Valentine Logue.

REFERENCES

1. Matson D. D. (1962) Craniopharyngioma. *Clin. Neurosurg.* **10**, 116-29.
2. Svolos D. G. (1969) Craniopharyngiomas: a study based on 108 verified cases. *Acta Chir. Scand.* Suppl. 404, 8-44.
3. Matson D. D. and Crigler J. F. (1969) Management of craniopharyngioma in childhood. *J. Neurosurg.* **30**, 377-90.
4. Bartlett J. R. (1971) Craniopharyngiomas – a summary of 85 cases. *J. Neurol. Neurosurg. Psychiatry* **34**, 37-41.

5. Michelson W. J., Mount L. A. and Renandin J. (1972) Craniopharyngioma: a 39 year study. *Acta Neurol. Lat. Am.* **18**, 100–6.
6. Kahn E. A., Gosch H. H., Seeger J. F. et al. (1973) Forty-five years' experience with craniopharyngiomas. *Surg. Neurol.* **1**, 5–12.
7. Katz E. L. (1975) Late results of radical excision of craniopharyngiomas in children. *J. Neurosurg.* **42**, 86–90.
8. Banna M. (1976) Review article. Craniopharyngioma: based on 160 cases. *Br. J. Radiol.* 49, 206–23.
9. Kerr A. (1968) Craniopharyngiomata. (Proc. Soc. Br. Neurol. Surg.) *J. Neurol. Neurosurg. Psychiatry* **31**, 646–50.
10. Kramer S., McKissock W. and Concannon J. P. (1960) Craniopharyngiomas: treatment by combined surgery and radiation therapy. *J. Neurosurg.* **18**, 217–26.
11. Kramer S., Southard M. and Mansfield C. M. (1968) Radiotherapy in the management of craniopharyngiomas, further experiences and late results. *AJR* **103**, 44–52.
12. Sharma U., Tandon P. N., Saxena K. K. et al. (1974) Craniopharyngiomas treated by a combination of surgery and radiotherapy. *Clin. Radiol.* **25**, 13–17.
13. Sweet W. H. (1976) Radical surgical treatment of craniopharyngioma. *Clin. Neurol.* **23**, 52–79.
14. Hoffman H. J., Bendrick E. B., Humphreys R. P. et al. (1977) Management of craniopharyngioma in children. *J. Neurosurg.* 47, 218–27.
15. King T. T. (1979) Removal of intraventricular craniopharyngiomas through the lamina terminalis. *Acta Neurochir.* **45**, 277–86.
16. Miles J. (1977) Sump drainage: a palliative manoeuvre for the treatment of craniopharyngioma. *J. Neurol. Neurosurg. Psychiatry* **40**, 120–6.
17. Le Gros Clarke W. E., Beattie J., Riddoch G. et al. (1938) *The Hypothalamus.* Edinburgh, Oliver & Boyd.
18. Ghatak N. R., Hirano A. and Zimmerman H. M. (1971) Ultrastructure of craniopharyngioma. *Cancer* **27**,1465–75.
19. Grcevic N. and Yates P. O. (1957) Rosenthal fibers in tumors of the central nervous system. *J. Pathol.* 73, 467–72.
20. Zulch K. J. (1965) *Brain Tumors: Their Biology and Pathology,* 2nd American ed. New York, Springer, pp. 228–33.
21. van der Bergh R. and Brucher J. M. (1970) L'abord transventriculaire dans les craniopharyngiomes du troisième ventricule. *Neurochirurgie* **16**, 51–65.
22. Timperley W. (1968) Histochemistry of Rathké Pouch tumours. *J. Neurol. Neurosurg. Psychiatry* **31**, 589–95.
23. Scatliff J. H. and Bull J. W. D. (1965) The radiological manifestations of suprasellar metastatic tissue *Clin. Radiol.* **16**, 66–70.
24. Naidich T. P., Pinto R. S., Kushner B. A. et al. (1976) Evaluation of sellar and parasellar masses by computed tomography. *Radiology* **120**, 19–99.
25. Ross Russell R. W. and Pennybacker J. B. (1961) Craniopharyngioma in the elderly. *J. Neurol. Neurosurg. Psychiatry.* **24**, 1–13.
26. Backlund E.-O. (1979) Stereotactic radiosurgery in intracranial tumours and vascular malformations. In: Krayenbuhl H. (ed.) *Advances and Technical Standards in Neurosurgery.* Berlin, Springer-Verlag, vol. 6, pp. 3–37.
27. Symon L., Logue V. and Jakubowski J. The results of surgical treatment in craniopharyngiomas. (In preparation.)

J. M. Rice Edwards

8 Syringomyelia and its Surgical Management

It would seem desirable that surgeons should have some idea of the nature of the diseases they are treating. In the case of syringomyelia, apart from accepting that the condition is one of cystic cavitation of the spinal cord, there is no general agreement about either the pathogenesis or the classification of the condition and this uncertainty, compounded by a lack of information about the efficacy of the various surgical manoeuvres employed, gives many surgeons a sense of insecurity in what they are doing. Any attempt to unravel the subject will have the imprint of the writer's bias, particularly regarding his position as an adherent of, or, in my case, an opponent of Gardner's hypothesis which has dominated thoughts about this strange condition for 20 years. It is inevitable, therefore, that I review the various operations that have been employed from the standpoint of my own understanding of the condition.

CLASSIFICATION

First of all, how is syringomyelia defined? The word has been used to include simple dilatation of the central canal (hydromyelia) or to apply only to cavitation with a glial lining. Barnett and Rewcastle [1] have proposed the following definition: 'Syringomyelia is a cavitation in the spinal cord which has a wall largely composed of glial tissue'. It is certainly useful to be able to distinguish hydromyelia, which is usually symptomless, from syringomyelia in this way. Cystic intramedullary tumours are sometimes included under the general heading of syringomyelia and sometimes not. It is tempting not to do so because the frequent clinical problem is to distinguish between 'syringomyelia' on the one hand and 'cystic or solid tumour' on the other. In fact, the question of whether an intramedullary tumour is cystic or not would seem a poor basis for classification. It is not used as such in the brain. Syringomyelia is a process peculiar to the spinal cord and cavitation due to a tumour is not. The wall of a tumour cyst may certainly be lined with glial tissue in parts but characteristically it is much thicker than a typical syrinx.

For these reasons I have distinguished between cystic tumour and syringomyelia (although it may well be that hydrodynamic factors aid

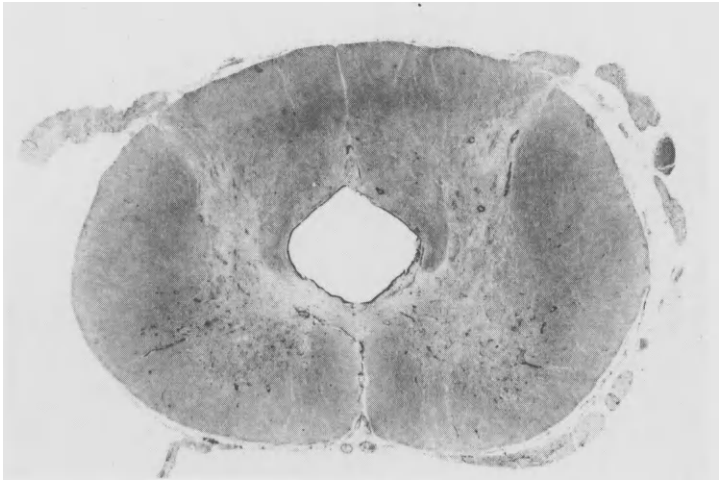


Fig. 8.1. Unsuspected hydromyelic canal with a complete ependymal lining with associated Chiari malformation in a young man dying of acute poliomyelitis.

the extension of tumour cysts in much the same way as they do syringomyelia) and I have modified Barnett and Rewcastle's definition as follows: 'Syringomyelia is a cystic cavity in the spinal cord with a wall free of tumour and largely composed of glial tissue'. It should be noted that this definition does not exclude the possibility that syringomyelia might *coexist* with intramedullary tumours.

It is now generally agreed that there are two basic types of syringomyelia; one, much the more common, stemming from a dilatation of the central canal (hydromyelia) and the other arising in the substance of the cord without primarily involving the canal. These have been called 'communicating' and 'non-communicating' by Williams [2] as it was assumed that a dilated central canal would be in free communication with the fourth ventricle. As discussed below, however, this is not always the case and the presence or absence of communication would therefore seem an improper basis for classification.

The appearance of the hydromyelic canal suggests a congenital lesion (*Fig. 8.1*) whereas the other type occurs as a result of well-recognized, acquired lesions. The two main types may therefore be called 'congenital' and 'acquired'. It may be objected that in the first of these the syrinx, though stemming from a congenital defect, is not itself congenital. It may therefore be reasonable to speak about a 'hydromyelic' type of syringomyelia.

On this basis the following classification is proposed:

Classification of Cystic Cavitation of the Spinal Cord

1. Hydromyelia and Syringomyelia
   (i) Congenital (*a*) Simple hydromyelia (assoc. Chiari type II malformation in hydrocephalic infants with spinal dysraphism)
   (*b*) Hydromyelia and syringomyelia (assoc. Chiari type I malformation in adults)
   (ii) Acquired (*a*) Post-traumatic syringomyelia
   (*b*) Post-arachnoiditic syringomyelia
2. Cystic Intramedullary Tumours

PATHOGENESIS

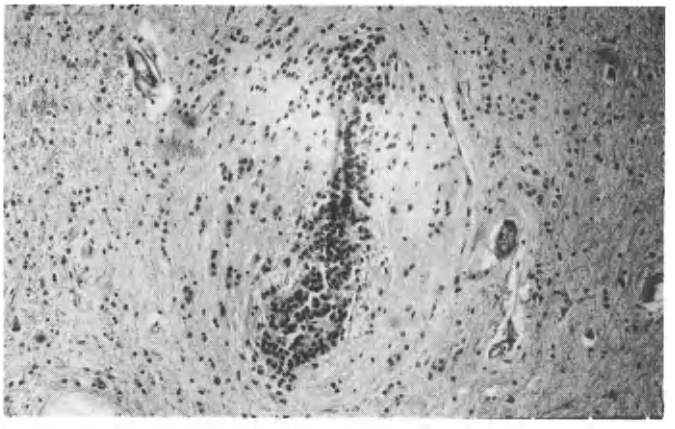
Congenital (Hydromyelic)

There have been many theories about the cause of syringomyelia and any lack of factual evidence has been made up for by ingenious speculation. The association of the Chiari I malformation with 'communicating' syringomyelia established by Gardner [3] led him to propose a theory that the craniovertebral anomaly established a disturbance of the CSF arterial pulse wave causing this to dilate the central canal to such a degree that the fluid would burst the bounds of the canal wall at various points and penetrate into the cord substance. Certain aspects of this theory were criticized by Williams [2] and du Boulay et al. [4] but the central idea that the syrinx fills in a pulsatile manner from the fourth ventricle in this type of syringomyelia was incorporated by them in other versions of what has become known as the hydrodynamic theory. The essential point of this theory is that the syrinx fills with clear, colourless fluid from the fourth ventricle and that this occurs because the associated Chiari malformation creates a disturbance of CSF hydrodynamics at the foramen magnum. It is crucial to these ideas that there should be an adequate passage between the fourth ventricle and the syrinx but over the years there has been some disagreement about the existence of this. Gardner [3] and also Conway [5] noted during operations that when they injected indigo carmine into a lateral ventricle they were able to retrieve it from the syrinx, indicating that the two chambers were in free communication. Although radiological studies have sometimes demonstrated such a communication, this is unusual and in most cases the syrinx appears to taper to a narrow canal at the C1 segment. Furthermore, pathological studies show that the communication is typically small or absent. Twenty-two cases were recently studied from the pathological records from a number of hospitals [6, 7]. These were all adult cases with advanced syringomyelia of the hydromyelic type. The cerebellar tonsils were abnormally low in fourteen, the information being incomplete about this in the remainder. In six cases the central canal was blocked completely at the upper cervical and lower medullary levels and in the others a very narrow communication existed

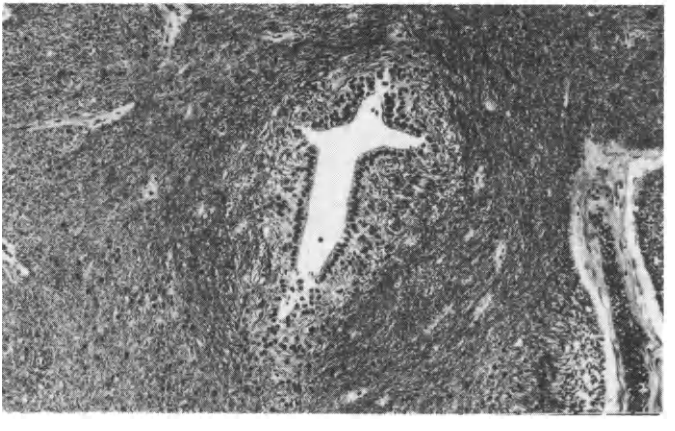
being usually invisible to the naked eye and measuring only a few micromillimetres in diameter (*Fig. 8.2*). Although it is possible that post-mortem shrinkage accounted for some diminution in the diameter of the canals it seems clear that even when the canal was patent it was so small that it could not have acted as a conduit for fluid during life in the manner envisaged by upholders of the hydrodynamic theory.

This lack of communication is at first sight surprising in view of the well-established fact that infants with Chiari II malformation and meningomyelocoele frequently have hydromyelia [8] and there is ample evidence in these cases that the dilated central canal is in free communication with the enlarged ventricles. Hydromyelia in free communication with the ventricles is also readily provoked by causing hydrocephalus in animals in whom the central canal normally remains patent during adult life [9]. In both these instances the canal and the ventricles may be thought of as one enlarged communicating ependymal-lined chamber. The association between the Chiari I malformation and syringomyelia in adults suggests that here the pathology is basically similar, being merely a less severe variety than in the Chiari II malformation encountered in infants. This may well be so but there are three important differences between the adults and infants. First, the ventricles are not usually enlarged in adults with syringomyelia [10]; secondly, the cavity in the adults is not usually a simple ependymal-lined hydromyelia as in the infants but consists of an irregular system of glial-lined extensions from the hydromyelic canal into the cord substance; and thirdly, there is no adequate communication between the central canal and the ventricles as mentioned above. It is a blind sac in most cases and it is interesting to speculate about how it arises, how it progresses and why the CSF remains clear and colourless, for these mechanisms may well have implications for correction by surgical treatment.

The pathology of this type of syringomyelia suggests that it is basically a congenital lesion. The association with the Chiari malformation and sometimes with bony anomalies of the foramen magnum would suggest this and it is often possible to find areas where the syrinx consists purely of a large patent central canal completely lined with ependymal cells: it has the appearance of a congenitally wide canal rather than one that has been forced open by hydrodynamic forces. In other words, it is a persistence of the fetal state of hydromyelia. Where does the fluid come from if not from the fourth ventricle? The idea that the fluid may cross the cord substance from the subarachnoid space [12, 13] has recently received some support from the observation that metrizamide may enter the syrinx some hours after introduction into the subarachnoid space [14]. It would seem more likely that the dye diffuses through the cord rather than enters the syrinx via the fourth ventricle though this question is under examination at the present time by sequential CT scanning of the fourth ventricle and spine after metrizamide has been injected into the lumbar subarachnoid space. An alternative idea is that CSF within the syrinx is actually formed



a



b

Fig. 8.2. The central canal in C1 segments in two patients dying with syringomyelia. In one (*a*) the canal is completely blocked and no communication exists between the syrinx and fourth ventricle. In the other (*b*) the canal is patent though extremely small. In both patients there was evidence that the syrinx stemmed from hydromyelia in lower segments. (× 84.)

by capillaries within the cord in the same way that ventricular CSF is partially a product of intracerebral capillaries, the CSF being in fact identical to cerebral extracellular fluid [6]. There is no evidence on the point but whatever the difficulties in theorizing on the source of the clear syrinx fluid it is noteworthy that Barnett [15] reported that the syrinx fluid may be clear and colourless even in the post-traumatic type of

syringomyelia where the central canal is not involved and where the syrinx is typically contained within the cord substance without communication with the subarachnoid space or with the fourth ventricle.

The fact that the syrinx expands with time may be presumed by the fact that symptoms and signs of an intramedullary lesion develop slowly (or sometimes acutely) during adult life. This may be caused by an imbalance between formation and reabsorption of syrinx fluid but might also be caused by a mechanism first suggested by Williams [16, 17]. He has studied the pressure changes in the lumbar sac during coughing and straining and it is quite possible that the transmission of these to the cord might cause the syrinx fluid to extend into the cord substance at the expense of the more compressible neural tissue: this is really another type of hydrodynamic theory. This might explain the extension of the cavity into the medulla above the foramen magnum and the complex way in which the syrinx appears to dissect into the cord parenchyma forming an irregular network of penetrating passages. In the vicinity of the syrinx the cord may be oedematous and contain areas of haemorrhage and these appearances suggested to Greenfield [18] that there had been tearing of tissues as if some violent process had been at work. The occasional experience of a patient with syringomyelia having a sudden exacerbation of symptoms on coughing or straining also suggests that the cavity may extend as a result of pressure changes. The effect of these may well be greater when there is no communication with the fourth ventricle and the irony of this is obvious in view of Gardner's strongly held and widely accepted views on the therapeutic need to block the canal. Further comments about these ideas are made below in relation to the radiological appearances and to Gardner's operation.

It may be argued that acquired lesions in the region of the foramen magnum may cause 'communicating' syringomyelia. In fact there is little evidence that this is so. All the craniovertebral anomalies in the series of Logue and Rice Edwards [10] were thought to be congenital. The case of Kosary et al. [19] concerns dilatation of the spinal cord which resolved after removal of a meningioma but, although the cause of this phenomenon is uncertain, the meningioma arose from the tentorium and did not therefore cause a craniovertebral anomaly in the manner suggested by Gardner unless prolapsed tonsils were responsible. If this were the case one would expect prolapsed tonsils to regularly cause syringomyelia. More difficult are the cases of syringomyelia described after tuberculous meningitis. One must distinguish between spinal and localized craniovertebral arachnoiditis. The spinal type may occur after meningitis and give rise to intraparenchymal cavitation unassociated with dilatation of the central canal [20]. Localized craniovertebral arachnoiditis is commonly found in the presence of congenital bony anomalies or the Chiari malformation. Giminez-Roldan et al. [21] described syringomyelia after tuberculous meningitis with evidence of a communication between the fourth ventricle and the syrinx

in two of these. However, one of these cases had hydrocephalus and there is no disputing that the upper end of the central canal may be wide open in hydrocephalics [22]. The evidence of a communication in the other case is not entirely convincing.

Appleby et al. [23] describe the pathological appearances in a patient who developed progressive neurological symptoms after an attack of tuberculous meningitis at the age of 13 years. Details of this infection are not given. No macroscopic communication between the upper end of the syrinx at C2 and the fourth ventricle was seen, but the canal was patent at C1 on microscopy. The ventricles were not dilated. However, the fact that he had 'gross scoliosis' suggests that the onset of spinal disease preceded the tuberculous meningitis at the age of 13 years.

Acquired

The mechanism of cyst formation in the case of spinal cord tumour is probably no different in most cases to that encountered in intracerebral tumours. In ependymomas, astrocytomas or haemangioblastomas the fluid leaks from tumour vessels and slowly collects around or within the solid component. I have given reasons for suggesting that cystic tumours should not be designated as syringomyelia but factors which aid the expansion of syringomyelia may also of course have the same effect in causing tumour cysts to extend.

In the case of syringomyelia following cord trauma or spinal arachnoiditis the origin of the syrinx is not certain. In trauma it is probable that the original cavity is formed by pulping of the central core of the cord [24] with subsequent reabsorption of blood and necrotic tissue and replacement by cord extracerebral fluid. Kao et al. [25] have suggested that the cavities are formed by the rupture and coalescence of microcysts in the myelin following trauma. If the same influences then bear upon the extension of these purely intramedullary syringes, as in the cases where the original cavity is congenital hydromyelia, it is not surprising that the gliotic wall eventually looks the same whatever the underlying cause.

Barnett [20] has suggested that cavitation of the cord in spinal arachnoiditis is due to ischaemic necrosis, and again once a cavity is established it may extend due to hydrodynamic factors.

CLINICAL FEATURES

Congenital (Hydromyelic)

It might be thought that there is nothing new to say about the clinical features of syringomyelia. There can be few medical students who do not

encounter, usually during a neurological demonstration, a case of syringomyelia with the characteristic clinical signs, but it must be remembered that syringomyelia is a pathological not a clinical description and that the classic signs, though usual, are not invariable and that conversely these classic signs may occur in other lesions such as solid intramedullary tumour. Logue and Rice Edwards [10] analysed the clinical findings in patients proved to have an intramedullary syrinx and found that the signs were usually of the classic variety but that some patients had a root entry syndrome affecting power and *all* modalities of sensation in one limb, that tendon reflexes are quite often retained, that occasionally the legs may be affected rather than the arms and that rarely there may be little or no sensory loss. The clinical signs are not stereotyped therefore. It is also important to realize that a Chiari malformation may also cause neurological disability independent of any associated syrinx. In a series of patients with the adult Chiari malformation in whom there was no clinical radiological or operative evidence that they also harboured a syrinx it was concluded that the signs were likely to be due to the Chiari malformation alone [11]. A common presentation was with benign cough headache – a sudden severe pain, usually occipital, which occurs momentarily after coughing, sneezing, laughing, bending or straining. Williams [17] has demonstrated the occurrence of a craniovertebral pressure differential during these manoeuvres in the presence of a Chiari malformation and it is quite possible that the symptom is due to downward displacement of the hind brain and dural stimulation because of this. My own experience is that this symptom is invariably associated with a lesion at the foramen magnum (commonly, though not invariably, the Chiari malformation) even though this may be difficult to demonstrate. In three patients with cough headaches who were explored on clinical grounds in the face of negative or questionable radiological findings a mild degree of Chiari malformation was found in each and the symptom eradicated by operative decompression (*Fig. 8.3*). In other patients evidence of medullary dysfunction was found, in particular difficulty in swallowing, vertigo and oscillopsia due to downbeat nystagmus. Cerebellar ataxia with horizontal nystagmus was also encountered and in the limbs a spastic quadriparesis with or without impaired joint position sense. All these findings alone or in various combinations appear to be related to the Chiari malformation. Why this should cause cough headache in one patient, dysphagia in another and pyramidal weakness in a third and why this congenital lesion should cause symptoms for the first time in patients 20-50 years old are questions impossible to answer.

Scoliosis, lower motor neurone signs and the classic suspended areas of dissociated sensory loss – signs associated with central cord lesions – are usually held to be due to associated syringomyelia although it is not always possible to confirm this radiologically or by observation of the upper two or three spinal cord segments during posterior fossa surgery. Lateralized pain, usually of an intense burning quality experienced within

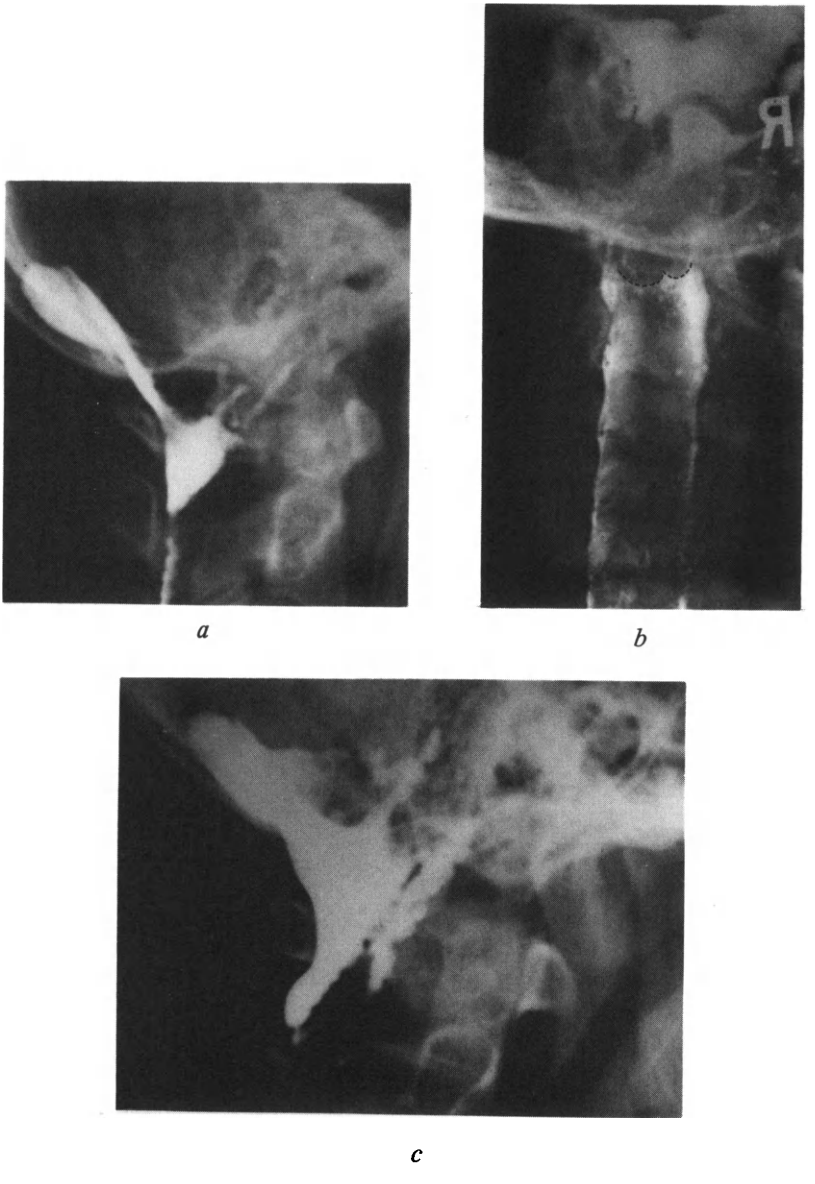


Fig. 8.3. Typical appearance of Chiari malformation demonstrated by supine screening of myodil in lateral (*a*) and anteroposterior (*b*) views. The cord is markedly dilated. In (*c*) the tonsils appear to be above the foramen magnum but the patient was explored on clinical grounds and proved to have a small Chiari malformation.

or at the borders of areas of cutaneous sensory loss, in contrast to benign cough headache, is also probably a symptom of cord cavitation.

In the individual case of syringomyelia there may well be a combination of the effects of medullary compression by the tonsils and of the presence of a syrinx. Some of the features such as spastic weakness of the legs might be caused by either of these lesions but in certain cases it may be found that signs are all compatible with compression by the Chiari malformation and that in others the signs of cord cavitation predominate. Therefore, in some patients the clinical analysis will strongly influence the question of whether a patient should have surgery or not (because the results of tonsillar decompression are likely to be more effective than drainage of a syrinx) and what type of surgery shall be performed. An important point is that the signs of 'syringobulbia' may well be due to compression by the tonsils rather than extension of fluid into the medulla and that far from being the end result of a progressive and fatal cavitation, the prominence of these signs might well influence a surgeon more towards decompressing the cerebellar tonsils than against surgery.

Hydrocephalus is found in approximately 25 per cent of patients with syringomyelia [10], but it is rarely severe enough to cause symptoms and is, in any case, of such chronicity that shunting is likely to carry a high risk of inducing subdural haematomas. Nevertheless, enlargement of the ventricles might sometimes contribute to the clinical picture particularly as a cause of postoperative drowsiness following surgery and justify ventricular shunting.

Associated bony craniovertebral anomalies act as markers to the probable underlying Chiari malformation and seldom contribute to the neurological deficit except in the case of significant basilar invagination.

Acquired

In about 2 per cent of patients with traumatic paraplegia or paraparesis (and a small number of quadriplegics) spontaneous pain, pain on coughing or sensory loss ascending from the level of the original deficit heralds the onset of post-traumatic syringomyelia. This occurs after an interval of months or years, the average being about 4 years. The onset of symptoms is typically unilateral but this progresses to bilateral sensory loss and increasing lower motor neurone weakness in the hands (and of course increasing weakness in the legs in those who are not already paraplegic). Excess sweating above the level of trauma is also quite common. The end result may be total quadriplegia but progression can be exceedingly slow in some cases and even spontaneous remission has been observed [26].

Cavitation occurring in the cord in the vicinity of severe spinal arachnoiditis is rare but, as in the case of the post-traumatic variety, may present as a progressive lesion of the cord ascending above the level of the arachnoiditis. Where arachnoiditis spreads throughout the spinal canal it

may be difficult to determine whether deterioration is due to arachnoiditis itself, to the development of arachnoid cysts or to cavitation [20].

RADIOLOGY

Congenital (Hydromyelic)

The advent of CT scanning and of a safer water-soluble contrast medium has changed the radiological management of these patients.

Plain X-rays are abnormal in approximately 30 per cent of the congenital type and the most common anomaly is posterior atlanto-axial fusion or apposition which nearly always indicates an associated Chiari malformation. Basilar invagination is more rarely encountered and is seldom severe enough to cause symptoms. A more common anomaly is a combination of a short clivus and odontoid process with upward tilting of the anterior part of the foramen magnum. This renders McGregor's line well below the tip of the odontoid process but does not imply invagination of the foramen magnum, a fact that can be established by anteroposterior tomography. The distribution of the radiological abnormalities is shown in Table 8.1. It is important to remember that plain X-rays will be normal in 70 per cent of cases.

Table 8.1. Craniovertebral Anomalies in 75 Cases of Syringomyelia

Wide cervical canal	14
Atlanto–axial fusion or apposition	9
Basilar invagination	2
Bifid C1	1
Bifid C6	1
Extra bone between clivus and dens	1
Fusion C2–3	1
Asymmetrical posterior fossa	1

Six patients had more than one abnormality.
Data of Logue and Rice Edwards [10].

CT scanning reveals that the ventricles are dilated in only about 25 per cent of cases [10]. Demonstration of the syrinx by CT scanning will depend on the sophistication of the equipment employed but it is to be expected that this method will be increasingly successful as time goes on. Already Bonafé et al. [27], using a modified EMI CT scanner, have reported that they were able to identify a syrinx in each of 32 cases of syringomyelia. As mentioned by Dr Kendall (Chapter 2, p. 49), the cord was of normal proportions in four of these and the syrinx would not therefore have been demonstrable by myelography. A Chiari malformation was demonstrated in 50 per cent where this aspect was investigated and it is possible, therefore, to identify all the important points – syrinx, Chiari malformation, bony anomaly, ventricular size – by plain X-rays and CT

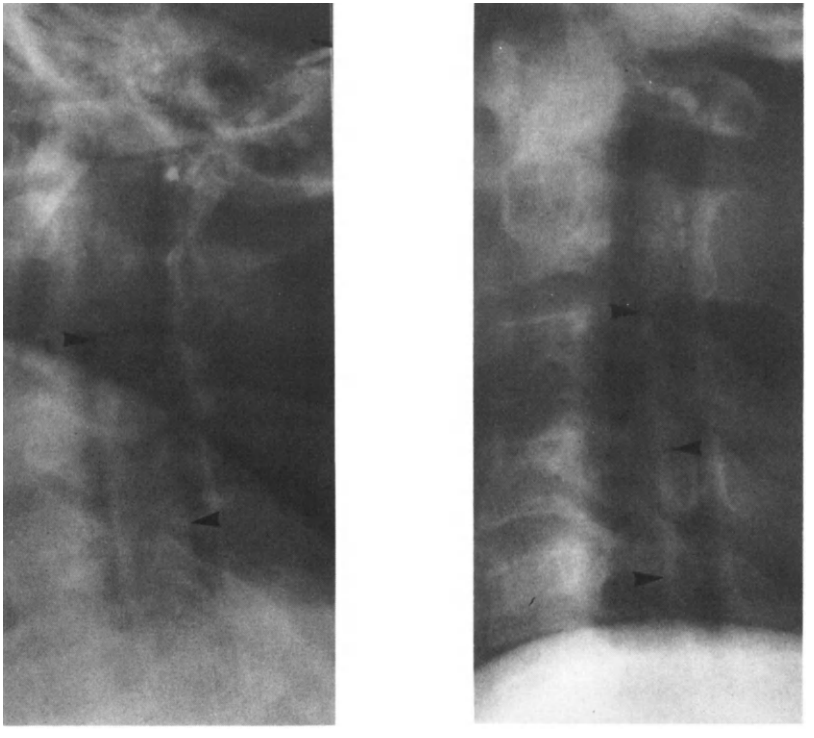
scanning alone. The demonstration of a syrinx or a tumour cavity by CT scanning may be aided by enhancement of the cord with intravenous xenon or by intrathecal metrizamide which may enter the syrinx itself after a delay of approximately 6 hours. The demonstration of nodules within cystic tumours may be helped by enhancement with intravenous metrizamide (Chapter 2, p. 49).

The delineation of the cerebellar tonsils by CT scanning is aided by direct or reconstructed coronal scanning and by the introduction of a low concentration of intrathecal metrizamide.

Conventional myelography, preferably using metrizamide, will be needed where CT scanning has failed to show these abnormalities. The position of the tonsils is demonstrated by screening the patient in the supine position (*Fig. 8.3*). There is virtually never an obstruction anterior to the medulla and cord. The lower borders of the tonsils may be demonstrated well below the level of the foramen magnum but it must be remembered that contrast medium may flow in the vallecula between the tonsils, obscuring the level of the tips. Oblique views may be helpful in demonstrating the tonsils jammed against the dura posterolaterally, and anteroposterior views are also needed to establish the position of the tonsillar tips. Even then the malformation may be missed. Very often the degree of protrusion is small and the tonsils may be wrapped around the side of the medulla like curtains, so that the main obstruction is lateral rather than posterior. The appearances may merely give a 'crowded' appearance or seem virtually normal. Air myelography with tomography of the foramen magnum region can also demonstrate the degree of tonsillar descent though a true comparison between air- and water-soluble contrast medium has not been made. *Fig. 8.3c* demonstrates a patient where the results of myodil myelography were reported as normal but where an air study suggested that the tonsils just protruded into the foramen magnum. At operation the presence of a small Chiari malformation was confirmed and the patient's severe and disabling cough headache was immediately cured by decompression.

The diameter of the cord is well assessed by metrizamide myelography but the limits of normality are arbitrary. It should be possible in many cases to distinguish the smooth outline of syringomyelia from the more localized widening caused by an intramedullary tumour. The presence of abnormal vessels may also be noted in the vicinity of a tumour.

The place of air myelography nowadays is uncertain. It has the advantage over metrizamide or myodil that it may show dynamic changes in the size of the cord, for when a flaccid cyst is surrounded by air the fluid in it will fall to its most dependent part, causing the cord to expand or to shrink according to whether the patient is tipped head-up or head-down (*Fig. 8.4*). Ellertson [28] claims that cystic tumours are more tense and change very little, if at all, with posture. It can be accepted that the collapsing cord is characteristic of the presence of syringomyelia. These dynamic



a *b*

Fig. 8.4. Air myelography. Variable diameter of cord in head-down (*a*) and head-up (*b*) positions. Air myelography has only a limited use nowadays.

changes have been widely misunderstood. The collapsing cord sign does not imply that the syrinx empties into the fourth ventricle but is merely a demonstration of how a flaccid fluid-filled cavity behaves when half of it is surrounded by air rather than fluid. It is similar to the behaviour of a balloon half-filled with water. When immersed in water the balloon has a gentle rounded shape, but when suspended in air the upper half collapses as the water gravitates to the lowest part. The dynamic changes do not imply the presence of a communication with the fourth ventricle rather the reverse because the syrinx typically collapses when the patient is in the head-up position whereas if a wide communication with the fourth ventricle were present it would be expected that the cord would fill rather than empty. Air myelography is unpleasant for the patients, carries a small risk of causing neurological deterioration and is not completely reliable as some patients with syringomyelia proved by other means do not show the typical collapsing cord sign [10].

Finally, puncture of the cord may be carried out during myelography or as a separate procedure. Dr Brian Kendall has carried out over 130 examinations of this type with one permanent deficit resulting from the procedure and five transient ones [29]. It is therefore a relatively safe procedure in experienced hands and will establish the diagnosis of syringomyelia by the withdrawal of clear, colourless CSF from the cord. (Fluid from a cystic tumour, and sometimes from a post-traumatic syrinx, is yellow and proteinaceous.)

The injection of metrizamide into the syrinx to perform an 'endomyelogram' will demonstrate the extent of the syrinx and demonstrate the existence, if any, of a communication with the fourth ventricle and whether or not the syrinx descends into the sacral segments if division of the filum terminale is being considered (*see below*). In cystic tumours endomyelography may demonstrate the mural nodule and the exact level where the surgeon will find tumour. Computed endomyelography is a refinement of this technique and is described by Dr Kendall in Chapter 2.

Which of these investigations should be employed, and in what order? Clearly the extent of radiological investigation will depend upon whether the patient is to be considered for operative treatment, but in those undergoing surgery it is advisable to have established the presence of the main anomalies by radiological means.

In some cases all the essential features can be established by a combination of CT scanning and plain X-rays. If not myelography is needed. A swollen cord in the presence of a Chiari malformation can be assumed to be due to syringomyelia and no further investigations needed. If the cord is small or of normal proportions in the presence of a Chiari malformation, it may not be therapeutically important to establish whether a small syrinx exists or not as syringostomy would be unlikely to help and might be hazardous. This point is usually decided on clinical grounds. If, however, it is considered essential to establish whether a syrinx is present, air myelography or puncture of the cord is probably the way to do it.

If there is no Chiari malformation and the cord is swollen in a smooth generalized manner, puncture of the cord or air myelography may be employed to establish whether one is dealing with syringomyelia or a cystic tumour, unless of course CT scanning has given information on this point. Endomyelography may be useful to demonstrate a tumour nodule or to indicate the lower extent of the syrinx if division of the filum terminale is being considered (*see below*). Analysis of the cyst fluid will usually establish whether syringomyelia or cystic tumour is present. It is important to avoid puncturing a vascular tumour and evidence of abnormal vessels should be looked for on the myelogram. If they are absent and the clinical findings suggest a high cord lesion as they do in most cases it should be safe to puncture the lowest part of the swollen cord away from the level of clinical suspicion. If signs suggest a low cord lesion, if the cord is swollen over a limited area only, or if abnormal vessels are seen, it is

more likely that a tumour is present and spinal angiography should probably be done first. Angiography may then obviate the need for cord puncture as a diagnostic manoeuvre by showing tumour circulation or may indicate that puncture is relatively safe in the absence of such vessels.

Acquired

Here there is no reason to expect radiological abnormalities at the foramen magnum. CT scanning is the method of choice to show the syrinx. Otherwise myelography should be employed to show the width of the cord above the level of trauma. Where the cord appears of normal dimension percutaneous puncture and endomyelography may be used to outline the syrinx itself. Both in the case of myelography and endomyelography the needle is passed just above the level of primary trauma [30]. Endomyelography is not a technique available everywhere and the clinical context is so characteristic that it may well be justified to explore the spinal cord above the level of primary trauma on clinical grounds alone.

In the case of post-arachnoiditic syringomyelia myelography is unlikely to be helpful and may well be detrimental in the presence of widespread arachnoiditis. CT scanning would be especially important in such a case but where this fails to show a syrinx it may be necessary to explore the cord on the basis of clinical findings.

OPERATIONS

Congenital (hydromyelic)

Ventriculo-atrial Shunt

Krayenbuhl and Benini [31] accepted the theories of Gardner [3] (*see below*) and proposed that a logical way of treating syringomyelia was to perform a ventriculo-atrial shunt. The logic is not, however, entirely clear for they proposed correction of CSF *circulation* rather than attempting to influence the CSF arterial pulse wave which was thought to be the crucial factor by Gardner. In fact there is little evidence that CSF circulation is usually impaired intracranially in patients with syringomyelia: it is not a condition associated with raised intracranial pressure and the ventricles are mostly of normal size. Nevertheless, the authors describe 7 cases who were treated by shunting and they all seem to have improved to some extent, sometimes dramatically. These results must be treated with caution. In 3 cases the ventricles were enlarged, in 2 others the CSF pressure was raised and in 1 other the ventricles may well have been enlarged as the patient had previously had meningitis. They are not, therefore, typical. In the remaining case there was no evidence of impaired CSF circulation and no objective neurological improvement occurred after shunting though the patient showed 'some recovery of swallowing'.

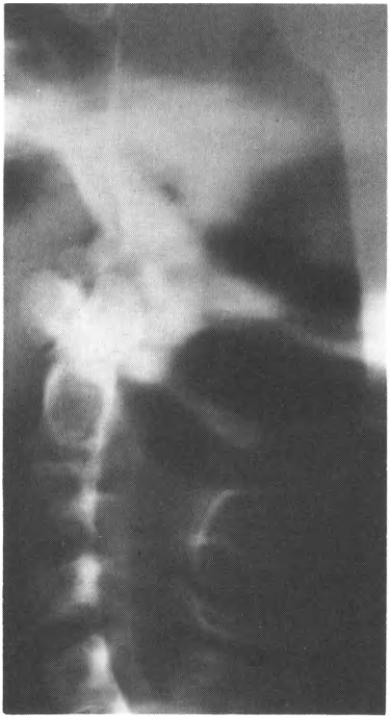


Fig. 8.5. In this case air was injected into a hugely dilated fourth ventricle and enters a syrinx within the cord. The patient could not be treated by shunting the lateral ventricles as there was also aqueduct stenosis. (Courtesy of Professor Valentine Logue.)

It is hard to see why shunting would help in cases where the ventricles are of normal size and where there is likely to be little or no communication between the ventricles and the syrinx. However, shunting should be considered when the ventricles are enlarged. Ventricular enlargement is usually of long standing and unlikely to be the source of neurological symptoms itself, but there may well be a communication in such cases and shunting may then be the most effective and surest way of drainage. Thus, hydrocephalic children with evidence of cord expansion should be treated in this way (*Fig. 8.5*). Shunting may also be needed when hydrocephalus complicates posterior fossa surgery (*see below*).

Gardner's Operation

Gardner's great contribution was to recognize the strong association between syringomyelia and the Chiari malformation. His operative findings

indicated that the foramen of Magendie was often occluded by a membrane and that the hind brain hernia also caused narrowing of the foramen. His theory is based on these observations and on the views of Bering [32] concerning the origin of the CSF arterial pulse wave which was thought to be caused by pulsation of the choroid plexus in the lateral ventricles. Gardner argued that this is normally dispersed via the outlets of the fourth ventricle into the subarachnoid space. When the rhombic roof is narrowed or occluded by a semipermeable membrane this may be competent to equalize the mean pressure within and without the fourth ventricle, thus not causing hydrocephalus, but not to equalize the pulse pressures – 'This may be compared to a window screen readily permeable to a breeze but which bulges in response to a sudden gust' [3]. The result is that the arterial CSF pulse wave is not dispersed via the foramina of the fourth ventricle and exerts an effect like a water-hammer on the lower end of the fourth ventricle which tends to dilate the central canal. Gardner's operation is a logical conclusion to this hypothesis and consists of opening the foramen of Magendie, enlarging the subarachnoid space in order to accommodate the CSF arterial pulse wave and blocking the communication between the fourth ventricle and the central canal by tucking a piece of muscle or a wisp of cottonwool into the lower reaches of the fourth ventricle. Gardner was able to establish that such a communication existed in some of his patients. He reported a series of 74 cases but the central canal was only plugged in the last 33 of these. There was improvement in 52, no change in 11, worsening of preoperative symptoms in 6 and operative death in 5. Of 17 patients followed for more than 15 years, 8 (half the survivors of the operation) had received lasting benefit. Details of this improvement are not given, however, nor is it stated whether those who had the central canal plugged did better than those who did not.

Decompression of the Cerebellar Tonsils

As a result of Gardner's ideas most surgeons have attempted to correct the hind brain anomaly that is so commonly found in patients with hydromyelia and syringomyelia. In the series reported by Logue and Rice Edwards [10] the early cases underwent Gardner's operation. However, it was noted that when the central canal was not blocked with muscle, for instance because arachnoid adhesions were too dense to justify exposing the fourth ventricle, the results were not inferior. Doubts about the validity of Gardner's hypothesis and the suspicion that the beneficial effects of the operation were due to decompression of the tonsils and not by influencing the syrinx led to a change in policy. Recent cases have been treated by tonsillar decompression alone. The procedure is done in the prone position. The lower part of the occipital bone and the laminae of C1 and C2, sometimes C3, are removed as widely as possible (taking care

Fig. 8.6. Simple decompression of Chiari type I malformation. The arrow indicates the level of the foramen magnum. The tips of the tonsils are outlined. The arachnoid was not opened in this case.

about the position of vertebral arteries) and the dura is opened. The arachnoid is left intact as any underlying anomaly is usually visible. If not, a small opening is made in the arachnoid to inspect the area and then reapproximated by clips. A small arachnoid incision will also be needed if a syringostomy is performed (*see below*). The dura is left open (*Fig. 8.6*).

Comparison of patients receiving Gardner's operation and simple tonsillar decompression reveals that the results are very similar: approximately 30 per cent are improved and 40 per cent stabilized. Improvement in long tract signs, pyramidal and posterior column, is the chief mode of recovery after each operation. Only rarely does sensory loss improve and neither muscle wasting nor lost reflexes usually return. Gardner's operation, however, is followed by frequent complications (usually of a temporary nature), such as hydrocephalus or sterile meningitis, whereas simple decompression is not [10].

It is envisaged that the relief of tonsillar compression alleviates the effect of pressure on the medulla and spinal cord but does not influence the syrinx. Whether or not the procedure influences the *progression* of the syrinx is uncertain. It is possible that rectification of the spinocranial pressure dissociation that occurs in the presence of a partial block of the foramen magnum may alter the effect of these pressure changes on the syrinx.

It should be noted that although approximately 30 per cent of patients improved after Gardner's operation or simple decompression the gain was modest and in less than one-half of the improved cases did function improve significantly to affect the patient's mode of life. It should be noted that this is in contrast to the situation in which this operation is performed in cases of Chiari malformation in the absence of syringomyelia when approximately 75 per cent of patients improve [11]. This is striking in the case of symptoms of medullary compression which are usually relieved in patients without syringomyelia by decompression of the Chiari malformation whereas similar symptoms occurring in the presence of syringomyelia (when the mechanism may either be tonsillar compression or extension of the syrinx into the medulla) are much less likely to be alleviated.

Syringostomy

An operation in which clear fluid was aspirated from the spinal cord was first carried out nearly 90 years ago [33]. Thereafter syringostomy became the usual operation until Gardner's work shifted attention to the posterior fossa. It may be employed as an additional measure during tonsillar compression if there is evidence of a large cavity in the exposed upper two or three segments of the cervical cord. Otherwise it is usually performed as a separate procedure via a high thoracic laminectomy below the cervical enlargement so as to avoid inflicting any damage to the arms even though the syrinx is usually largest at the cervical level. The incision is made at any point where the syrinx is visible on the surface. Otherwise an entry may be made in the midline or at one posterior root entry zone where typically the syrinx comes nearest to the surface. If the incision is made away from the midline the presence or absence of impaired joint position sense in the legs may determine the side on which the cut is made, it being preferable to operate on the side already affected rather than risk involving a limb with normal proprioception.

In the past the operation has consisted of either making a hole into the syrinx or inserting a variety of setons to ensure patency. Nowadays it is preferable to insert a length of narrow Silastic tubing which is then anchored to the arachnoid or to the dura. The inner wall of the syrinx is seen to be smooth but typically forms a series of sausage-like bulges with sharp constrictions between. The results of this operation have been reviewed by Love and Olafson [34]. They grade the results as 30 per cent 'excellent' (showing subjective or objective improvement); 40 per cent 'good' (status unchanged); 30 per cent 'poor' (progressive deterioration). Although it is not possible to make an accurate comparison with posterior fossa surgery (especially as the cases may not all be of the same type of syringomyelia), it would seem that the results are not dissimilar.

Percutaneous Puncture

Temporary improvement can certainly occur after tapping a tumour cyst but it is only rarely that this significantly helps patients with syringomyelia (*see Case Report below*).

Syringo-peritoneal Shunt

If the syrinx is a non-communicating chamber and if progression occurs as a result of the effects of pressure changes on the fluid within the syrinx as envisaged by Williams [16, 17] it might be logical to attempt shunting the fluid into another cavity in order to obtain collapse of the syrinx. The following case of very advanced syringomyelia was treated by my colleague Mr R. D. Illingworth by a percutaneous technique under local anaesthetic.

Case Report (M. A. B., male, aged 27)

The patient had a 7-year history of progressive limb weakness. There was gross wasting and weakness of the arms and he was unable to use his hands at all. The upper limb tendon reflexes were absent. He was breathless owing to weakness of the intercostal muscles and was unable to lie down. There was gross spastic weakness of the legs and he was unable to walk. Pain sensation was lost from C2 downwards bilaterally and joint position sense was absent in the hands.

X-rays showed a wide cervical canal, severe kyphoscoliosis, an expanded spinal cord and a Chiari malformation. Percutaneous aspiration of clear fluid from the syrinx (Dr Brian Kendall) resulted in definite but transient improvement. His respiratory function was so poor that it was thought unlikely that he would withstand a major operation. Under local anaesthetic a paediatric Ryle's tube was introduced into the syrinx percutaneously through a large aspirating needle and then taken subcutaneously and introduced into the peritoneal cavity. Following this procedure there was sustained improvement in his breathing and he was able to lie flat. There was also some improvement in the power of his limbs although not to a degree producing any real functional benefit. The patient lived abroad and it is not known whether this improvement has been maintained.

Division of Filum Terminale

In 1977 Gardner and co-workers [35] reported a series of cases of syringomyelia treated by division of the filum terminale at its junction with the conus medullaris by what was called 'terminal ventriculostomy'. The terminal ventricle is a dilatation of the central canal in the tip of the conus extending into the upper portion of the filum terminale [36]. Gardner and his colleagues found evidence of such a cavity in 3 of 11 adult patients with no known neurological disease examined at autopsy, a surprising finding in view of the fact that the central canal is normally closed in adults, and in 10 of 11 operated patients with syringomyelia in whom the filum was examined histologically. It was therefore claimed that making an opening into the terminal ventricle is an effective way of draining a syrinx.

In 7 of the cases described the operation was carried out in addition to the posterior fossa approach previously described by Gardner [3] and was used as the primary operation in the remaining 5, though no reasons were given for favouring it. The operation has the advantage of simplicity and safety but the question must remain as to how frequently the syrinx extends as low as the filum terminale. My own experience of 2 operative cases is that in one there was no cavity and in the other a microscopical channel which did not appear to communicate with the main syrinx. Examination of pathological material in patients dying with the diagnosis of syringomyelia of the hydromyelic type shows that the syrinx usually does not extend as low as the sacral segments let alone into the filum terminale [7]. Nevertheless the syrinx may occasionally be drained by this route.

Case Report (S. F., female, aged 37)

This patient, who was under the care of Professor Valentine Logue, developed a scoliosis as a child with progressive weakness of the limbs at the age of 18. When she was 21 investigations revealed a severe degree of basilar invagination and an expanded cervical cord. A foramen magnum decompression was done at which the tonsils were found to be matted together but above the foramen. Clear CSF was aspirated from the cord and an upper cervical syringostomy made. The patient then remained stable for 8 years but deteriorated relentlessly over the subsequent 2 years when a second syringostomy, this time at the mid-dorsal level, was performed, with improvement in her gait. However, within 2 years her walking had again become worse and this deterioration continued slowly for the next 5 years. At this stage in 1977 the conus was exposed and a thickened filum terminale found to contain a cavity from which clear, colourless, CSF drained. An adequate T-shaped incision was made which gaped open. There was temporary improvement following this procedure and she was able to lift her right leg high in the air whereas previously she had not been able to raise it at all. However, within 6 months this improvement had not been maintained.

Operation for Basilar Invagination

Detailed description of this is beyond the scope of this review but it must be remembered that syringomyelia may be associated not only with the Chiari malformation but with other malformations, in my experience always congenital, or occasionally with no abnormality [10]. The only bony anomaly which is likely to cause neurological symptoms is basilar invagination which usually compresses the brain stem anteriorally. If this is demonstrated radiologically to be the case and if it is thought that the clinical signs are more compatible with this than with the effects of cord cavitation, an anterior transoral removal of the odontoid process is likely to be the best procedure. In some cases posterior fusion is then needed to maintain stability [37].

Choice of Procedure

As mentioned above, a true comparison between posterior fossa surgery and syringostomy cannot be made. In the past, results have usually been

quoted in vague terms such as 'improved' or 'unchanged'. For a condition which often has a constellation of symptoms and signs the description 'improved' is imprecise when the clinical features may include pain, difficulty in swallowing, oscillopsia, weakness or sensory loss. For instance, walking may be improved after surgery but the pain made worse. Furthermore the follow-up in many series is short. It is notorious that patients often describe improvement immediately following operation which is not maintained after a few months. Such patients cannot be described as 'improved'.

Patients who are already severely disabled seldom show much improvement and one must be cautious about treating those whose disease is already static. Thus, the best patient would be young and not severely disabled with cough headache in whom long tract signs, quite likely to be related to tonsillar compression, predominate.

In most cases syringomyelia will be associated with a Chiari malformation and I believe that decompression of the cerebellar tonsils is the best procedure if the signs are compatible with that. Simple decompression leaving the arachnoid intact is a safe procedure and unlikely to make the patient worse. This is an important point in treating a condition where the results of operation are modest. It is essential to treat patients with cough headache as this symptom is very likely to be cured. If a syrinx is visible in the exposed upper two or three cervical segments and if it is judged that this can be entered reasonably safely then syringostomy with insertion of a Silastic tube should be performed as part of the initial procedure.

In the event of no improvement or relapse following this operation a dorsal syringostomy should be considered as present evidence suggests that this is more effective than syringostomy by division of the filum terminale. That procedure should probably only be performed where an endomyelogram has demonstrated that the syrinx extends to the bottom of the spinal cord and where other methods have failed.

Associated hydrocephalus and craniovertebral bony anomalies should be treated on their own merit and it cannot be overemphasized that the radiological features must be correlated carefully with the clinical findings to analyse which of these is most likely to be helped by which operative procedure.

Acquired

Posterior fossa surgery has no place in these cases. The syrinx does not communicate with the central canal and only very rarely with the subarachnoid space. In those with complete post-traumatic lesions the choice of procedure lies between syringostomy just above the level of trauma (bringing the distal end of the tube into the subarachnoid space upwards well away from the site of primary trauma) and complete cord transection. In the latter case the upper end of the cord may retract when it is freed

from arachnoiditis at the site of the primary trauma. A catheter may be placed into the stump to ensure patency. When the lesion is incomplete only syringostomy, of course, can be employed. Barnett and Jousse [26] report good results in these procedures. Six of 7 patients suffered from pain which was relieved by operation. Power improved in 6. Shannon et al. [30] also report good relief of pain which occurred in 10 of their 13 patients. They noted improvement in power in 4 but no improvement in sensation and they concluded that no definite statement could be made about the effect of operation on the natural history of this disease.

REFERENCES

1. Barnett H. J. M. and Rewcastle N. B. (1973) Syringomyelia and tumours of the nervous system In: Barnett H. J. M. et al. (ed.) *Syringomyelia.* Philadelphia, Saunders, p. 361.
2. Williams, B. (1969) Hypothesis: the distending force in the production of 'communicating syringomyelia'. *Lancet* **2**, 189-93.
3. Gardner W. J. (1965) Hydrodynamic mechanism of syringomyelia: its relationship to myelocoele. *J. Neurol. Neurosurg. Psychiatry* **28**, 247-59.
4. du Boulay G., Shah S. H., Currie J. C. et al. (1974) The mechanism of hydromyelia in Chiari type I malformation. *Br. J. Radiol.* **47**, 579-87.
5. Conway L. W. (1967) Hydrodynamic studies in syringomyelia. *J. Neurosurg.* **27**, 501-14.
6. Rice Edwards J. M. Syringomyelia and the central canal. (To be published.)
7. Rice Edwards J. M. Extension of the central canal into the filum terminale. (To be published.)
8. Keiller V. H. (1922) A contribution to the anatomy of spina bifida. *Brain* **45**, 31-103.
9. Hall P. V., Kalsbeck J. E., Wellman H. N. et al. (1976) Radioisotope evaluation of experimental hydrosyringomyelia. *J. Neurosurg.* **45**, 181-7.
10. Logue V. and Rice Edwards M. (1981) Syringomyelia and its surgical treatment – an analysis of 75 patients. *J. Neurol. Neurosurg. Psychiatry* **44**, 273-84.
11. Logue V. and Rice Edwards M. (1981) (To be published.)
12. Ball M. J. and Dayan A. D. (1972) Pathogenesis of syringomyelia. *Lancet* **2**, 799-801.
13. Aboulker J. (1979) La syringomyélie et les liquides intra-rachidiens. *Neurochirurgie* **25**, Suppl. 1.
14. Forbes W. and Isherwood I. (1978) Computed timography in syringomyelia and associated Arnold Chiari type I malformation. *Neuroradiology* **151**, 73-8.
15. Barnett H. J. M. (1973) Syringomyelia as a late sequel to traumatic paraplegia and quadriplegia – clinical features. In: Barnett H. J. M. et al. (ed.) *Syringomyelia.* Philadelphia, Saunders, pp. 148-50.
16. Williams B. (1970) The distending force in the production of communicating syringomyelia. *Lancet* **2**, 41-2.
17. Williams B. (1976) Cerebro-spinal fluid pressure changes in response to coughing. *Brain* **99**, 331-46.
18. Greenfield J. G. (1963) *Greenfield's Neuropathology,* 2nd ed. London, Arnold, p. 332.
19. Kosary I. Z., Braham J., Shaked I. et al. (1969) Cervical syringomyelia associated with occipital meningioma. *Neurology* **19**, 1127-30.

20. Barnett H. J. M. (1973) Syringomyelia associated with spinal arachnoiditis; and The pathogenesis of syringomyelic cavitation associated with arachnoiditis localized to the spinal cord. In: Barnett H. J. M. et al. (ed.) *Syringomyelia.* Philadelphia, Saunders.
21. Giminez-Roldan S., Esteban A. and Benito C. (1974) Communicating syringomyelia followed cured tuberculous meningitis. *J. Neurol. Sci.* **23**, 185-97.
22. Kasantikul V., Netsky M. G. and James A. E. (1979) Relation of age and cerebral ventricle size to central canal in man. Morphological analysis. *J. Neurosurg.* **51**, 85-93.
23. Appleby A., Bradley W. G., Foster J. B. et al. (1969) Syringomyelia due to chronic arachnoiditis at the foramen magnum. *J. Neurol. Sci.* **8**, 451-64.
24. Barnett H. J. M., Jousse A. T. and Ball M. J. (1973) Pathology and pathogenesis of progressive cystic myelopathy as a late sequel to spinal cord injury. In: Barnett H. J. M. et al. (ed.) *Syringomyelia.* Philadelphia, Saunders.
25. Kao C. C., Chang L. W. and Bloodworth J. R. (1977) The mechanism of spinal cord cavitation following spinal cord transection. *J. Neurosurg.* **46**, 745-55.
26. Barnett H. J. M. and Jousse A. T. (1973) Syringomyelia as a late sequel to traumatic paraplegia and quadriplegia: clinical features; and Nature, prognosis and management of post-traumatic syringomyelia. In: Barnett H. J. M. et al. (ed.) *Syringomyelia.* Philadelphia, Saunders, pp. 129-53 and 154-64.
27. Bonafé A., Ethier R., Melancon D. et al. (1980) High resolution computed tomography in cervical syringomyelia. *J. Comput. Assist. Tomogr.* **4**, 42-7.
28. Ellertson A. B. (1969) Syringomyelia and other cystic spinal cord lesions. *Acta Neurol. Scand.* **45**, 403-17.
29. Kendall B. E. and Symon L. (1973) Cyst puncture and endomyelography in cystic tumours of the spinal cord. *Br. J. Radiol.* **46**, 198-204.
30. Shannon N., Symon L., Logue V. et al. (1981) Clinical features, investigation and treatment of post-traumatic syringomyelia. *J. Neurol. Neurosurg. Psychiatry* **44**, 35-42.
31. Krayenbuhl H. and Benini A. (1971) A new surgical approach in the treatment of hydromyelia and syringomyelia. The embryological basis and the first results. *J. R. Coll. Surg. Edinb.* **16**, 147-61.
32. Bering E. A. (1955) Choroid plexus and arterial pulsation of cerebrospinal fluid: demonstration of the choroid plexuses as a cerebrospinal fluid pump. *Arch. Neurol. Psychiatry* **73**, 163-72.
33. Abbe R. and Coley W. B. (1892) Syringomyelia operation – exploration of cord, withdrawal of fluid, exhibition of patient. *J. Nerv. Ment. Dis.* **19**, 512-20.
34. Love J. and Olafson R. (1966) Syringomyelia. A look at surgical therapy. *J. Neurosurg.* **24**, 714-18.
35. Gardner W. J., Bell H. S., Poolos P. N. et al. (1977) Terminal ventriculostomy for syringomyelia. *J. Neurosurg.* **46**, 609-17.
36. Kernohan J. W. (1924) The ventriculus terminalis: its growth and development. *J. Comp. Neurol.* **38**, 107-25.
37. Menezes A. H., Vanglider J. C., Graf C. J. et al. (1980) Craniocervical abnormalities: a comprehensive surgical approach. *J. Neurosurg.* **53**, 444-55.

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