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Preface

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

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

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

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

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

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

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

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

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

The Editors

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A. Advances

Post-Traumatic Brain Swelling

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With 13 Figures

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Introduction

Brain swelling is a general term to denote an increase in the volume of the brain. It may be defined as any increase in brain volume produced by an increase in volume of any or all of the constituents of the brain. Brain swelling may be due to an increase in the cerebral blood volume (CBV) (engorgement or hyperemia), to an increase in the amount of extra or intracellular water (oedema) or to an extra mass.

Historically, increased cerebral volume following head injury was divided into oedema and swelling. These terms were used interchangeably in clinical practice until the advent of computerized tomography (CT), when they have been increasingly used to refer to more specific conditions. Brain oedema, which is a specific state consisting of fluid retention and

decreased blood volume in the involved cerebral substance, may be seen as a particular form of swelling. Traumatic oedema may be a combination of cytotoxic oedema, which involves primarily cellular elements, and vasogenic oedema, which affects the extracellular spaces resulting primarily from increased capillary permeability to plasma proteins[73]. Interstitial oedema may also occur when there is obstruction to CSF flow. Oedematous brain tissue appears as normal density or a radiolucent area on the CT scan which does not enhance after intravenous contrast injection[25, 45, 64, 81–83, 105, 115, 156]. By contrast, hyperemic brain shows slightly elevated CT numbers and postcontrast enhancement, mostly of the cerebral cortex[21, 75, 151, 156, 158]. The distinction of oedema from hyperemia is of more than academic interest as therapeutic management may differ in accordance with the underlying pathophysiology. However, differentiation between normal and oedematous brain, or between normal and hyperemic brain may be difficult or impossible. Increased protein and lowered lipid content in oedematous brain may offset the effect of increased tissue water rendering recognition of oedema difficult[81, 83, 115]. On the other hand, a low density area in the brain may not reflect brain oedema but ischaemia[81, 82, 104].

Brain swelling, local or universal, is the most frequently noted secondary change following head trauma[86]. Clinically there are three independent syndromes of post-traumatic brain swelling (primarily defined in terms of volume), i.e. diffuse, hemispheric and focal[1, 20, 25, 36, 37, 47, 64, 69, 75, 83, 87, 88, 90, 128, 151, 156, 158]. The latter is the syndrome of "contusion plus oedema", which consists of a radiolucent area that develops about an intracerebral haematoma or a contusive focus[1, 69, 82, 104, 105]. This ring of decreased density spreading through the white matter within hours or days after injury, probably represents vasogenic oedema similar to that accompanying brain tumours or experimental cold lesions and will not be discussed here.

The other two brain swelling syndromes develop acutely after trauma involving one cerebral hemisphere (acute cerebral hemispheric swelling = ACHS), or both cerebral hemispheres (acute generalized brain swelling = AGBS). The first is typically seen in patients operated for acute extracerebral haematoma in a deep coma in whom the underlying cerebral hemisphere expands to fill the space so created leading to raised ICP[1, 11, 25, 47, 68, 69, 81, 87, 88, 90, 112, 124, 128, 135]. The syndrome of AGBS mainly occurs in children and adolescents, and consists of diffuse bulk enlargement of both cerebral hemispheres without midline shift; ICP may be within normal limits but it is somewhat elevated in two third of the cases[14, 20, 21, 25, 37, 61, 71, 87, 157, 158]. This phenomenon, which has been considered to be the commonest CT finding in head injured children[20, 158], has been given different names such as "diffuse cerebral swelling", "diffuse brain swelling", "generalized oedema" or "acute generalized cerebral swelling". This paper considers the possible pathophysiological mechanisms involved in the pro-

duction of these acute brain swelling syndromes as well as their clinical incidence, radiological diagnosis, prognosis and management.

Acute Cerebral Hemispheric Swelling

Definition, Incidence, Clinical Significance, and Radiological Presentation

It has been recognized for a long time that following the removal of an acute extracerebral haematoma the ipsilateral cerebral hemisphere may remain slack or show varying degrees of focal swelling which persists after the clot is evacuated. This regional swelling, an almost constant accompaniment of acute subdural haematoma, is the pathogenic mechanism for the persistent postoperative shift which vexed neurosurgeons for many years[19, 31, 68, 69, 107, 123]. This phenomenon is most commonly seen in patients undergoing operation for a large extraaxial haematoma, but may be also observed with very thin, "smear" subdural haematoma causing a midline displacement much greater than the thickness of the clot[1, 25, 68, 90, 128]. At surgery the brain herniates through the craniotomy window and the postoperative control CT scan shows cerebral hemispheric enlargement with persistent or even increased midline shift. ACHS is almost always associated with severe intracranial hypertension which may lead to death within hours or few days after trauma[90, 128].

The incidence of ACHS in series of patients operated on for an acute extraaxial haematoma before the advent of the CT scan may be estimated only approximately. Jamieson and Yeland[68] classified 40.5% of 553 traumatic subdural haematomas in their series as "complicated haematoma"; this type of lesion was most often observed after severe acceleration-deceleration injuries and carried the highest mortality rate (2.5 times greater than simple subdural haematoma and 1.3 times more than haematoma plus contusion). According to these authors, "the swelling of the damaged brain added to the sometimes relatively minor accumulation of blood in the subdural space may explain the rapid course of complicated subdural haematoma". Britt and Hamilton[18] found "massive cerebral oedema or extensive contusion" at necropsy in the majority of their cases of acute subdural haematoma suggesting that extensive direct trauma to the underlying brain existed in addition to the pressure effects of the clot. Richards and Hoff[123] described "gross disruption of the brain" underlying the haematoma in 61% of the fatal cases in their series of 100 acute subdural haematomas. McKissock *et al.*[99] found "hemisphere pulping and massive oedema" in 11 fatal cases in their series of 125 epidural haematomas. Heiskanen[57] observed "widespread diffuse cerebral contusion of the ipsilateral cerebral hemisphere" in 7 out of 10 patients dying after being operated on for epidural haematoma. However, neither in these reports, nor in other studies on extracerebral haematoma performed during the CT

era was a clear distinction made between multifocal contusions haematoma and diffuse swelling as the cause of cerebral hemisphere enlargement[150].

With the advent of the CT ACHS has been defined as cerebral hemispheric enlargement causing marked midline shift (septal and pineal displacement) in the absence of associated focal lesions in the initial and follow-up CT scans[82,87,88,90,128,135]. Shigemory *et al.*[135] described 15 patients with acute subdural haematoma causing large midline displacement, collapse of the ipsilateral ventricle and obliteration of the cisterns at the tentorium in whom the postoperative CT scan showed persistent cerebral hemisphere enlargement with low density areas suggestive of oedema accompanied by elevated ICP; however, these authors did not mention the incidence of this CT pattern in their global head injury series. Lanksch *et al.*[81] found cerebral oedema, seen as a zone of low density with attenuation values lower than that of normal white matter in 9 (8%) of 118 patients with epidural haematoma and in 26 (15%) of 168 patients with acute subdural haematoma; oedema associated with epidural haematoma was limited to the white matter, but oedema accompanying subdural haematoma affected both the grey and the white matter and often extended

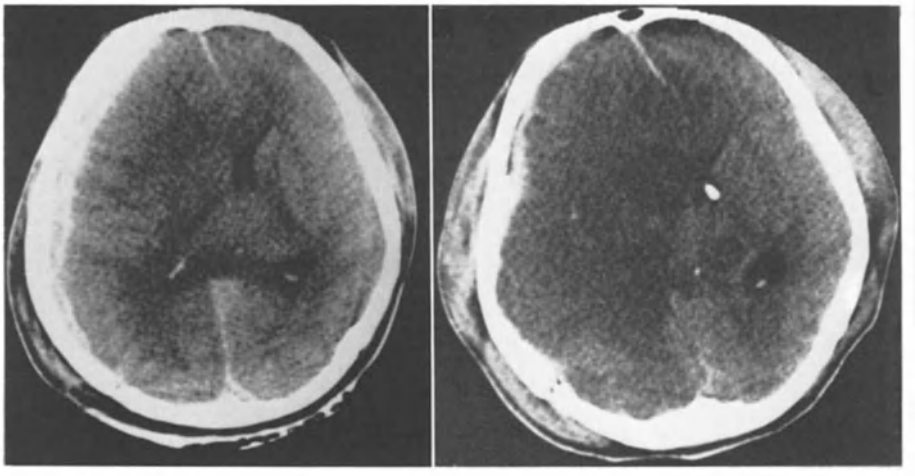

Fig. 1. This 25 year-old man was admitted 20 minutes after suffering a traffic accident. He showed bilateral fixed delated pupils and the GCS score was 3. There was moderate arterial hypotension and hypoxia. The admission CT scan (left) showed an acute subdural haematoma over the whole hemispheric convexity causing marked midline displacement. Despite of rapid haemodynamic stabilization and haematoma removal, the patient's condition did not improve. The postoperative control CT scan (right) showed persistent midline shift with diffuse hypodensity of the ipsilateral cerebral hemisphere; haematoma reaccumulation was visible only in one CT slice. Raised ICP could not be controlled and the patient died within two days after injury

through the entire hemisphere; when swelling followed the evacuation of an acute subdural haematoma, the postoperative CT scan usually showed generalized hemispheric enlargement with decreased density. These authors attributed the normal CT density values seen in some patients to vasodilatation with increased CBV and cerebral blood flow (CBF), or to oedema containing protein. Clifton *et al.*[26] described "hemispheric oedema isolated or associated with a previous extracerebral haematoma"as a cause of further neurological deterioration in their series of severely head-injuried patients. Bruce *et al.*[21] observed ipsilateral cerebral hemispheric swelling in 2 out of 5 children operated on for large acute epidural haematoma who developed high postoperative ICP. Occasionally, ACHS has been found in patients without extracerebral haematoma who made a rapid and complete recovery[75, 151].

Using the CT scan to exclude associated intracranial pathology we observed the CT pattern of ACHS in 132 (16%) of 819 consecutive severe head injured patients. ACHS was associated with a more or less voluminous ipsilateral subdural haematoma in 83.5% of the cases (Figs. 1 and 2) and with a large epidural haematoma in 10.5% of the cases (Fig. 3); the remaining 6% of the patients showed ACHS as the unique finding. The mechanism of injury is shown in Fig. 4. 73% of the patients were unconscious from the moment of the impact, 86% scored 3 or 4 points on the GCS (Fig. 5), and 74% showed uni- or bilateral mydriasis at admission.

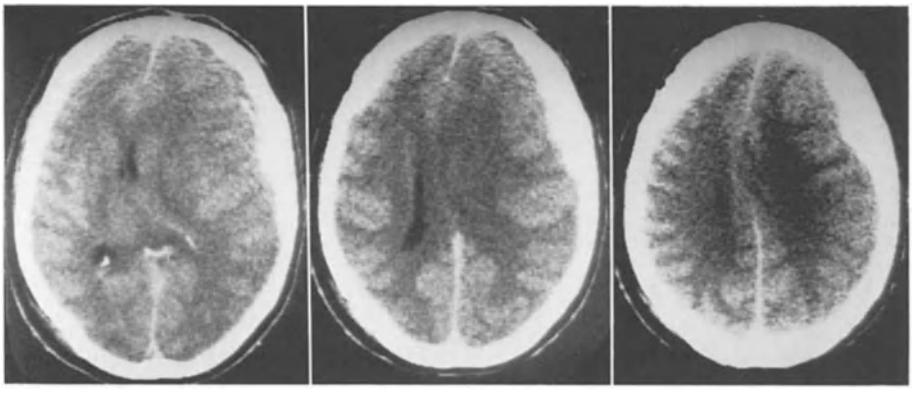

Fig. 2. This 22 year-old man injuried in a traffic accident lost consciousness at the moment of the impact. Associated extracranial injuries caused arterial hypotension and hypoxia. He arrived in our unit 3 hours after injury showing bilateral fixed delated pupils and a motor score of 2. The admission CT scan showed a laminar subdural haematoma which was immediately evacuated; the preoperative midline shift, which was disproportionate for the size of the clot, did not change after the operation. ICP was above 35 mmHg leading to patient's death on the third day after trauma

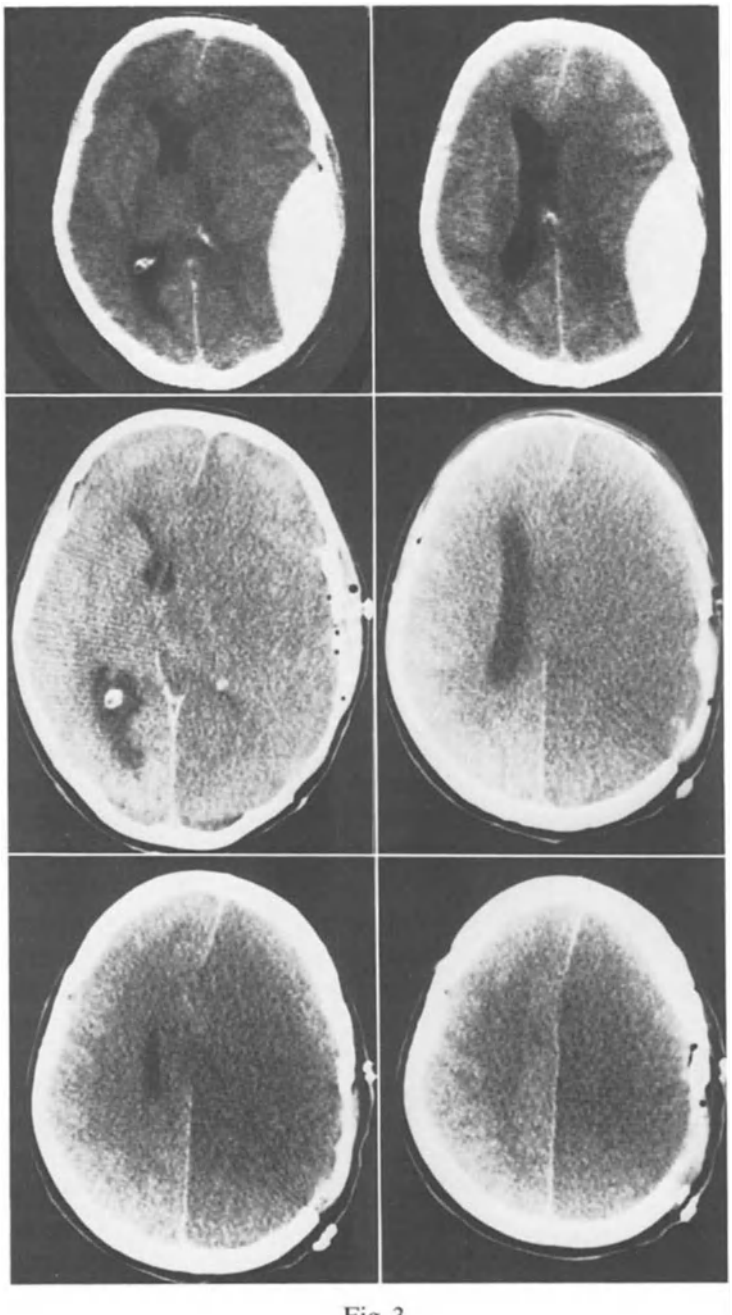

Fig. 3

Patients with ACHS associated with a subdural haematoma were younger on average (72% under 40 years of age) (Fig. 6) were more frequently involved in traffic accidents and had a higher incidence of peritraumatic

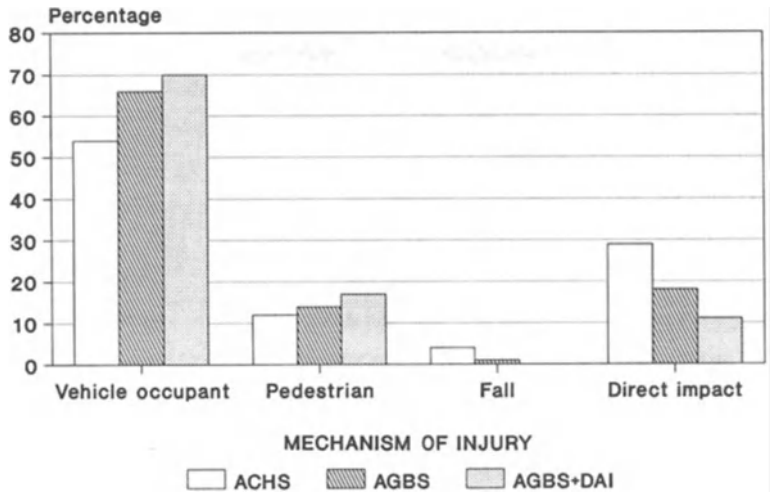

Fig. 4. Mechanism of trauma in severe head injury patients showing acute cerebral hemispheric swelling (*ACHS*) (132 cases), acute generalized brain swelling (*AGBS*) (80 cases) and AGBS plus signs of diffuse axonal injury (*DAI*) (100 cases)

hypotension-hypoxia than other patients with acute subdural haematoma (cases of pure haematoma or haematoma associated with brain contusion).

The involved cerebral hemisphere appeared either isodense (29% of the cases), or hypodense (69% cases), in comparison to the contralateral hemisphere. Preoperative midline shift was over 10 mm in 78% of the cases and patients with laminar subdural collections showed a striking disproportion between clot thickness and the degree of midline displacement (Fig. 2).

At surgery, rapid brain reexpansion with variable degrees of herniation through the craniotomy opening was usually observed. Following haematoma evacuation midline displacement diminished in only 19% of the cases and initial postoperative ICP was above normal limits in 80% of the patients; half of these had an ICP over 40 mmHg (Fig. 7). 38% of the

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Fig. 3. This 45 year-old woman injured in a traffic accident was seen in a local hospital. The GCS was 15 and skull X-ray was normal. Twenty-four hours later she developed severe headache and rapid neurological deterioration. A CT scan showed an epidural haematoma causing marked midline shift (upper part). She arrived in our unit three hours after deterioration showing bilateral fixed dilated pupils and decerebration. Following haematoma removal the clinical status did not change. The postoperative control CT scan (middle and lower) showed cerebral hemispheric swelling with persistent midline shift. ICP was above 40 mmHg and could not be controlled. The patient died two days after the operation

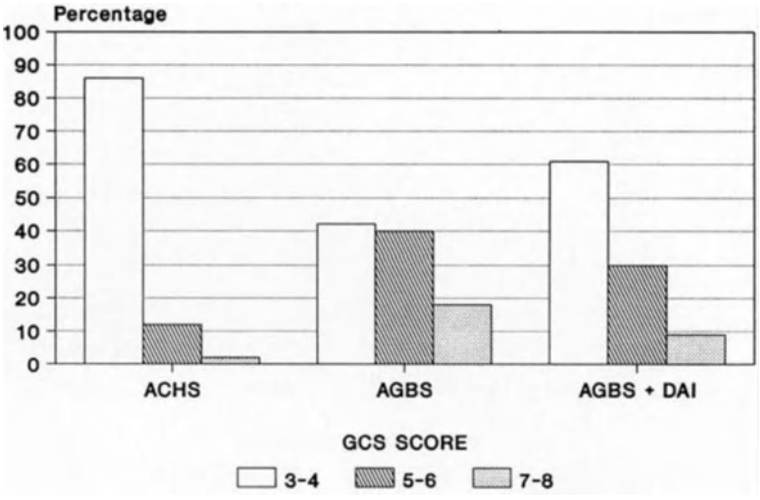

Fig. 5. Glasgow coma scale (*GCS*) score in severe head injury patients showing acute cerebral hemispheric swelling (*ACHS*) (132 cases), acute generalized brain swelling (*AGBS*) (80 cases) and AGBS plus signs of diffuse axonal injury (*DAI*) (100 cases)

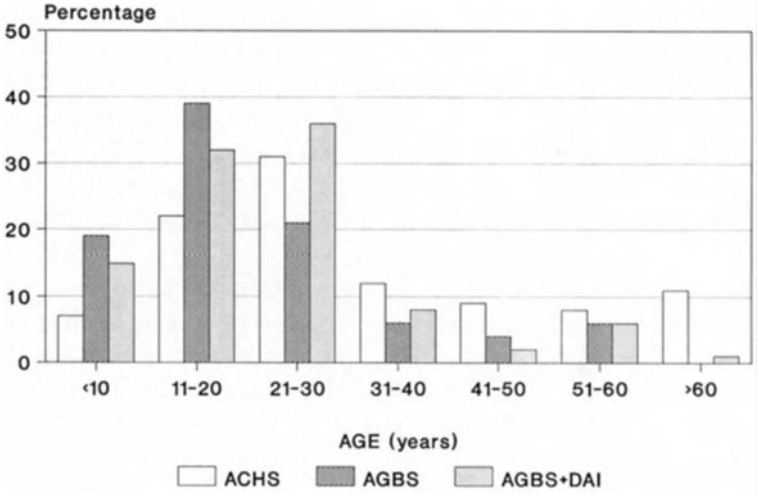

Fig. 6. Age distribution in severe head injury patients showing acute cerebral hemisphere swelling (*ACHS*) (132 cases), acute generalized brain swelling (*AGBS*) (80 cases) and AGBS plus CT evidence of diffuse axonal injury (*DAI*) (100 cases)

patients died within 1 to 3 days after admission because of fulminant intracranial hypertension. In one third of the patients, ICP was normal immediately after surgery but then rose until it became uncontrollable. ICP could be controlled in the remaining patients who showed persistent hemi-

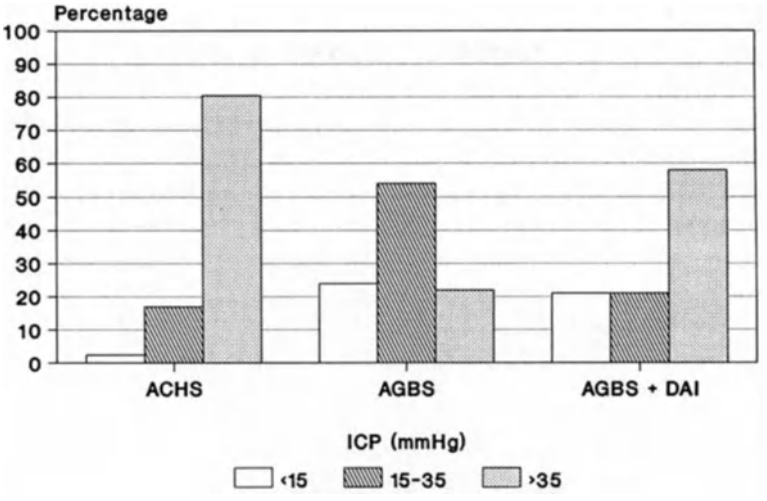

Fig. 7. Intracranial pressure (*ICP*) levels in severe head injury patients showing acute cerebral hemisphere swelling (*ACHS*) (132 cases), acute generalized brain swelling (*AGBS*) (80 cases) and AGBS plus CT evidence of diffuse axonal injury (*DAI*) (100 cases)

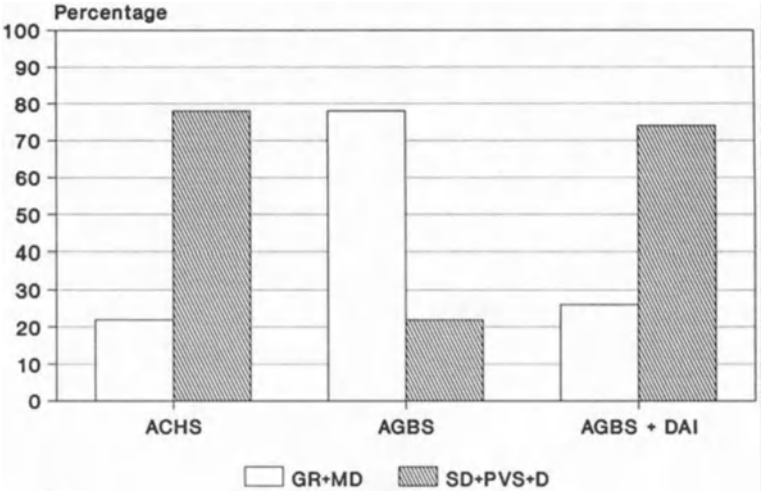

Fig. 8. Final outcome in severe head injury patients showing acute cerebral hemisphere swelling (*ACHS*) (132 cases), acute generalized brain swelling (*AGBS*) (80 cases) and AGBS plus CT evidence of diffuse axonal injury (*DAI*) (100 cases). *GR* Good recovery; *MD* moderate disability; *SD* severe disability; *PVS* persistent vegetative status; *D* death

spheric enlargement for several days after admission. Similar ICP courses were described by Shigemori *et al.*[135] in three subgroups of patients with acute subdural haematoma treated with decompressive craniectomy. Mor-

tality rate with ACHS reached 78% in our series (Fig. 8), while it was 61% in the total group of patients with acute subdural haematoma and 37.4% in the total severe head injury series.

In summary, the syndrome of malignant ACHS, a most dreaded complication in neurotraumatology, is more likely to develop in patients with acute subdural haematoma showing a low preoperative GCS score, pupillary changes, large midline displacement on the admission CT scan and bulging of the brain during surgery, but independent of the interval between trauma and operation or the thickness of the clot[87, 90, 128]. By contrast, ACHS associated with epidural haematoma was seen only in patients with very large clots removed late after the onset of coma[88, 124].

Pathophysiology

It has been debated whether cerebral hemisphere enlargement is the result of oedema or hyperemia[23, 25, 40, 41, 46, 47, 59, 63, 65, 74, 80, 82, 86, 90, 104, 116, 127, 143, 156]. Taking into account its rapid development after injury, a sudden increase in CBV resulting from cerebrovascular dilatation seems more likely than acute oedema formation. Cerebral hemispheric swelling occurring as early as 20 to 30 minutes after trauma has been documented in patients showing higher CT numbers in the involved hemisphere than in the contralateral one[75, 151]. Both the increased density and the relatively rapid resolution of swelling in these cases, support the interpretation that hemispheric enlargement is due to hyperemia[20, 79, 80, 113, 158]. In a series of experiments on acute subdural haematoma, measurements of brain tissue water, blood-brain barrier studies with labelled sucrose and electron microscopy observations failed to find evidence of cerebral oedema in the swollen brain, suggesting that acute hemispheric swelling is not due to cerebral oedema but to increased CBV[50]. However, laboratory studies and direct measurements of brain water content in head-injured patients indicate that post-traumatic brain oedema may occur much more rapidly than is usually thought[49, 63, 74, 144, 154]. Densitometric[25, 64, 81, 82] and dynamic[156] CT studies also indicate that acute oedema formation is a common cause of brain swelling in cases of fatal head injury and that oedema associated with acute subdural haematoma is much more marked in the ipsilateral cerebral hemisphere than in the contralateral one. The prolonged duration of the mass effect and the null effect of hyperventilation on elevated ICP observed by us and other authors in the majority of patients with ACHS, support oedema formation as the underlying mechanism[90, 128, 135, 156].

Clinical and laboratory studies have shown that the local pressure exerted by an intracranial expanding mass on the underlying cerebral hemisphere, added to the decrease in cerebral perfusion pressure caused by ICP elevation may result in critical reductions of CBF leading to hemispheric

ischaemic oedema within a few hours of injury[1, 23, 29, 39, 65–67, 114, 127, 130, 141]. In one study[144] hemispheric oedema with passage of Evans blue was observed as early as 30 minutes after a mechanical insult. Other experiments showed that the combined effects of hypoxia and impact insults produced a substantial reduction in CBF immediately under the site of impact as well as significant reductions in other regions of the hemisphere with widespread increase in brain water throughout the ipsilateral cerebral cortex[62, 116]. In one experimental study using the balloon compression model, increased water content was observed in both cerebral hemispheres, though it was much greater ipsilateral to the site of compression[127]. Neuropathological studies in fatal head injury have also shown that ischaemic neuronal damage is more frequent in the cerebral hemisphere underlying an acute extracerebral haematoma than in the contralateral hemisphere[93].

The mechanism of cerebral hemispheric swelling following the removal of a large extraaxial haematoma is likely to be the same as that following epidural balloon deflation in laboratory animals, which is basically an ischaemic lesion with restoration of blood flow after decompression[23, 25, 29, 39, 40, 58, 65–67, 92, 93, 130, 141, 153, 159]. Both haematoma formation and balloon inflation result in elevated hydrostatic pressure and structural stresses leading to compression of microcirculation and secondary ischaemia. It has been shown that the time course of the uptake of iodinated dye in the compressed cerebral hemisphere closely parallels that seen in swelling accompanying ischaemic infarction in humans[25, 134]. Morphological findings are also consistent with the type of damage seen in ischaemic models in which the leakage of Evans blue occurs in the late phase of reperfusion when vasogenic oedema develops[6].

A series of experiments with the epidural balloon model have shown that the postdecompression hemispheric swelling and rebound of ICP is an "all or none" phenomenon that occurs at critical time-cerebral perfusion pressure thresholds related to extreme degrees of ischaemia ocurring in the supratentorial compartment during mass compression[40, 65–67]. For the response to occur a critical reduction in the perfusion pressure should be reached, but the intensity of the response is graded in relation to the duration of compression[65–67], as occurs with the time of arterial occlusion in ischaemic models[4, 13, 16, 59, 139, 143]. ICP rebound follows a uniform course increasing exponentially towards a plateau, but the final plateau seems to be a function of the duration of compression and independent of the reduction in cerebral perfusion pressure. During the period of ischaemia in the compression phase, vasoparalysis develops[66]. When perfusion pressure is restored by decompression there is an initial state of hyperperfusion with CBF values 2–3 times the control, which is replaced by hypoperfusion resulting from rebound in ICP and increased cerebrovascular resistance caused by capillary compression by developing brain oedema[67]. Increasing

oedema in previously ischaemic areas of the brain was demonstrated both by magnetic resonance imaging and analysis of tissue water content[65].

The threshold nature of the postdecompression response explains that it may or not occur in patients undergoing operation for acute extracerebral haematoma in an apparently similar clinical condition of advanced tentorial herniation depending on whether or not they have reached the time-cerebral perfusion pressure ischaemic thresholds[66]. This reveals the importance of the rapid removal of acute extraaxial haematomas (time factor), and maintaining an adequate perfusion pressure before surgery (treat arterial hypotension and administer hyperosmolar solution to lower ICP). In one epidural balloon study[29], in which a standardized brain injury in terms of magnitude of ischaemia, brain oedema and venous obstruction was produced, the incidence of post-deflation brain swelling was significantly higher in animals developing transtentorial herniation and secondary midbrain haemorrhages than in those without herniation.

In cases of ACHS not associated with an extracerebral haematoma a direct vascular mechanical injury or a neural mechanism disturbing the vasomotor control of the involved hemisphere may be postulated.

Management

The management of ACHS in patients undergoing evacuation of an acute extracerebral haematoma represents a most difficult problem[11, 18, 47, 50, 53, 69, 87, 90, 112, 119, 128, 135, 149]. Mannitol 20% (0.25–0.5 g/kg), as a rapid infusion over 20–30 minutes is administered just before or during endotracheal intubation. Anesthesia is induced with a combination of nitrous oxide, barbiturates, narcotics and droperidol which have minimal effects on ICP. As thiopental may prevent swelling from developing, high doses (7–12 mg/kg body weight), are used at induction. In one experimental study[17], using epidural balloon compression, pretreatment with barbiturates prevented postdecompression brain swelling and barbiturates given following decompression alleviated intracranial hypertension without decreasing perfusion pressure. Brain tension, which most frequently manifests during haematoma evacuation or when removal has just been performed, is almost always due to ACHS, but one should be aware of anesthetic problems such as hypoventilation due to ventilator or tube disconnection, pneumothorax or obstructed cerebral venous outflow. The possibility of new acute haematoma formation, either on the side opposite the craniotomy or in an ipsilateral area hidden from the operative window must be also considered[100]. When the brain is swollen at operation a postoperative control CT scan should be performed to confirm ACHS and exclude new haematoma formation[23, 90, 128, 135].

Arterial blood pressure, which is frequently elevated before haematoma

evacuation, usually drops as the skull and dura are opened but sometimes remains very high. Since loss of autoregulation with cerebrovascular dilatation is usually involved in the etiology of ACHS, a carefully controlled arterial hypotension to 60–80 mmHg may be induced to achieve brain relaxation[11]. Following brain shrinking blood pressure is allowed to return to normal and both arterial hypotension, which may further compromise cerebral perfusion in ischaemic regions, and arterial hypertension, which may increase hemispheric engorgement and oedema, should be avoided[11, 42, 95, 102, 106, 121, 132]. There is evidence that arterial hypertension may increase postischaemic and post-traumatic brain oedema as the pressure head is communicated downstream increasing capillary pressure and water passage towards brain tissue[5, 42, 80, 97, 98, 131]. It should also be noted that a fall in arterial pressure occurring during haematoma removal is not always related to ICP decrease but may result from bleeding caused by associated extracranial injuries.

High-dose barbiturates is a major tool for the control of intraoperative brain swelling[96, 133]. An initial bolus of 20 mg/kg of thiopental is given and the drug is continued until the swelling is controlled or blood pressure drops below critical levels. Doses totaling as much as 75–80 mg/kg may often be required to control massive intraoperative swelling[96]. Though excessive hyperventilation may provoke oligemia in areas of the hemisphere with already critically reduced CBF[30], further lowering of pCO_2 (it is preferable to increase tidal volume rather than the rate), plus additional doses of mannitol and nonosmotic diuretics may be used simultaneously. Mannitol improved cortical CBF in animals exposed to epidural mass expansion[41], and suppressed brain swelling following recirculation in experimental brain infarction[138]. When barbiturates, hyperventilation and mannitol fail to relocate the brain back into the skull a frontal or temporal lobectomy may be indicated for achieving internal decompression.

The value of decompressive surgery in patients showing post-traumatic brain swelling remains controversial. Different types of craniectomy or hemicraniectomy with or without lobectomy or dural patching have been performed to provide room for movement of the swollen brain laterally away from the brain stem with variable benefit[18, 33, 53, 72, 107, 112, 119, 135, 149]. Some authors recommended decompressive craniectomy as the best method to relieve transtentorial herniation, but others argued that such an operation usually results in additional brain damage and that intensive medical management without craniectomy produces better results[11, 39]. In the presence of blood-brain barrier disruption, craniectomy may decrease tissue pressure, increase hydrostatic pressure gradients between capillaries and tissue, thereby markedly enhancing oedema formation in the decompressed hemisphere[32, 39, 56]; further hemispheric swelling will rapidly return intracranial volume-pressure relationships to the preoperative situation and the

entire exposed hemisphere may become irreversibly damaged. We have seen with the CT scan increasing hypodensity of cerebral tissue developing over time at the craniectomy site which may correspond to infarction.

Though there is not definitive information indicating that any type of surgery can acutely return the displaced midline to the normal position, decompressive craniectomy may be used for dealing with raised ICP and avoid secondary brain stem compression associated with acute subdural haematoma[18, 135]. According to Ransohoff *et al.*[119] this type of surgery should be reserved for patients who enter the hospital without demonstrable brain stem compression only to deteriorate subsequently because of increasing subdural haematoma or hemispheric swelling. Shigemori *et al.*[135] resorted to decompressive craniectomy in patients with acute subdural haematoma showing progressive signs of impending transtentorial herniation. Though it may be impossible to determine which patients undergoing acute extracerebral haematoma removal will develop ACHS, the occurrence of arterial hypotension and hypoxia prior to admission, a low preoperative GCS score, a large midline shift on the admission CT scan and the bulging of brain during operation all increase the probability of postoperative hemispheric swelling and high ICP. Limited temporal lobe resection and temporal craniectomy led to only transient control of elevated ICP in some of our patients. Recently, a large temporal lobe resection with dural closure has been successfully employed in patients with ACHS[112].

With or without decompressive craniectomy, intracranial hypertension associated with ACHS may be extremely difficult or even impossible to control[90]. High-dose thiopental achieved only a transient decrease of ICP in many of our patients. However, some nonresponders perhaps did not receive adequate doses or received adequate doses for only short time[128], and it should be noted that most survivors were among the initial responders to thiopental. Once ICP is controlled, barbiturates should not be discontinued until much improvement or complete disappearance of the mass effect is seen on the following CT scan, which may occur as late as 12 days after the onset of therapy. Recently, indomethacin was found to be effective in lowering ICP resistant to all other forms of therapy, barbiturates included[70]. The value of calcium antagonists for treating postischaemic brain swelling remains equivocal[59].

Acute Generalized Brain Swelling

Definition

CT-defined AGBS consists of a generalized increase in volume of both cerebral hemispheres with more or less marked obliteration of internal (lateral and third ventricles), and external (perimesencephalic cisterns), CSF spaces and can be considered a distinct clinicopathological entity[158].

Though AGBS tends to be greater in patients with more severe injuries, it also occurs in association with mild or moderate trauma indicating that the magnitude of the swelling does not always correlate with the severity of injury[50].

According to the classical description by the Philadelphia head injury group[20, 21, 157, 158], the clinical course in children with AGBS is as follows: after suffering an apparently trivial head injury, the patient falls into coma immediately or after showing a lucid interval lasting several hours. Increased CT numbers suggest that the brain contains more blood than normally so diffuse hyperemia is considered responsible for the patient's clinical picture. As cerebrovascular reactivity is preserved, hyperventilation is effective in reducing CBV and despite the seemingly devastating neurologic picture the final result is usually good. However, AGBS does not always occurs as a benign, self-limiting phenomenon and both children and adults may develop generalized brain swelling with normal or decreased CT numbers associated with severe intracranial hypertension and fatal outcome[36, 37, 60, 61, 64, 81, 82, 87, 156, 157]. Though brain hyperemia may occur initially after trauma in these cases, other mechanisms eventually leading to brain oedema must be involved[25].

Incidence and Clinical Significance

The clinical significance of AGBS is a matter of great controversy. As stated above, AGBS may follow head injuries of variable severity and the first problem is to determine whether the swelling is merely an epiphenomenon coexisting with the basic process that leads to the patient's neurological deterioration or is itself the cause of deterioration. Discordances between the magnitude of the swelling seen on the CT scan and the severity of injury estimated clinically or the final outcome, suggests that the pathophysiology differs from patient to patient. The diagnosis of AGBS at necropsy on the basis of the presence of convolutional flattening, obliteration of sulci and small symmetrical ventricles is made difficult by the fact that brain swelling occurs after the onset of brain stem death and after death[1, 86]. On the other hand, necropsy studies in patients showing the CT picture of AGBS are scarce. In some cases the classical pathological picture of minimal or no structural damage, with diffuse cerebral swelling and congestion of the blood vessels was observed[27, 86], but in other cases multifocal contusions, brain oedema, shearing injury and hypoxic-ischaemic encephalopathy are described[60, 136]. Because of the poor understanding of the basic pathophysiology and the lack of a definite diagnostic radiological criteria, the exact incidence of AGBS cannot be defined.

The majority of patients showing the CT picture of AGBS are injured in traffic accidents[20, 21, 37, 87, 157]. A recent epidemiological study[3], confirmed

that this syndrome is more related to the age (young patients), than to the mechanism of injury as its incidence was similar in the groups of patients suffering motor vehicle accidents or falls. AGBS is seen in 4 to 44% of the patients in head injury series depending on the severity of injury and the age groups considered. Zimmerman and Bilaniuk[157] found AGBS in 16.1% of the cases in their global head injury series and in 25% of the patients below 18 years of age, respectively; overall, 37% of the patients

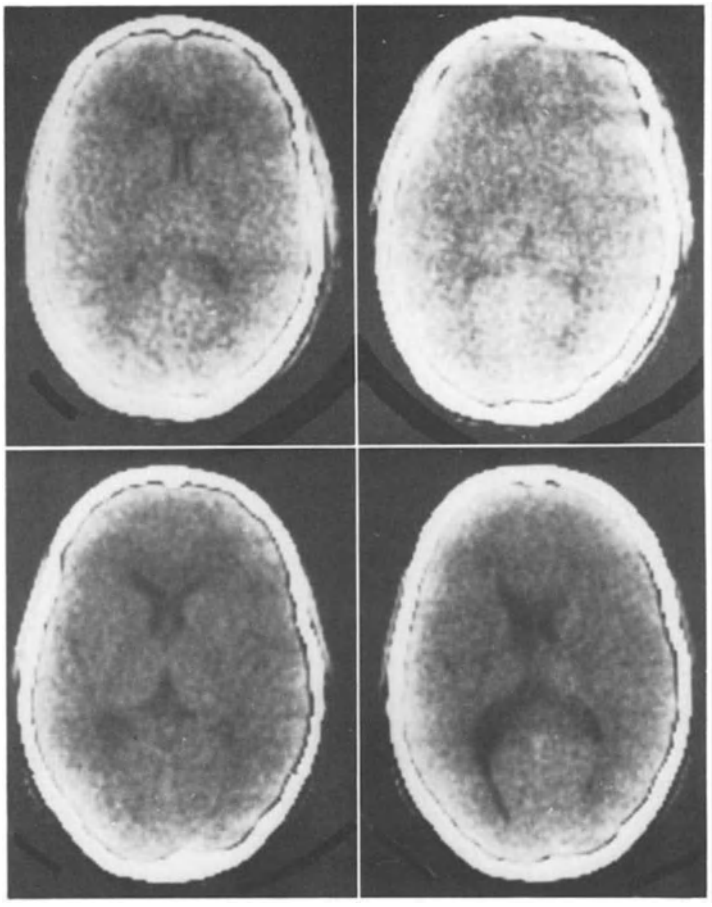

Fig. 9. This 12 year-old boy was injured in a traffic accident. The GCS score on admission was 13 points and the CT scan showed generalized brain swelling (upper left). Six hours after admission sudden neurological deterioration occurred (score = 7). A control CT scan showed increased diffuse brain swelling (upper right). Initial ICP was 45 mmHg but could be easily controlled with hyperventilation and mannitol. The patient recovered consciousness within few days. A further CT scan performed 9 days after injury showed reexpansion of the CSF spaces (lower). The final outcome was good recovery

with AGBS were comatose and 45.6% showed significant disturbances in the level of consciousness; 20% of the children showed focal deficits indicative of associated primary brain damage[1, 2]. Patients with isolated AGBS, most of whom were young, tended to do well, while those with associated small haemorrhages of the deep white matter and the corpus callosum (diffuse axonal injury) had a poor prognosis (62% mortality and 23% severe disability rates, respectively). In the series of Lanksch *et al.*[82] 12% of all head injured patients showed AGBS and 95% of them had disorders of consciousness indicating that they had suffered severe injuries; mortality was related to the severity of injury as only 4% of the somnolent and stuporous patients died in comparison to 50% of those who were comatosed.

The incidence of AGBS in severe head injury series including patients of all ages ranges between 13.9 and 24%[45, 48, 82, 87, 125]. In our severe head injury series, 180 of 819 patients (21.9%) presented the CT picture of AGBS (Figs. 9–12); in 80 patients (44.4%), AGBS was the only finding and in the remaining 100 cases (55.5%), brain swelling was associated with small haemorrhages of the deep and subcortical white matter or the brain stem (Fig. 12). Subarachnoid hemorrhage was visualized in 8.8% of the patients with isolated AGBS and in 55% of those showing signs of diffuse axonal injury[36, 87]; 37% of this last group also had intraventricular haemorrhage[35]. Some patients in both subgroups had small extracerebral haematomas. The mechanism of injury was similar in both subgroups (Fig. 4), but patients with isolated AGBS had a significantly higher incidence of lucid interval

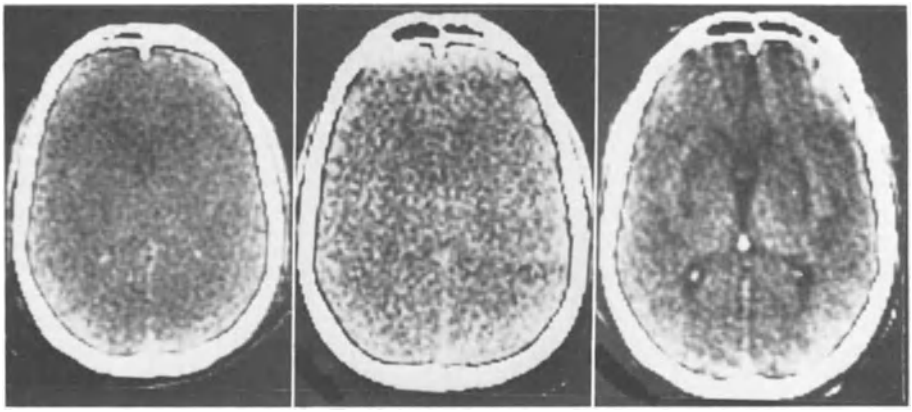

Fig. 10. This 7 year-old boy involved in a traffic accident scored 6 points on admission to our unit. The initial CT scan showed generalized brain swelling (left). Despite hyperventilation ICP remained above 25 mmHg and the patient showed further neurological deterioration (score = 4); a further CT scan revealed a complete collapse of the ventricles and cisterns (middle). Mannitol and barbiturates controlled raised ICP and the patient made a good recovery. A further CT scan ten days after trauma showed slightly enlarged ventricles and cisterns (right)

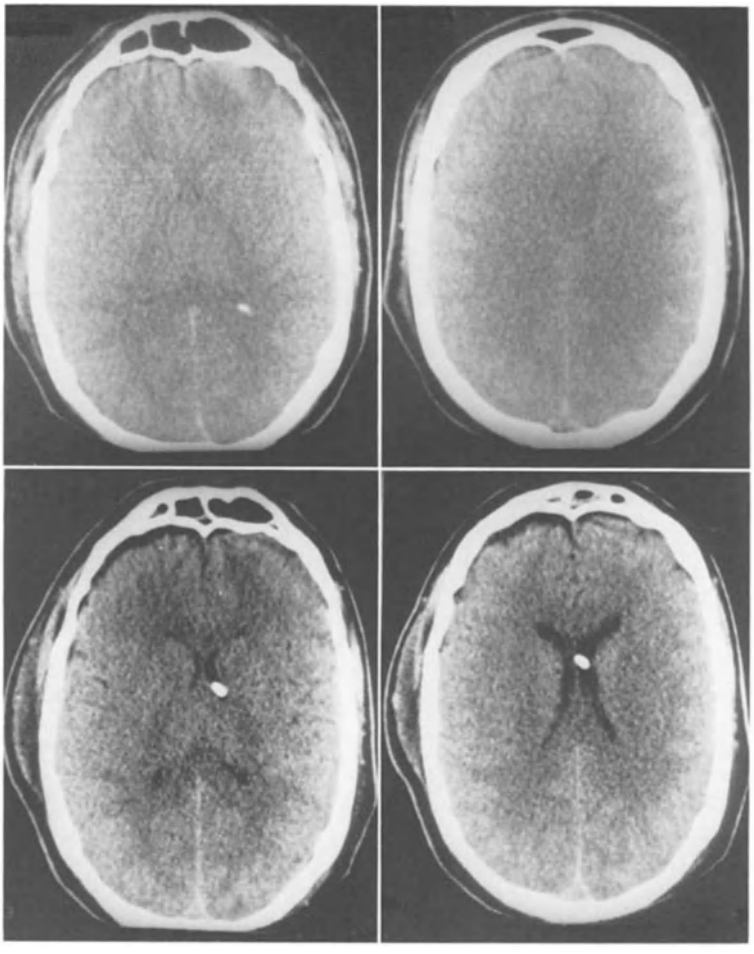

Fig. 11. This young adult injured in a traffic accident scored 7 points when admitted to a local hospital. The admission CT scan showed generalized brain swelling (upper part). ICP ranged between 25 and 35 mmHg. Six days after trauma ICP was normal and the next CT scan (lower part) showed normal ventricles and cisterns with discrete frontal hygromas which disappeared on a later CT scan

(26.3% vs. 14%). Average age was lower in patients with isolated AGBS than in those with associated signs of primary brain damage (57.5% vs. 25.3% under the age of 20 years, respectively) (Fig. 6). Patients with isolated AGBS scored higher on average (Fig. 5), had a lower incidence of pupillary changes (26.6% vs. 46%) and raised ICP (22% vs. 58%) (Fig. 7), and made a significantly better outcome than those with associated diffuse axonal injury (77% vs. 26% made a functional recovery) (Fig. 8). The CT pattern

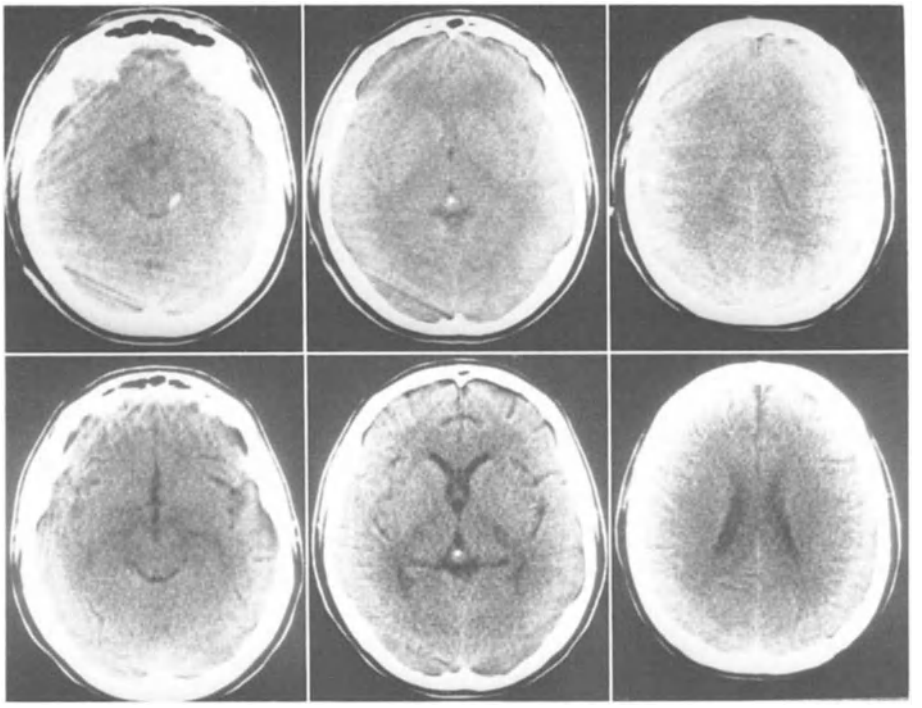

Fig. 12. This adolescent injured in a traffic accident scored 5 points when admitted to our unit. He showed alternating pupillary changes during the first three days after injury. The admission CT scan showed discrete generalized brain swelling with small intraparenchymal haemorrhages in the corpus callosum and the dorsolateral mesencephalon. ICP ranged between 20–30 mmHg and was easily controlled. Coma lasted for three weeks and the final outcome was moderate disability

of isolated AGBS ranked among the more benign in our head injury series together with monofocal brain contusion and pure extracerebral haematoma. Richard[122] observed AGBS in 44 (16.1%) of 273 severe head-injured patients and also noted that this CT picture associated with a lower age and better prognosis than other CT patterns. Uzzel *et al.*[147] also found that AGBS carried a lower mortality rate than diffuse axonal injury or focal mass lesions (15%, 40%, and 22%, respectively). In the severe head injury series of Roberson *et al.*[125] 80% of the patients showing AGBS made a good recovery.

In the pediatric head injury series of Bruce *et al.*[20] the CT picture of AGBS was seen in 29% of children and adolescents and the incidence was higher in comatose patients (41% of those with a GCS score of 8 or less) than in non-comatosed patients (15% of those with a score greater than 8). Overall, 77.7% of the children with AGBS scored 8 or less and those

with lower scores had a higher incidence of associated subarachnoid haemorrhage. A minority of children also had small extracerebral haematomas or small intraparenchymal hemorrhages indicative of primary brain damage. All but one child developing AGBS, after showing a lucid interval between trauma and subsequent deterioration, made a good recovery, while 5 (14.7%) of the 34 rendered comatose immediately after trauma died. According to these authors[20,21], AGBS seems to be the most frequent cause of delayed post-traumatic neurological deterioration in young patients in contrast to adults, who most commonly have an expanding mass lesion either intra- or extraaxial[89]. Kalff *et al.*[71] observed AGBS in 26.4% of 253 head-injured children; of these 85.1% made a good outcome. In the series of Berger *et al.*[14] 44% of the patients showed AGBS indicating that this CT pattern may be present in nearly one-half of all severely head-injured children; 75% of the children with AGBS in this series made a satisfactory outcome which is in keeping with the findings of Bruce *et al.*[20]. Finally, AGBS was seen in one third of the cases in one series including only infants and toddler[118].

In the pediatric severe head injury series of Cordobes *et al.*[37], 30% of children showed AGBS either isolated or associated with diffuse axonal injury; all children with pure AGBS made a functional recovery while 54% of those with associated primary brain damage died. In the severe head injury series of Humphreys *et al.*[61] 26 of 75 children (34.6%) unconscious from the moment of impact showed AGBS; of these 10 died (38.4%), and only 3 made a complete recovery. In a recent analysis of the Traumatic Coma Data Bank, patients with CT evidence of brain swelling in the absence of lesions greater than 25 ml had a mortality approximately equal to patients with surgically evacuated mass lesions (34% vs. 39%, respectively) (LF Marshall, unpublished observations, 1989).

Although intracranial compliance is likely to be reduced in most children showing the CT pattern of AGBS, ICP is not always high, particularly during the initial period. ICP was elevated in 59% of the children in the series of Bruce *et al.*[20] and could be controlled with conventional measures or barbiturates, so no child died from uncontrollable intracranial hypertension. In the series of Cordobes *et al.*[37] only 28.5% of children showing isolated AGBS had moderate intracranial hypertension, whereas 63.6% of those with associated diffuse axonal injury had elevated ICP which could not be controlled in the majority of the cases. Humphreys *et al.*[61] pointed out that the presence of diffuse cerebral oedema carries a poor prognosis when it is seen on the first CT examination in severely head-injured children. Toutant *et al.*[145] also reported that the final result is worse when diffuse brain swelling is observed soon after injury that when it occurs in later stages.

Radiology

The CT criteria for defining AGBS used by Bruce *et al.*[20] were an initial CT scan (within 24 hours) showing small ventricles and cisterns with compression or absence of perimesencephalic cisterns and a follow-up scan 7–20 days later showing return of the ventricular system and cisterns to normal size. As partial volume averaging of brain and CSF may artificially reduce the size of the ventricles and cisterns, thin CT sections are more adequate for diagnosis[158]. When the collapse of the ventricles and the subarachnoid spaces is complete the CT diagnosis of AGBS is straightforward, but the problem arises when compression is less marked as children and young adults normally have small ventricles and the normal dimensions of the CSF spaces are still not clearly defined[109, 120, 155]. Though obliteration of the CSF spaces may not always be initially obvious, the changes can become more convincing on viewing of serial studies after resolution of swelling. The more severely affected patients develop extracerebral fluid collections as the swelling resolves. These hygromas, respresenting accumulation of CSF within the subarachnoid or the subdural spaces, coexist with a slack brain, are without tension and disappear spontaneously. Later on, the CT picture shows variable degrees of ventricular and cortical sulci enlargement suggestive of cerebral atrophy but further CT follow-up eventually reveals that the ventricles and sulci return to normal in most cases. Some patients show varying degrees of ventricular dilatation which depends on the extent of brain damage[21, 36, 87, 157].

In most cases of AGBS the brain tissue lacks the normal structure and shows an homogeneous isodense or faintly hyperdense appearance. In one study[158], the average density of the white matter was 34.6 to 36.4 HU in 12 children with hyperdense swelling, while it was 29.2 to 33.2 HU in 18 normal (control) cerebral hemispheres. Typically there is a measurable increase in the CT numbers of the white matter of about 3 HU and a subsequent decrease to normal values over a 5–7 days period[20, 158]. However, there are patients with AGBS who show normal or slightly decreased brain density[37, 60, 64, 82, 87, 156, 158]. Ito *et al.*[64] using planimetric sequential CT scanning in a group of 51 patients with post-traumatic brain swelling and oedema, found that diffuse hyperemic swelling appeared within 2–4 hours of injury, while the first signs of oedema developed only 24 hours later increasing in size during 3–10 days; brain swelling subsided within 3–5 days, while oedema did not reach its maximum before days 5–8 suggesting that these two pathological events can be separated. Yoshino *et al.*[156] using dynamic CT scanning found that patients with hypodense AGBS due to brain oedema had a poorer outcome than those with AGBS due to hyperemia.

The degree of brain swelling as estimated by the CT scan correlates

with the level of ICP[44, 145], but there may be discrepancies and caution is needed as once the basal cisterns have been obliterated ICP can increase significantly without any further change in the CT appearance. Slit ventricles are not necessarily associated with elevated ICP[55, 126] and the collapse of the basal cisterns and the third ventricle are more reliable indicators of raised ICP[109, 142]. MR, which shows the alterations in the flow void of the third ventricle caused by higher pressure, may be able to estimate ICP non-invasively.

Though MR is not yet routinely used in severe head-injured patients, initial studies have shown that it is more sensitive than the CT scan for detecting brain contusion and oedema and brain damage of the impact type, all of which may occur in patients showing the CT picture of AGBS[51]. MR seems the best available method to study the formation and resolution of brain oedema, as it may detect oedema formation within 2 hours of injury[10], quantitate oedema fluid and distinguish between various types of oedema, i.e. cytotoxic, vasogenic and interstitial[8, 9, 12, 15]. Vasogenic oedema is better appreciated on T 2-weighted images and gadolinium demonstrates blood-brain barrier breakdown with greater sensitivity than contrast-enhanced CT[78]. The analysis of the alterations in CBF and CBV, which influence T 1 and T 2 relaxation times, seems a very promising way of elucidating the mechanism of brain swelling.

Pathophysiology

Clinical and experimental evidence supporting either oedema or hyperemia as the underlying mechanism of AGBS is multiple and conflicting[20–27, 29, 34, 36, 37, 39–41, 45–47, 50, 52, 54, 59–67, 74, 75, 79–83, 87, 88, 90, 97, 98, 101, 102, 104–106, 110, 111, 113–118, 128–131, 135–137, 140–144, 151–154, 156–159]. Both the immediate and the delayed forms of AGBS may represent a special form of vascular reaction of the child's brain to injury rather than a primary type of injury[21]. The higher cerebral metabolic rate and greater vasoreactivity in childhood might explain the comparatively higher incidence of AGBS in the pediatric population. However, the basic triggering mechanisms of AGBS are unknown. Either the mechanical effects of trauma on the brain or on the cerebral vessels, or the liberation of chemical mediators may influence brain stem vasomotor centres resulting in intraparenchymal vasodilatation, lowered cerebrovascular resistance and elevated CBF[7, 20, 22, 25, 38, 50, 63, 75, 79, 101, 110, 111, 117, 129, 152, 154]. Another explanation is that hyperemia is the result of transient hypoperfusion of the brain or hypoventilation related to the occurrence of peritraumatic arterial hypotension and hypoxia[140]. Redistribution of CBV could stiffen the brain, reduce intracranial compliance and put the patient at risk of cerebral herniation. However, some investigators believe that raised ICP cannot be explained by changes in the

vascular compartment only, and that varying combinations of hyperemia, brain oedema and obstruction to CSF outflow must concur.

The arguments supporting diffuse brain hyperemia (congestion) as the mechanism of AGBS are diverse. The rapidity with which AGBS develops and resolves, particularly in less severely injured children suggests that it is a transient, reversible physiological process which fits better with a transient vascular engorgement than with development of brain oedema. Increased CBF with or without increased metabolic rate for oxygen was measured in patients with AGBS[20, 113, 157]. The occurrence of hyperemia is also supported by the previously mentioned measurements of brain attenuation values showing higher CT numbers in children with AGBS than in the normal pediatric population and that initially increased CT numbers diminish in follow-up scans at the time when the swelling disappears[20, 158]. It has been claimed, however, that to increasing the CBF an amount equivalent to the reported increase of 3 HU in CT attenuation numbers measured would mean an increase of around 75% which is physiologically unlikely[142]. Clasen *et al.*[24] calculated that doubling the CBF would increase the CT number by only 0.7 HU and that for a ventricular collapse to develop it would be necessary to triple the CBV. According to Clasen and Penn[25] the increased CT numbers of white matter observed in AGBS result from the reduction of the extracellular space of the white matter secondary to compression by the swollen oedematous grey matter. The extracellular space is larger in the immature brain and would be more subject to compression than in the adult. On the other hand, clinical studies have demonstrated normal or even decreased CBF in children with AGBS and emission tomography has shown decreased CBV[77, 108].

Measurements of white matter specific gravity values in patients with diffuse head injuries employing microgravimetric methods showed either normal[22], or increased[49], brain water content. In any case, there is clinical and experimental evidence indicating that brain oedema may complicate head trauma[25, 46, 49, 62–64, 75, 82, 83, 91, 131, 144]. Oedema can appear as early as 3–5 hours after the traumatic insult and may develop even more quickly than ischaemic oedema[75, 76]. It has been hypothesized that acute vasomotor changes leading to increased capillary permeability and fluid passage towards the extravascular space may result from, a) Stimulation of certain diencephalic areas, the midbrain reticular formation and the locus coeruleus, b) Leaking of transmitters into the CSF and c) Brain acidosis secondary to systemic hypoxia and hypotension occurring prior to the patient's admission to hospital[1, 102, 103, 116, 140]. In one study[44], the occurrence of prehospital arterial hypotension and hypoxia was associated with the presence of diffuse symmetrical swelling. It has been shown that the brain may become severely swollen with pale flattening of convolutions within 15 to 30 minutes after the onset of traumatic shock in patients without

relevant intracranial lesion[86], and that the combined effects of hypoxic and traumatic insults may produce a widespread increase in brain water[62, 116]. Impaired vasoreactivity may limit compensatory vasodilatation normally induced by hypoxia and hypotension thus increasing the risk of brain ischaemia and oedema formation[84, 85]. Finally, iatrogenic fluid overloading may also contribute to development of oedema.

The two hypothetical basic mechanisms of diffuse brain swelling, i.e. hyperemia and oedema are not mutually exclusive and might occur sequentially in some cases. It has been postulated that brain trauma may damage the hypothalamic centers[110] triggering vasomotor paralysis and a sudden increase in CBV which in turn would lead to raised ICP, compression of the cerebral veins, increased cerebrovascular resistance, CBF decrease to ischaemic levels and oedema formation. There is experimental evidence that vascular engorgement that is severe and persistent enough may result in widespread brain hypoxia and oedema[25, 38, 46, 79, 116, 143, 152]. Histopathological examination in patients with acute malignant brain swelling not responding to aggressive treatment of raised ICP disclosed diffuse ischaemic damage (homogenizing necrosis), but no evidence of shearing injury or generalized ischaemia because the basal ganglia were not involved[27]. Correlations of CT and histological findings in brain obtained at autopsy along with positron emission tomography and MR studies should clarify the pathophysiology of AGBS and resolve the enigma of whether there are different types of acute brain swelling.

Management

There seems to be a turning point in the course of brain swelling at which it becomes irreversible and irreversibility seems to be correlated with the level of ICP. Thus early detection of swelling and ICP control are of critical importance to prevent brain stem compression. Until the precise causes of brain swelling can be identified specific therapies are not contemplated and treatment is applied on the basis of CT visualization of compressed CSF spaces and the findings with ICP monitoring[145, 148].

Children diagnosed as suffering a moderate head-injury (GCS score of 9–12 or abnormal metal status) who show AGBS in the initial CT scan are at risk of developing increased swelling and sudden deterioration into coma[60, 89]. Thus, they should be placed under close observation and have blood gases, electrolytes and fluid balance measured during the first 48 hours after trauma. If further neurological deterioration occurs, endotracheal intubation, hyperventilation and ICP monitoring should be started at once.

Intracranial hypertension is a potentially fatal but treatable component in comatosed patients showing the CT picture of AGBS. Though epidural

or subdural ICP monitoring are preferable, intraventricular measurement is also feasible in the majority of the cases in spite of the reduced ventricular size. Monitoring is continued for at least 72 hours as an initially normal ICP is no guarantee that pressure will remain normal. A following CT scan 24 and 48 hours after trauma is advisable to exclude the presence of new pathology and monitor the state of the CSF spaces. When ICP is elevated, therapy measures aimed to reduce the bulk in one or more of the three components of intracranial volume are initiated[21, 25, 50, 95, 103, 121].

Treatment should be initially directed toward reduction in CBV and at present hyperventilation with high O 2 mixture appears the most effective method to control AGBS associated with incipient vasoparalysis[21]. With preserved autoregulation the vasoconstrictive effect of hypocarbia (pCO_2 = 25 mmHg) leads to a fall in ICP which begins rapidly after hyperventilation. Effective CBF can be maintained with pCO_2 as low as 16–20 torr, and CBV can be reduced while still maintaining effective brain perfusion. The beneficial effects of hyperventilation may be due not only to a reduction in CBV but also to a decrease in end-capillary pressure which facilitates clearance of fluid from brain to the vascular compartment and the reversion of tissue acidosis. Hyperventilation may be ineffective when vasoreactivity is impaired or oedema has developed. In these cases additional therapy measures are required[95, 103, 121].

Water content represents more than 77% of the most important component of intracranial volume, i.e. brain tissue, and the water proportion is higher prior to complete myelination, so that the brain of infants and younger children has a higher water content than that of the adults. Though some authors do not use mannitol if possible within the first 24 hours after trauma in children with AGBS because it may increase CBF[20, 21], both hyperosmolar and nonosmotic diuretics such furosemide and ethacrynic acid are indicated when the patient is hyperventilated and ICP is still increased[52, 94, 95, 121]. The amount of fluid removed by the osmotic gradient established between the intravascular and the interstitial brain compartments may have dramatic effects on intracranial compliance. In any case, the patient should not be dehydrated as dehydration predisposes to impaired microcirculation. Monitoring of CBF or the arterial-jugular venous O 2 difference may show which patients are hyperemic and thereby do not warrant hyperosmolar treatment[50].

Despite of the reduced ventricular size, CSF drainage through the ventricular catheter can still be used to control ICP. CSF should be removed intermittently to avoid catheter obstruction. Because of the high intracranial elastance, venting very small volumes (0.5–1.5 ml) of fluid from "tight" ventricles may result in dramatic ICP reductions. The movement of extracellular fluid into the ventricular cavities represents a major mech-

anism for the resolution of vasogenic oedema and venting ventricular CSF encourages bulk flow of fluid in the appropriate direction.

Barbiturates may be effective in controlling elevated ICP when conventional therapies have failed[21, 25, 37, 43, 94, 95, 116, 121, 133, 146]. Apart from decreasing brain metabolic demands and reducing CBV, barbiturates may also inhibit brain stem neurogenic mechanisms responsible for vasoparalysis[17, 28], and by lowering ICP, they reduce end-capillary pressure and the secondary passage of fluid to brain tissue[17]. Barbiturate therapy should not be initiated with evidence of hypovolemia measured by direct central venous line or pulmonary artery pressure monitoring. Systemic arterial pressure in children tends to be lower than in adults and barbiturate administration plus the dehydrating effects of diuretics may cause arterial hypotension compromising brain perfusion pressure[146]. However, when the patient is adequately fluid-loaded (central pressures within normal ranges) high-dose barbiturates may decrease ICP prior to any change in blood systemic blood pressure being recorded. Either pentobarbital[94, 95], or thiopental[87], can be administered until ICP is brought below 20 mmHg (Fig. 13). Serum levels of barbiturate should not exceed 5 mg%. Once the ICP has remained normal for 2 days and the CT scan shows some degree of im-

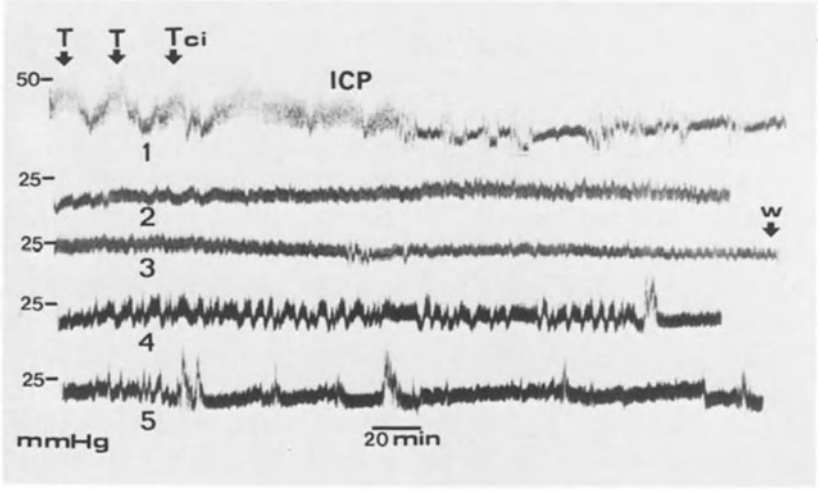

Fig. 13. Intracranial pressure recording in a 16 year-old girl who was unconscious from the moment of the impact and showed generalized brain swelling on the admission CT scan. Initial ICP was 50 mmHg. A bolus of thiopental (*T*) decreased ICP for brief periods but continuous infusion of this drug (*T ci*) led to stabilization and definitive control of raised ICP. Four days after initiation of treatment, when the next CT scan showed decreased swelling, thiopental was withdrawn; ICP recording became unstable but ICP remained below 20 mmHg. The final outcome was good recovery

provement in the swelling effect, barbiturate is tapered off by dividing the dose in half for the first 24 hours. The second day, the dose is halved again and the drug is stopped on the third day.

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Transcranial Doppler in Neurosurgery

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With 5 Figures

Contents

Summary

This chapter describes the use of the transcranial Doppler apparatus in neurosurgery. The principles of Doppler insonation, the techniques of recording and the use of activation techniques is described. The relationship between blood flow and blood velocity is discussed, and the interaction of various pharmacological agents. The establishment of normal values for the laboratory and various vessels insonated is emphasised. The use of indices particularly the pulsatility index is described together with its variations. Cerebral vascular reactivity measurements and the interaction of Doppler recordings with raised intracranial pressure, useful in assessment of cerebral perfusion pressure as in head injury and in terminal cases, is documented.

The use of transcranial Doppler in management of head injury and subarachnoid haemorrhage is described. The latter is probably the most useful routine place for Doppler measurement in neurosurgical practice and the documentation of the onset and progress of vasospasm is the final portion of the chapter.

Introduction

The normally functioning brain demands continuous and adequate perfusion. Correspondingly, brain disorders frequently present with circulatory changes which under certain circumstances may lead to irreversible brain damage or even death. Insight into the haemodynamics of the normal and malfunctioning brain thus contributes to a sound basis for therapeutic strategies and for the management of the individual patient.

The cerebral circulation can be investigated at different levels: along the arterial inflow channels, at the microcirculatory level, or at different levels of venous outflow. Several techniques have been developed for such studies in humans; however, they imply either highly invasive procedures, expensive equipment, and/or use radioactive tracers. Thus, the need had remained for a method for investigating the cerebral circulation noninvasively and innocuously, yet relatively inexpensive, and which may be performed at the bedside whenever needed. This goal came nearer when Aaslid, Markwalder and Nornes in 1982 introduced transcranial Doppler (TCD). Originating from the field of neurosurgery with a particular view

to the assessment of vasospasm after aneurysmal subarachnoid haemorrhage (Aaslid *et al.* 1984, Aaslid *et al.* 1986, Lindegaard *et al.* 1987), TCD is now used in clinical anesthesiology, cardiology, pediatrics, and vascular surgery, in aerospace medicine, and for studies of normal human physiology.

This presentation briefly describes the principles and investigation techniques of TCD. Following a consideration of cerebral haemodynamics in the normal situation, some of the experiences that have emerged from its application in clinical neurosurgery will be reviewed.

Instrumentation Principles and Investigation Techniques

The TCD technique comprises a pulsed Doppler ultrasound instrument usually operating at 2 MHz. The time interval of the instrument is adjustable thereby allowing sampling depth control between 15 and 155 mm from the transducer. Using a transducer probe with ultrasonic focusing, the sampling volume is 5–12 mm long (depending on the sampling depth) with a diameter of 3–4 mm. For a given emitted frequency, the Doppler-shift (in Hz or KHz) is a function of the velocity of the ultrasonic reflectors within the sampling volume, the blood corpuscles. When used to obtain information about the behaviour of the blood flow it nevertheless seems logical to convert the Doppler-shift frequency into a term with a more explicit meaning to workers in the medical field, blood flow velocity, or more simply: blood velocity (in $cm \cdot s^{-1}$).

Blood velocity in intracranial vessels is measured through so-called "ultrasound windows"; specific areas where the cranium usually is quite thin and devoid of cancellous bone. These areas (Fig. 1) include the region just above the zygomatic arch (the transtemporal window), the orbit (the transorbital window), and the small area above and lateral to the occipital notch (occipital window). When considering the posterior circulation, measurements are performed through the foramen magnum (the suboccipital window). The clinical examination also includes measurements from the distal extracranial internal carotid artery (ICA), with the probe below the jaw angle. The ultrasound window selected for a given purpose depends both on the adequacy of the windows and the vessels of interest. The principles for intracranial vessel identification have been discussed thoroughly by Fujioka and Douville (1992).

When recording through intact cranium of adults, the conditions required for measuring the cross-sectional average blood velocity (V_{mean}) are seldom obtained. The parameter commonly used to describe blood velocity with TCD is therefore the envelope, or the spectral outline velocity (V_{max}). This conforms to the maximal velocity component of the velocity profile, which usually corresponds to the lumen centerline blood velocity. Com-

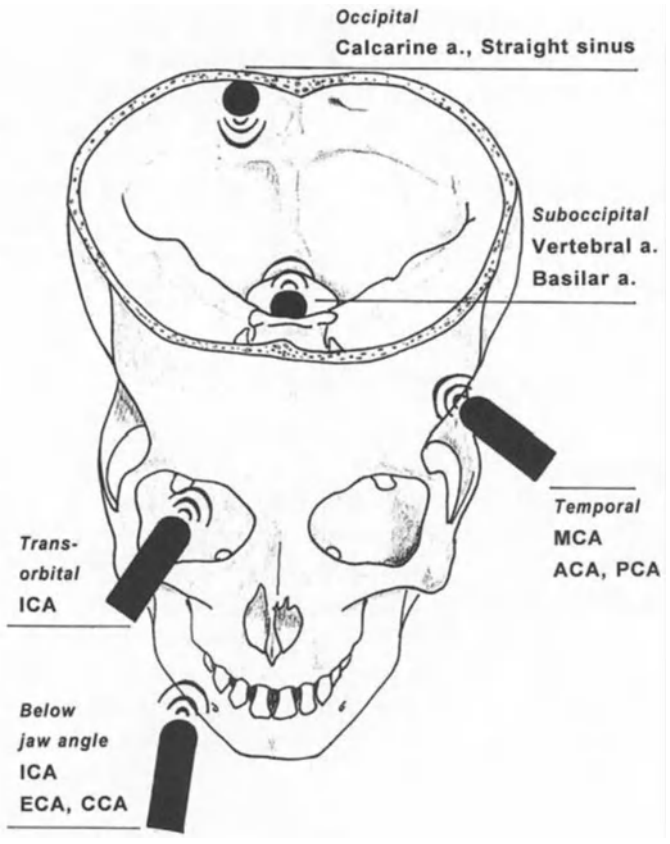

Fig. 1. Ultrasound windows and natural openings of the skull used in transcranial Doppler examination. For recording in the position below the jaw angle the probe is kept as parallel as possible to the vessel, sampling depth 35–45 mm. *MCA, ACA, PCA*: Middle, anterior, and posterior cerebral arteries. *ICA, ECA, CCA*: Internal, external, and common carotid arteries

parison of V_{max} and V_{mean} recorded simultaneously from normal human brain arteries during step changes in arterial blood pressure (ABP) (Aaslid *et al.* 1989, 1991) and cerebral activity (Aaslid 1987), have shown minimal discrepancy between these two variables, which suggests that the velocity profile changes very little under such circumstances. Hence, relative changes in V_{max} may be interchanged for relative changes in V_{mean}. Given no change in arterial lumen area, relative changes in V_{max} will also reflect similar changes in arterial volume flow.

The Examination

The TCD examination is performed either using a hand-held probe or taking advantage of the fixed probe technique. With the hand-held probe

the vessels of interest are investigated in sequence, selecting for each vessel the probe position and the sampling depth providing the highest blood velocity reading. Findings in different arteries can be considered indepently or they may be evaluated together. When evaluated together, stable hemodynamic conditions are required for the findings to be valid.

With the fixed probe technique, a self-retaining probe becomes mounted and locked in a position, providing a strong and clear blood velocity signal (good signal to noise ratio). It may be readjusted prior to, or between recordings; however, it must remain stable during the examination period proper for the findings to be valid.

While the hand-held probe technique is used in considering absolute blood velocities, the fixed probe technique is superior when investigating relative changes in the cerebral circulation. When monitoring continuously, the MCA is the prime choice because this artery is large, it may be considered as the clinically most important branch of the carotid system, and it is favourably situated for investigation with TCD. Continuous monitoring with TCD can be performed in periods up to days (Lundar *et al.* 1990). If the probe becomes accidentally displaced or when deliberately removed, the blood velocity signal is most easily retrieved by choosing the same probe position and sampling depth as before.

Blood Velocity Versus Blood Flow

Absolute Values

The human brain receives blood through defined cerebral artery systems; each system consisting of a cerebral artery with its branches extending down through the level of the capillaries. As blood neither becomes added nor subtracted in the cerebral circulation, the amount of blood Q (in $ml \cdot sec^{-1}$) that flows through a cerebral artery will seconds later pass through its microcirculation or perfusion territory. This amount thus equals $V_{mean} \cdot A$ (V_{mean} in $cm \cdot sec^{-1}$ and the arterial lumen area A in cm^2) as well as $1/60 \cdot rCBF \cdot T$ [rCBF is the brain tissue perfusion in ml (100 g tissue)$^{-1}$(min)$^{-1}$ and T the size of the perfusion territory in hundred of g]; or simply: $V_{mean} \cdot A = 1/60 \cdot rCBF \cdot T$ (Sorteberg *et al.* 1989 a). By introducing a constant K to interchange V_{max} for V_{mean}, and by correcting for the angle of incidence (α) between the blood flow and the ultrasound beam axis, the relationship between the TCD obtained blood velocity V in a cerebral artery and the regional blood flow rCBF in its perfusion territory becomes:

$$V = K \cdot \alpha \cdot 1/60\,(rCBF \cdot T)\,A^{-1} \quad (1)$$

Sorteberg *et al.* (1989 a) tested empirically this relationship between V and rCBF in defined cerebral artery systems of normal subjects. Technical

limitations precluded simultaneous investigations of V and rCBF, hence the two examinations were carried out separately. Since the end-expiratory pCO_2 was significantly higher during the rCBF than in the TCD examination, data were normalized to a standard pCO_2 (5.3 kPa) using accepted formulas (Alexander *et al.* 1964, Markwalder *et al.* 1984). There were significant positive correlations between V and rCBF for all investigated arteries (MCA, ACA, PCA, and ICA). Furthermore, the estimated blood velocity given rCBF = 0 was not significantly different from 0. These findings support the validity of expressing the relationship between V and rCBF in defined cerebral artery systems as in Eq. 1. From Eq. 1 one can also see that in order to calculate rCBF in a region perfused by a cerebral artery from the TCD obtained blood velocity of this artery, one must know the luminal area A and the perfusion territory T of the artery, the factor K and the angle of incidence between the blood flow and the ultrasound beam.

Relative Changes

When investigating the cerebral circulation of a subject in two different situations, the relationships between V and rCBF become:

$$V_1 = K_1 \cdot \alpha_1 \cdot 1/60\,(rCBF_1 \cdot T_1)\,(A_1)^{-1} \text{ and}$$
$$V_2 = K_2 \cdot \alpha_2 \cdot 1/60\,(rCBF_2 \cdot T_2)\,(A_2)^{-1}, \text{ respectively}$$

Expressing the relative changes in V and rCBF from situation 1 to situation 2 as indices, and rearranging, we obtain:

$$V_2/V_1 = (K_2/K_1)\,(\alpha_2/\alpha_1)\,(rCBF_2/rCBF_1)\,(T_2/T_1)\,(A_1/A_2)$$

A any change in the velocity profile between the two examinations would be minor (Kirkham *et al.* 1986, Aaslid 1987, Aaslid *et al.* 1989, Aaslid *et al.* 1991), hence K_2/K_1 can be considered 1. Moreover, if there is no change in the angle of incidence between the blood flow and the ultrasound beam (obtained e.g. by using a fixed probe in a locked position), α_2/α_1 also equals 1. Given these assumptions, relative changes in V and rCBF of a defined cerebral artery system relate as follows:

$$V_2/V_1 = rCBF_2/rCBF_1 \cdot T_2/T_1 \cdot A_1/A_2 \qquad (2)$$

Relative changes in V thus correspond to relative changes in rCBF when the luminal area A and the perfusion territory T of the examined artery remain constant. Given an increase in T or a decrease in A, relative changes in V will exceed relative changes in rCBF; with increases in A or decreases in T having the opposite effect.

Vasoactive drugs may induce complex alterations in individual haemodynamic states. Sorteberg *et al.* (1989 b) findings in normal subjects

indicate that acetazolamide induces narrowing of the basal cerebral arteries and dilatation of the distal resistance vessels. Moreover, the composite effect on the brain's arterial system seemed to be an disturbance in the balance between the larger areas so that a given artery temporarily supplied adjacent areas ordinarily perfused by a neighbour; acetazolamide hence seemed to induce changes in A as well as in T of the basal cerebral arteries. Dahl *et al.* (1989) observed that 1 mg nitroglycerin administrated sublingually caused a reduction in the V_{MCA}, but induced no significant change in the corresponding rCBF. This indicates that nitroglycerin caused a dilatation of the mainstem MCA. As they measured blood velocity in the MCA only, the question of T constancy could not be addressed. When clinically investigating relative changes in cerebral artery blood velocity versus relative changes in CBF, the aspect of possibly of induced changes in A and T of the investigated artery should hence always be born in mind.

Normal Values

When considering cerebral haemodynamics in the normal situation, we will first present findings obtained at rest, then discuss the cerebral vasomotor responses to certain test stimuli.

The Resting Situation

Blood velocity in a given cerebral artery varies with age. While it is low shortly after birth, it rises rapidly in the first days of life (Bode and Wais 1988). There is a further slow rise towards a peak at the age of 4–6 years; average value for the V_{MCA} then reaching about $95\,cm \cdot s^{-1}$ (Bode and Wais 1988). Blood velocity thereafter steadily declines. For the V_{MCA} this decline is about $1–2\,cm \cdot s^{-1}$ per year from 6 to 16 years, and about $0.75\,cm \cdot s^{-1}$ per year during adult life (Adams *et al.* 1992). This age dependent variation in blood velocity corresponds with and probably mainly reflects similar age-related changes in CBF (Adams *et al.* 1992).

From the equation $V = K \cdot \alpha \cdot 1/60\,(rCBF \cdot T)\,A^{-1}$ one sees that several factors exert influence on the V reading. Therefore, when investigating a group of subjects, one could anticipate wider ranges for the blood velocity than for the blood flow data in the various defined cerebral artery systems. This is indeed what Sorteberg *et al.* (1989 a) found when they compared blood velocity and rCBF findings in defined cerebral artery systems of normal subjects. One may assume individual differences in T, α, and K, although these are difficult to quantify. However, there is considerable individual variation in the lumen area A of a given cerebral artery (Gabrielsen and Greitz 1970). Individual difference in A is therefore a main contributor to the individual difference in TCD obtained blood velocity. From these considerations it follows that in the present state of technology,

clinically worthwhile estimations of rCBF from TCD blood velocity is precluded.

To recognize only the upper and lower limits of normal blood velocities is of limited value. On the other hand, to know in the same individual how blood velocities may differ within a hemisphere, or how TCD parameters may differ between the sides, or vary from one examination to the next, would be important. In the normal individual the V_{MCA} is less than $120\,cm \cdot sec^{-1}$ (Aaslid *et al.* 1982), but higher than the ipsilateral V_{ACA} or V_{PCA} (Sorteberg *et al.* 1990, Lindegaard *et al.* 1985). Moreover, the V_{MCA}/V_{ICA} hemispheric ratio (ratio between blood velocity in the MCA and the distal extracranial segment of the ICA) is $\leqslant 3$ (Lindegaard *et al.* 1986, 1989; Sorteberg *et al.* 1990 a). Finding at rest the V_{ACA} higher than the ipsilateral V_{MCA} indicates an increased ACA volume flow (Lindegaard *et al.* 1986), a reduced ACA diameter (Lindegaard *et al.* 1986, 1989), or a reduced MCA volume flow (Mattle *et al.* 1988). The same applies to the PCA. The presence of a V_{MCA}/V_{ICA} hemispheric ratio > 3 signals MCA vasospasm (Lindegaard *et al.* 1986, 1989).

In the normal individual there are only minor side-to-side differences and day-to-day variations in blood velocity and blood velocity ratios. A side-to-side difference exceeding some $\pm$ 20% for the V_{MCA} (Grolimund and Seiler 1988, Zanette *et al.* 1989, Sorteberg *et al.* 1990), the V_{ICA} (Grolimund and Seiler 1988, Sorteberg *et al.* 1990) and the V_{MCA}/V_{ICA} hemispheric ratio (Sorteberg *et al.* 1990) can be considered outside normal limits. Somewhat higher values are accepted for the V_{ACA} and the V_{PCA} (Grolimund and Seiler 1988, Sorteberg *et al.* 1990). A day-to-day variation in blood velocity or blood velocity ratios within the anterior circulation (MCA, ACA, and ICA) of less than $\pm$ 20% should be considered normal (Sorteberg *et al.* 1990). Such variations from one examination to the next can be explained by the composite effect of genuine changes in blood velocity and in methodological errors. While genuine changes in blood velocity reflect changes in blood flow, possibly also in the vascular calibre, methodological errors include variations due to changes in the incidence angle between the blood flow and the ultrasound beam, and in alterations in the signal intensity and/or manual assessment of blood velocity (Lindegaard 1992).

The pulsatility describes the degree of variability in V_{max} that occurs during a cardiac cycle (Fig. 2). This waveform results from the interaction of two variables, the input signal and local organ-related factors. Thus, the observed waveform contains information about the dynamics of the blood flow both proximal and distal to the point of observation. Pulsatility can be quantified according to several indices, of which the Pulsatility Index (PI) (Gosling and King 1974) is the most commonly used in TCD. The PI is the difference between the systolic and diastolic velocity divided by the time-mean value. Unlike absolute blood velocity, the pulsatility does

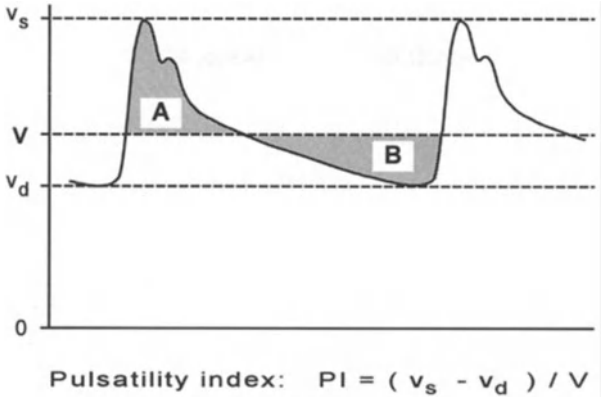

Fig. 2. Pulsatility denotes the excursion of the spectrum outline (maximum velocity, V_{max}), during one cardiac cycle

not depend on the angle of incidence between the blood flow and the ultrasound beam axis.

With no apparent trend with age, the normal PI usually falls within 0.5 and 1.1 (Adams *et al.* 1992). It seems to be of the same size in all intracranial arteries and artery segments within reach with the current TCD technique (Sorteberg *et al.* 1990). However, the extracranial ICA has a small, but significantly higher PI (Sorteberg *et al.* 1990), possibly because this artery also supplies an artery with a clearly higher pulsatility; the ophthalmic artery (Lindegaard *et al.* 1986 a). There are no significant side-to-side differences (Lindegaard *et al.* 1985, Sorteberg *et al.* 1990) or day-to-day variations (Sorteberg *et al.* 1990) in the PI. Standard deviation (SD) for the side-to-side difference of PI in the MCA was 10% when calculated from one PI annotation, 9% when averaged from four observations, and 4% when averaged from 10 PI annotations (Lindegaard *et al.* 1986, Sorteberg *et al.* 1990). This emphasizes the importance of pooling data from a larger number of observations when evaluating the PI.

Cerebral Vasomotor Responses

It is crucial for the brain that it can adequately handle acute alterations in cerebral circulatory demand or supply. This is obtained through mechanisms such as cerebral autoregulation and an ability to alter perfusion in response to acute changes in pCO_2. A knowledge of normal cerebrovascular responses to acute changes in arterial blood pressure (ABP) and in CO_2 would contribute to a sound basis when evaluating the individual patient.

Aaslid *et al.* (1989) investigated the cerebrovascular responses of normal subjects to step decreases in arterial blood pressure. Blood velocity was

monitored in the MCA using the fixed probe technique while the ABP was measured noninvasively in the brachial artery using a servo-cuff method capable of recording the ABP waveform continuously over 1–2 minutes (Aaslid and Brubakk 1981). Step decreases in ABP were induced by rapid deflation of cuffs around both thighs after a 2-minute inflation. Upon deflation, there was a rapid 20% drop in blood pressure which lasted for about 5–7 seconds, whereupon reflexes started to restore the ABP. The time course of the cerebrovascular resistance (CVR) was determined by dividing ABP by V for each time point. During the time interval from 1 to 3.5 seconds after the abrupt fall in cuff pressure, the CVR changed with time (T) in an approximate linear fashion. The rate at which the CVR changed during this time interval (dCVR/dT) was dependent on the relative blood pressure drop (dABP); Aaslid *et al.* (1989) therefore introduced a parameter they denoted rate of regulation (RoR). This parameter was calculated accordingly: (dCVR/dT)/dABP. A RoR of 20% implies a per second adjustment of 20% of the full CVR change needed to completely compensate for the dABP. On the other hand, a RoR of 0% reflects a setting where the CVR remains unchanged, and where cerebral artery blood velocity changes passively with alterations in ABP. In the study of Aaslid *et al.* (1989) the normal volunteers had a RoR of 20 ± 3% during normocapnia (37.1 ± 0.8 mmHg), 38 ± 4% during hypocapnia (22.2 ± 0.6 mmHg) and 11 ± 2% during hypercapnia (46.9 ± 0.5 mmHg). Thus, while moderate hypocapnia decreased the response time, hypercapnia slows down the cerebral autoregulatory responses to step changes in ABP.

Markwalder *et al.* (1984) have studied the effect of acute changes in CO_2 on the V_{MCA} of normal subjects. The study comprised 31 volunteers, 11 between 5 and 15 years, 10 between 16 and 40 years, and 10 between 41 and 73 years. The end-expiratory pCO_2 was altered within the ranges of 20–55 mmHg. Obtaining a 3.4 ± 0.5% increase in the V_{MCA} per mmHg increase in pCO_2, there were no marked distinctions between the three age groups. The CO_2 reactivity of the V_{MCA} closely resembles the CO_2 reactivity of CBF previously demonstrated with tracer methods (Olesen *et al.* 1971). This suggests that the MCA diameter does not seem to vary unduly during acute changes in CO_2. Moreover, the cerebrovascular CO_2 reactivity seems to be independent of age.

Cerebral Perfusion Pressure

The cerebral perfusion pressure (CPP) is the difference between arterial blood pressure and the intracranial pressure (ICP) (CPP = ABP − ICP). Together with the cerebrovascular resistance (CVR) it sets the premises for the cerebral circulation. Within normal limits of CPP (usually within the ranges of 50–150 mmHg) CPP changes induce alterations in the CVR so that the cerebral perfusion remains relatively constant.

It seems reasonable to assume that healthy subjects with normal ABP also have normal intracranial pressure. Therefore, when inducing step changes in the ABP of normal volunteers (Aaslid *et al.* 1989), one may infer similar step changes in CPP.

Cerebral Circulation and Intracranial Pressure

With increased intracranial pressure (and decreased cerebral perfusion pressure), characteristic changes occur in cerebral artery blood velocity and the blood velocity waveform. These changes seem to be independent of whether the cause is a head injury, cerebral or cerebellar haemorrhage, subarachnoid haemorrhage, brain tumour, pseudotumour cerebri, encephalitis or hydrocephalus (Hassler *et al.* 1988, 1989; Lundar *et al.* 1990). The alterations have been thoroughly discussed by Hassler *et al.* (1988, 1989), and Lundar *et al.* (1990) and the present Fig. 3 is thus a synopsis of their findings.

Compared with the normal situation (Fig. 3 a), during moderately increased ICP, the blood velocity waveform shows increased pulsatility with increased systolic peak velocity and decreased diastolic velocity (Fig. 3 b). However, there is little change in the time-mean value. When the ICP approaches, or reaches the diastolic ABP (actually the diastolic pressure at the level of the cerebral microcirculation), the diastolic part of the velocity spectrum disappears (Fig. 3 c). This is due to a functional obstruction, probably at the microcirculatory level (Newell *et al.* 1992 a). With ICP surpassing the diastolic pressure, the diastolic blood velocity reappears; however, this time in a reversed direction (Fig. 3 d). Such a situation indicates severe impairment of the intracranial circulation with systolic/diastolic alternating blood flow in the basal cerebral arteries. When the ICP equals the ABP (with hence zero CPP), there exists a situation of cerebral circulatory arrest.

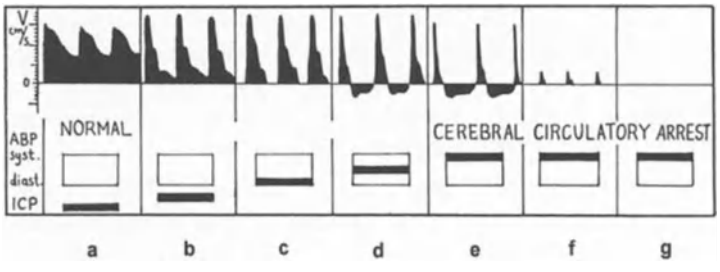

Fig. 3. Graphical illustration of blood velocity recordings in cerebral arteries in (a) the normal situation, (b–d) with increasing intracranial pressure (ICP), (e–g) in brain tamponade with cerebral circulatory arrest

A sequence of three different TCD patterns can be observed during cerebral circulatory arrest (Figs. 3 e–g). During the early phase, the blood velocity oscillates with antegrade flow in the systole, retrograde flow in diastole, and with zero net flow (Fig. 3 e). In the intermediate stage only sharp and narrow systolic spikes are obtained (Fig. 3 f). One may speculate that this stage also reflects a situation of oscillating blood flow; however, the amplitude of the retrograde diastolic flow is so small that the signal during diastole becomes filtered by the TCD instrument (in order to obtain good blood velocity signals TCD instruments contain a filter which removes the lowermost frequencies received). In the end stage of cerebral circulatory arrest, no TCD signals are obtained intracranially (Fig. 3 g).

Correlation of TCD data with angiographic findings during cerebral circulatory arrest (Hassler *et al.* 1989) have shown that the further the ultrasonic pattern has progressed from the oscillating type to the no flow type, the more caudal is the angiographic termination of the contrast material column. The typical angiographical correlates to the three TCD stages of cerebral circulatory arrest are as follows: During the oscillating net zero flow there is a delayed, tapering stasis filling of the basal cerebral arteries, with no antegrade drainage. In the ICA, contrast flow can also terminate at the anterior clinoid process with preserved filling of the ophthalmic artery. When the narrow systolic spikes are present, the usual angiographic finding is an extradural cessation of contrast media in the cavernous or petrous portion of the ICA. When the intracranial blood velocity signals have totally disappeared, the contrast media column ends extracranially.

TCD recordings have been obtained in patients during intracranial A pressure waves (plateau waves) (Lundar *et al.* 1990) and B pressure waves (Lundar *et al.* 1990, Newell *et al.* 1992 b). During A pressure waves the mean blood velocity was sometimes reduced; however, the amplitude of the blood velocity invariably increased with the decreasing CPP. The B pressure waves are characterized by repetitive alterations in ICP at frequencies of 0.5 to 2 waves per minute. Simultaneous recording of TCD and ICP signals in patients with head trauma (Lundar *et al.* 1990, Newell *et al.* 1992 b) have demonstrated synchronous variations in the MCA blood velocity and the ICP during such intracranial B pressure waves. Moreover, in one patient where the blood velocity was monitored simultaneously in both MCA's, the velocity fluctuations were completely synchronous with one another, and in phase with the ICP B wave (Newell *et al.* 1992 b). Analyzing their data carefully, Newell *et al.* (1992 b) could delineate that commonly the blood velocity wave started immediately prior to the intracranial B pressure wave. This suggests the presence of a central control mechanism or a synchronizing mechanism which initiates the blood velocity waves; probably through vasomotor waves altering the cerebral blood flow.

The vasomotor waves would produce fluctuations in cerebral blood volume, which would again be reflected in ICP. Newell *et al.* (1992 b) also demonstrated similar synchronous variations when relating blood velocity in the distal extracranial ICA to the intracranial B pressure waves.

Since the waveform of the blood flow in cerebral arteries shows increasing amplitude when the cerebral perfusion pressure falls (Greenfield and Tindall 1965), it is an attractive possibility to estimate the CPP through analysis of the intracranial blood velocity waveform. Investigating 10 patients undergoing testing of CSF pressure dynamics by the intraventricular route for suspected non-communicating hydrocephalus, Aaslid *et al.* (1986 b) compared the first harmonic component of the MCA blood velocity waveform and the systemic arterial blood pressure. Through computer-assisted Fourier waveform analysis they estimated the CPP (CPP_e) accordingly: $CPP_e = F_{1(\text{velocity})}/F_{1/\text{blood pressure})}$. The measured CPP fell from a mean of 81 to 31 mmHg. A correct differentiation between low (< 40 mmHg) and normal (> 80 mmHg) CPP values was achieved in all patients. In six patients the CPP_e was within $\pm$ 5 mmHg of the measured CPP. In the remaining four, findings were within a range where they could still be considered useful.

Cerebral Circulatory Arrest and Brain Death

With the possibility to detect and recognize the characteristic progression of changes that occur from a state of increased intracranial pressure to the situation of cerebral circulatory arrest, the TCD method may provide valuable clinical information. The importance of the TCD investigation in patients with increased ICP lies in alerting the clinician to situations where countermeasures can be carried out, and to evaluate their effect. Given a situation of uncontrollable and escalating ICP, the examination can recognize when the situation of cerebral circulatory arrest has developed. However, it has been observed that cerebral circulatory arrest may be a reversible phenomenon if it occurs for only 1–2 minutes. Grote and Hassler (1988) hence recorded TCD signals during rebleeding episodes in patients with cerebral aneurysm, and observed oscillatory blood flow which gradually returned to normal in parallel with clinical recovery.

From the above mentioned it is thus clear that the diagnosis of brain death remains clinical. Nevertheless, to be able to recognize cerebral circulatory arrest at the earliest possible time should aid in the timing of agonal angiography. The use of TCD can hence eliminate situations where a terminal angiographic examination is performed prematurely, or very late, and thereby improve the possibilities for organ salvage and transplantation.

having RoR values of 5 or below spontaneous blood pressure changes produced passive changes in the MCA blood velocity.

Lundar *et al.* (1990) and Newell *et al.* (1992) also evaluated the responsiveness of the cerebral circulation to acute changes in CO_2 in their head injury patients. Lundar *et al.* (1990) observed that during hyperventilation most patients showed a CO_2 reactivity in the MCA blood velocity within normal limits (2.5 – 5% change in blood velocity per mmHg change in pCO_2). Severely impaired CO_2 reactivity (below 1%) was considered present in four patients in coma after the severe head trauma. Three of these four patients died, with the fourth patient surviving in a persistent vegetative state. This subject showed a CO_2 reactivity within normal limits two months following the head injury. All four patients with severely impaired CO_2 reactivity also demonstrated pressure-passive blood velocity changes throughout the observed CPP range (up to 120 mmHg), thus suggesting abolished cerebral autoregulation. In the group of head injured patients studied by Newell *et al.* (1992) the MCA blood velocity response to hyperventilation varied between 0% and 4.5%. The zero CO_2 reactivity was generally found in patients with very severe brain injury or in MCA distributions with extensive focal lesions. Knowledge of the integrity of the CO_2 response was helpful in determining the potential effectiveness of hyperventilation for ICP control in the individual patient.

Angiographic examinations have demonstrated cerebral vasospasm following head injury; vasospasm that can lead to ischemic neurological deficit (Wilkins 1980). However, as cerebral angiography was usually performed soon after the head injury, the real incidence and time course of posttraumatic cerebral vasospasm could not be delineated. The TCD method enables longitudinal investigation of the individual patient, thereby allowing a delineation of this problem. Using a V_{MCA}/V_{ICA} hemispheric ratio $\geqslant 3$ as a criterion for cerebral vasospasm, Weber *et al.* (1990) found that 14 of 35 patients (40%) developed vasospasm and the occurence of vasospasm correlated with the amount of blood seen on computer tomography (CT) scans. Maximum values occurred 5 – 7 days after injury. The two patients having a ratio > 5 died. Martin *et al.* (1992) investigated 30 patients and defined vasospasm as MCA blood velocity > 120 cm/s. In patients with CT-scans showing blood the maximum blood velocities occurred during the second week, resembling the course of blood velocities in vasospasm after spontaneous SAH (Aaslid *et al.* 1986b).

Subarachnoid Haemorrhage

Subarachnoid haemorrhage (SAH) is a dramatic event, – the intracranial pressure approaches systemic blood pressure levels during the first seconds after the rupture of an arterial aneurysm (Nornes 1973a) with near arrest

in cerebral blood flow (Nornes 1978). Aside from the direct brain damage from initial and recurrent bleed, a substantial amount of the morbidity and mortality from SAH is being attributed to the narrowing of cerebral arteries, or so-called vasospasm, which occurs in the wake of the haemorrhage (Kassell and Torner 19884). This vasospasm is probably a multifactorial process, and, while a review of its pathogenesis is beyond the scope of this presentation, it is generally accepted that if vasospasm is severe and the compensatory mechanisms are depleted it can become the decisive factor in the total equation that determines if and how the brain will recover.

The *raison d'être* of transcranial Doppler was the neurosurgeon's desire to assess individual patients with regard to the presence and degree of vasospasm. From measurements obtained by using miniature Doppler probes in the operating field, Nornes *et al.* (1979 b) had shown that the blood velocities were increased in arteries appearing to be in vasospasm. Velocities of 150–200 $cm \cdot s^{-1}$ were observed in such vessels; 2–4 times the velocity recorded from vessels appearing as normal. A reduction in blood velocity and an increase in diameter was seen following the topical application of papaverine 3% on spastic artery segments.

Following the introduction of transcranial Doppler (Aaslid *et al.* 1982), the capabilities of the new technique were directed towards the assessment of vasospasm in patients with aneurysmal SAH. Typically, the Doppler audio signal from severely vasospastic arteries has a high-pitch quality, resembling the sound of air from a jet. This is apparent also from the Doppler-shifted spectral display. When vasospasm is very severe the reflected signal becomes weak because blood flow is reduced. Musical murmurs (Aaslid and Nornes 1984) may be recorded from sites near the circle of Willis.

The first study on the diagnosis of cerebral vasospasm with TCD was presented in 1984 (Aaslid *et al.* 1984). For the middle cerebral artery (MCA) the authors demonstrated an inverse relationship between blood velocity and residual lumen diameter measured from angiographic films. Grading angiographical vasospasm as an absent/present phenomenon, proximal MCAs with evidence of vasospasm had blood velocities from 120 to more than 200 $cm \cdot s^{-1}$. From these observations the authors suggested velocities $> 120\,cm \cdot s^{-1}$ as indicating MCA spasm. Two other studies also comparing blood velocities and angiograms have supported this view (Grolimund *et al.* 1987, Harders and Gilsbach 1987). Hence, MCA blood velocities of 120–140 $cm \cdot s^{-1}$ have been adopted as the empirically based limit by other authors (Sloan *et al.* 1989, Romner *et al.* 1989, Romner *et al.* 1990, Martin *et al.* 1992). Higher and lower cut-off limits have been proposed as well, 155 $cm \cdot s^{-1}$ (Sekhar *et al.* 1988), and 100 $cm \cdot s^{-1}$ (Compton *et al.* 1987). These limits are based on observation and are, therefore, provisional.

Head Injury

The aim of the management of patients suffering from head injury is to provide the brain with optimal conditions for recovery and to prevent secondary injury. This involves providing adequate oxygenation and circulatory perfusion; it hence includes lowering of increased intracranical pressure and surgical removal of intracranial mass lesions that threaten to cause additional brain damage. In the handling of these patients it therefore becomes valuable to know the adequacy of the cerebral circulation. Moreover, to identify individuals with deranged cerebral vasomotor responses or those developing cerebral vasospasm allows a further delineation of patients at risk for additional brain damage.

The cerebral perfusion is highly dependent on the ICP and the cerebral perfusion pressure. Using injected radioactive xenon and external detectors, Obrist *et al.* (1984) showed that the CBF following head injury could be normal, increased or decreased. Moreover, the CBF may or may not be as closely linked to the cerebral metabolism as it is under normal circumstances (Obrist *et al.* 1984). When considering the adequacy of the cerebral circulation by means of TCD, most information is obtained by considering the blood velocity and the blood velocity waveform combined. Typical findings during increased ICP/decreased CPP have been discussed in the section considering cerebral artery blood velocity versus ICP and is therefore not repeated here. However, when investigating cerebral perfusion by monitoring cerebral artery blood velocity on a continuous basis, one must bear in mind that only when the lumen area A and the perfusion territory T of the investigated artery remain constant will changes observed in V reflect corresponding relative changes in rCBF (Eq. 2).

Several groups (Lundar *et al.* 1990, Newell *et al.* 1992) have investigated the autoregulatory responses by means of TCD in patients suffering from head injury. Lundar *et al.* (1990) observed that increased ICP/decreased CPP deranged cerebral autoregulation in all their 12 patients when the CPP fell to values below 40 – 45 mmHg. Moreover, five of them demonstrated pressure passive blood velocity changes throughout the observed CPP range (up to 120 mmHg). Thus, under less extreme conditions cerebral artery blood velocity seems to be autoregulated with a lower regulatory limit of about 40 – 45 mmHg.

Inducing step changes in the ABP of 20 head injury patients by deflating thigh cuffs, Newell *et al.* (1992) observed RoR values between 0 and 29.4%. The range of values indicate that in head injury patients the autoregulatory response can be completely absent, completely intact, or impaired to various degrees. They also observed that in the patients with RoR values of 15% or above, spontaneous blood pressure changes of at least 30 s duration produced minimal changes in velocity. On the other hand, in those patients

When we discuss velocity threshold values in the context of cerebral vasospasm it is prudent to remember that by assessing MCA spasm, or diameter, from the absolute MCA blood velocity one implicitly presumes a predictable relationship between MCA diameter and blood velocity. Indeed, MCA blood flow variations compromise this assumption. Consider the following: for a V_{MCA} of $64\,cm \cdot s^{-1}$ in the normal situation, the V_{MCA} given 25% diameter reduction becomes $115\,cm \cdot s^{-1}$. Given a 50% diameter reduction the predicted V_{MCA} becomes $256\,cm \cdot s^{-1}$, – this value exceeded the highest blood velocity observed in our clinical series (Lindegaard *et al.* 1989). However, after SAH the cerebral perfusion may differ substantially from the normal (Grubb *et al.* 1978, Ishii 1980, Mickey *et al.* 1984, Powers *et al.* 1985, Jakobsen *et al.* 1989). Therefore, if we assume a 40% blood flow reduction in all patients with severe MCA spasm, one obtains $150\,cm \cdot s^{-1}$ for a 50% calibre reduction instead of $256\,cm \cdot s^{-1}$. Spasm assessment from MCA blood velocity alone may hence be difficult to interpret or even misleading in settings with hyperperfusion (Jakobsen *et al.* 1990 a, b) as well as when the perfusion is reduced due to vasospasm with or without intracranial hypertension (Jakobsen *et al.* 1990 b, Klingelhöfer *et al.* 1991). Such error may be serious when TCD is used as a clinical management tool.

Hemispheric Index

To lessen the impact of blood flow variations in the practice of stand-alone Doppler one may consider the following: the ICA blood flow (Q_{ICA}), and blood velocity (V_{ICA}) could be expected to reflect these changes in cerebral perfusion. The relationship between blood flow and blood velocity in a vessel segment may be written as:

$$V = \text{const} \cdot Q \cdot (D)^{-2};$$

thus:

$$V_{MCA} = \text{const} \cdot Q_{MCA} \cdot (D_{MCA})^{-2},$$

and:

$$V_{ICA} = \text{const} \cdot Q_{ICA} \cdot (D_{ICA})^{-2}.$$

Calculating the ratio V_{MCA}/V_{ICA} eliminating the constant:

$$V_{MCA}/V_{ICA} = (Q_{MCA}/Q_{ICA}) \cdot (D_{ICA})^2 \cdot (D_{MCA})^{-2}.$$

If the MCA can be regarded as an end artery from the ICA, then variations in blood flow should not change the ratio Q_{MCA}/Q_{ICA}. Provided a constant D_{ICA}, the expression $(Q_{MCA}/Q_{ICA}) \cdot (D_{ICA})^{-2}$ will be constant as well. The ratio V_{MCA}/V_{ICA} then emerges as:

$$V_{MCA}/V_{ICA} = \text{const} \cdot (D_{MCA})^{-2} \quad (3)$$

The hemispheric index V_{MCA}/V_{ICA} therefore seems attractive for predicting MCA lumen narrowing. Similar considerations were obviously important to Weir *et al.* (1978). They assessed angiographical spasm employing the indices of Gabrielsen and Greitz (1970) to compensate for individual variation of the cerebral artery tree. The hemispheric V_{MCA}/V_{ICA} index can be considered as introducing similar principles in blood velocity measurements.

Comparing angiograms and blood velocity recordings in 80 patients with SAH we found that compared with the MCA blood velocity, the hemispheric index showed less variation with age and gender (Lindegaard *et al.* 1989). This grees with studies in normal persons (Grolimund and Seiler 1988). With angiographical vasospasm of the MCA mainstem scored as severe, moderate, suspected, or absent, the better correlation was obtained with the hemispheric index. Our series suggested an index of $\geqslant 3.0$ as denoting the presence of angiographical MCA spasm, with values of $\geqslant 6.0$ indicative of severe spasm (Lindegaard *et al.* 1989).

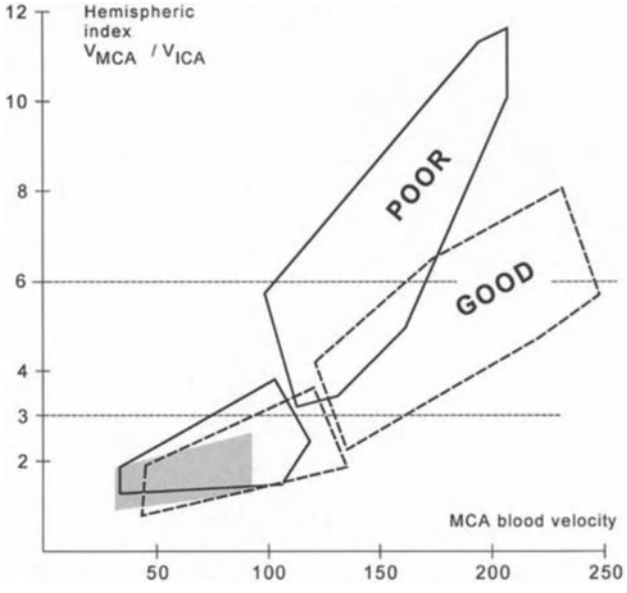

Fig. 4. Patients with recent SAH. Comparison of MCA blood velocity (in cm s^{-1}) and the hemispheric index V_{MCA}/V_{ICA} in patients in Grade I–II* (good condition, broken outline) and Grade II–IV (poor condition, drawn outline). In the presence of angiographical MCA spasm clear differences in index were revealed for a given absolute velocity (right). The groups overlapped when MCA spasm was absent (left). Shaded: patients in good condition investigated within 48 hours after SAH

* Grades according to Hunt and Hess (1968)

The advantage of the index was most evident in patients in poor clinical grade (Hunt and Hess' Grade III–IV, Hunt and Hess 1968). Some of these patients had a V_{MCA} about 120 cm · s^{-1} despite severe angiographical MCA spasm. In these patients the V_{ICA} was very low, about 20 cm · s^{-1}, probably indicating a low blood flow, yet the hemispheric index V_{MCA}/V_{ICA} was about 6.0 (Fig. 4). This we interpret as confirming that the hemispheric index adds information of significant clinical value, and therefore maintain that to reduce misjudgement it is essential to obtain an insight into the blood flow in the artery system of interest. Using the hemispheric index this may be achieved in a clinical TCD routine.

A close conseptual relation to the hemispheric index is the spasm index of Jakobsen (Jakobsen *et al.* 1990 b). This is obtained from dividing the V_{MCA} by the CBF in the MCA perfusion territory: V_{MCA}/CBF_{MCA}. The CBF_{MCA} may be estimated by means of the initial slope algorithm with 133-Xe inhalation. This index remained stable even in cases with great day to day variation in V_{MCA} and CBF.

The First Minutes and Hours After SAH

It is now generally accepted that an early phase of vasospasm does not occur during the first 24 hours after a first aneurysm rupture in humans. This conclusion follows from angiograms obtained during and immediately after aneurysmal rupture (Wilkins 1976) and from recordings of blood velocity obtained during the first minutes (Grote and Hassler 1988) and hours (Romner *et al.* 1989) after the bleed.

During the first critical seconds after SAH the blood velocities drop precipitously (Grote and Hassler 1988). This reflects the drop in cerebral blood flow as shown by means of electromagnetic flowmetry (Nornes 1973 a, Nornes 1978), which is due to the dramatic increase in intracranial pressure (Nornes and Magnæs 1972) during this momentous phase. In a patient who ultimately had a good recovery, Grote and Hassler (1988) observed reverberating MCA blood velocities (see Fig. 3 e) compatible with total or near-total cerebral circulatory arrest (Hassler *et al.* 1988) for the first 100 seconds following a rebleed. The blood velocities became normalized within the next 2–3 minutes. Another patient showed reverberating blood velocities and total or near-total blood flow arrest persisting for 10 minutes. Thereafter net forward flow returned, however, the patient died from the resulting ischemic brain damage. Romner *et al.* (1989) investigated 19 patients within 12 hours after SAH and found MCA blood velocities within normal limits bilaterally in all.

Time Course After Aneurysmal SAH

Vasospasm, as seen from the X-ray films, appears three days after aneurysmal SAH and reaches a maximum incidence during the second week

(Kwak *et al.* 1979, Symon 1980, Weir *et al.* 1978). Angiography is, however, not clinically acceptable as a means to follow the course of vasospasm in the individual patient at risk. On the other side, serial blood velocity measurements by TCD can provide the information required for individualized patient management during this critical stage, atraumatically and with no cooperation from the patient apart from lying relatively still.

The time-course of blood velocities seems to follow the pattern demonstrated from serial angiograms. Increased velocities are rare within the first two days after a single bleed, while the velocities escalate from the end of the first and well into second week (Aaslid *et al.* 1986 a, Seiler *et al.* 1986, Harders and Gilsbach 1987, Sekhar *et al.* 1988, Hutchinson and Weir 1989). High velocities persist for days and thereafter recede more slowly. There seems to be a relationship between the increase in blood velocities (i.e., vasospasm) and the extent of the bleed (Fisher *et al.* 1980, Seiler *et al.* 1986, Harders and Gilsbach 1987, Brouwers *et al.* 1992). However, the correlation with clinical grade seems to be poor (Seiler *et al.* 1986, Compton *et al.* 1987, Sekhar *et al.* 1988), i.e. some patients remain in good clinical condition despite blood velocities well above $200\,cm \cdot s^{-1}$ (Seiler *et al.* 1986). It has been established that patients in poor condition have lower CBF and lower blood velocities (Sekhar *et al.* 1988, Matsuda *et al.* 1990). It seems reasonable to assume that some of these patients, possibly all, have intracranial hypertension (Klingelhöfer *et al.* 1991).

Similar data pertaining to the hemispheric index V_{MCA}/V_{ICA} have not been reported as yet. Aaslid *et al.* (1986 a) noted significantly reduced ipsilateral ICA blood velocity in patients when the MCA velocity was $> 200\,cm \cdot s^{-1}$. From this it may be inferred that the time profile of the hemispheric index can be expected to improve the visualization of the escalation and decrease of cerebral vasospasm.

With current TCD equipment the aneurysm itself can be detected only when large and favourably situated (Lindegaard *et al.* 1986 b).

Distal Artery Spasm

Distal cerebral arteries, i.e. the pericallosal artery and the MCA branches beyond the Sylvian fissure, are out of reach with current TCD techniques. Thus, if vasospasm involves these vessels only, it may be overlooked with TCD. An assessment of the incidence and significance of predominantly distal artery vasospasm is therefore important.

In their series of 34 patients investigated with TCD within 24 hours of angiography, Sloan *et al.* (1989) had 12 false negative findings. These were attributed to distal MCA spasm (four), proximal or distal anterior cerebral artery spasm (six), and supraclinoid ICA spasm (two). Hutchinson and Weir (1989) claimed that in their experience, severe narrowing of distal

MCA branches in the absence of proximal spasm was "exceedingly rare". In Newell's series (Newell *et al.* 1990) of 136 angiograms from 68 patients with ruptured aneurysms of the anterior circulation, 40 showed angiographical vasospasm defined as $\geqslant 25\%$ lumen narrowing. Of these, one half had vasospasm of the basal arteries, 42.5% had evidence of spasm of both basal and distal segments, and 7.5% showed vasospasm involving the distal segments only.

Delayed Ischemic Dysfunction

The incidence of delayed ischemic dysfunction (DID) is about one half of the incidence of angiographical vasospasm, – and the degree of angiographic vasospasm does not necessarily correlate with the patient's clinical condition. TCD findings corroborate the latter observation (Seiler *et al.* 1986), however TCD data also indicates that vasospasm is more prevalent than known from angiography studies (Aaslid *et al.* 1986 a). DID has been observed with V_{MCA} values as low as $120\,cm \cdot s^{-1}$, while in other patients, a V_{MCA} twice as high may be well tolerated. High velocities seem to precede DID by at least 1–2 days (Seiler *et al.* 1986). During this time-window the situation seems to proceed from the "prodromal" to the "symptomatic" stage (Sekhar *et al.* 1988).

Seiler and Aaslid (1986) reported on 39 patients. Ten of 11 patients with reversible DID had $V_{MCA} > 200\,cm \cdot s^{-1}$. Three of the 20 asymptomatic patients had $V_{MCA} > 200\,cm \cdot s^{-1}$. Harders and Gilsbach (1987) observed DID in 14/50 patients treated with early surgery and nimodipine. DID occurred between six and 12 days after SAH and all these patients had $V_{MCA} > 120\,cm \cdot s^{-1}$.

Klingelhöfer *et al.* (1991) also observed that the outline of the envelope of the blood velocity spectrum showed augmentation of pulsatility with increasing ICP levels in excess of 20 mmHg. This valuable clinical information may give clinicians an explanation to unexpectedly low absolute blood velocities in patients in poor clinical condition. The results from the study also emphasize that when intracranial hypertension and vasospasm concur, the risk for DID, brain infarction, and death increases dramatically.

Steep velocity increases during the first three days (i.e., $> 20\,cm \cdot s^{-1}$ per day) may signal an increased risk for DID (Seiler *et al.* 1986, Harders and Gilsbach 1987). In Seiler's series, three patients died from brain infarction, and the mean V_{MCA} increase exceeded $30\,cm \cdot s^{-1}$ per day in these patients (Seiler *et al.* 1986). Out of a series of 121 patients, Grosset *et al.* (1992) observed DID in 47. The average of the highest MCA or ACA blood velocity in patients with DID was $186\,cm \cdot s^{-1}$, significantly higher than in patients not developing signs of DID. The hemispheric index was also significantly higher in patients with DID, 6.0 versus 4.5. Extra steep

velocity increases, in the order of $50\,cm \cdot s^{-1}$ per day, were observed in a substantial proportion of the patients. The average increase in the 47 patients with DID was $67\,cm \cdot s^{-1}$ per day, with an average of $47\,cm \cdot s^{-1}$ per day in the others. Twenty patients with steep velocity increases were selected for CBF studies with the HMPAO-SPECT technique. DID developed in 10 of 15 patients studied before the onset of any deficit. The CBF pattern showed low perfusion areas in 14 of these 15 patients and in a further five patients with already manifest DID. These findings correlated with the arteries showing elevated blood velocity (Grosset *et al.* 1992).

It may be difficult to appoint an "ischemic threshold" for blood velocities, and this is not surprising. In view of the leptomeningeal collateral system of the brain one could expect that one spastic artery, even an MCA, may be well tolerated. However, this delicate balance may become decompensated if spasm afflicts the other input channels, the anterior and posterior cerebral arteries as well. To obtain a better insight into the haemodynamics of DID it is therefore prudent to consider the circle of Willis and its inlets and outlets as a system with considerable potential for flow redistribution. The average hemispheric index, i.e. the average of the ipsilateral MCA and ACA values suggested by Sekhar *et al.* (1988) may be useful. Jakobsen's spasm index (V_{MCA}/CBF_{MCA}) seems promising, but sacrifices the technical simplicity and the short response time which are important advantages with the stand-alone TCD approach.

The Effect from Surgery

To assess the effect of aneurysm surgery on cerebral artery blood velocities, Hutchinson and Weir (1989) investigated 12 patients operated electively (no recent bleed). After the operations they observed only very moderate velocity increases, up to about $60\,cm \cdot s^{-1}$. Seiler *et al.* (1987) reported MCA blood velocities up to $110\,cm \cdot s^{-1}$ in patients operated for asymptomatic aneurysms or sellar/parasellar tumour.

The timing of surgery and its haemodynamic effects were addressed by Romner *et al.* (1990). In their 36 patients the preoperative MCA blood velocities were similar in the patients operated upon at < 48 hours and at 49–96 hours after SAH. The allocation mechanism was not explained, but the average clinical Grade was very similar in the two groups. No signs of DID and no velocities $> 120\,cm \cdot s^{-1}$ were observed in the 18 patients operated upon within 48 hours. In the other patients, velocities of $120\,cm \cdot s^{-1}$ were seen in three at 5–7 days after SAH, and in seven at 10–12 days after the bleed (difference statistically significant). Two patients died from delayed ischemia and brain infarction. They had been operated upon at 76 and 96 hours after SAH and had velocities $> 170\,cm \cdot s^{-1}$.

Correlation with Angiography

Basically, the term vasospasm refers to the narrowing of brain arteries seen from angiographical images. First described by Ecker and Riemenschneider (1951), the diagnosis by cerebral angiography continues to be the reference standard with regard to this condition. Comparisons with angiographical findings have therefore been performed to validate the TCD findings (Aaslid *et al.* 1984, Harders and Gilsbach 1987, Sekhar *et al.* 1988). However, in order to assess how TCD and angiographical findings correlate (using angiography as the standard of reference) we need answers to the following questions: 1) How should angiographical vasospasm be defined? 2) How accurate and consistent is the assessment of vasospasm from the angiograms films?

1) Standard measurement points for basal brain arteries have been devised by Gabrielsen and Greitz (1970), but these points may not coincide with the narrowest vessel segments. The calibre of cerebral arteries is individually variable, and the assessment of angiograms obtained after an SAH is difficult since only in very exceptional cases will angiograms have been obtained pre-SAH. It seems realistic to assume that when comparing with the corresponding vessel on the other side, only diameter differences exceeding 20% will be recognized (Symon 1980). Diffuse vasospasm, more or less involving all basal cerebral arteries, will complicate this estimation.

2) The inter-observer variability while reading angiograms has been addressed in two reports. Using Kappa statistics (correlation of categorical data with correction for agreement by chance), Eskesen *et al.* (1987) confirmed that two independent judges may read one and the same angiogram very differently. This may explain why the reported incidence of vasospasm after SAH ranges from 21 to 78% (Chyatte and Sundt 1984). Even when angiographic spasm is evident, deciding if it is moderate or severe may be intricate. Probably illustrating a best-case situation, Lindegaard *et al.* (1989) found agreement between two independent judges (radiologist and surgeon from the same institution) in 105/124 hemispheres (Kappa = 0.67) for spasm of the MCA and in 62/124 (Kappa = 0.43) for the ACA. It seems that no intra-observer variability data have been reported.

Since the assessment of angiograms by eye is categorical (vasospasm is present/absent or either severe, moderate, mild or absent) while blood velocities and the derived indexes are reported on continuous scales, these two methods will remain very difficult to reconcile. It may be suggested that at least for research purposes judgement by eye should be replaced by measurements of the contrast-filled column on angiograms and corrected for magnification (du Boulay 1980). This would be very relevant if the deleterious effects of vasospasm are due mainly to the loss of inflow pressure from viscous drag in the narrowed vascular segments and disturbed flow

(or so-called turbulence). Indeed, reports of the relief of DID symptoms within minutes after the successful transvascular balloon dilatation of severely spastic brain arteries documented angiographically and with TCD (Newell *et al.* 1989) seem to support this, however, more evidence from larger series will be necessary. If this can be confirmed it does not seem unrealistic to estimate the diameter of the artery in question using a nomogram with premediated confidence limits, and a physiological variable connected with blood velocity.

SAH from Other Causes

Vasospasm after rupture of an arteriovenous malformation is considered rare (Parkinson and Bachers 1980), but may have clinical importance (Lindegaard *et al.* 1986). In two AVM patients with haemorrhage mainly to the basal cisterns we have seen typical signs of vasospasm in the MCA opposite to the hemisphere harbouring the malformation. In these remote and normal MCA's blood velocity increased to about $150\,cm \cdot s^{-1}$ and the V_{MCA}/V_{ICA} index rose to about 5. No signs of DID were observed. After rupture of an AVM even its feeding artery may develop vasospasm (Hassler 1986).

Using the V_{MCA}/V_{ICA} hemispheric index, Weber *et al.* (1990) found vasospasm in 14 of 35 severely head injured patients. Moreover, vasospasm correlated with the amount of blood seen from CT scans. A high index value was an ominous prognostic sign, the two patients with values of > 5.0 died. Martin *et al.* (1992) investigated 30 head injury patients, vasospasm occurred in eight. Three of these had no blood on the CT scans and a brief course of spasm. In patients with CT scans showing traumatic SAH the maximum blood velocities occurred during the second week, resembling the course of blood velocities in vasospasm after spontaneous SAH (Aaslid *et al.* 1986 a). This may be interpreted as reflecting that both conditions involve diffuse and direct trauma to the brain and the collection of blood in the basal cisterns.

Special Considerations

Hemispheric Index

We have considered a V_{MCA}/V_{ICA} index of $\geqslant 3.0$ as denoting angiographical MCA spasm, with values $\geqslant 6.0$ indicating severe spasm (Lindegaard *et al.* 1989). The latter value emerged through taking repeated angiography into consideration: a slimming of the ICA (average about 7%) seemed to occur with increasing cerebral vasospasm, probably reflecting the vascular adaptation to lower rates of flow. In patients in very poor condition, precluding angiography, this slimming could be even more pronounced. Al-

though it may be difficult to obtain angiographical proof in such situations, we surmise that especially if a high priority is given to avoid underdiagnosing severe vasospasm in high-risk patients, a slightly lower threshold, 5.0–5.5, could be used.

Examination Technique

The MCA branches in the Sylvian fissure can often be detected at depths between 30 and 45 mm. By changing the probe position slightly it seems possible to differentiate between different branches. Occasionally, unexpectedly high velocities may be found corresponding to one branch, while other branches, and the MCA mainstem, have lower velocity. Such findings probably indicate spasm at the M 2 level, and we regard this as being equal to a similar velocity found more proximally. In such a situation we calculate two index values. However, finding one vasospastic MCA branch may have less clinical consequence because of the potential for collaterals within the MCA territory.

Cerebral Vasospasm – Physiology and Pharmacology

By virtue of mobility and relative simplicity, TCD enables physiological investigation of patients with SAH on a greater scale. The vasomotor reactivity to hyper- and hypocapnia was investigated by Hassler and Chioffi (1989). The authors classified vasospasm according to the MCA blood velocity. Patients with mild vasospasm, defined as velocities 80–120 $cm \cdot s^{-1}$ in eucapnic situations, seemed to have about half the vasomotor response observed in normal individuals. With severe spasm, MCA blood velocity $> 160\,cm \cdot s^{-1}$ (mean $214\,cm \cdot s^{-1}$), the peripheral vascular bed seemed near maximally dilated (at least to hypercapnic stimulation). However, the vascular constrictive capacity was about one third of the normal. The authors considered these findings as suggesting that these patients had no vasoparalysis. However, since the hypocapnia was produced voluntarily one may suspect that the authors were prevented from investigating patients where vasoparalysis might have been well expected: those in very poor clinical condition, with multi-vessel spasm, and probably, also with intracranial hypertension (Lundar *et al.* 1990).

The TCD method may be used as an aid in the investigation of the pathophysiology of SAH. The effects of therapy designed to relieve vasospasm or to abate the effect of vasospasm on the brain have been investigated. In an open study in 37 patients given nimodipine i.v. within 4 days after SAH and compared with 33 patients who did not, Seiler *et al.* (1987) concluded that nimodipine did not prevent vasospasm but significantly reduced the blood velocities, especially in patients who, from clinical and radiological scores, were considered as having a high risk for ischemia.

Among the high-risk patients the incidence of DID was significantly lower in the nimodipine group while no difference was obtained in low-risk patients. The effect of nimodipine on the vasomotor response to CO_2 has also been investigated; – no significant effect was found (Seiler and Nirkko 1990). Using TCD to assess patients with SAH, Juul *et al.* (1990) reported evidence of increased neuropeptide Y activity with cerebral vasospasm.

Clinical Implementation

In patients with subarachnoid haemorrhage from aneurysm rupture TCD blood velocity measurements allow definition of location and severity of cerebral artery spasm in a standardized way whenever needed. In good-risk patients we operate within 72 hours after SAH. Vasospasm remains a threat following operation, an escalating V_{MCA}/V_{ICA} index underscoring the need for intensified medical treatment. If surgery is delayed for any reason, we determine the timing of the operation individually with the aid of TCD. Combining clinical data and blood velocity measurements is important when the V_{MCA}/V_{ICA} index is between 3 and 6. Repeated observations are of value because from Day 3 the course and the spread of vasospasm become important as well. Although we use nimodipine only in strictly selected cases, we agree with Seiler *et al.* (1988) who operate upon alert patients admitted after 72 hours provided that no indication of severely escalating vasospasm appears over the next 12–24 hours.

During the second week, a stable index of about 5 on one side does not preclude operation if the technical risk is considered small and the patient's clinical condition is acceptable. Surgery is withheld if the hemispheric V_{MCA}/V_{ICA} index is above 6.0, or rises sharply during the first week. In our view such findings overrule even a good clinical grade. We operate on these patients when the index recedes, indicating remission of spasm. Blood velocity measurements also reduce guesswork in deciding whether or not a clinical deterioration is due to vasospasm. We submit that repeated angiography for these purposes is no longer indicated.

Proper selection, pre- and postoperative care and timing of surgery are cornerstones in the management of these patients, – equal in importance to their treatment in the operating room (Nornes and Wikeby 1979). In 1975 Drake recommended that aneurysm surgery during the first week should be immediately preceded by an angiogram (Drake 1975). The time may have come to rephrase that advice: if vasospasm cannot be ruled out from immediately preceding diagnostic angiography, surgery should not proceed without a TCD investigation.

Surgical Occlusion of the Carotid Artery

Despite continuous development in the fields of microsurgery and interventional radiology a place remains for deliberate occlusion of one carotid

artery (Swearingen and Heros 1987). However, as dangerous derangements in brain perfusion may result, it is of utmost importance to foresee the haemodynamic and clinical consequences of a such occlusion.

The mainstay monitoring techniques, EEG recordings (Sharbrough *et al.* 1973) and isotope measurements of CBF (Sundt 1983), have distinct shortcomings. It takes time before the effects from moderate ischemia transpire to the EEG record. With CBF techniques the time-resolution is poor unless the tracer is being injected directly into the carotid artery, and even so a beat to beat haemodynamical analysis is not possible. Simultaneous bilateral electromagnetic recording of carotid blood flow has provided valuable insight into the behaviour of the blood flow in the anterior circulatory system during gradual carotid occlusion (Nornes 1973 b). It would be desirable to assess the blood flow in the perfusion territory of the MCA, where ischemia from deliberate carotid occlusion is most likely to occur, within a short time span and with the information available immediately. The TCD method seems promising for this purpose, although the absolute blood flow can not be addressed with current TCD instrumentation. However, since trial occlusions of the ICA in the neck seem to incur only very minor changes in MCA diameter (Aaslid *et al.* 1991), the relative changes in MCA blood velocity should reflect relative changes in MCA blood flow.

Based on their experience in monitoring blood velocities during carotid clamping for endarterectomy, Powers *et al.* (1989) performed permanent ICA occlusion in six patients, abrupt occlusion in two, and a gradual occlusion by Crutchfield clamp in four patients. Reductions in MCA blood velocity of from 7 to 38% were tolerated without difficulty.

In the carotid endarterectomy series by Powers *et al.* (1989), slowing of the EEG was observed during ICA occlusion in three patients. Two patients had velocity drops of 57 and 79%. The EEG changes disappeared when ICA blood flow was restored. In one patient with a velocity drop of 71% EEG slowing occurred after four minutes and remained stable during a total of 58.5 minutes' occlusion time. Postoperatively there was a contralateral hemiparesis which resolved almost completely, with CT scans revealing a lucency in the ipsilateral parieto-occipital region suggesting a haemodynamical etiology. Since the tolerance to ischemia also is a function of time the authors proposed as a guideline the following perfusion velocity index: $PV_i = (V_o/V_i)(100/t)$ where V_o is the velocity during occlusion, V_i denotes pre-occlusion velocity, with t the occlusion time in minutes (Powers *et al.* 1989). For permanent occlusion ($t \rightarrow \infty$), this index cannot be used.

Ungersböck *et al.* (1991) performed manual trial occlusion of the carotid artery in 11 patients. Immediately after occlusion MCA blood velocity was between 26 and 78% (mean 52%) of the baseline value. After 30 seconds' occlusion the velocity had been restored to within 10% of baseline in six,

a moderate increase was seen in one, while in four patients velocities persevered at between 25 and 43% of baseline, suggesting poor Willisian collaterals and, presumably, a high risk for neurological deficit should a surgical carotid occlusion be needed. No information on treatment and results was presented.

Our protocol in patients who may require permanent surgical occlusion of one ICA includes manual trial occlusions of the common carotid artery with monitoring of MCA blood velocity. Two patients have undergone ICA trap-ligation to allow radical surgery for malignant extracranial tumour. During trial occlusions the MCA blood velocity in these patients remained between 60–70% of pre-test values. Similar values were obtained when occluding the ICA by using a Selverstone clamp applied under local anaesthesia. No neurological deficits were seen following the permanent ICA trap-ligation. Permanent occlusion was withheld in a third patient whose MCA blood velocity dropped to below 50%.

In our opinion data are not yet available to say precisely the degree of blood velocity changes that is compatible with an acceptable risk in surgical ICA occlusion. Nevertheless, the findings of Powers *et al.* (1989) and our own experiences could be interpreted as suggesting that a velocity drop of 40% or less denotes a situation where gradual carotid occlusion may be safe. This is also compatible with findings from bilateral simultaneous electromagnetic flowmetry (Nornes 1973 b); – the blood flow in the opposite ICA increased by between 50 and 75% in patients who tolerated ICA occlusion, while increases of 20% or less indicated a poor tolerance. Our view is corroborated by observations that EEG changes develop when CBF drops below 30 mm/100 g/min (Sharbrough *et al.* 1973), i.e. to some 40% below normal levels.

Examination Technique – Special Considerations

To assess the behaviour of MCA blood flow during carotid trial occlusions it is prudent to insonate the MCA exclusively, and to avoid the supraclinoid segment of the ICA and the circle of Willis in the sampling field. To this end we prefer a short sampling distance (typically 35–45 mm in the average adult patient).

Carotid occlusion modifies the haemodynamical balance not only between the anterior and posterior circulation, but also between the two anterior cerebral and the ipsilateral middle and posterior cerebral arteries. This implies that the bulk of tissue perfused from each of these vessels (T in Eq. 1) will change. Recordings from two vessels at the same time, as previously described (Nornes *et al.* 1990, Nakstad *et al.* 1992), could be used to build a broader conceptual framework and improve the guidelines for clinical practice.

Arteriovenous Malformations

A cerebral arteriovenous malformation (AVM) can be regarded as consisting of two parts: the basically normal feeding arteries and draining veins, and the nidus – the shunt vasculature proper. The involved arteries and veins usually also have branches responsible for the nutritive perfusion of normal brain tissue. Angiography provides the essential anatomical map of the vasculature and remains the basis for therapy by interventional radiology and/or surgery. From angiograms, AVM feeding arteries may be viewed as showing or not showing the successive tapering towards the periphery which is a characteristic of the normal arterial tree. While the feeders to small shunts and the minor contributors to larger ones do taper more or less in the normal manner, the wide feeding arteries to high-flow AVM's seem to lack this feature. This is believed to reflect that a high proportion of the blood flow passes straight through the shunt into the draining veins ("waste-flow"), and that, by comparison, only a small part of the bulk flow is being diverted to the nutrition of normal brain. To reconcile findings from angiography and TCD, the classification into "tapering" and "non-tapering" AVM feeding arteries therefore seems logical.

Arteries supplying a medium-sized or large AVM are wide with a high blood flow, they are thus well suited for detection with TCD. Compared to normal brain arteries the characteristical features of these vessels include a high blood velocity with a low pulsatile amplitude (Nornes *et al.* 1979 a, Nornes and Grip 1980). The low pulsatility is usually attributed to the low resistance to flow through the shunt, however it probably also reflects that the AVM proper is haemodynamically more rigid than the microvasculature of normal brain (Aaslid and Lindegaard 1986). TCD investigation of these patients has two goals: 1) to differentiate between feeders and normal arteries near the base of the brain (this is fundamental in order to recognize an AVM), and 2) to assess these vessels haemodynamically.

Recognition of AVM

The Doppler audio signal from typical AVM feeding arteries is immediately apparent from the Doppler-shifted audio signal and from the spectral display. Low-frequency "gruffy" bruit is often obtained corresponding to the vascular bifurcations near the circle of Willis. These contribute to an impression of high flow in tortuous arteries. Musical murmurs (Aaslid and Nornes 1984) are absent except in vasospasm following AVM rupture and SAH.

In a series of 22 patients with AVM's with diameter > 2 cm, Lindegaard *et al.* (1986 a) found significant differences between AVM-feeding arteries and normal arteries without AVM involvement. Further, significant dif-

Table 1. *TCD Findings in 22 Patients with Unruptured Cerebral AVM**

Variable	Normal remote MCA	Tapering AVM feeders	Nontapering AVM feeders
Velocity ($cm \cdot s^{-1}$)	44–94 (65)	75–124 (95)	90–237 (136)
Velocity (%)		106–225 (145)	100–443 (223)
PI	0.65–1.10 (0.87)	0.41–0.74 (0.62)	0.22–0.70 (0.44)
PI (%)		52–79 (67)	32–66 (51)

Table shows ranges with median values in brackets.
Percentages denote AVM feeding artery blood velocity and pulsatility index (*PI*, see Fig. 2) expressed as percentages against values obtained from the normal remote middle cerebral artery (*MCA*) in individual patients.
* Data from Lindegaard *et al.* (1986 a).

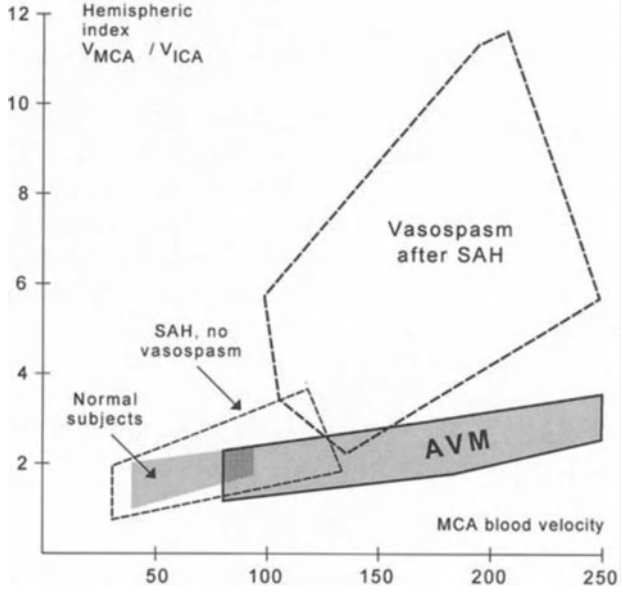

Fig. 5. Graph illustrates the value of the hemispheric index V_{MCA}/V_{ICA} to differentiate between high blood velocities in feeding arteries to arteriovenous malformations and in cerebral vasospasm (data from Lindegaard *et al.* 1986 c and 1989)

ferences were found between tapering and non-tapering AVM feeders (Table 1).

High blood velocities are characteristic features of both spastic arteries and AVM feeders. The differentiation between the two conditions may be

difficult from only one recording from one vessel. However, in general the pulsatility is higher (more near the normal or even increased) in vasospasm. The assumption of unilateral involvement in AVM is unreliable, – large AVM's often have multiple feeders while vasospasm may involve just one vessel. Further, after the rupture of an AVM vasospasm may develop in remote normal arteries (Lindegaard *et al.* 1986 c) as well as in the AVM feeding artery (Hassler 1986). Typical of the inflow channels to large AVM's is that the high velocity is present also extracranially. It is therefore not surprising to find ICA blood velocities approaching 90 or even 100 $cm \cdot s^{-1}$ in the distal extracranial ICA. While the hemispheric index V_{MCA}/V_{ICA} seems to be only slightly elevated on the side of the AVM (median value 2.1), the difference from findings in hemispheres without AVM involvement (median 1.5, within normal limits) is still highly significant (Lindegaard *et al.* 1986 a). Of greater importance is the finding that despite extremely high MCA velocities the index V_{MCA}/V_{ICA} rarely exceeds 3.0 in patients without recent AVM haemorrhage (3.4 being the highest index value observed in our series). The hemispheric index should therefore facilitate a differential diagnosis versus high velocities due to vasospasm. In vasospasm the ICA velocities are within or below the normal range (Fig. 5). In our experience residual problems can be solved through combining the findings from TCD with clues from the case history and the CT scans.

In patients with multiple feeding arteries, the vessel with the highest velocity also show the lowest PI value. Using nonparametrical statistics we obtained a trend towards higher velocities (and lower PI values) with AVM diameters > 4 cm, though no significant difference was obtained (Lindegaard *et al.* 1986 a). By means of parametrical correlation, Hassler (1986) found highly significant positive association between AVM volume and velocity and an inverse relationship between pulsatility and AVM size. The above findings have been corroborated in other studies (Schwartz and Hennerici 1986, Pasqualin *et al.* 1991).

Since an AVM probably arises from persisting direct connections between the arterial and the venous sides of the embryonal vascular plexus (Wilkins 1985), one might postulate that the location of the AVM can be obtained from considering the pattern of its feeding arteries. Our findings confirmed this: AVM's situated near the center of the perfusion territory of an artery were rarely supplied from other basal cerebral arteries (apart from collateral flow in the circle of Willis). On the other hand, multiple feeders were the rule in large AVM's covering the borders between adjacent perfusion territories (Lindegaard *et al.* 1986 a). Thus, it is possible to obtain a useful impression of the localization of the AVM proper from the TCD findings.

In the Sylvian fissure the MCA can often be detected at depths between 30 and 45 mm. By changing the probe position slightly it is possible to

differentiate between the MCA branches. When situated within the sectors of the intracranial space accessible through the patient's "ultrasound windows" (Fig. 1), the AVM proper and its draining veins can be delineated (Lindegaard *et al.* 1986 a). The Doppler audio signal from the shunt and its vicinity typically has a rough "machine-hall" quality which is due to disturbed flow conditions locally and the tortuous vascular channels comprising the AVM nidus. As demonstrated previously from recording in the surgical field (Nornes *et al.* 1979 a, Nornes and Grip 1980), the draining veins show a higher velocity and more residual pulsatility compared with normal intracranial veins.

The identification of an artery (or a vein) as being involved in the AVM complex basically relies upon one physiological parameter, the ratio of shunt flow versus nutritive blood flow. It is evident that there will be a downward limit as to the AVM size, or more correctly, the degree of shunt involvement, which can be detected. In an early series of 16 patients, TCD permitted a correct diagnosis in 14 patients (87%) 27/31 (93%) of the angiographically verified feeding arteries (Lindegaard *et al.* 1986 c). Recently, Sommer *et al.* (1992) presented advanced techniques combining transcranial and extracranial Doppler to relieve some of the difficulties associated with the recognition of low-capacity shunts.

Haemodynamical Assessment

Very high velocities, 170–220 $cm \cdot s^{-1}$ or even more, can be encountered (Lindegaard *et al.* 1986 a). Although such feeders may be long, extending from the circle of Willis through the Sylvian area to an AVM situated high on the convexity of the hemisphere (Grolimund *et al.* 1987), these high velocities are more often seen in relatively short feeders to more proximally located AVM's. In fact there seems to be an inverse relationship between the length of the feeder and the blood velocity (Hassler 1986). Further, the inverse relationship between blood velocity and pulsatility has been well established (Lindegaard *et al.* 1986 a, Hassler 1986). This probably reflects that these variables are inseparable as far as AVM's are concerned, the relationship being characteristic of blood flow in a low resistance system with a high volume stiffness.

The CO_2 reactivity of non-tapering feeders is near zero, probably reflecting a high shunt flow. However, this does not necessarily mean that vasoparalaysis prevails in the surrounding normal brain (Hassler and Steinmetz 1987). The reactivity of the flow in tapering feeders ranges from significantly or moderately reduced to near the normal reactivity level. Investigation of vascular reactivity provides further clues as to distinguish between feeding arteries to the AVM and purely nutritional arteries perfusing normal brain.

The correlation between anatomical size and haemodynamical variables

in AVM's suggests increasing velocity and decreasing pulsatility with increasing size of the nidus. Further, large AVM's more often have multiple feeders. However, a comparison with information from vascular images remains clinically important since blood velocity varies substantially. A medium-sized AVM in the strict anatomical sense may hence have wide feeder arteries with blood flowing at very high velocity and a low pulsatile amplitude (Nornes and Grip 1980, Lindegaard *et al.* 1986 a, Hassler 1986). The haemodynamical dimension of a such lesion can thus exceed its anatomical size. The knowledge on AVM haemodynamics obtained through ultrasound methods has therefore improved our understanding of angiography as a method to investigate the haemodynamics of the normal and abnormal brain circulation.

Postoperative Findings

In our previously reported series (Lindegaard *et al.* 1986 a), the highest MCA blood velocity was $186\,cm \cdot s^{-1}$. This AVM had a diameter about 6 cm and was situated in the left parietal region behind the central sulcus. Immediately after AVM excision, the brain showed signs of incipient swelling, and in the ICU symptoms of possible hematoma developed over the following hours. Emergent reoperation revealed a small clot and a taut brain. The postoperative aphasia and hemiparesis finally subsided. Control angiography at three months confirmed total removal of the AVM. It is noteworthy that this AVM received three long and enlarged MCA feeding arteries, each giving off numerous nutrient branches toward the periphery.

Three months after excision of the AVM the PI was within the normal range in previous feeding arteries in 11 patients reported by Lindegaard *et al.* (1986 a). The blood velocities were lower than in the remote normal arteries used as reference. Any signs of collateral flow in the circle of Willis had disappeared. Control angiography confirmed total removal of the AVM and normal flow conditions in all these patients. These findings have been corroborated by Petty *et al.* (1990); in six patients investigated at an average of 16 days after AVM excision, blood velocity had dropped by an average of 46% ($56\,cm \cdot s^{-1}$). The pulsatility had increased in all previous feeding arteries.

Superselective embolization of large AVM's are being increasingly employed to obtain a step-by-step obliteration thereby allowing the normal brain vasculature a gradual adaptation to normal levels of perfusion pressure. When used in preparation for surgery it seems to reduce the risk of postoperative hyperperfusion and breakthrough (Spetzler *et al.* 1987). Petty *et al.* (1990) investigated nine patients approximately three days after AVM embolization. While the pulsatility increased, the average velocity drop was 31% ($38\,cm \cdot s^{-1}$). After superselective embolization in 11 patients Harders

et al. (1988) reported normalization of cross-filling and a slow reduction in the blood velocity in AVM-feeding arteries.

Results from follow-up after radiotherapy of AVM's have been reported. In six patients the blood velocity in feeder arteries decreased by an average of 15% over the first three months. By the end of the first year, the drop amounted to 24% of the values obtained before irradiation (Mehdorn and Grote 1988).

Clinical Implementation

The problems encountered when attempting to describe blood flow in exact fluid dynamic terms are considerable. However, for practical working purposes the application of relatively simple physical principles nevertheless reveals some clues to the understanding of important haemodynamical mechanisms. A useful model to integrate the information obtained from angiography and blood velocity measurements is obtained through the Hagen-Poiseuille equation which, solved with regard to blood velocity (V), reads:

$$\triangle P = V \cdot (8 \cdot L \cdot \mu / r^2)$$

where $\triangle P$ denotes the pressure loss due to viscous drag, with L the length, r the radius of the vessel, and μ the viscosity (Nornes and Grip 1980; Hassler 1986, Lindegaard *et al.* 1986 a).

At normal rates of flow and velocity, very little of the potential energy that is transmitted by means of pressure is actually spent in the transport of blood from the aorta and up to the circle of Willis (Bakay and Sweet 1952). However, the high velocity (V) of the flow in feeding arteries to an AVM, increases the pressure drop from the viscous drag (Nornes and Grip 1980). Since the pressure loss also increases with the length of the feeding artery (L), brain areas perfused from the nutrient branches of AVM feeders may have chronically impaired perfusion. This may explain postoperative hyperperfusion and brain swelling, and the so-called normal perfusion pressure breakthrough (Spetzler *et al.* 1978). The factor of greatest significance is probably whether these nutrient branches emerge from the feeder trunk proximally (near the circle of Willis) or distally where the perfusion pressure is at the lowest. There is evidence that postoperative redistribution of blood flow and hyperemic complications, occur more often following the embolization or excision of large AVM's with long feeding arteries (Nornes and Grip 1980, Lindegaard *et al.* 1986 a, Batjer *et al.* 1989, Pasqualin *et al.* 1991). Small AVM's are more prone to rupture and the explanation may be that the small AVM's are perfused at near normal CPP levels (Spetzler *et al.* 1992). Findings of low velocities, and by inference high pressures, in feeders to small AVM's contribute to explain this.

There are several systems for grading AVM's in terms of its location, arterial supply and venous drainage and size (Shi and Chen 1986, Spetzler and Martin 1986, Pertuiset *et al.* 1991). Ideally, haemodynamical factors should also be included. With the length and the calibre of the feeding artery or arteries being known from angiograms, the haemodynamical information available through TCD provide insight into the "haemodynamical dimension" of AVM's. An AVM may thus be considered in three dimensions: clinically, anatomically, and haemodynamically. Our experience has convinced us that considering clinical features and angiograms together with the TCD findings is a rational platform for clinical risk analysis and the planning and staging of diagnostic and therapeutic procedures in the individual patients.

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Clinical and Molecular Neurogenetics in Neurosurgery

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Contents

Summary

This chapter describes the basic principles of molecular genetics, particularly in relation to gene mapping and isolation (positional cloning). The application of this technology is illustrated by progress in elucidating the molecular basis of inherited tumour syndromes, including neurofibromatosis types 1 and 2 and von Hippel-Lindau disease, and molecular studies of tumourigenesis in malignant gliomas.

Introduction

Molecular neurogenetics represents a growth area in neuroscience, and its techniques are already applicable to the management of patients with neurological disease, as well as increasing our understanding of their aetiology. This review will provide an introduction to molecular genetic principles and techniques and their applications to diseases of interest to the neurosurgeon, particularly the neurofibromatoses and von Hippel-Lindau disease, as well as discussing the management of patients with these disorders in terms of genetic counselling and the screening of their families.

Mendelian Inheritance and Nucleic Acids

Genes are arranged linearly on the chromosomes, each having its own position or locus. They are transmitted via the parental gametes to each offspring, so are usually present in pairs. As a result of genetic variation, different forms of a gene (alleles) may exist at a given locus, giving different characteristics to individual members of a population. Human diploid cells (all cells except gametes) contain a pair of each of 22 chromosomes which are called the autosomes, and either two X chromosomes or one X and one Y chromosome, depending on the sex of the individual. During cell division, the process of mitosis results in two identical daughter cells. Gametogenesis involves the more complex process of meiosis which occurs in two stages. During meiosis stage one, homologous chromosomes pair and an exchange of genetic material takes place. This is known as crossing over. In meiosis stage two, the homologous chromosomes undergo reduction division in which the chromatids separate resulting in haploid daughter cells, the gametes.

Mutant genes on the autosomes may be inherited as dominant or recessive traits. Autosomal dominant genes affect the phenotype despite the presence of a corresponding normal allele on the homologous chromosome. Thus all offspring of an individual carrying an autosomal dominant disease have a 50% chance of inheriting the mutant allele, and therefore the disease. In autosomal recessive inheritance it is necessary for both alleles to be abnormal for the disease to be expressed, i.e. the affected individual is homozygous. Thus the parents of an individual affected by an autosomal recessive disease are obligate heterozygotes for the mutant allele at that locus, i.e. one of the chromosome homologues in each parent carries the mutant gene. If two heterozygotes for the same autosomal recessive gene mate, on average 1 in 4 of their children will be affected, 2/4 will be carriers and 1/4 will be normal. Defective genes on the X chromosome show a distinctive pattern of inheritance, in which males are most severely affected, and females carrying the gene may be moderately or mildly affected or clinically normal. An important feature of X-linked inheritance is that male

to male transmission never occurs, but all female offspring of affected males inherit the abnormal gene. The variation of expression of X-linked disorders in females is due to the process of lyonisation, in which the expression of one X chromosome is suppressed randomly in each cell. The distinction between X-linked recessive and X-linked dominant disorders is rather loose, although these terms are often used.

The classical observations of mendelian inheritance led to the concept of the gene as the fundamental unit of heredity, and postulated that it must have three basic properties: a specific function in the organism; the capacity for exact self replication; and, although usually stable, to be susceptible to sudden change, or mutation, resulting in a new allele which is also self replicating and may possess a new function in the cell. The molecule which endows a gene with these properties is deoxyribonucleic acid (DNA). The primary role of DNA is the direction of synthesis of proteins via ribonucleic acid (RNA). The base pair sequence in a gene determines the sequence of amino acids in a corresponding polypeptide chain. An excellent review of the structure and function of nucleic acids is provided by Alberts and colleagues (1989).

DNA consists of two very long polynucleotide strands coiled round a common axis to form a double helix. The backbone of each chain consists of phosphate and sugar (deoxyribose) groups. A nitrogenous base is attached to each sugar group, projecting inwards. The base may be one of four types: adenine (A) or guanine (G) which are purines, and thymine (T) or cytosine (C) which are pyrimidines. A and T always pair together by means of hydrogen bonds and the same applies to G and C. Mammalian chromosomal DNA is supercoiled around proteins called histones. The human genome, i.e. all the chromosomal DNA, consists of approximately 3×10^9 base pairs (bp) of DNA.

Only about 1% of genomic DNA forms structural genes comprising unique sequences (single copy genes). About 50% of human DNA consists of short repetitive sequences which either encode small high abundance proteins such as histones or are not transcribed. The function of the remaining 50% is not well understood. Some of it codes for introns, the non-coding parts of genes; the coding parts are called exons. A series of processes is involved in translation, the conversion of the sequence of bases in the DNA of a gene into a corresponding sequence of amino acids in a polypeptide chain. They are mediated by different types of RNA molecules. The DNA strands unwind so that one can act as a template for a complementary RNA chain. In this process, transcription, synthesis takes place using the available pool of ribonucleotides, and the same rules for base pairing apply as in DNA, except that uracil (U) is paired with adenine instead of thymine. The RNA strand is then processed to form messenger RNA (mRNA). This involves splicing, the removal of intervening non-

coding sequences, formation of a "cap" structure (methylated guanine residues) and the addition of a sequence of adenylated residues to the 3′ end of the mRNA being synthesized. The mRNA strand then enters the cytoplasm of the cell, and after attaching to ribosomes, serves as a template for polypeptide synthesis. The relationship of base sequences in DNA to amino acid sequences is known as the genetic code. Each amino acid is specified by three bases, referred to as base triplets or codons. The four bases of DNA can occur in 64 different base triplets; 61 of these specify one of the 20 amino acids which occur in proteins, so a particular amino acid is usually coded by two or more base triplets. There are also three triplets which specify chain termination.

In DNA replication, the two strands of the double helix separate and each strand then acts as a template for the formation of a complementary sequence, catalysed by DNA polymerase. This enzyme can also read and correct errors, allowing a high degree of accuracy in replication. If this mechanism fails, mutation occurs, either by substituting a single incorrect nucleotide (point mutation), or by adding or skipping a number of bases (insertion or deletion). Point mutations may lead to an amino acid substitution in a protein or a truncated protein. Deletions of one or more bases (but not 3 or multiples thereof) lead to frame shift mutations, with misreading of the genetic code downstream from that site.

Genetic Variation

Mutation may result in alleles with abnormal products and thus result in disease, but many give rise to normal variation, or polymorphism. This may be externally apparent, such as differences in hair and eye colour, or may only be evident at the protein level, for example in the different blood group systems. With the introduction of molecular genetic techniques, it has become possible to study DNA variation directly, and it is now known that an enormous amount of phenotypically silent variation exists in human populations. This is of great value in mapping and isolating neurological disease (and other) genes, and will be described in some detail for this reason. As has been mentioned, mammalian genes are arranged as a series of non-contiguous coding blocks, known as exons. Intragenic non-coding sequences are called introns. It is within the non-coding regions, both within and between genes, that most normal variation can be found. This is partly because of its abundance, but also because the evolutionary forces which limit mutation within coding sequences operate to a lesser degree upon non-coding DNA.

Many techniques are now available for the detection of variation in DNA. Most depend upon the resolution of DNA fragments on the basis of size or base sequence by solid phase electrophoresis, and the ability to

isolate defined stretches of human DNA as a homogeneous species. The latter is loosely termed cloning.

One of the most critical developments in molecular genetics was the discovery of restriction endonucleases. These enzymes occur in microorganisms, and recognise specific sequences of the DNA molecule and cleave it at these sites and nowhere else. With these enzymes, DNA can be cut into fragments and inserted into prokaryocyte vectors such as bacteriophage (often called phage, a virus which infects bacteria), cosmids (plasmid DNA packaged into phage), or plasmids. Plasmids are small circular DNA molecules which are found in the cytoplasm of bacteria and replicate independently of the host chromosomal DNA. Foreign DNA can be inserted into plasmids cleaved by restriction endonucleases using the enzyme DNA ligase. This hybrid DNA molecule is called a recombinant, and it is replicated on a large scale (cloned) by transfecting bacteria (usually *Escherichia coli*) and culture, allowing the production of multiple copies of the inserted DNA fragment.

A human genomic library is produced when sequences from the entire human genome are cloned in a given vector, usually phage or cosmid. It is often useful to construct libraries containing the DNA sequences complementary to mRNA transcribed in different tissues such as muscle or brain. mRNA is extracted from the tissue and complementary DNA (cDNA) to the mRNA sequences is synthesised using the enzyme reverse transcriptase. The cDNAs are then cloned into a vector, producing a cDNA library; this only contains sequences of DNA that are transcribed in the tissue studied.

A gene probe is a fragment of DNA which detects complementary sequences. Probes may be produced synthetically, the nucleotide sequence inferred from the amino acid composition of the gene product if this is known, or isolated from genomic or cDNA libraries.

Detection of DNA Polymorphism

Polymorphism may be detected in both repeated and single copy sequences. Repetitive DNA is widely dispersed throughout the genome. Tandemly repeated sequences vary in copy number between individuals because of unequal recombination (VNTRs = variable number tandem repeats). A restriction fragment containing the whole block of tandem repeats will vary in size considerably between different people, and the number of possible alleles makes these hypervariable loci very useful in linkage analysis (Nakamura *et al.* 1987). Smaller sequences which share the characteristics of VNTRs are often referred to as minisatellites, and they are used in genetic fingerprinting. A further refinement in the development of hypervariable loci is the identification of microsatellites, very short sequences which

contain a variable number of repeated dinucleotides, usually GT repeats. These occur frequently throughout the genome and are very useful in gene mapping (Weber and May 1989, Wong *et al.* 1986). They are analysed by high resolution electrophoresis after amplification of the relevant DNA sequence, using the polymerase chain reaction (PCR; Saiki *et al.* 1988, Eisenstein 1990). First the DNA sequences flanking the sequence of interest are determined. Then short oligonucleotide primers are synthesized which will anneal to one DNA strand on each side of the repeat. Successive cycles of denaturation of the DNA template, annealing of synthetic primers, and strand elongation by thermostable DNA polymerase, results in exponential amplification of the target sequence. The final number of template molecules is typically a million or more times the starting number. The PCR product is analysed by agarose or acrylamide gel electrophoresis, depending on its size.

As restriction enzymes each recognize a specific sequence of bases in human DNA, point mutations in single copy sequences may lead to the creation or loss of these sites. This results in differences in the fragment sizes generated on digestion of genomic DNA with restriction enzymes. This type of polymorphism is referred to as restriction fragment length polymorphism (RFLP). VNTRs, minisatellites, and point mutations can be detected as RFLPs by the hybridization of probes to DNA immobilised on a solid support matrix such as nitrocellulose or nylon filters in a procedure known as Southern blotting (Southern 1975). The probes are usually labelled with radioactive phosphorus using techniques known as nick translation or oligolabelling (Rigby *et al.* 1977, Feinberg and Vogelstein 1983). The position of the DNA fragments can then be determined by exposing X-ray film to the filter.

Point mutations, insertions and deletions can also lead to alterations in the physicochemical properties of small DNA fragments. These altered properties are detectable under conditions in which the double-stranded DNA fragment will denature, such as salt concentration or temperature, by denaturing gradient gel electrophoresis (Noll and Collins 1987), or in the type of intra-strand conformation adopted by single stranded DNA under non-denaturing conditions, detected as single strand conformation polymorphisms (Orita *et al.* 1989).

Gene Mapping and Isolation

The approach of "reverse genetics", localising a disease gene locus to a chromosomal region with the aim of identifying the abnormal gene product, has been applied to many neurological disorders, and is particularly useful in autosomal dominant disorders in which there are rarely identifiable metabolic markers. Genetic linkage analysis (gene mapping) has two major

requirements: sufficient family material for the disease in question, and sufficient variable DNA markers scattered throughout the genome at close intervals. One vital requirement for linkage analysis is that key individuals in the pedigree are informative for the marker studied, i.e. heterozygous. Thus the best genetic markers for linkage studies are highly polymorphic, such as VNTRs or microsatellite polymorphisms. Many RFLPs have the disadvantage of having only two possible alleles, and even if the gene frequency for each allele is 50%, the chance of any individual transmitting the disease locus being homozygous for the RFLP, and thus uninformative, is 50%.

If two independent genes are located close together on the same part of a chromosome, they are said to be linked. If they are very close together, they are tightly linked, and it is unlikely that they will be separated as a result of the exchange of genetic material which occurs between homologous chromosomes during meiosis (crossing over). The likelihood of linkage between two genetic loci is assessed statistically using lod scores (Ott 1986). Lod stands for the "log of the odds"; linkage between two loci at a given distance is usually considered to be proven or excluded if the lod score is greater than + 3 or − 2 respectively. A lod score of 3 means that the odds in favour of linkage are 1000 to 1, although, because of the low prior probability of two loci being linked, the overall probability of linkage with a lod score of + 3 is 95% (Davies and Read 1988).

Lod scores are calculated using computer programmes for a number of theoretical genetic distances (recombination fractions) between the marker and disease loci. If two loci are far apart, they should be transmitted together or separately in roughly equal proportions. The highest lod score would therefore be observed at a recombination fraction (θ) of 0.5. If the maximum lod score is 3 or greater at, for example, $\theta = 0.01$, this indicates that the two loci are linked and that recombination will occur, on average, during 1 in 100 meioses. Segregation of a disease locus may be investigated in relation to a number of markers in the same chromosomal region. The results are analysed using multilocus (or multipoint) analysis, which is a much more powerful technique than two-point lod scores, as individuals in the same pedigree who are informative for different markers contribute more information (Davies and Read 1988).

The distance between two loci is defined genetically in terms of potential recombination, and is measured in centimorgans. Crossing over between two loci 1 centimorgan (cM) apart will occur in 1% of meioses. Genetic distance is not identical to physical distance, as some parts of the genome appear to be more prone to recombination than others, but a distance of 1 cM approximates to 1 million base pairs.

Isolating Disease Genes

The ultimate object of reverse genetics is the isolation of a defective gene, and to study its abnormal product, in order to understand disease pathophysiology and possibly develop a rational approach to therapy. Progressing from linkage to isolating a mutant gene is not easy. Even closely linked markers, e.g. 1 cM distant, are likely to be at least one million base pairs away from the gene. In attempting to move from a linked marker to a gene it is useful to have a physical map of the region of interest. This can be achieved by the use of pulsed field gel electrophoresis (PFGE) which allows the resolution of DNA fragments up to 2 million bp or more in length (Schwartz and Cantor 1984). These are produced by digesting DNA with enzymes which cut it very infrequently and thus produce exceptionally large restriction fragments. Because such large DNA fragments are obviously few in number in the genome, DNA probes which hybridise to the same region of the gel are assumed to be located on the same restriction fragment.

Gene isolation is made easier if patients who have a chromosome translocation or deletion associated with the disease of interest can be identified, as it can usually be assumed that the chromosomal defect disrupts the disease gene. This approach was very useful in identifying the NF 1 gene. If no such individuals are identified, it is necessary to isolate and move in from flanking linked markers. This involves the use of sophisticated molecular genetic techniques, such as chromosome walking and jumping (Collins 1988). Chromosome walking isolates a series of adjacent, overlapping clones, typically proceeds in steps of 30 kb or less, and thus is very labour intensive. Chromosome jumping proceeds more rapidly via the isolation of genomic clones containing sequences that were originally 100–200 kb apart in the genome, without the inclusion of the sequences between them. One limitation of these cloning techniques has been the length of foreign DNA which can be inserted into conventional cloning vectors, which in cosmids (plasmids which have been manipulated to allow the cloning of larger DNA fragments) is up to about 50 kb. More recently, DNA fragments up to several hundred kb in length have been cloned into yeast chromosomes, and propagated as yeast artificial chromosomes (YACs) (Burke *et al.* 1987). The techniques of PFGE, chromosome jumping and YAC cloning have narrowed the gap in resolving power between molecular approaches and cytogenetic techniques.

DNA sequences isolated from the vicinity of the disease gene locus can be analysed to assess their potential as the disease locus itself. A number of approaches are used. Vertebrate genomes are highly methylated due to the presence of 5-methyl cytosine in the sequence CpG. About one per cent of the genome is nonmethylated at CpG and relatively high in GC

content; it was detected by its cleavage into tiny fragments by the methyl-sensitive restriction enzyme *Hpa II*. Sequences with these characteristics occur as discrete "islands", usually 1–2 kb in length, which occur throughout the genome approximately every 100 kb (Bird 1987). These islands are called HTF islands, CpG islands, and methylation free islands (MFIs). Many are associated with genes, and can be detected by restriction enzymes with recognition sites that are GC rich and contain one or more CpGs. The use of these provides a useful method for the mapping and cloning of genes, since CpG islands are detected as a cluster of restriction sites in the construction of long range physical maps in candidate areas.

Comparative hybridization of DNA probes from candidate areas to genomic DNA from several species (zoo blots) may also be used to detect the presence of conserved sequences, which by virtue of being conserved are likely to possess important functional properties. Alternatively cDNA clones may be isolated from tissue specific libraries, using the genomic clone as a probe, and used in expression analysis by hybridization to RNA (northern blotting) from different tissues.

Proof that a cloned gene is the disease gene can only ultimately come by demonstration of mutation at that locus which does not occur in the normal population. Deletions, insertions or duplications are often detectable as alterations in fragment size, using Southern blotting or PFGE. It is possible to screen rapidly for more discrete nucleotide changes, including point mutations, using techniques such as single strand conformation polymorphism analysis referred to earlier (Orita *et al.* 1989). Gene segments (usually from exons) 100–400 bp in length are amplified by the PCR, heat denatured, and electrophoresed on high resolution polyacrylamide gels. Each single stranded fragment assumes a secondary structure determined in part by its nucleotide sequence under these conditions, and single base changes can alter electrophoretic mobility. The sequence of a candidate gene, either cloned or amplified using the PCR, can be determined in detail, usually using the dideoxy method of Sanger and colleagues (Sanger *et al.* 1977). Short stretches of sequence can be compared to known genes and proteins using established databases, and the protein product of any unknown gene predicted from its sequence. Antibodies to corresponding synthetic peptides can then be used to study the distribution of the gene product in normal and affected tissues. Arguably the most elegant way of demonstrating the effects of a mutant gene, and eventually investigating pathogenesis of the disease in question, is by producing transgenic animal models of the human condition by micro-injecting the gene into the fertilised ova of mice. This has been achieved in one form of inherited spongiform encephalopathy (Hsaio *et al.* 1990).

The Clinical Application of Linked DNA Markers

The identification of a genetic marker linked to a disease locus has important clinical applications in presymptomatic and prenatal detection of gene carriers, even before the gene itself has been isolated. Once linkage has been established, it is often relatively easy to generate more closely linked DNA markers, thus enhancing the accuracy of gene tracking which is so important in clinical practice. The diagnosis of genetic diseases using linked genetic markers is obviously an indirect method and has a number of disadvantages, not the least of which is the inaccuracy generated by the possibility of recombination during meiosis. It is necessary to study several family members in order to establish how the genetic marker is segregating with the disease locus, and these are not always available, particularly in late onset life limiting disorders such as Huntington's disease. Nevertheless, the clinical use of linked markers is well established in this and several other neurological diseases. When a disease gene and its defects have been identified, molecular genetic diagnosis is more precise.

Molecular Genetic Studies of Inherited Tumour Syndromes

Random linkage analysis, i.e. screening the whole of the human genome for linked markers, is extremely time consuming and labour intensive. Often attempts are made to accelerate gene mapping by focusing on candidate genes or chromosomal regions. This approach has been particularly fruitful in inherited tumour syndromes, in which analysis of tumour tissue may provide clues for gene localization.

There is evidence that some tumours are produced by two genetic events in a single cell, predicted by the "two hit" hypothesis of Knudson (1971). This especially applies to tumours which are clearly inherited in some cases, for example retinoblastoma and acoustic neuroma. In familial cases, one mutation is inherited and the other is in the tumour stem cell (e.g., the retinoblast), a somatic cell mutation. Both "hits" occur in the stem cell in sporadic cases. These observations were first made in retinoblastomas, following the identification of deletions in the long arm of chromosome 13 in some patients with these tumours (Vile 1989). Retinoblastomas may be familial (40% of cases) or sporadic in occurrence. Tumour growth in the embryonic retina is due to a loss in function of both copies of the Rb gene which maps to chromosome 13. In familial cases, one allele of the Rb gene is defective or deleted in the germ line of the individual, and this is inherited as an autosomal dominant trait. Tumour formation only requires a mutation in the other Rb allele, hence the bilateral and multifocal occurrence of inherited retinoblastomas. In sporadic cases, mutations occur in both Rb genes in a single cell, which, being a statistically less likely event, leads to unilateral, unifocal lesions.

There is evidence that in normal cells the function of the Rb gene relates to the control of stem cell division and differentiation, that is it acts as a potential tumour suppressor gene. Retinoblastoma cells in culture express both neuronal and glial markers, suggesting that they have arisen from bipotent stem cells; it appears that this mechanism for malignant transformation can occur in other types of stem cells. In patients with familial retinoblastoma lesions can occur in sites other than the retina, including the brain and bone (osteosarcoma). Structural rearrangements of the Rb gene have also been reported in some breast cancers, melanomas, and small cell lung carcinomas (Vile 1989).

Both random linkage analysis and the candidate gene approach have been used in isolating the genes causing neurofibromatosis and von-Hippel-Lindau disease, which will be discussed in some detail here, along with the clinical and classical genetic features of these disorders.

Neurofibromatosis 1

Neurofibromatosis comprises a heterogenous group of disorders of up to seven or more different conditions characterized by cutaneous pigmentation and tumour formation in various tissues, the most frequent of which is von Recklinghausen's neurofibromatosis (NF 1). Only this and bilateral acoustic neurofibromatosis (NF 2), are common in clinical practice (Riccardi 1982). NF 1 accounts for more than 90% of cases of NF and has an incidence of at least 1 in 5,000 in the UK (Huson *et al.* 1988). It is an autosomal dominant disorder and is virtually fully penetrant but with very variable expression. About 50% of cases represent fresh mutations.

Clinical Features

The major defining features of NF 1 are cafe au lait (CAL) spots, peripheral neurofibromas and Lisch nodules. These are found in virtually all adult patients. CAL spots are obvious at or soon after birth, increasing in number and size later; in childhood they may be the only manifestation of the disease. They are brown macules, varying in size from 0.5 to 50 cm. The majority of patients with NF 1 have six or more CAL spots, whereas 10 per cent of the population have one or two (Crowe *et al.* 1956). A further type of cutaneous lesion which is common in NF 1 is axillary freckling. This is also seen in the groins, the base of the neck and below the breasts in females (Huson *et al.* 1988). Subcutaneous neurofibromas usually first appear at around the time of puberty and gradually increase in number, from a few to several hundred, and size with age. They are common on the trunk, particularly around the areolae in females and these may increase in number and size during pregnancy or when taking the oral contraceptive pill.

Plexiform neurofibromas have a diffuse appearance resulting from localized enlargement of several nerve trunks which form a plexus. There is usually hypertrophy of the overlying skin, which is very vascular, or underlying bone. They may be present at birth or develop during childhood and most frequently occur on the trunk; if present on the face they cause severe cosmetic disfigurement. Surgical treatment is usually impossible.

A relatively poorly recognized but important physical sign in the diagnosis of NF 1 is the Lisch nodule. These are melanocytic hamartomas of the iris which are best seen on slit lamp examination. They are brown in colour and have a dome shaped appearance. They develop in early childhood and again increase in number with age, being present in 100% of patients with NF 1 by the age of 20 years (Lubs *et al.* 1991).

Tumours of the central nervous system are well recognized as a complication of NF 1 but population studies suggest that they are rare (Huson *et al.* 1988). They are most commonly gliomas, particularly affecting the optic nerve and chiasm. Most optic nerve gliomas have a very benign course and should really be considered as hamartomatous malformations; the 5 year survival rate is more than 95% (Illgren *et al.* 1985). Overall, gliomas occur in about 3% of patients with NF 1; other sites, in decreasing order of frequency, include the cerebellum, the region around the third ventricle, the cerebral hemispheres, brain stem and spinal cord. Although acoustic neuromas have been associated with NF 1, there is little evidence that these occur more commonly in NF 1 (as opposed to NF 2) than in the general population. The same applies to meningiomas. Single or multiple spinal neurofibromas are also relatively uncommon, occurring on the posterior roots more frequently than the anterior. They have a characteristic dumb-bell appearance when they grow out through an intervertebral foramen. They most commonly present with root pain and evidence of motor or sensory root dysfunction, with a varying degree of spinal cord compression. The symptoms are particularly likely to arise during pregnancy.

Other neurological features of NF 1 include macrocranium, usually due to diffuse macroencephaly, but occasionally hydrocephalus arises as a result of aqueduct stenosis. Intracranial artery stenosis and occlusion may also occur, particularly in children. Epilepsy without obvious structural cause occurs in approximately 4% of patients with NF 1 (Huson *et al.* 1988). Intellectual handicap is a significant problem associated with the disease; 18 per cent of patients require remedial class education and 10% special schooling, although only 1–2% are severely retarded (Huson *et al.* 1988). Intellectual handicap is thought to be related to the disturbed cortical architecture and neuronal heterotopia which is found in this disease (Rosman and Pearce 1967).

Non-neurological complications of NF 1 include short stature, bone dysplasia, and phaeochromocytoma. Malignant nerve sheath tumours are

seen in about one per cent of patients and other malignancies include rhabdomyosarcoma and various forms of childhood leukaemia (Sorensen *et al.* 1986).

Two of the other proposed types of neurofibromatosis may give rise to diagnostic confusion in relation to NF 1. One is segmental NF in which CAL spots and dermal neurofibromas are confined to one or several dermatomes in a restricted area of the body. This may result from somatic mutation of the NF 1 gene (Miller and Sparkes 1977). Multiple cafe au lait spots may be inherited as an autosomal dominant trait without any other features of NF (Riccardi 1980).

Genetic Aspects

The pathogenesis of NF 1 is not entirely understood. Although often considered as a disorder of neural crest cells, many of the disease complications arise in tissues of mesodermal or neural tube origin. Studies suggesting that nerve growth factor concentrations were elevated in this disorder (Siggers *et al.* 1975) have not been confirmed. The gene was mapped to the long arm of chromosome 17 by means of linkage analysis with RFLPs (Barker *et al.* 1987, Seizinger *et al.* 1987 a). The latter paper reported linkage of the NF 1 locus to that for the nerve growth factor receptor (NGFR) gene, a candidate gene for NF 1. However, crossovers between the two loci indicated that a defect of NGFR was unlikely to be the basis of NF 1.

Studies of 30 benign tumours from NF 1 patients, including 22 neurofibromas, did not show loss of heterozygosity with chromosome 17 markers. Most neurofibrosarcomas show loss of sequences from chromosome 17, but in some these have been derived only from the short arm and have thus not included the NF 1 locus (Menon *et al.* 1990). Losses of 17 p are also observed in all grades of glioma, which occur in some patients with NF 1 (see below). It thus seems likely that more complex mechanisms than the two hit system are operative in the pathogenesis of NF 1.

A detailed genetic map of the region containing the NF 1 locus was obtained in a collaborative effort involving 142 families (Fain *et al.* 1989), and two patients with translocations involving chromosome 17 were identified (Collins *et al.* 1989). The translocation breakpoints were shown to lie about 60 kb apart by PFGE. Candidate sequences for the NF 1 gene were isolated by means of chromosome jumping, and also by cloning the translocation region in a YAC. These fragments of DNA were then searched for conserved sequences by hybridizing them to zoo blots. Most single copy genes exhibit conservation between species. Conserved sequences were then used to screen cDNA libraries, derived from peripheral nerve, fetal brain, and non-neurological tissues, for evidence of expression. Six exons spanning at least 33 kb of genomic DNA were identified by one group

(Wallace *et al.* 1990), and nine exons over 100 kb by another (Viskochil *et al.* 1990).

Studies of NF 1 patients showed that the gene transcript was interrupted by one of the previously identified translocations. A 500 bp insert in or close to one exon was found in one patient with genetically normal parents (representing a fresh mutation; Wallace *et al.* 1990). Six of 72 NF 1 patients had variant alleles in exons 4–9, detected by SSCP analysis (Cawthon *et al.* 1990). A 2485 amino acid NF 1 peptide was then predicted from the reading frame sequence. A 360 residue region showed homology to both human and bovine GTPase activating protein, an intermediate in the cellular transduction of extracellular signals which is involved in the regulation of cell growth (Xu *et al.* 1990).

Prognosis and Management

Overall, 20% of patients develop complications during childhood which cause lifelong morbidity such as large plexiform neurofibromas, pseudoarthrosis, scoliosis and mental retardation. Fifteen per cent have others which are potentially treatable, including aqueduct stenosis, renal artery stenosis and visceral or endocrine tumours, and 6% develop malignant lesions including CNS tumours. In view of the high incidence of complications of NF 1 it has been suggested that affected children should be reviewed 6 monthly and that adults should be followed up on an annual basis (Huson *et al.* 1988). Genetic counselling is an important aspect of management and prenatal diagnosis is now possible. It is essential that mildly affected adults are aware of the fact that there is a risk of having a severely affected child, particularly the risk of mental retardation. Unfortunately there is currently no way of predicting which gene carriers will be severely affected.

Bilateral Acoustic Neurofibromatosis (NF 2)

Clinical Features

Also known as central NF, NF 2 is an autosomal dominant disorder. It has only been clearly recognized as a distinct entity in the last 10 years or so. A substantial but unknown proportion of patients appear to represent fresh dominant mutation and it can be safely assumed that virtually all patients with bilateral acoustic neuromas have NF 2. The cardinal clinical feature of this form of NF is bilateral acoustic neuromas which may present at any time between the early teens and the seventh decade of life with an average age of onset of about 20 years (Kanter *et al.* 1980, Martuza and Eldridge 1988). Bilateral deafness is the initial symptom in about 50% of cases but this can be unilateral and presentation may be with ataxia or

other features of a posterior fossa mass. The diagnosis may be overlooked unless bilateral acoustic neuromas are considered as a cause of progressive bilateral sensorineural deafness and this is a particular problem in middle aged or older patients. Diagnostic delay is associated with poor outcome in such patients who eventually present with brain stem compression and hydrocephalus. The tumours are often asymmetrical in size and a small contralateral lesion may be overlooked in patients presenting with the features of a unilateral acoustic neuroma. Often posterior fossa tumours are multiple, with what may appear to be a diffuse neuromatous process involving a number of the lower cranial nerves. Other central nervous system tumours occur in this disorder, including meningiomas, spinal neurofibromas and gliomas of the spinal cord or brain. These occur in about one-fifth of patients and meningiomas are the most frequent (Kanter *et al.* 1980, Martuza and Eldridge 1988). The diagnosis of NF 2 should be considered in any child with a meningioma or Schwann cell tumour.

Cutaneous features are subtle or absent in NF 2, and Lisch nodules do not occur. Forty per cent of patients have one or more CAL spots but none have more than five; 20% have one or up to a few peripheral neurofibromas (Kanter *et al.* 1980, Martuza and Eldridge 1988). The appearance of the peripheral neurofibromas is rather different from those in NF 1. They are slightly raised plaques with an irregular surface, often with more prominent hair over the skin. They are best seen by oblique illumination (Martuza and Eldridge 1988).

Genetic Aspects

The two hit hypothesis led indirectly to localizing the gene for NF 2. The difference in presentation between sporadic and familial acoustic tumours parallels the situation in retinoblastoma. Early cytogenetic studies showing that loss of chromosome 22 was frequent in meningiomas; these tumours also occur in NF 2. These observations led Seizinger and colleagues (1986) to look for heterozygosity in acoustic neuromas by means of RFLP analysis. In seven of 16 informative tumours (one bilateral, six unilateral), there was loss of genes from chromosome 22 which were present in the patients' leukocyte DNA. Further analyses of one meningioma and cervical root neurofibromas from NF 2 patients showed selective loss of all or part of chromosome 22, and the pattern of allele loss in NF 2 acoustic neuromas suggested that the long arm of 22 was most consistently involved (Seizinger *et al.* 1987 b). Genetic linkage studies subsequently established that the gene for NF 2, which is presumed to be a tumour suppressor gene, is near the centre of the long arm of chromosome 22 (Rouleau *et al.* 1987, Wertelecki *et al.* 1988).

Diagnosis and Management

The diagnosis of bilateral acoustic neuromas is much as in unilateral tumours, although hearing is often suprisingly preserved and normal pure tone audiograms are sometimes found. Magnetic resonance imaging (MRI) with gadolinium enhancement, together with auditory evoked potentials, comprise the most accurate means of diagnosis of bilateral tumours, particularly small ones. These are thus the most useful investigations for screening individuals at risk. Management is not straightforward. It has been suggested that bilateral small (less than 2 cm) tumours should be removed as early as possible, although the chances of preserving any hearing are small and patients should be taught to lip read before surgery (Hughes *et al.* 1982, Huson and Thrush 1985). This obviously applies largely to those who are identified as being affected by virtue of family screening or present with other lesions. Most patients who are symptomatic will have medium size tumours, and they should probably be followed over a period of months in order to identify those who have very slow progression as it is thought that surgery is best deferred in such cases (Young *et al.* 1970, Huson and Thrush 1985). Clearly surgery is indicated if there is any evidence of brain stem compression or hydrocephalus. In patients who show marked increase in tumour size over an assessment period of months or a small number of years, and those with severe symptoms at the time of presentation, early operation on the most affected side is indicated. There is a 50% risk of transmitting NF 2 to offspring and individuals at risk should be screened approximately every two years, starting around puberty. Genetic markers closely linked to the NF 2 locus will be useful in genetic counselling and prenatal diagnosis although this has not as yet been applied on a large scale.

Von Hippel-Lindau Disease

This is another autosomal dominant disorder with variable manifestations. The mean age of onset of symptoms is 26 years, with retinal angioma as the presenting lesion in 43 per cent of cases. These are often multiple and can present with visual loss as a result of retinal detachment and/or haemorrhage. The second commonest presentation, in 39 per cent, is with cerebellar haemangioblastoma, usually between the ages of 20 and 40 years. The third most important lesion in this syndrome is renal cell carcinoma; this will occur in 70 per cent of patients by the age of 60 years (Maher *et al.* 1990). Other features include renal adenoma, phaeochromocytoma, pancreatic, renal and hepatic cysts, and epididymal cysts and tumours. There is a tendency for phaeochromocytomas to cluster within families. Haemangioblastomas are situated most commonly in the cerebellum but may also arise in the spinal cord or medulla. Supratentorial lesions are

uncommon. Haemangioblastomas are often multiple and many are asymptomatic for long periods, being detected during investigation of presenting lesions. However, approximately 25% of patients have single haemangioblastomas which is of relevance to the issue of the frequency of von Hippel-Lindau disease (VHLD) in patients presenting with a solitary lesion. The interval after the initial presentation before the appearance of a second VHLD lesion is very variable, between 3 and 11 years. This is a seriously disabling disease, often requiring multiple neurosurgical procedures. Severe disability and early death are common; median actuarial survival is 49 years. Renal cell carcinoma is the commonest cause of death, followed by haemangioblastoma (Maher *et al.* 1990).

It is clear that VHLD sometimes occurs as the result of fresh mutation and the gene varies in expression and is not fully penetrant; some patients present over the age of 60 years and others are only diagnosed at autopsy (Go *et al.* 1984). Between 20 and 40 per cent of patients, diagnosed as having VHLD on the basis of having either multiple haemangioblastomas or one haemangioblastoma and another relevant lesion, give no history of similarly affected relatives (Boughey *et al.* 1990, Maher *et al.* 1990).

The gene locus for von Hippel-Lindau disease (VHLD) has been mapped to the short arm of chromosome 3 and is linked to that for the human homologue of the raf 1 oncogene (Seizinger *et al.* 1988, Maher *et al.* 1991). This is of interest given that renal cell carcinomas had previously been shown to exhibit loss of heterozygosity for chromosome 3 p markers. The VHLD gene probably acts as a tumour suppressor gene, as loss of 3 p alleles has been demonstrated in 11 renal cell cancers, one phaeochromocytoma, and three haemangioblastomas from cases of VHLD (Tory *et al.* 1989). The clustering of certain VHLD lesions within families may be explicable on the basis of different mutations within a complex genetic locus (Neumann and Wiestler 1991).

A question of substantial clinical importance arises when a haemangioblastoma is diagnosed in the absence of a family history or a lesion elsewhere. Does the patient have VHLD? Single cerebellar and spinal haemangioblastomas are numerically more common than those due to VHLD but diagnosis of the latter is of considerable importance for two reasons. There may be other surgically treatable lesions such as phaeochromocytoma or renal carcinoma, or retinal angiomas which should be treated with early photocoagulation if appropriate to avoid visual loss. Also, if the patient has VHLD there is a 50% risk of transmission to offspring and possibly also a risk to other relatives. It is clear that patients presenting with seemingly single haemangioblastomas are often inadequately investigated for the possibility of VHLD (Boughey *et al.* 1990). This study showed that a diagnosis of VHLD could be made in 12 of 34 patients who presented with apparently isolated cerebellar lesions, but this may have been an under-

estimate. Only 10 patients with seemingly isolated cerebellar tumours had been investigated appropriately and two had evidence of VHLD. Of interest is the fact that four of 26 cases with apparently completely resected isolated cerebellar tumours later developed recurrent tumours which could have been second lesions, hence suggesting VHLD. There are no specific clinical features of the cerebellar or spinal haemangioblastomas seen in isolation or in VHLD, and the range of age of onset overlaps considerably. The presence of a brain stem or supratentorial haemangioblastoma is nearly always a feature of VHLD.

Boughey and colleagues (1990) suggested that all patients presenting with a seemingly isolated haemangioblastoma should be investigated by means of abdominal CT (looking for hepatic, renal or pancreatic lesions), indirect ophthalmoscopy (for retinal angiomas which often cannot be seen by direct ophthalmoscopy), and urinary VMA estimations. This assessment should be repeated at about 3 yearly intervals for 15 years or until the age of 65, together with CT of the posterior fossa to exclude recurrent or second tumours. MRI could be used in preference to CT for non-invasive screening. If a patient develops a second lesion, or a relative is diagnosed as having VHLD, then first degree relatives should also be investigated.

Maher and coworkers (1990) have provided screening protocols for patients with VHLD (annual physical examination, urinary VMA estimations, renal ultrasound and indirect opthalmoscopy, and MRI or CT brain and abdominal scanning every three years until the age of 50, five yearly thereafter), and their relatives at risk. The latter included: annual examination and renal ultrasound from the age of 15 and indirect ophthalmoscopy from the age of five; MRI or CT scanning of the head every three years between the ages of 15 and 40 years, then every five years to the age of 60; and MRI or CT scanning of the abdomen every three years between the ages of 20 and 65 years. Huson and colleagues (1986) and Jennings and co-workers (1988) suggested that screening could cease at the age of 50 but this is probably unwise in view of the fact that some patients do not present until the seventh decade of life (Boughey *et al.* 1990, Maher *et al.* 1990). Renal cell carcinoma is a frequent complication in older VHLD patients. The detection of retinal lesions is particularly important as early treatment can prevent blindness, and clinical neurological assessment will not detect intracranial lesions which could give rise to fatal subarachnoid haemorrhage. It is now possible to apply DNA markers linked to the relevant region of chromosome 3 in clinical practice, which makes it possible to define the population at high risk, and thus particularly in need of screening, more precisely (Maher *et al.* 1992). Prenatal diagnosis is also possible (Payne *et al.* 1992).

Molecular Genetics of Gliomas

The use of molecular genetic techniques in the investigation of tumourigenesis is well illustrated by studies of gliomas, although many questions remain unanswered. The results from molecular genetic studies of gliomas have confirmed the findings of earlier cytogenetic analyses and have brought to light additional changes not detected by karyotyping. Southern blotting and hybridization can be used to detect the presence or absence of a specific sequence in gliomas from individuals whose normal cells are found to be heterozygous but have a deletion in their tumour cell DNA, as was done in acoustic neuromas (Seizinger *et al.* 1986). This can also be determined by a reduction in signal intensity of around 50% in a fragment from a tumour sample in a homozygous individual. In addition, this technique can detect amplification of a sequence, as in these circumstances the hybridization signal will be increased, or in some cases a rearrangement in the DNA if this either involves a restriction site or creates a restriction fragment of different size from that found in normal cells from the same individual.

Studies of gliomas have so far shown that loss of sequences on chromosomes 10, 13, 17, and 22 is common (James *et al.* 1988). There is an indication that losses of chromosome 10 sequences are restricted to tumours of high malignancy grade, whereas those on other chromosomes occur in tumours of all grades. James and colleagues used a total of 51 polymorphic DNA probes, including at least one from each chromosome, to look for loss of heterozygosity in 53 gliomas. Chromosome 13 losses occurred in 5 cases (14%), and losses from 17 and 22 occurred in 8 (22%) and 7 (19%) cases, respectively. These losses were found in tumours of each malignancy grade, but those on chromosome 17 were found only in tumours of astrocytic differentiation. Loss of sequences on chromosome 10 was found in 28/29 glioblastomas, but not in gliomas of lower malignancy grades. These results suggest that the loss of a tumour suppressor gene on chromosome 10 could be the genetic mechanism by which a lower grade tumour progresses to become a glioblastoma.

Further investigations into the loss of chromosome 17 sequences in astrocytic tumours were carried out by James and colleagues (1989). Thirty five gliomas were included in this study, of which 24 displayed astrocytic differentiation. Chromosome 17 losses were detected in eight tumours, all of which showed astrocytic differentiation, using a total of seven RFLPs. These included two grade II tumours, two grade III tumours and four grade IV tumours. The region of loss and reduplication in these tumours varied but commonly involved the short arm from p11.2-pter. Loss of heterozygosity for chromosome 17 sequences was also observed in 40% of anaplastic astrocytomas and glioblastomas by Fults *et al.* (1989). These

results imply the existence of a tumour suppressor gene located within the common region of loss (p 11.2-pter).

It is of interest in relation to these observations that the p53 gene maps to chromosome 17 p 13.1. The deletion of sequences from chromosome 17 and the finding of p53 gene mutations in colon tumours (Baker *et al.* 1989) prompted a search for p53 mutations in other tumours which show losses of 17 p sequences, including gliomas (Nigro *et al.* 1989). Amongst five glioblastomas which showed loss of heterozygosity for 17 p alleles, four were found to have point mutations in the remaining p53 gene. The one tumour in which no mutation was detected was found to express p53 mRNA, but no protein product could be detected, implying that a mutation elsewhere may have affected p53 mRNA translation or stability. These results, and those from other tumours, support the hypothesis that p53 is a tumour suppressor gene, the loss of function of which (by deletion or mutation) may play a role in the development of many cancers. Further evidence for this comes from a study by Sidransky and colleagues (1992), which showed that progression from low to high grade malignancy was associated with a p53 mutation. Cells containing the mutation were present in low abundance in low grade tumours, but such cells had become predominant in high grade recurrences.

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B. Technical Standards

Surgery for Hindbrain Related Syringomyelia

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With 42 Figures

Contents

Summary

Syringomyelia is a condition with many possible causes, the commonest of which seems to be an abnormality at the foramen magnum. Such cases may be grouped under the heading of "Hindbrain related syringomyelia" and the principles of treatment for all such cases are largely similar. The commonest of these foramen magnum region abnormalities is hindbrain herniation which may be associated with a history of birth difficulties, a small posterior fossa, segmentation abnormalities of the cervical vertebrae or the base of the skull, arachnoiditis of the subarachnoid spaces, subarachnoid pouches, hydrocephalus and intracranial tumours or tumours partly blocking the foramen magnum.

Other causes of syringomyelia include conditions which could be grouped under the heading of "non-hindbrain related syringomyelia", these mostly produce blockage of the spinal subarachnoid spaces, especially spinal "arachnoiditis" or meningeal fibrosis, including that secondary to

traumatic paraplegia. Intraspinal tumours are sometimes cystic and some authors have included this association under the heading of syringomyelia.

Syringomyelia of all kinds is almost always a surgical condition, the destructive forces are those of fluid distending the tissues. As a principle, treatment directed against the cause of the accumulation and the intracord propagation of the fluid by normalising the CSF pathways is more likely to be successful than drainage of the cavities. Drainage operations have an inevitable failure rate and a further incidence of complications attends myelotomy and the leaving of any drainage tube within the narrow confines of the spine.

Correction of craniospinal pressure dissociation and re-establishment of a cisterna magna appears to be the most successful treatment strategy and is likely to be immediately and permanently successful in correcting not only the pressure problems such as long tract involvement and syringobulbia features but also in producing satisfactory clinical and radiological improvement in the syringomyelia. The recommended technique includes radical means to gain space at the foramen magnum by creating a large artificial cisterna magna, resecting part of the tonsils, preventing the descent of the cerebellum and avoiding the use of space occupying or fibrosis producing dural grafts. Because the pathogenesis of the cavities remains in doubt, the method by which this treatment stratagem is effective is unclear. It may be that change in the closure conditions of parts of the neuraxis, i.e., alteration in the capacitance and consequent change in pulsation characteristics afforded by the decompression may be the factor which predicates success.

Surgical management of hindbrain related syringomyelia is not easy, there are hazards associated with operation, hydrocephalus demands priority in it's management. Neurological losses are likely to be permanent as are orthopaedic problems such as Charcot's joints and kyphoscoliosis.

Future management problems will include cases where syringomyelia comes to light as an unexpected finding during MRI and for those cases it should be borne in mind that neurological deficits, if allowed to develop, are likely to be irreversible.

Keywords: Arnold-Chiari Deformity; syringomyelia; syringobulbia; craniovertebral decompression; syrinx shunting; hindbrain herniation.

Introduction

Definitions

Syringomyelia is the condition of longitudinal cavities within the spinal cord extending over several segments[15]. Since the writings of Gardner[13] it has been recognised that the commonest cause of syringomyelia is a struc-

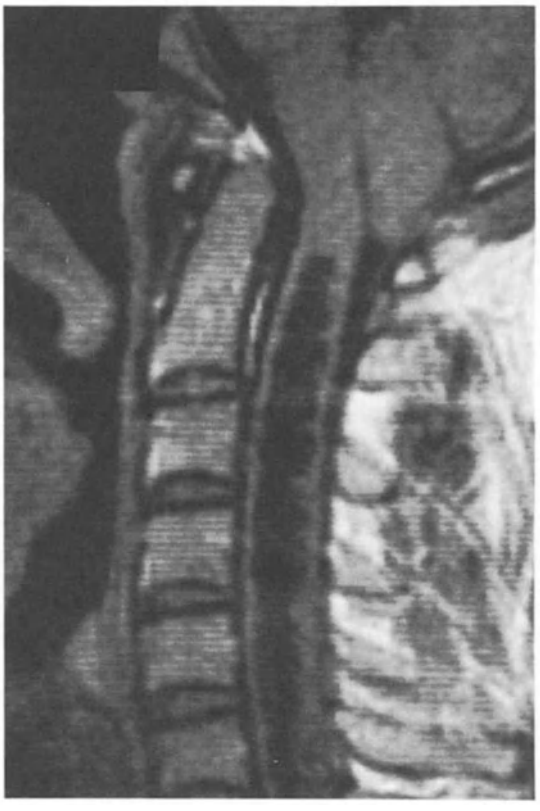

Fig. 1. Typical appearance of hindbrain related syringomyelia without any known associated condition. Note the valvular configuration of the hindbrain hernia, the narrowing of the subarachnoid pathways at the foramen magnum, the absence of the cisterna magna, the numerous partial septations and the tension in the syrinx

tural lesion at the foramen magnum (Figs. 1 and 2). It has been perhaps Gardner's greatest contribution to show that operations on the hindbrain may produce improvement in the clinical features and the morphology. The surgery of benign, non-tumorous hindbrain hernia is closely linked to hindbrain related syringomyelia and since such conditions as syringobulbia may be found with no syringomyelia, surgery of hindbrain herniation itself is covered here. The hindbrain related cases and those with herniation but no syrinx have many identifiable causes[2, 45, 47, 50, 56].

The descent of the tonsils through the foramen magnum, which is sometimes called the Arnold-Chiari Deformity or Chiari Type I malformation, is a herniation of the hindbrain. The term Arnold Chiari deformity is sometimes used to describe the severe deformities of the hindbrain and upper cord found in association with spina bifida and hydrocephalus. This

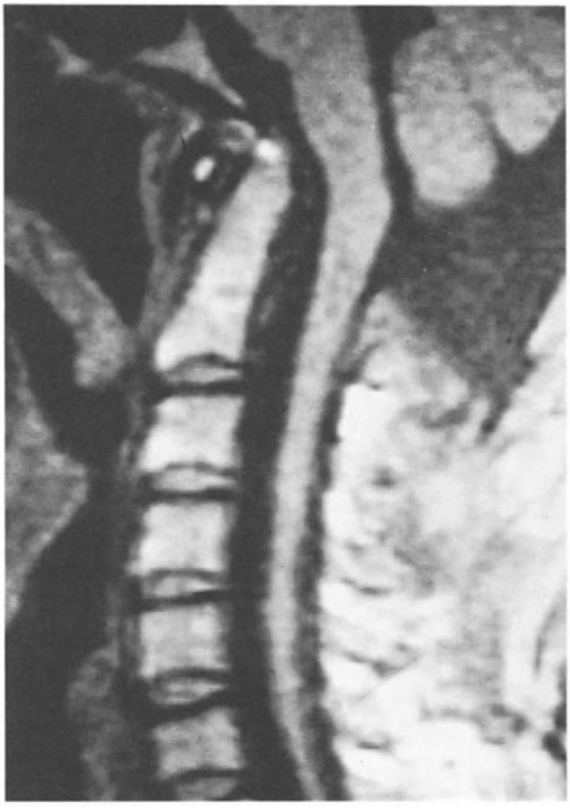

Fig. 2. Typical post-operative appearance in the same case as shown in Fig. 1. Note the rounding of the lower border of the tonsils, the widening of the midline outflow tract of the fourth ventricle, the large cisterna magna and the collapse of the syrinx

is sometimes called Chiari Type II. It is not possible to delineate the two conditions precisely and many intermediate forms may be found. The aetiology of both types is likely to be pressure differences[45]. The term hindbrain hernia will be used here for both variants.

Syringobulbia is a term which has been used with several different meanings[15, 21, 27]. The commonest cases described as having syringobulbia are those with bulbar symptoms, lower cranial nerve features, giddiness, syncope, nystagmus and so forth. The term has also been used to describe clefts running from the floor of the fourth ventricle (Fig. 3) into the substance of the lower pons and medulla[27]. These may be described as fourth ventricular clefts and although they have been correlated well with clinical features they are uncommon (Figs. 4–7). Neither of these types of syringobulbia is necessarily associated with syringomyelia[27, 32]. The third type

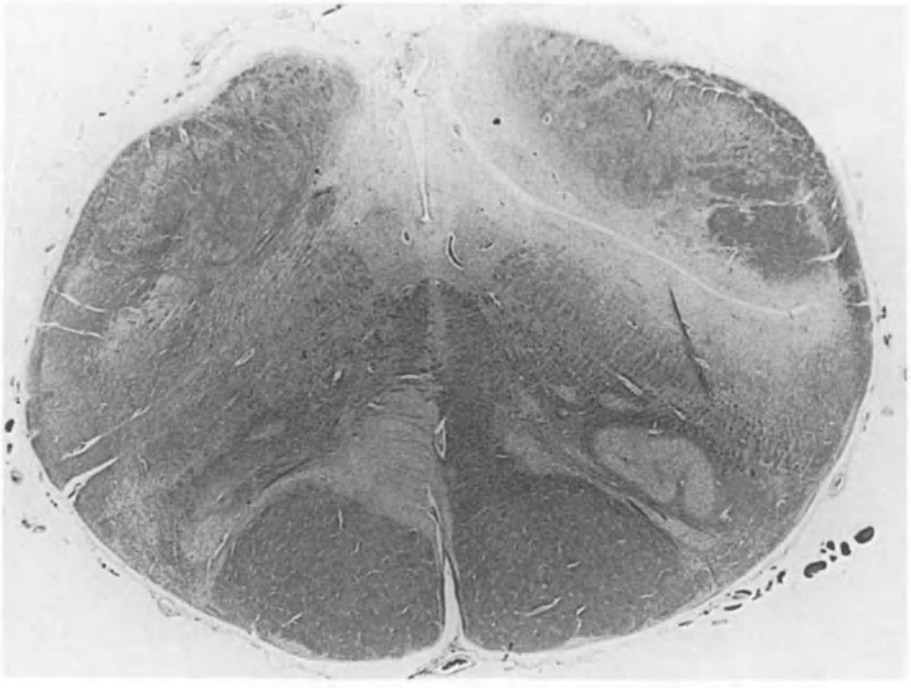

Fig. 3. Histological preparation of syringobulbia with clefts running from the fourth ventricular floor in the region of the midline sulcus. The split on the right is in a typical location, running into the zone of the trigeminal nucleus. The midline cleft is running in the region of the hypoglossal nucleus and in some cases may lead to a communication with an associated syrinx. Cf. Fig. 7. Note that the splits are collapsed, which is typical after death but not during life

of case is that in which there is a syringomyelia cavity, often of a primarily spinal cause, which tracks upwards from the syrinx, into the grey matter of the medulla and sometimes up into the pons or higher[18, 19, 20, 27, 29]. This may be called ascending syringomyelia, or the ascending form of syringobulbia. It is commoner in the non-hindbrain related group of cases, presumably because the compression of the upper end of the cord by tissue impaction at the foramen magnum tends to prevent the cord from splitting or else helps it to heal if splitting should begin.

"Arachnoiditis" is a term which is often incorrectly used to describe excessive fibrosis in the subarachnoid space[2]. There is sometimes adhesion from the arachnoid to the dura and sometimes between the pia and the arachnoid with occasionally almost complete blockage of the subarachnoid space from these adhesions alone. The suffix "itis" implies an active inflammation rather than the residuum or scarring after such an inflammation

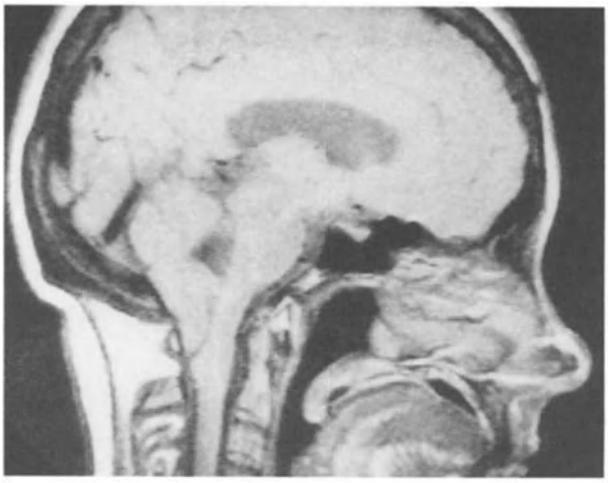

Fig. 4. Hindbrain herniation in a patient presenting with bulbar features of 20 years duration including diplopia, voice disturbance, gait imbalance and dysphagia. Note there is no syringomyelia and only modest hydrocephalus

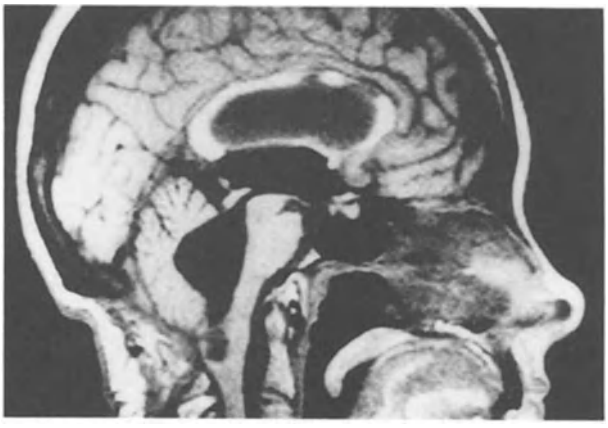

Fig. 5. Same case as Fig. 4 some weeks after operation. The hydrocephalus was not detected initially and the symptoms worsened. There is no cisterna magna due to technical failure of the operation (post-operative haemorrhage). Note that the midline outlet of the fourth has closed off and that the hydrocephalus is attacking the floor of the fourth. There is lower pressure within the spine and this accounts for the excavation of the syringobulbia

but the term is much used. The term "meningeal fibrosis" will be used here, since the collagenous adhesions involve all of the meninges including the dura and the pia. The causes of such meningeal fibrosis include meningitis, chemical insults and the late effects of head injury, especially birth

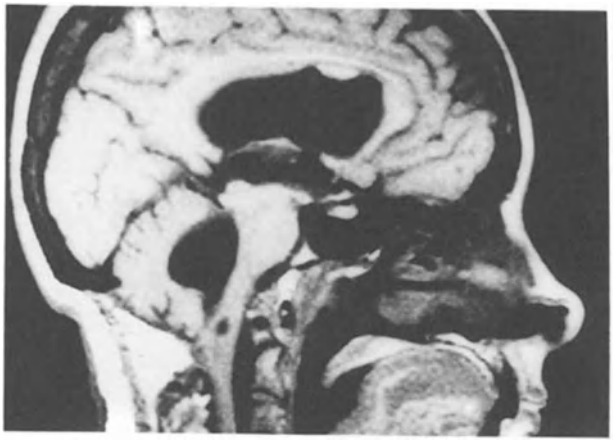

Fig. 6. A sagittal cut parallel to the midline in the same case as Figs. 4 and 5

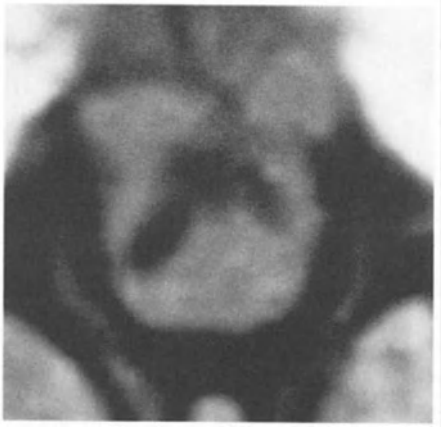

Fig. 7. Axial cut through the region of the lower end of the fourth shows the appearance of clefts going along the line of weakness. Note that in comparison with Fig. 3 the clefts are actively distended during life. After treatment of the hydrocephalus this lady was little different from before her first operation, at which time the clefts were probably not present

related perinatal head trauma. Meningeal fibrosis low in the spine has some points of difference from that at the hindbrain and may be associated with syringomyelia by different mechanisms[34, 37, 53].

There are often collections of cerebrospinal fluid in the vicinity of the foramen magnum and these are commonly referred to as "cysts". The majority of these cavities are a cul-de-sac or diverticulum rather than the isolated collection implied by the word cyst (Figs. 8 and 9). When there is

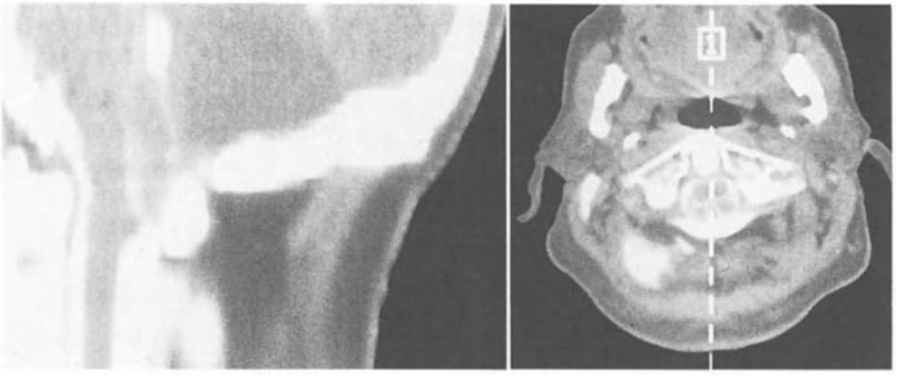

Fig. 8. A post myelogram CT of a posterior fossa retrocerebellar pouch in association with a hindbrain hernia. Such pouches commonly fill in the region of the hindbrain hernia. The tonsils fit closely into the foramen closing off the entrance/exit to the pouch. This patient had a complete resolution of his symptoms and his hydrocephalus after radical decompression and re-establishment of a cisterna magna. Note the close fit of the tonsils in the axial cut

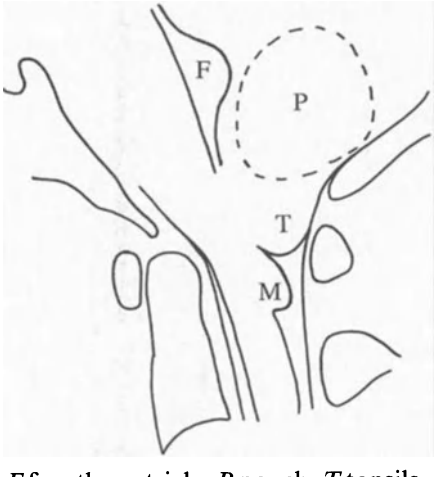

Fig. 9. Key to Fig. 8. *F* fourth ventricle, *P* pouch, *T* tonsils, *M* medullary deformity due to the moulding of the medulla by the tonsils acting under the influence of suck

one opening which is both entrance and exit the term "pouch" may be chosen[50].

The mechanisms which cause the syrinx are not necessarily those which maintain it. It is possible that after the cavity is created it is kept going by a different mechanism. Therapy is only to a limited extent directed towards the concept of cause of the syringomyelia.

Historical Concepts

Ollivier, who named syringomyelia in 1827, understood that cavitation followed the weaknesses along which fluid tracked through the grey matter of the spinal cord; he carried out air injection to support this notion[30]. The idea later became prevalent that the disease was due to degenerative changes in glia. The cavities become surrounded by gliosis, but Greenfield[15], pointed out that the cavities appeared to be due to tearing of tissues by the spread of fluid. Studies on human cadaver, subsequent to that of Ollivier, and also by injections of saline or CSF into the grey matter of living animals produced cavities mimicking syringomyelia. Kaolin induced hydrocephalus is a reliable animal model but the relevance to the human condition is limited[53].

The relationship between abnormalities of the base of the brain which cause pressure differences between the head and the spinal subarachnoid space was noted by Gardner[13]. He suggested that the majority of cases have a communication from the fourth ventricle to the syrinx in the initial stages of syringomyelia.

Gardner showed that operative craniovertebral decompression was often accompanied by improvement in the patient's clinical state; and produced a theory which attempted to explain spina bifida, anencephalus, iniencephalus, Dandy-Walker cysts and syringomyelia, on the basis of failure of the fourth ventricle roof to perforate during embryogenesis. This concept seems unsound, but has been of value in stimulating subsequent workers.

Spina bifida and other forms of dysraphism clearly have a resemblance to syringomyelia. The hydromyelia found in much of the cord above a spina bifida aperta is likely to be secondary to hydrocephalus acting through a communication. The hindbrain herniation of spina bifida aperta, Chiari type II may act like a Chiari I, but there are two additional mechanisms which are not so clear, cord cysts above lipomata, which are not rare, and cystic cord beneath spina bifida occulta which is rare. The pathogenesis is likely to be "dysraphic" but of course the morphology of the dysraphic lesions is always dominated by disorders of CSF pressure so that the picture is confused, theory is highly speculative and dogma is out of place.

Classification

The classification of syringomyelia is, thus, not agreed upon, but a suggested classification with some idea of the frequency of instances is given in Table 1.

Pathogenesis

The pathogenesis of syringomyelia is not understood. Theoretical concepts abound but surgery is currently practised based upon an empirical or pragmatic background rather than certain knowledge of causation.

Table 1. *Classification of Syringomyelia According to Presumed Cause*

Hindbrain related syringomyelia 71%
Hindbrain herniation
Idiopathic herniation (Chiari type 1) 32%
Secondary to birth injury 39%
Secondary to tumours 1–2%
Bony or meningeal tumours of the posterior fossa
Tumours forming the hindbrain hernia
Intrinsic brain tumours
Secondary to bony abnormality
Basilar invagination (idiopathic or birth injury) 10%
Sclerosteosis
Rickets
Acro-osteolysis
Osteogenesis imperfecta
Associated with hydrocephalus 10%
Intracranial arachnoid pouches 2%
Dandy-Walker cysts
Early onset hydrocephalus (aqueduct stenosis)
Secondary to spina bifida (Chiari type 2) 4%
Meningeal fibrosis
Birth injury related 9%
Post inflammatory
Post-traumatic (post-natal) 1%
Infections
Unknown cause
Non-hindbrain related cases 19%
Spinal tumours 5%
Intramedullary 3%
Cysts wholly or partly within the tumour
Cysts outside the tumour
Extramedullary tumours, including disc disease
Meningeal fibrosis 15%
Post-inflammatory
Pyogenic meningitis
Epidural abscess
Post-traumatic 12%
Tuberculous meningitis
Myodil (pantopaque) 1%
Secondary to spinal body deformities
Post-traumatic 11%
Tuberculous bone disease
Idiopathic scoliosis

Percentages given in parentheses are from a database of syringomyelia and related diseases. Diagnoses with no percentage given have an incidence of less than 1%. They do not add up to 100% because of intersections. Some factors much as perinatal or post-natal head injury are difficult to interpret. Others such as hydrocephalus or basilar impression are matters of degree.

The observation of it's occurrence in association with the disorders shown in Table 1 almost certainly indicates a causative connection between the syringomyelia and the other structural abnormalities; or that both are due to a common cause. Most patients who have syringomyelia secondary to post traumatic paraplegia for instance, had a normal central nervous system in all respects prior to the injury. In the pathology associated with the hindbrain related cases the factor which links them seems not so much something protruding through the foramen magnum or even forming a valvular configuration there, but more the absence of the cisterna magna.

It is relevant to consider the forces which are brought to play on the tissues of the neuraxis through the CSF.

The Hydrodynamic Forces

The CSF within the neuraxis is in continual movement. Cardiac pulsation in the capillary bed of the brain is constant throughout the nervous system. Of greater significance and power are the effects of the venous plexuses. These have free connection through valveless veins present at each vertebra of the neuraxis and up to the head. Any increase in pressure in the abdominal and thoracic cavities is transmitted into the spine. Compression of the dura by venous distension of the epidural plexus produces rapid movements of CSF with associated pressure changes. Williams found that the pressures produced by a cough may exceed the pressures produced by cardiac pulsation by a hundred times[46]. The energy imposed upon the tissues of the neuraxis affects the formation and the maintenance of syringomyelia[52].

"Suck"

The first mechanism is the creation of pressure differences between CSF compartments by venous pulsation. If the patient has a spinal tumour, for example, energetic coughing will force fluid upwards past the tumour more efficiently than it can run back down again.

This leads to a collapsed theca below the tumour with a high protein content and a low pressure, Froin's syndrome. If fluid can find its way into the cord at the site of the obstruction then this may be the mechanism which gives rise to a syrinx. Tumour outside the cord, fracture, Pott's disease or other partial blockage of the subarachnoid spaces caused by the formation of pathological arachnoid adhesions are the common causes.

When measurements are made at rest in the majority of adults with hindbrain related syringomyelia, or even patients with well developed herniation due to tumour, pressures are substantially equal in the head and the spine.

When coughing and sneezing, the pressure in the lumbar sac rises higher and quicker than it does in the head. In the majority of patients with hindbrain hernia, however, the CSF is delayed in its return downwards past the foramen magnum[45, 46, 51, 52]. In normal cases the half life of the return of pressure differences to normal, i.e., equal in the spine and the head, is less than 1/10th of a second. With hindbrain herniation the equalisation of pressure may be delayed, sometimes with a half life of over 30 seconds. During a post Valsalva rebound after staining the pressure dif-

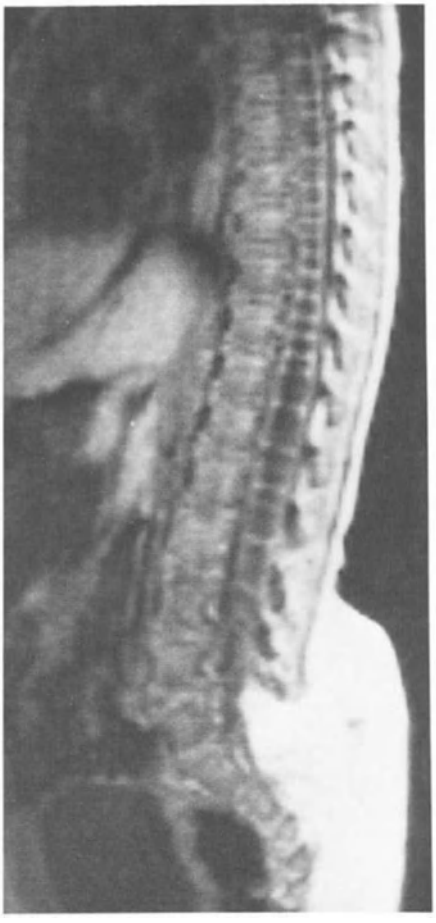

Fig. 10. Ascending syringomyelia in a child with a spinal lipoma lesion and a marked hindbrain herniation. Operation on the cord, perhaps combined with syringopleural shunting may be recommended for such cases when there is no hindbrain hernia

ferences may be high across the foramen magnum and may remain high for a significant period. Pressure differences across the foramen may be called craniospinal pressure dissociation, but with pressure differences across the site of any obstruction lower in the neuraxis, may be conveniently described as "suck". This exerts a force which continues to mould the hindbrain hernia as well as sometimes being concerned with the pathogenesis of syringomyelia. Correction of the hindbrain hernia will commonly produce radiological and clinical improvement in hindbrain problems and also in the syringomyelia[1, 4, 7, 8, 10, 11, 13, 19, 22, 24, 26, 31, 32, 33, 35, 48, 53, 57].

The Communicating Hypothesis

The idea of Gardner that the embryological communication between the fourth ventricle and the central canal was usually the means by which the syrinx filled had immediate appeal once the nature and severity of the suck mechanism between the head and the spine was measurable. Widespread acceptance of this idea led to a following for the operative step of blockage of the site of presumed communication, as advocated by Gardner[13]. The search for such communication in life was, however often fruitless. West and Williams[42] reported seventy ventriculograms with either water soluble or oily contrast media. They found the communication in only seven cases.

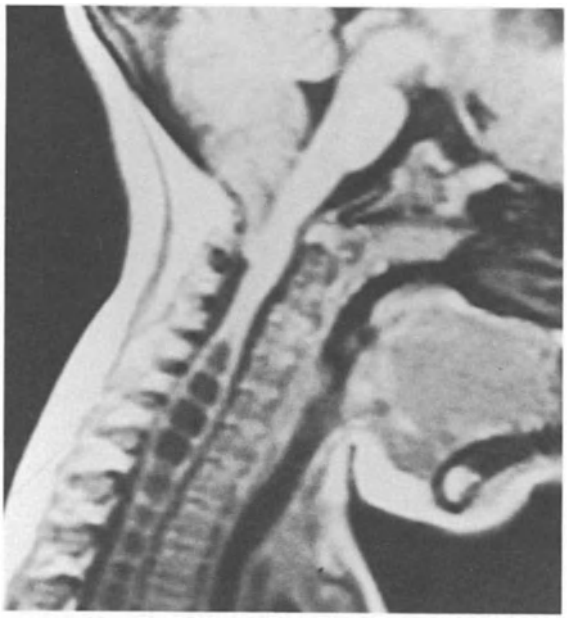

Fig. 11. Note the tight fit of the hindbrain in the top of the spine, in the same case as Fig. 10. Operation at the bottom end of the tethered cord, was thought inadvisable because of the hindbrain herniation

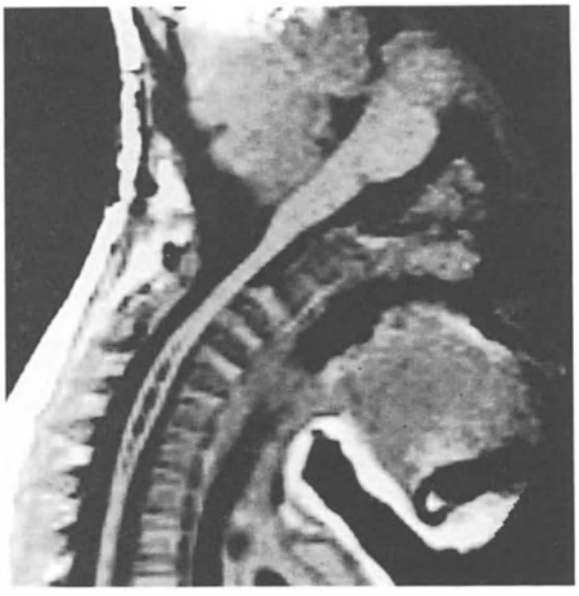

Fig. 12. Appearances after craniovertebral decompression in the same case as Figs. 10 and 11. Note the collapse of the syrinx. It does not seem possible that the fluid could have been distending the syrinx by entering through a communication at the top in this case. The fluid was almost certainly entering from below and yet the hindbrain hernia decompression was effective both clinically and a radiologically

This figure of about 10% of cases of detectable communications in "communicating syringomyelia" accords well with other estimates. The objection that there was no communication demonstrable might be met, for some cases, by proposing that there had been a communication in the past which had been closed, perhaps partly by the compression of tissues in the foramen magnum in the hindbrain related cases. There seems however to be a proportion of cases in which the communication could never have been present. These include hindbrain tumour cases and also cases where the top of the syrinx is well away from the hindbrain (Figs. 10–12).

The "communicating" hypothesis may not be dead, but it is not adequate as an universal explanation for the association between hindbrain abnormalities and the syrinx.

"Slosh"

Energy imposition upon the spine by manoeuvres which raise the intrathoracic and intra-abdominal pressure is probably a usual mechanism in syringomyelia. If the cord contains fluid it is likely that the fluid within

will move more readily than that outside, because of the greater impediments to movement outside the cord from the dura, the pia, dentate ligaments, arachnoid strands, blood vessels and nerve roots as well as the narrowing of the subarachnoid space. Fluid surging on the inside can stress the walls of the cord and lead to tearing of the tissues in the same way as injection of fluid. Pathological preparations showing the collapsed cord are misleading. Most syrinx cavities in life are at least partially filled. It was stressed by Williams after creation of an analogue model, that cord fluctuations could be violent and the fluid inside is free to surge upward and downwards in an undulating manner imposing ballistic distending stresses[44]. The phenomenon of surging, impulsive intracord fluid movements is difficult to name tersely, the term "slosh" is used here. If a cavity is being maintained by slosh than it is likely that the natural shape of the cavity will be kept in existence by the diffusion of fluid through the walls of the cord. Septations within the syrinx cavity, sometimes called haustrae,

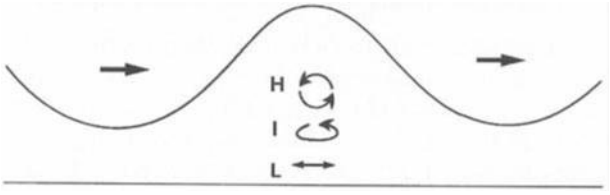

Fig. 13. Wave motion above a flat surface produces horizontal movement (*L*) close to the bottom, sinusoidal movement (*H*) close to the surface and ellipsoidal movement (*I*) between. The diagram may be similar to what happens in a syrinx if there is a rotation, that is to say the bottom of the picture becomes the midline of the syrinx

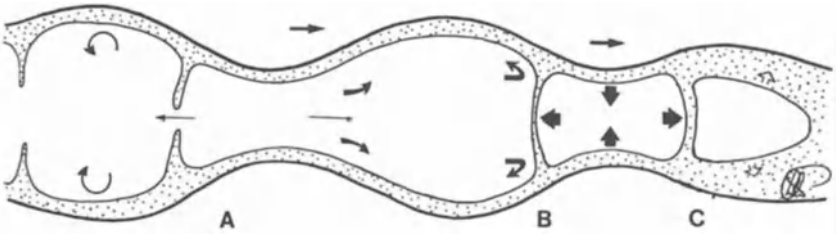

Fig. 14. If the fluid is forced up and down the cord it probably almost always displays wave phenomena of short wavelength compared to the length of fluid which the energy traverses. From *A–B* is one wavelength, the amount of fluid between *A* and *B* is therefore almost the same during the passage of a wave. The cell between *B* and *C* suggests how change in the shape of the walls of a cell might allow transmission of energy. Energy causing undulation in the wall of the intact cord might generate new cavities when there is no gross communication either through the septum or through the walls. Compare with Fig. 11

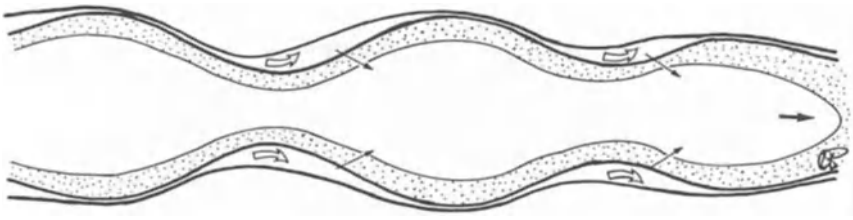

Fig. 15. The easy passage of fluid up the centre of the cord compared with the difficulty in movement within the subarachnoid space means that there may be forces, probably acting intermittently as part of the wave phenomena, which tend to force fluid to migrate across the wall and take an easier pathway moving up and down the spine via the syrinx cavity

are of interest (Figs. 11 and 12). They probably represent nodes or no flow areas in the cord. The "slosh" occurs in limited zones and the walls may tend to heal or else not break down at the site of septation. Their existence naturally leads to the contemplation of wave phenomena and the existence of standing waves as part of the pathology; as illustrated in Figs. 13–15. These septae may be surgically important; they make it difficult for the surgeon to pass a drainage catheter and sometimes lead to persistence of a short section of syrinx after other parts of the cavity have been drained.

Transmural Pressure Gradients

It may be simplistic to try to think of "filling mechanisms" as applicable to this class of problem. Syrinxes are not necessarily in a state of active filling at all times. It may be more reasonable to seek an analogy with the Starling equations describing the behaviour of tissue fluid as being a state of balance representing the equilibrium point of several interacting forces. The cord is a porous structure. There are no tight junctions in the gliotic lining of the syrinx cavity and fluid can enter readily, as may be observed by looking at the behaviour of water soluble contrast material in post-myelography CT scans.

Ball and Dayan in a critique of the "communicating" hypothesis, drew attention to the porous state of the cord, particularly to the sizeable spaces alongside the vessels which are sometimes called the Virchow Robin spaces. They suggested that the fluid was driven into the syrinx by the nature of the blockage at the foramen magnum[3]. This seems at first an unlikely suggestion. Why should it be that the obstruction of the subarachnoid pathways should force the fluid into a solid structure? Imaging the cord as being completely porous and passive suggests only that the cord would flap slightly if the fluid outside it should slosh up and down the spine. The

Ball and Dayan hypothesis deserves close consideration however although the reasons that they gave themselves do not seem to be the best. They remarked that the pressure differences between the head and the spine were insufficient to cause filling of the syrinx along a tiny communication. The pressure differences are however enormous; Williams has recorded pressures of over 100 mm Hg between the head and the spine[52].

Fluid is unlikely to track along the proposed communication in a majority of cases for the reason that there just is no communication. The behaviour of water soluble contrast which enters the cord cavities easily as shown on post-myelography CT, illustrates the likelihood that the cord is acting in a porous way, perhaps as suggested by Fig. 15.

Synopsis of Present Views of Pathogenesis

The pathogenesis of syringomyelia is presently obscure, the views held by individual surgeons affect the treatment which they espouse, the results of many forms of treatment are encouraging and give support to almost any view which the surgeon may hold. It may be that the benefits of laminectomy or of hindbrain decompression may be due to alteration in the balance of forces which maintain the syrinxes in a state of filling. The effects of terminal ventriculostomy for instance may be due to the alteration in the capacitance of the spinal canal affecting the suck and the slosh mechanisms. As a result

Table 2. *Bulbar Features with Hindbrain Related Syringomyelia.* 54 patients with hindbrain features in addition to pain, giddiness or nystagmus

	As a presenting feature	Resolved	Improved	Unchanged	Worse, or onset after surgery
Hindbrain headache	35	28	7	–	–
Vertigo or giddiness	27	10	14	3	2
Nystagmus	26	1	9	16	4
Hearing impairment	9	–	8	–	1
Tinnitus	11	4	6	1	2
Ptosis	11	8	1	2	1
Diplopia	16	12	2	2	–
Facial paresis	5	4	–	1	–
Palatal palsy	13	6	4	2	1
Accessory palsy	1	1	–	–	–
Hypoglossal palsy	9	–	6	2	3

From Morgan and Williams, [27].
Some of these patients also feature in Tables 3–5.

there is no present consensus, the empirical observations of the surgeon remain the guide to future success.

Clinical Presentation

The presentation is variable, no dogma can be offered (Tables 2 and 3). Patients may present either with features of the hindbrain hernia or of the syrinx[1, 4, 7, 9, 11, 12, 17, 19, 27, 31, 33, 35, 40, 49].

Table 3. *Presenting Symptoms in 100 Cases of Symptomatic Hindbrain Hernia (63 Syrinxes)*

Symptom grouping	Symptom	Number
Pain	headache	52
(82%)	nuchal pain	49
	limb pain	16
	trunk pain	8
	impulse related	44
Motor symptoms	weakness	52
(70%)	wasting	16
	spasticity	12
	clumsiness	22
	drop attacks	2
Sensory symptoms	numbness	42
(65%)	paraesthesiae	27
	dissociated loss	38
	posterior column	6
	other sensory	15
Stem symptoms	diplopia	5
(39%)	oscillopsia	4
	other visual	2
	trigeminal loss	4
	deafness	3
	tinnitus	9
	giddiness	19
	voice	9
	swallowing	9
Other symptoms	gait disturbance	30
(39%)	hyperhidrosis	4
	bladder symptoms	5
	syncope	4
	sexual problems	1

From Byrne and Williams, unpublished.

Hindbrain Herniation

These include intracranial symptoms, pain, medullary symptoms such as vertigo, oscillopsia, or any complaint of lower cranial nerve involvement. The symptoms related to the medulla are often thought of as "syringobulbia". There are different possibilities for the pathology, as discussed above[27]. The sort of clefts shown in Figs. 3–7, which are sometimes described as syringobulbia, are different from upward progression from the main syrinx. The majority of cases with brain stem signs have no clefts, only dysfunction due to compression of tissues in the foramen magnum or traction upon lower cranial nerves aggravated by suck (Fig. 16).

Strain related headache is a characteristic presentation. The pain is usually nuchal and bilateral, radiating into the occiput or vertex. It may be strictly unilateral. It is commonly brought on by suddenly rising from the lying or sitting position, by coughing, straining, lifting, shouting and only rarely by emotional tension[28]. It is characteristically pounding and patients may be able to draw a graph of the pain which they experience after blowing in a sphygmomanometer to raise the mercury to a height of

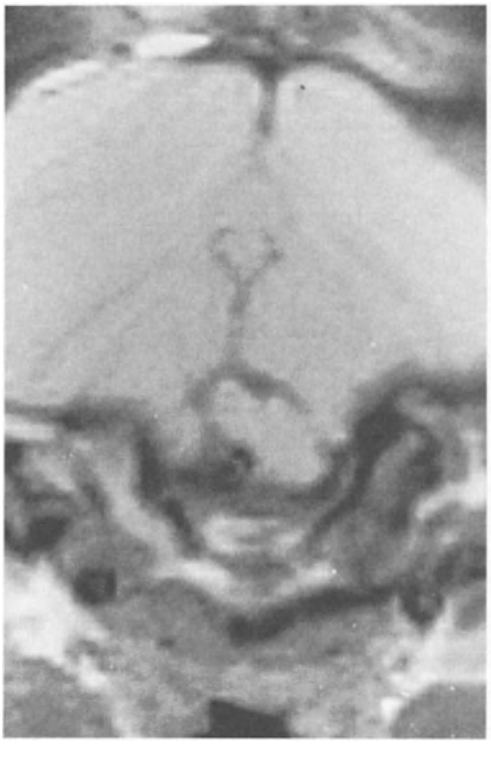

Fig. 16. Severe compression of the medulla with indentation of the medulla by the basilar artery. This patient has dizziness, syncope, nuchal pain, vomiting, disordered eye movement and trigeminal features

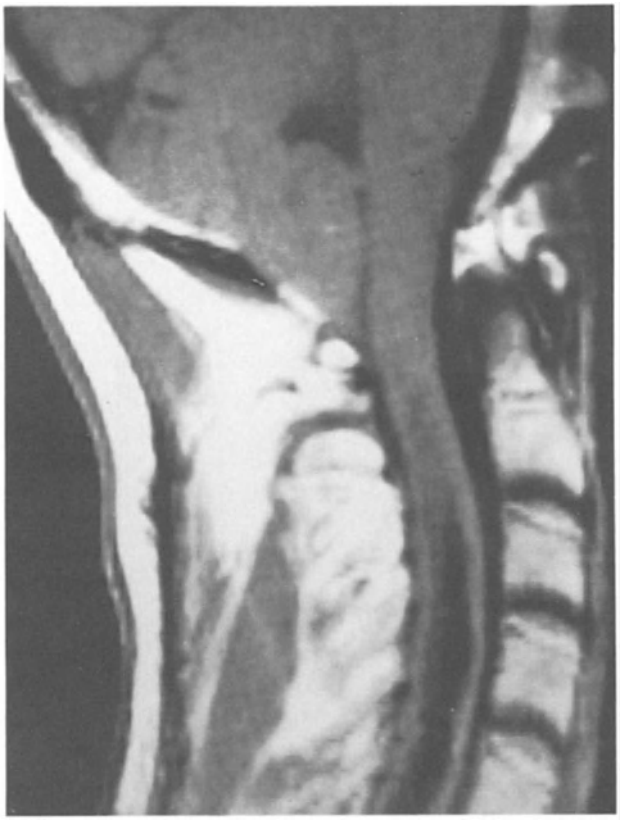

Fig. 17. Sagittal MRI through the same case as Fig. 16. The syrinx was almost asymptomatic compared with the bulbar features although there was a little dissociated sensory loss on testing

40 mm for 5 seconds, or of the similar pain produced after an individual event such as a sneeze. This type of headache is the same as that found when patients have a hindbrain hernia due to brain tumour always the first consideration in cases presenting in this way.

Cord Presentation

Any manifestation of spinal cord disorder may be the first symptom, including scoliosis, trophic, sensory or motor features[7, 17, 49]. Sensory changes present in the majority in the upper limbs, but stiffness in the legs was the commonest symptom reported by Barnett *et al.* and presentation with leg symptoms alone is not uncommon. Pain occurs in the majority of patients and many present to an orthopaedic surgeon before seeing a

neurologist or neurosurgeon[49]. Pain may be associated with slosh, for instance sudden pain in the trunk or limbs after coughing or sneezing.

Scoliosis is present in more than half the patients with hindbrain related syringomyelia[17, 49]. It is correlated with early onset, and usually precedes other neurological features. The side and level of the cord cavity are not related to the curve[17]. Paraplegia during correction of scoliosis may be the first declaration of syringomyelia. The history is paramount. Taking a birth history in adult life is not common, since most birth related injuries are diagnosed in paediatric practice. Hydrocephalus, epilepsy and syringomyelia are causes of late neurological presentation. Difficult birth is related to over half the cases of adult syringomyelia and of those who have no other cause detectable it is probable that the majority are birth related[47].

Similarly, complaints such as giddiness, syncope, drop attacks sweating changes, transient double vision, swallowing difficulties, hypersalivation, stiffness of the legs and so on, may not be linked by the patient to their presenting complaint if that is a different type of symptom, such as pain or scoliosis. The characteristic dissociated sensory loss is often not present in the early stages, but enquiry may include asking if an underarm deodorant feels the same on the two sides, and asking women if their hair rollers burn the backs of their necks, or if the drying of nail varnish on the nails fells different on the two sides.

On examination, scoliosis, hemiatrophy, asymmetries of the face and upper limbs, wasting, Charcot's joints, trophic changes often with severe finger involvement, are all late manifestations. Slight trophic changes, such as burns or ulceration from brassiere straps, may precede the patient's noticing that they have dissociated loss. Tendon jerks are commonly lost early in the arms and brisk in the legs, abdominal reflexes tend to be lost. Wasting and fasciculation may be present in the arms.

Radiological Assessment

Plain Radiographs

In the hindbrain related cases the x-ray findings may be rich and variable. Plain radiographs of the lateral skull may show effects of hydrocephalus, platybasia or basilar invagination[33]. There may be segmentation abnormalities with fusion of the occiput and atlas or fusion of cervical vertebrae. Encephalocele or spina bifida are uncommon. It has been suggested that these bony changes indicate a primary role for bone dysplasia in some cases. They are only associated anomalies, however, and probably due to a common cause. Finding a small posterior fossa is not necessarily support for the concept of primary osseous dysplasia.

Kyphoscoliosis is a common finding and is frequently the first clinical sign. The increased use of MRI scanning may well lead to the earlier

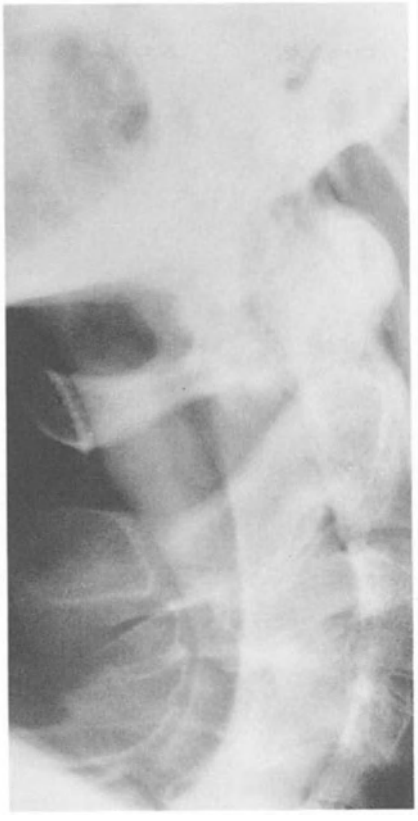

Fig. 18. Lateral radiograph during water soluble myelography in a man who had been neurologically stable for 23 years. Note the large size of the cervical canal and the atrophic cord. There is still a hindbrain hernia visible, the tonsil tips are just above the arch of C1. There were no hindbrain features clinically. Since the cord has collapsed and partly calcified the probability is that the hindbrain has permanently disimpacted and does not need treatment

diagnosis of such cases. Early treatment of an associated syrinx may lead to improvement in scoliosis.

Enlargement of the vertebral canal is often seen (Fig. 18), this may also be due to intraspinal tumours without syringomyelia, or to neurofibromatosis. Comparing the AP diameter of the canal and body at C5, then there is a 25% chance of pathology if the canal is more than 4 mm bigger than the body and a 98% chance of pathology if the difference is more than 6 mm[49].

In cases with meningeal fibrosis plain radiographs show only the changes of the paraplegia, or associated disease. Some tumour cases may have had

syringomyelia for sufficiently long, or at an early enough age, to have affected the growth of the bones.

Computerized Tomography

The ventricles should be scanned all cases, even those with a spinal presentation. Patients with walking difficulty, for example, may have vertex meningiomas or hydrocephalus. In around 1/3 of cases of syringomyelia there is some ventricular enlargement[42] and in 10% this is hydrocephalus which may be symptomatic. Head pouches may be related also, and show well on CT (Figs. 8 and 9). Mid-brain and posterior fossa tumours are known causes of syringomyelia, but tumours at the foramen magnum are more common and are sometimes missed on CT.

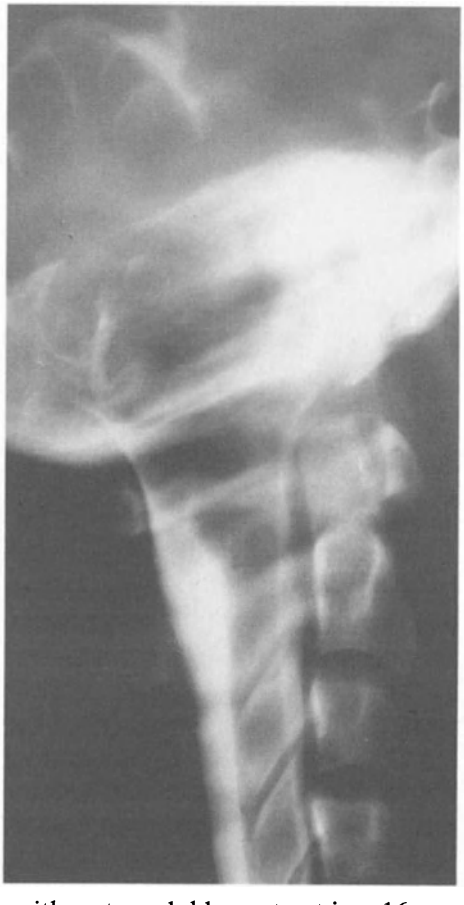

Fig. 19. Myelography with water soluble contrast in a 16 year-old girl with severe hindbrain herniation and clinical features of a syrinx cavity. Note the normal diameters of the cord. A tiny syrinx was seen on delayed post myelography CT

Water Soluble Myelography

Water soluble myelography is a valuable technique. Since the diagnosis of hindbrain hernia has been recognised as more common than previously suspected, it has been recommended that in any mysterious neurological case the contrast agent should be run up to the cisterna magna and the position of the tonsils and the 4th ventricle checked.

Postmyelography CT scanning is of value in showing hindbrain compression and tonsillar descent. It may show typical deformities such as are associated with features of syringobulbia (Figs. 8, 19, 20). Convenient times for CT scanning are 1 hour after the myelogram, then at the end of the radiographer's working day, usually 4 to 6 hours post-myelography,

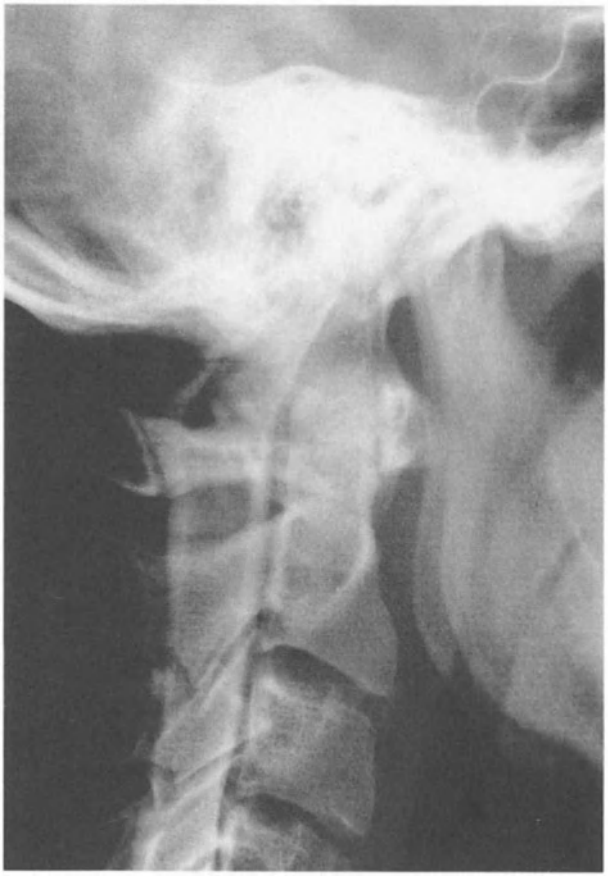

Fig. 20. Water soluble contrast myelography in a man of 31 with probable syringomyelia, but no radiological confirmation of a cavity by any technique. The patient had suggestive left arm pain as well as bulbar features. Note that the midline outflow path of the fourth is filling with contrast

and the following morning, about 20 to 24 hours after myelography. The cavity within the spinal cord may opacify, commonly at 6 hours. Occasionally it will enhance best at 24 hours. The great flexibility of the cord and its susceptibility to slosh are readily demonstrated[37]. These investigations however have largely been supplanted by magnetic imaging.

Magnetic Resonance Imaging

This shows the ventricles, including the 3rd and 4th, hindbrain descent and the spinal cord[6, 10, 16, 25, 36]. Scanning patients with severe scoliosis or other alignment problems may be difficult and skill is required in interpretation (Figs. 20 and 21). Platybasia is difficult, the skull bone does not show well. MRI scanning is invaluable as an outpatient surveillance tool (Figs. 2 and 22). When good MRI scans are available myelography and CT scanning may be dispensed with provided that the whole brain is imaged: plain radiographs remain useful.

Operation: Indications

Tumours

The cause of fluid collecting in and adajcent to tumours is probably as for tumour cysts in other parts of the neuraxis; since the fluid is proteinous, secretion from the substance of the tumour seems most likely. Management

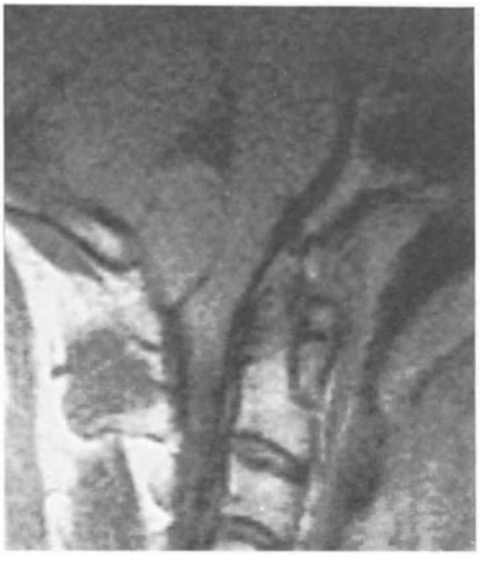

Fig. 21. MRI appearances of the same case as Fig. 20. Note the difficulty in cutting the midline neatly. The demonstration of the fourth is better than in Fig. 20

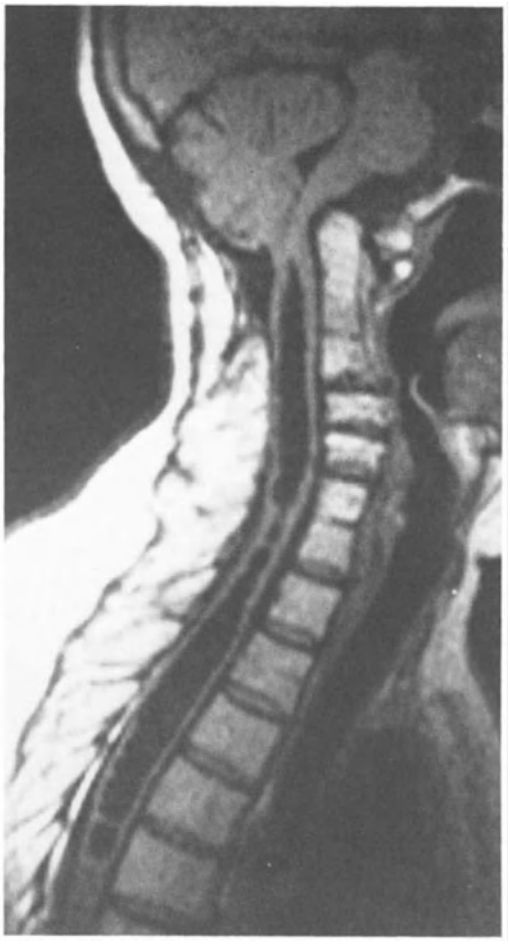

Fig. 22. A woman with spina bifida, encephalocele, hydrocephalus, aqueduct stenosis, basilar impression, Klippel Feil fusions and odontoid peg compressing the front of the medulla, all accompanying hindbrain related syringomyelia. MRI is invaluable in assessing cases of this kind which have to be followed for many years. This scan was taken after craniovertebral decompression and valved ventricular shunting for the hydrocephalus. The syrinx remains formidable in size and persistent neurological features invite shunting of the syrinx. Odontoid peg resection might have been helpful in this case

of tumour cystic cavities is linked to that of the tumour, as is that of head tumours, and the usual course is exploration and removal if possible.

Hindbrain Related Syringomyelia

The progression of syringomyelia is often slow. Many patients have become accustomed to their disabilities and do not want an operation. Careful

advice is necessary, not to minimise the difficulties. Younger patients have a better prognosis; early operation is, thus, ideal. Unfortunately many cases do not present until they are very disabled, and often it may be suspected that they are "burnt out" (Fig. 18). Fortunately, with MR scanning it is possible to see cases with tonsils which no longer appear impacted and syrinx cavities which appear collapsed. If the syrinx cavity is small and occluded at several points along its length, there is no hydrocephalus and the hindbrain hernia seems disimpacted, and if the wall of the cord is calcified in parts, then even recent neurological deterioration is not an indication for operation. If such a radiological result had been obtained by operation, then the surgeon would be well pleased. Even so, arrest of progression could not be promised. Such decisions will be increasingly necessary now that MRI scanning can lead to incidental diagnosis of hindbrain hernia with syringomyelia.

Ventricular Shunting

Sizeable hydrocephalus with neurological symptoms is an indication for correction usually by ventriculo-extrathecal shunting; occasionally by hindbrain hernia decompression or removal of a tumour. Objective improvement of syrinx size and correction of craniospinal pressures associated may often be achieved by ventricular shunting, as well as occasional improvement in the limbs.

The benefits of ventricular shunting are likely due to moving the patients to the left along the pressure volume curve, i.e., by reducing the overall volume of CSF and pre-distending the veins[44,53]. Kruse *et al.* have suggested that measurement of CSF conductance to outflow may be a predictor of which cases will benefit from shunting[23], but this is a difficult technique. Hydrocephalus or a communication from the fourth ventricle to the syrinx may favour shunting of the hydrocephalus.

Craniovertebral Decompression

Indications for operation on hindbrain abnormalities include not only syringomyelia, but also the clinical hindbrain hernia features such as headache. The most impressive measurement is to show suck between the head and the spine. Unfortunately, this is a difficult test and is not a reliable predictor[52]. It seems that many patients who have suck cannot be made to show it under test and also, patients who have had a careful hindbrain hernia decompression with good clinical results may sometimes show persisting suck, a salutary observation to those practising craniovertebral decompression.

One laudable objective of operation is that it should be simple. If operative intervention includes hindbrain hernia decompression, plugging

of the central canal at the obex as described by Gardner, a "stent"* from the fourth ventricle, a dural graft and a syringostomy, then it is difficult to attribute the surgical result, be they good, bad or mixed, to any particular procedure. If there is a disaster then it is not possible to guess accurately if anything further needs to be done. It is not unreasonable to carry out ventricular shunting and hindbrain decompression at the same time if it seems impossible to decide which is best. In the spinal meningeal fibrosis cases it is sensible to open up the spaces and to drain cavities at the same time, but otherwise it seems best do only one manoeuvre at a time. Also the author has a prejudice against dural grafts, insertions of nerves into myelotomies, terminal ventriculostomy and "wicks". A "wick" is something which works where fluid meets air, it is a surface tension utilizing device. A "wick" immersed in fluid will only tend to block up the hole and if it is made of an irritant substance such as silastic it may contribute to further meningeal fibrosis.

Transpharyngeal Removal of the Odontoid Peg

This is a procedure which is seldom necessary but when there is pronounced cranial "settling" and compression of the pons anteriorly then the procedure may be chosen. Dyste *et al.* reported 7 resections in 50 cases of symptomatic hindbrain herniation. They write that when there is ventral brain stem compression then transoral clivus-odontoid resection is indicated[11].

Consideration of the axial cuts at the level of hindbrain compression almost always indicates that a posterior approach will give a bigger decompression, it affords the opportunity to deal with the tonsils not only posteriorly but also laterally. Not only that but interference with the stability of the atlanto-occipital joint sometimes requires a posterior approach to the hindbrain anyway, if this is the case might it not be possible to get away with one operation from the back and should that at least not be given the opportunity to take effect before an anterior approach is chosen? A case such as shown in Fig. 22 with multiple abnormalities affords many therapeutic options. When the bony abnormalities are so widespread then odontoid peg removal probably should be followed by a posterior fusion. These considerations have led to the author having no experience of odontoid peg resection for syringomyelia.

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* Stent was a British Dentist who described how the healing of the palate may be helped by a cast similar to a denture. Stent's compound is still used for the wax which may make a firm temporary cast to assist the healing of tissues. A "stent" therefore is a firm support which holds tissues in place while they heal, it is then removed. The word seems to be used sometimes as if it meant drainage tube, this usage should be resisted.

When Should a Hindbrain Hernia Be Left Alone?

Hindbrain hernia should never be left alone if cord drainage to a low pressure is contemplated. Shunting the lumbar CSF to the peritoneal space for example is highly dangerous if the hindbrain can impact.

The question often arises as to whether a minor degree of hindbrain herniation might be contributing to a clinical problem. Cases with multiple sclerosis for example may have nystagmus and cord signs and if a sizeable hindbrain hernia is present it is tempting to decompress it even if there is no syrinx present. The degree of descent which is symptomatic is difficult to determine. Measurement of the degree of descent is stressed by Barkovitch[6], but the author prefers to look at the shape of the herniation and to decide if it seems likely to be responsible for suck. Minor degrees of tonsillar herniation may be symptomatic if they are shaped so as to cause suck or especially if there is some adhesive meningeal fibrosis present. Barkovich *et al.* suggested that less than 5 mm of descent below the foramen magnum may be normal[6]. In a group of patients with symptomatic hindbrain herniation they found the tonsils to be 3 mm to 29 mm below the foramen, with a mean descent of 13 mm. Dogma of this sort may be misplaced.

In cases where the hindbrain does not seem to be impacted and where the syrinx is flattened or partly flattened or calcified then the patients are likely to have a non-progressive or slowly advancing neurological deficit and surgery is contraindicated. Such cases have probably had a spontaneous cure of syringomyelia and are not rare (Fig. 18).

Which Operation for Patients with Hindbrain Hernia?

Overwhelmingly the best operation is hindbrain hernia decompression. If there is a big hydrocephalus or features of raised intracranial pressure then a valved ventriculo-atrial or ventriculo-peritoneal shunt is safer before the hindbrain is decompressed. Immediately sequential operation may be made, but the effects of the individual procedures are then more difficult to disentangle. There are often problems deciding whether hydrocephalus is relevant, when there is merely detectable enlargement then it is difficult to be sure. A suggested decision tree is given as Fig. 23.

If the syrinx is big and if there is a problem with the hindbrain, especially dense fibrosis of the cisterna magna then it may be tempting to shunt the syrinx first. This is dangerous in the presence of suck and generally is not recommended for hindbrain related syringomyelia until the situation at the hindbrain is fully corrected.

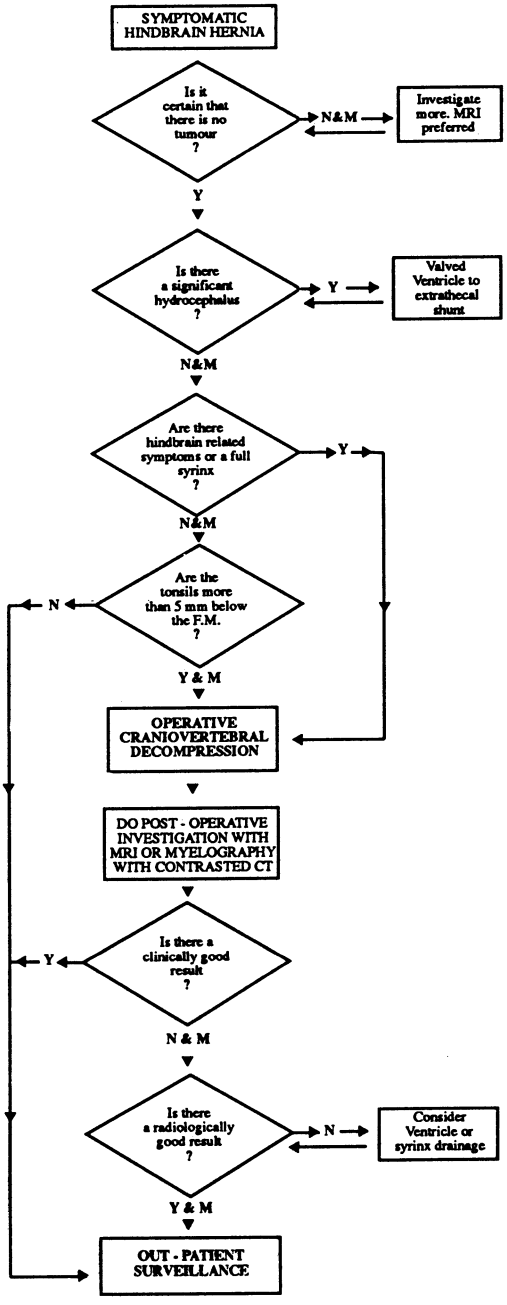

Fig. 23. Decision tree for hindbrain hernia surgery suggesting questions which may be posed in management. The answer to many questions, such as whether symptoms are due to hindbrain compression, is often "Maybe" and the decisions may then be influenced by other factors

Technique

Ventricular Shunting

The techniques are as for hydrocephalus. The author presently slightly favours Codman Medos adjustable valves which do not degrade MR images of the hindbrain and the syrinx. The objective is to create the lowest pressure without producing slit ventricles or intracranial haematoma.

Hindbrain Decompression

Objectives

The aims of operation may vary with the surgeon's ideas of the pathogenetic mechanisms, which are not universally agreed. The main benefit is probably produced by decompressing tissues within the foramen magnum so that they no longer impact. This stops suck and downward traction on the tonsils and the cranial nerves, prevents vascular loops being pressed into the medulla and probably lessens or stops the flow into the syrinx in some cases.

The objective, therefore, is to provide a communication between all the normal CSF containing spaces; the cisterna magna should be in communication with the subarachnoid spaces around the cord, the fourth ventricle and also the spaces alongside the upper medulla leading up to the cerebellopontine angles (Fig. 1 cf. Fig. 7). Minor hydrocephalus may sometimes be relieved by this decompression. An additional benefit of leaving a large artificial cisterna magna is the provision of a reservoir into which fluid from the spine may move during the surges of pressure occurring during exertion. The movements of fluid may be diverted there instead of washing past the lower cerebellum. The damping effect of the decompression provides a mechanism whereby the pressure is prevented from rising; the energy is dispersed in moving the occipital musculature, or lifting the cerebellum, which does no harm; instead of being imposed on central nervous system structures.

Blockage of the presumed communication is of doubtful value. The plug is likely to be dislodged by CSF movement in the post-operative period and there is a complication rate attached to fixing of tissue into the region of the obex[19, 26, 48]. Also the lack of a visible communication in radiological studies makes this manoeuvre less popular than it was, but some surgeons claim good results.

Other procedures such as putting in a syringostomy drain[32] or a fourth ventricle drain[8, 57] are probably not helpful, they have a complication rate and they make it difficult to attribute the results to any particular part of the operation.

The comparison of results is of course difficult in such a complex disorder and there is no proof that results are any better than those gained by leaving out obex blockage, drains or "stents".

Caveats

Patients with syringomyelia may have been neurologically stable for many years and be coping with their problems competently. They are nevertheless sometimes fragile and liable to severe or fatal complications[19, 48]. Respiratory arrest may be sudden and unexpected. Major neurological deficits may come on without any warning or observed operative mishap. The assumption must be, in such cases, that there has been a vascular event.

The use of hindbrain hernia decompression in the hope that it may help minor degrees of hydrocephalus is not always successful; relapse of the hydrocephalus may be slow or sudden, mild or severe.

The use of too large a decompression in the occipital bone may lead to "slump" of the lower parts of the cerebellum in the wound[8, 25, 48]. This may be aggravated by the mechanisms of suck persisting if the tissues reimpact around the edge of the decompression. Too small a decompression may lead to impaction of tonsils and post-operative respiratory arrest.

Position

The sitting position gives good conditions with the shoulders dropping well down, the head is easy to flex, the surgeon is standing comfortably for viewing the field the bleeding from the venous system is lessened. Blood and CSF flows away from the operation site to keep the field clear. The use of the sitting position may be dangerous for patients with sizeable hydrocephalus. The brain may fall away from the dura lining the skull and cause supratentorial subdural haematoma. The usual caveats for the sitting position apply and precautions must be taken against air embolism and fall in blood pressure. Instability of the craniocervical junction and a prominent odontoid peg threatening the ventral ponto-medullary junction need to be considered. In patients with doubtful control of respiration the anaesthetist may opt for spontaneous respiration.

Exposure

A vertical midline incision exposes the occiput and posterior lamina of the atlas. Removal of about 3–4 cm of occipital bone from side to side, and a similar distance above the foramen magnum, gives a good decompression without provoking slump. The arch of the atlas is removed well laterally, avoiding the vertebral arteries. In most cases it is possible to leave the spinous process of the axis in position with those muscles which run downwards from it still in position Fig. 24.

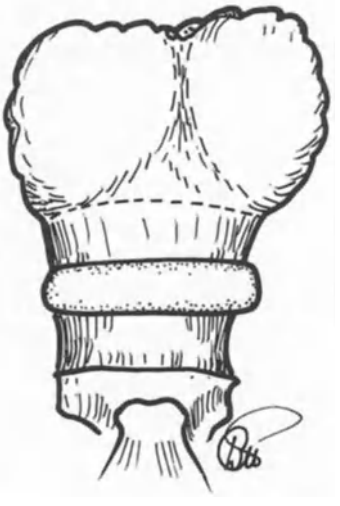

Fig. 24. Exposure of the dura in the posterior fossa need not be extensive. The bone is only removed to gain access to the structures. The cerebellum must continue to be supported at the end of the procedure so that an exposure of about 3 or 4 cm in height and 3 or 3.5 cm in width seems sufficient

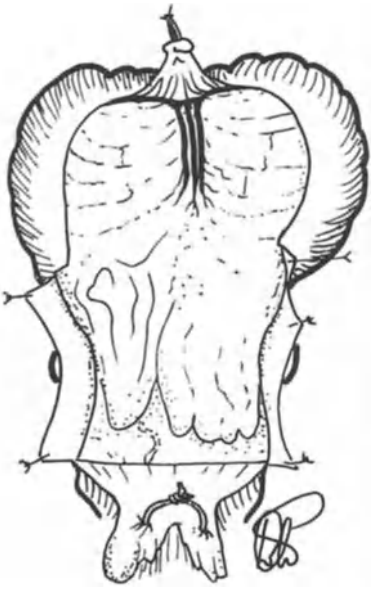

Fig. 25. The dura within the occipital bone may also be left to support the cerebellar hemispheres. The arachnoid may be left intact up to this stage. Note that the dura over the lower parts is securely fastened, but not pulled tightly

The incision in the dura may be made well inside the craniectomy so that the dura continues to support the cerebellum, but is taken well laterally below. There is sometimes a central sinus which may be transected and fastened upwards (Fig. 25).

The central part of the dura may be hinged downwards above the arch of C2. It will reach to the spinous process of the axis where it may be stitched. The posterior surface of the posterior spinal subarachnoid space may thereby be brought into alignment with the artificial cisterna magna planned for the closing stages. The dura at the sides is then gently stitched backwards, if it is stitched forcefully then the anterior spaces may be narrowed. Thought should be given to the effect of slackening off the retractors at the end of the procedure, if the dura is stitched to muscle away from the bone it may slacken and adhere to the cerebellum.

Dealing with the Arachnoid

In the majority of cases the arachnoid can be partly resected and partly sutured back. A 6 "0" suture is convenient. This is an important part of the operation; the arachnoid may look insubstantial, it may also lie down under the influence of surface tension and appear to be out of the way. If

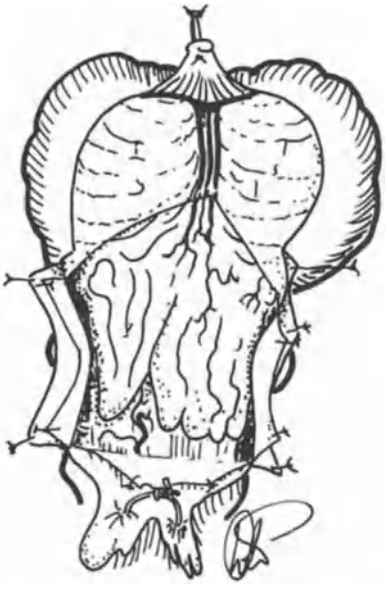

Fig. 26. The arachnoid may be resected over the area shown. If possible it should be sutured back as suggested. It should not be left to float about in the CSF after the wound has closed. There is no value in removing the arachnoid from the back of the hemispheres

it is left to float about in the CSF it tends to adhere to whatever it can, and then to thicken up. It is, therefore, important to stitch the arachnoid back at the bottom of the exposure to ensure permanent communication between the spinal spaces and the artificial cisterna magna (Fig. 26). Leaving the arachnoid intact is sometimes advocated[33] although correction of suck is probably not so effective if this is done. It is important not to leave arachnoid with a small hole in it. If fluid can collect between the arachnoid and the inside of the artificial cisterna magna, then the arachnoid may be pressed against the back of the tonsils and form a dense adhesion here. If a small hole remains to link the main pathways to the artificial cisterna magna then fluid cannot get in and out easily (Figs. 34–37). Such features may destroy the benefits of operation.

Dealing with the Tonsils

When herniated the tonsils exert a malevolent influence in several ways. They form the valve and thus maintain the suck mechanism, exerting downward traction and causing such features as the headache. Tonsillar distortion may be responsible for the headache of hindbrain hernia. Tonsils may compress stem structures and contribute to bulbar and long tract dysfunction. The more radical the clearance of the tonsils, the more certainly are these two factors dealt with. The tonsils may also obstruct the outlet of the fourth ventricle. Even in cases where the foramen of Magendie is completely occluded by a membrane, hydrocephalus is not necessarily a problem, it seems that the drainage of the fourth can be via the foramina of Luschka in most cases. Nevertheless the opening up of the fourth ventricle is a worthwhile objective. The midline opening at the bottom of the vermis is certainly bigger than the foramen of Magendie which is a discrete zone at the obex, where the ependyma of the fourth ventricular meets the pia. In the normal the cerebellar hemispheres may be a little way apart, leaving a valley, or vallecula, between the hemispheres with the vermis visible, like a worm at the bottom. When the tonsils are herniated they are pressed together and CSF may have an impaired escape route from the canal formed by the medulla in front and the cerebellar tonsils to either side. This may be called the midline outflow canal of the fourth ventricle, opening it is a worthwhile objective for all these reasons.

In the majority of cases the tonsils are not bound down and they may be picked up, sometimes after division of a few strands of arachnoid, to expose the obex. Most commonly there is a patent foramen of Magendie. This is obscured by the tonsils dropping back when they are released. Under these circumstances it is recommended to remove part of the tonsils to ensure that the pathways are maximally opened. In elevating the tonsils, the access to the lateral spaces is improved, the situation looks so much

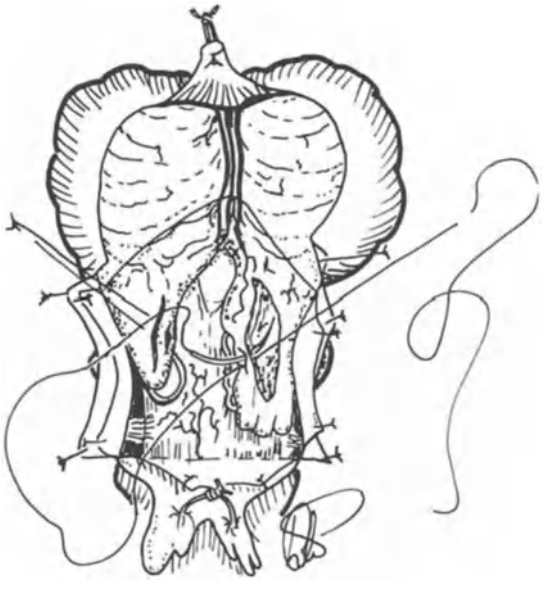

Fig. 27. The left tonsil has been partly evacuated and stitched upwards and laterally. Note the opening of the subarachnoid space under the tonsil tip, past the vertebral arteries and the lower cranial nerves into the prepontine cisterns. This passageway is as important as the central outflow pathway of the fourth ventricle. The right tonsil requires more exergetic elevation than the left to make a sound, capacious cisterna magna in this case

better that it is tempting to remove either the largest tonsil or both. Batzdorf recommends lightly diathermying the pia over the surface of the tonsils. This may make them shrink upwards and reform the outside impressively[8]. Creating an artificial cisterna magna is best effected by a more substantial removal. There is no morbidity after evacuation. A vertical incision may allow most of the inside to be sucked out. Leaving some septa on the inside gives stronger tissue to stitch. The suture may be passed through the medial wall of the tonsil and its pia once or twice (Fig. 27). The tissues should be pulled upwards, considering that the cerebellum will tend to move upwards after operation. The stitches should not be over tight or they may tear out if the tonsils develop post-operative swelling. In pulling the tonsils upwards and outwards to open the midline outflow canal it is possible to crowd the tissues lateral to the tonsil tips. Patients have been seen in whom second operations may be necessary to deal with this problem. Clearance of the lateral pathways may be helped by elevation of the tonsils by Batzdorf's manoeuvre but more radically and certainly by a positive attitude to tonsillar diminution.

If there is meningeal fibrosis the tonsils may be left alone. If they are bound together and to the back of the medulla with arachnoid adhesions, then dissection may imperil vessels such as branches of the posterior inferior cerebellar arteries. Not infrequently it seems best to rely upon the opening up of the anterior CSF spaces and the artificial cisterna magna. If dense adhesions are present the cerebellum is not likely to slump and the benefits of the operation are not thereby negated (Fig. 28).

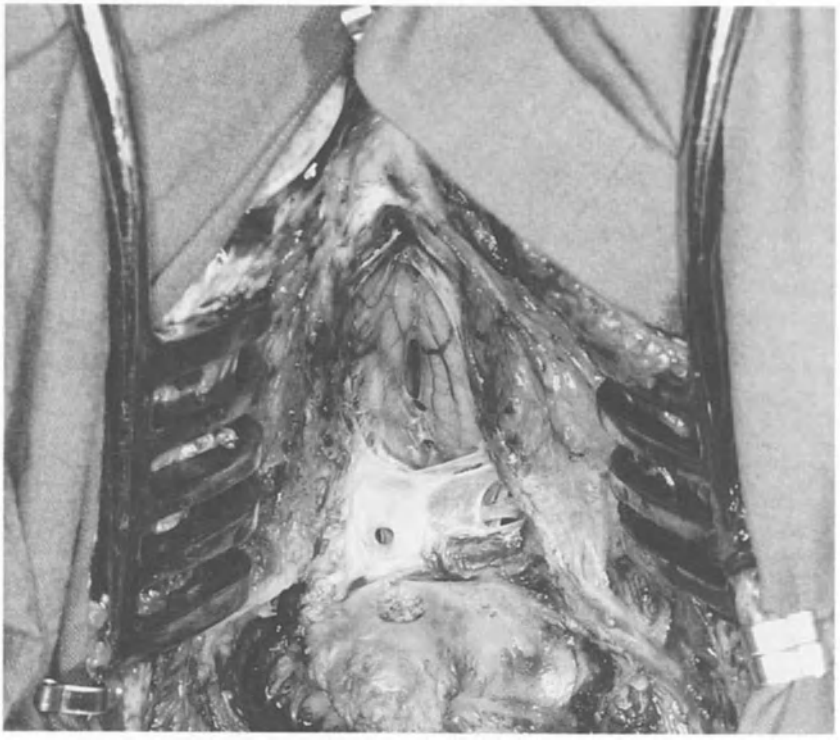

Fig. 28. Operative appearances of a case with dense white adhesions of meningeal fibrosis in the region of the tonsillar tips. This adhesive area will help to hold the hindbrain up, it may be easy to dissect but care must be taken. In this case there is an opening into the fourth above the meningeal fibrosis which will lead CSF readily from the fourth to the artificial cisterna magna. Prior to removal of the bone and dura this opening was effectively closed during episodes of suck

The fourth ventricle may be opened up above the zone of arachnoiditis either by the disease process, or if the fourth is large, by the surgeon. If the situation is difficult then the compromise between courage and caution is individual to each surgeon and each situation.

The anterior spaces often open up well but if there is a large cystic cord which collapses, the nerve roots, the dentate ligaments and the flattened cord all tend to separate the anterior spinal subarachnoid space from the new, artificial cisterna magna. The upper part of the cord may be moved backwards and forwards by pulsation as fluid is forced in and out of the artificial cisterna magna under these circumstances. It is possible to combat this by excising a part of the dentate ligaments or stitching them lightly backwards as in Fig. 29.

Fig. 29. The dentate ligaments attached to the upper cord may impede access for fluid from the artificial cisterna magna to the anterior spaces around the spinal cord. The ligament may be divided at its tip and lightly sutured backwards to open the spaces between the nerve roots

Closure

The muscle should not be tightly sutured close to the cerebellum. The spinous process of the axis gives a firm attachment point for resuturing and the remainder of the upper part of the muscle may be closed so as to leave a sizeable artificial cisterna magna.

The dura should be left open. If it is closed then the advantages of the operation are lost; to expose the patient to the risks of the procedure and then carefully reconstruct the valvular mechanism and re-establish suck is a negation of present understanding of this disorder. Some surgeons like to graft the defect. The suturing cannot be watertight. The graft may be pushed forwards against the back of the cerebellum with the artificial cisterna magna behind it instead of in front. If a fascia lata graft is used it is looking for a blood supply and may develop adhesions at that site. The result may be a constrictive arachnoiditis worse than the original. If a graft such as silastic is used, subsequent reopening shows a cavity, filled

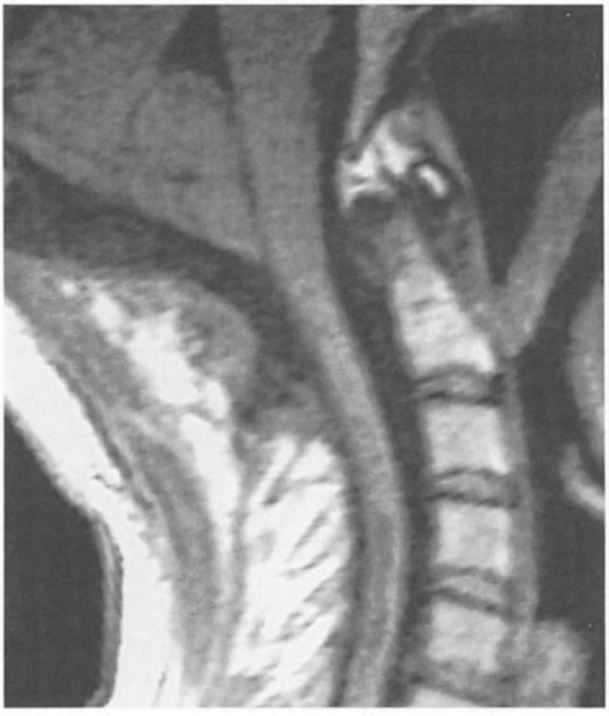

Fig. 30. A patient treated with a silastic sheet sutured across the site of dural opening. The pre-operative appearances were similar to those of Fig. 1. Compare this post-operative MRI with Fig. 2. The Silastic has provoked fibrosis and the tonsils are still held in a firm grip with a conical moulding. The patient was worse in almost all respects, the hindbrain headache was incapacitating, arm neurology deteriorated, but the syringomyelia cavity, interestingly, was objectively improved

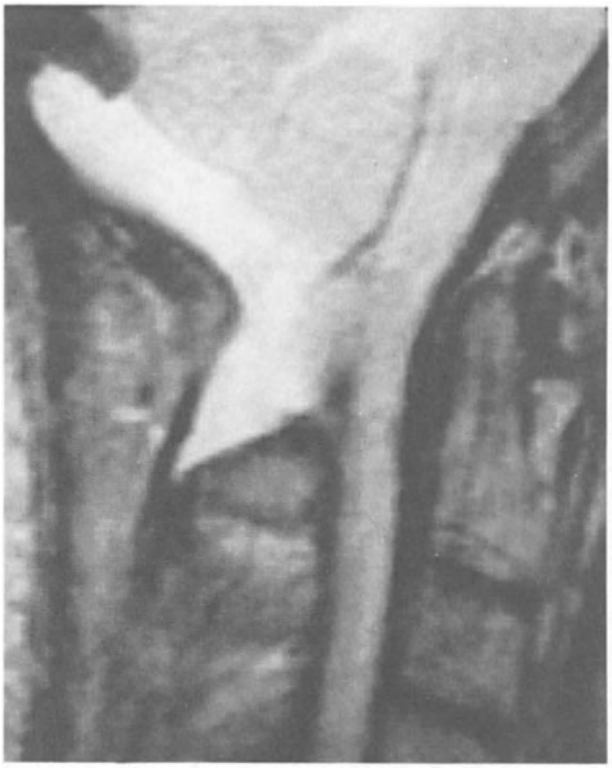

Fig. 31. The post-operative MRI of the same case as shown in Figs. 20 and 21. This is a T2 weighted image so that the artificial cisterna shows as white. Observe the flow void in the central outflow channel of the fourth ventricle

with CSF and lined with a thick reactive membrane. The graft may be curled up in this cavity, sometimes pressing on neural structures. The front membrane of the cavity may be dense fibrosis, tightly adherent to the cerebellum (Fig. 30). A graft is not necessary, a membrane grows in the right place, away from the surface of the cerebellum (Figs. 2, 5, 12, 22, 31). All that is required is that the muscle is closed in a reasonably watertight manner and not touching the brain. If a CSF leak develops, or the decompression bulges, then the patient may need a valved shunt. If a graft is used, it may be best to use fascia lata but to tent it firmly backwards so as to prevent forward displacement and re-adhesion to the back of the cerebellum. Batzdorf recommends tissue glue to make the graft watertight[8].

Syrinx Drainage

Syrinx drainage when the hindbrain abnormality is still in place is not advisable. Even though the idea of a filling mechanism which needs to be

disabled may be specious, the natural history of drains is that they become blocked. Even ventricular drains may block off, when the space around the catheter tips is greater than in a syrinx. If the drain works then it tends to flatten the walls of the cord around it and if the drain goes to a low pressure area such as the peritoneum or the pleura then the flattening around the catheter will be more emphatic.

No variety of syrinx drainage will address the problems of the hindbrain compression and extrathecal drainage may make the matter disastrously worse if low pressure in the spine is exaggerated. Byrne and Williams[9] found that in 100 consecutive unselected non-tumorous cases of hindbrain herniation, 63 of whom had syringomyelia, only four cases justified later syrinx shunting to the pleural space.

Syrinx to Subarachnoid Shunting

Myelotomy is a simple form of syrinx to subarachnoid shunt, one of the oldest operations for syringomyelia and is successful. Syringo-subarachnoid shunts have been praised[37], and a wide variety of technical variants have been proposed[5, 32, 39, 43]. The reason why a syrinx should empty through a syringostomy rather than fill through it, is that there is some residual elasticity in the wall. The majority of syrinxes which come to operation are too big to empty through their elasticity. Thus syringostomy, whether with a drain or just left open, may allow fluid to enter the cavity. Additional

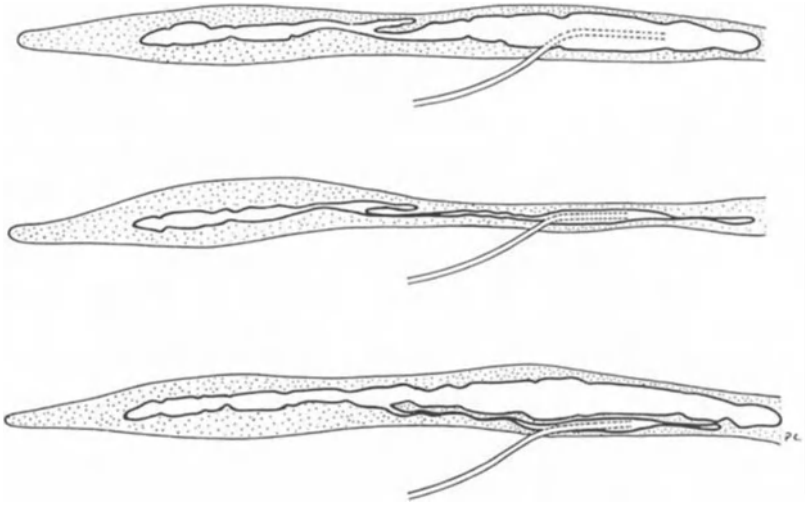

Fig. 32. A syringomyelia drainage operation is not advisable if the cord is still being inflated by an untreated filling mechanism or if it continues to exist, uncollapsed, in another part of the spine. A drain will block if it works well, and another cavity may develop alongside a collapsed syringomyelia

to that it is probably preferable to flatten all of the syrinx. If the syrinx is only partly drained, even if part of it may heal, then re-dissection may occur from another part which either has a life of its own, or where a filling mechanism still exists (Fig. 32).

Excision of the tip of the spinal cord, called by Gardner "terminal ventriculostomy" is sometimes advocated[14]. This may be criticised[54]. Now that MRI allows the imaging of the cord, the detection of a well filled

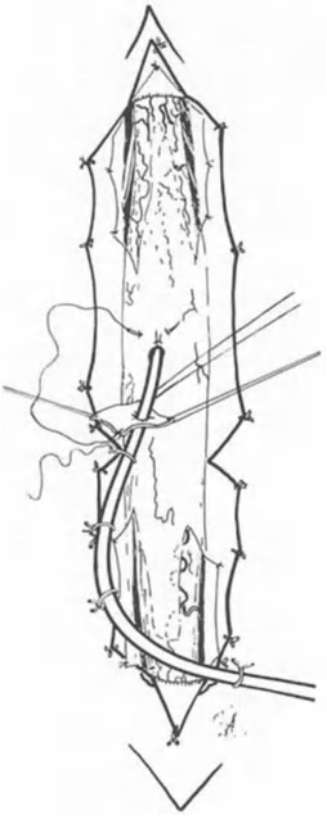

Fig. 33. Drainage of a syrinx to pleura or peritoneum is not good primary treatment for hindbrain related syringomyelia. Provided the spinal subarachnoid spaces are not obliterated by arachnoiditis a much smaller laminectomy than this can be used. The drawing here is of the sort of laminectomy used to treat a post-traumatic syrinx with arachnoiditis, the arachnoid is dissected and sutured back in a manner analogous to Fig. 26 and the dura left open to form an artificial meningocele. Note that the catheter must be securely fastened in position and that there must be a patch over the myelotomy. Tisseel tissue glue will attach this well and provide a watertight seal to prevent the CSF from overdraining. If drainage of all the CSF in the neuraxis is allowed then low pressure headaches and a risk of subdural haematoma may result

cavity down to the conus certainly invites consideration of this procedure. The original contention of Gardner that this was a safe procedure remains true, the benefits may be those of decompression and alteration of cerebrospinal dynamics rather than of drainage and it is probably best to leave the dura unclosed at such an intervention.

Syringopleural Shunting

Drainage to a low pressure area outside the theca has been used both peritoneum[5, 38] and pleura[55]. Pleura is a more convenient site, there is no need to change the operating position, the pleural pressure is satisfactorily low and the absence of omentum may be helpful.

A valve complicates the system. A hydrocephalus valve is designed to lower the CSF pressure to normal, so that if the initial pressure was already normal, a likely state if there was no hydrocephalus, then a valve may stop the system from working. A simple system is advocated. Care should be taken to close the pathways through which the CSF from outside the syrinx might enter the pleura. The catheter, a Cordis lumbar drainage catheter is a convenient size, is pulled through a small hole in the musculature, and the entry to the cord is patched (Fig. 33). Catheters of complex shapes have disadvantages, a "T" or "K" tube may require a large myelotomy and even a bayonet shaped catheter will be prone to distortion if the catheter becomes twisted during fixation. A well documented illustration is given by Wester[41].

It seems likely that such a drain will work for only a few days before the tissues obliterate the end of the catheter, no matter how well perforated it is. Reservoirs to test function are superfluous.

Outcome: Complications

Hindbrain-Related Syringomyelia

Respiratory Problems

Many patients have a diminished respiratory reserve due to kyphoscoliosis or impaired function either of the phrenic nerves or of the respiratory centres. Matsumoto and Symon reported a mortality after attempts to block the presumed communication at the obex of two cases out of 22. They related these deaths to respiratory problems[23]. In their cases with simple craniovertebral decompression they had no mortality. Williams has reported a case with sudden arrest, the patient being found dead[48]; in cases where there is anxiety an apnoea alarm or anoxia monitor is justifiable. Additional problems arise from damaged lower cranial nerves in many cases, sometimes with risk of inhalation. Careful pre-operative assessment is needed and close post-operative observation. Physiotherapy, vigilant

trials of drinking clear water before thick fluids or solids are tried and the use of tracheostomy for bronchial lavage, all have their place.

Hydrocephalus

If the development of hydrocephalus is due to re-impaction at the foramen magnum then the re-establishment of suck at this level may be diastrous with the development of fourth ventricular clefts and clinical features of syringobulbia (Figs. 4–6).

Inadequate Decompression

Occasionally, nervous surgeons may remove inadequate amounts of bone and leave the tonsils substantially in place (Figs. 34 and 35). The complication of respiratory inadequacy or arrest may result. If the dura is sutured or grafted re-impaction may occur. This is likely to lead to progression of the neurology in the later stages sometimes with persistent enlargement of the syrinx.

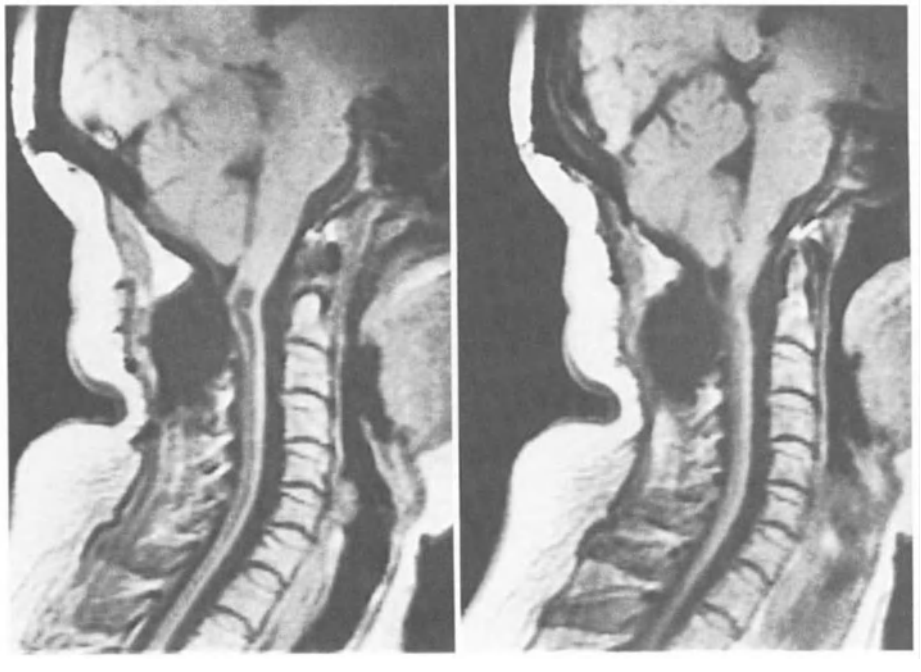

Fig. 34. A craniovertebral decompression which was too low and inadequate. The tonsils were not resected and the arachnoid was not removed. The result is that the outflow channel of the fourth has not been opened up, there is a sheet of thickened arachnoid forming a post-operative pouch behind the cord, and the syrinx itself is involved in post-operative adhesions

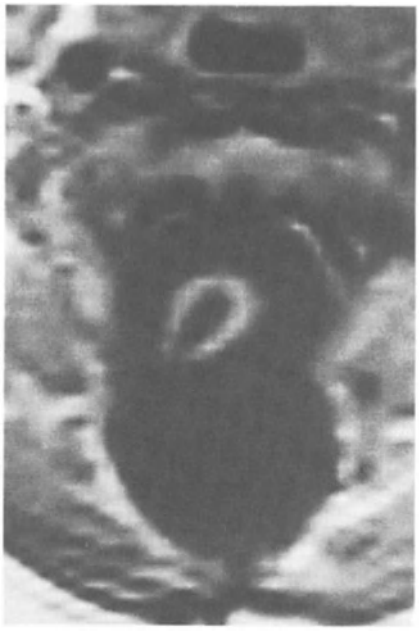

Fig. 35. Section through the same case as Fig. 34. The syrinx is tented backwards by the adhesions but there is little tension evidenced in the longitudinal images. The posterior cyst is under some tension, the front wall is thin and not visible on this image

The use of grafts may have a similar effect, the grafts may adhere to the cerebellum or the back of the cord establishing dense meningeal fibrosis, the use of silastic is, if anything, worse because fibrosis will develop on the anterior and the posterior surfaces of the graft (Fig. 31). A poorly formed artificial cisterna magna may give problems (Figs. 5, 36–38). Sometimes adhesions appear to be symptomatic, failure to control head pain is not unusual and sometimes this may be worse than pre-operative.

Slump

Over-decompression of the hindbrain with lack of support for the cerebellum may lead to its falling down into the decompression. Batzdorf prefers the term "ptosis of the cerebellum". This is more probable if suck is not eliminated. The hitching up to emptied tonsils may help to prevent this, but the size of the decompression is primary. The commonest symptom of slump is headache. If there is no hydrocephalus there seems to be little to do (Figs. 5, 36, and 39).

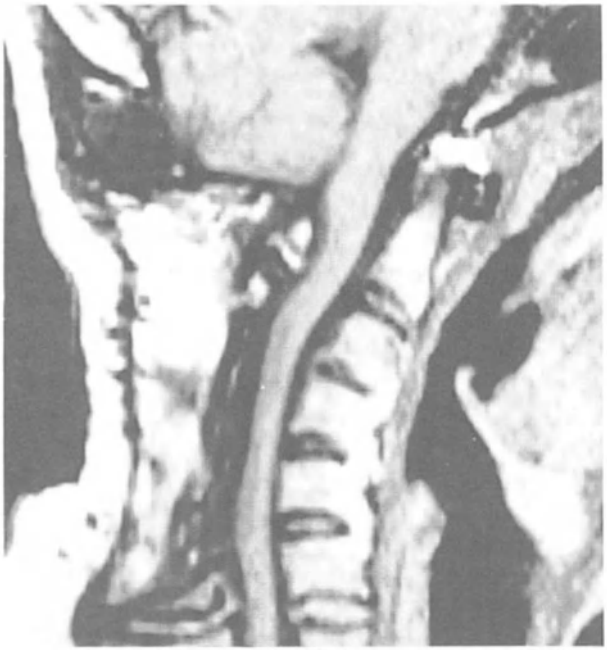

Fig. 36. On this T1 weighted image there is slump of the cerebellum, the artificial cisterna magna looks an uncomfortable shape but the midline outflow tract of the fourth is patent. The syrinx is flat, the laminectomy done in this case has produced a cervical kyphosis which does not require treatment

Persistent Tension in the Syrinx

A syrinx which has not collapsed as might be hoped may pose problems, such as illustrated in Figs. 40 and 41.

If the hindbrain is still causing suck it is possible that success will not follow a second attempt at dissection. The adhesions are commonly severe, the vessels are sometimes hidden and attempts to further free the suck mechanisms may be dangerous. A ventricle to extrathecal shunt is a safe next step. If the syrinx remains tightly full then a syringo-pleural drain may be used. Matsumoto and Symon report better results with syringo peritoneal shunts than with the use of syringotomy to the subarachnoid space[26]. In the majority of cases the syrinx is present, but relatively slack; any attempt to get a drainage tube into such a cavity may encounter haustrae and healing of parts of the cavity, with difficulty in inserting the drainage tube[5, 54].

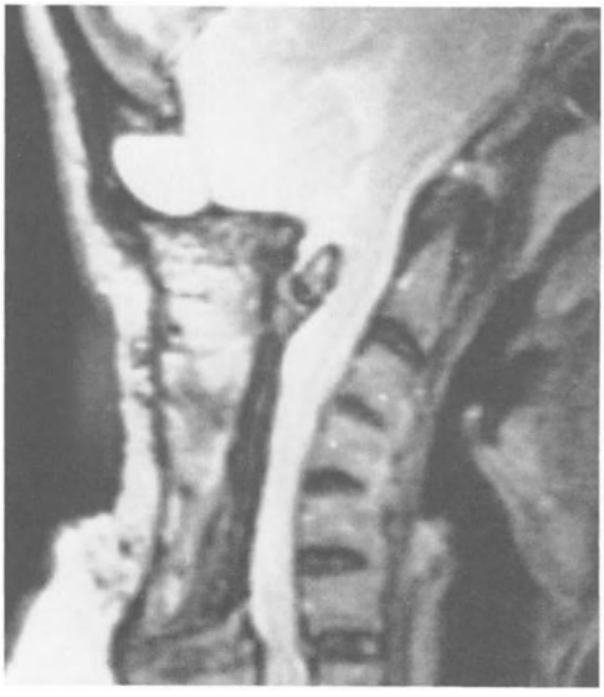

Fig. 37. MRI with a T2 weighted image of the same case as Fig. 36 shows that the cisterna magna has become partly walled off because of inadequate decompression. This may be due to the arachnoid attempting to make a neo-dura. It is the same sort of pouch as in Figs. 34 and 35. Pouches of this kind may occur after attempts to leave the arachnoid intact and may also fill up tightly and give rise to hindbrain compression. This man is clinically satisfactory despite the ugly appearances

Results

Spinal Instability

Patients who have an unstable spine with developing kyphoscoliosis may improve after surgery to the hindbrain[11, 17]. Clearly some of them will also progress despite neurosurgical intervention and orthopaedic surveillance is required.

Forward angulation of the cervical spine may occur after laminectomy. Laminoplasty is of doubtful benefit. Laminectomy of more than C1 should be avoided if possible, the spinous process of C2 may be used as a peg to resuture muscles to. The atlanto axial articulation is usually stable if the odontoid peg is unattacked.

There are few reports on outcome over satisfactory periods of outpatient

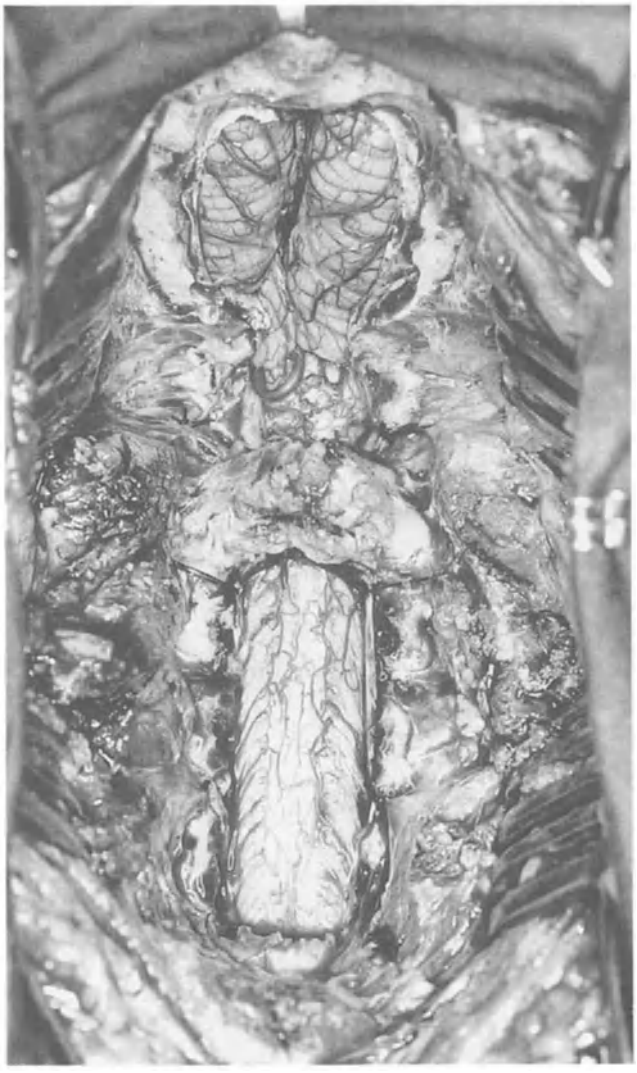

Fig. 38. Operative appearances of the same case as shown in Figs. 16, 17, 36, and 37. The removal of the occipital bone is excessive, it extends almost to the inion. The dura has been opened too widely over the cerebellum and the foramen magnum region has not been opened widely enough. Even so it is surprising that the cerebellum has come down as low as the spinous process and arch of the atlas. The laminectomy does not seem to help the result. Current practice is to bring the central area of the dura down and stitch it to the spinous process of C2

review, possibly because of the shortage of cases in well funded centres, and the converse. Chronic neurological deficits are difficult to record objectively, placebo effects of operation are powerful and the natural history

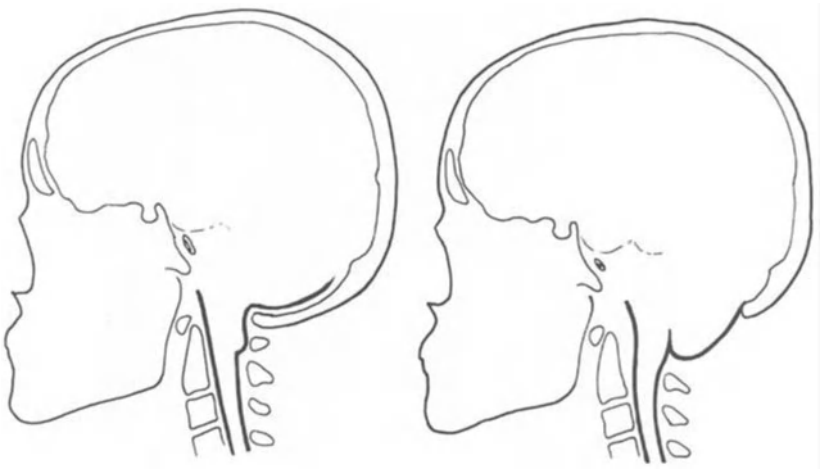

Fig. 39. Slump of the cerebellum into the wound is a consequence of too large a decompression of the cerebellum and too small a decompression of the tonsils, allowing the suck mechanism to become re-established. This drawing is of such a case before (left) and after (right) a decompression which was too large

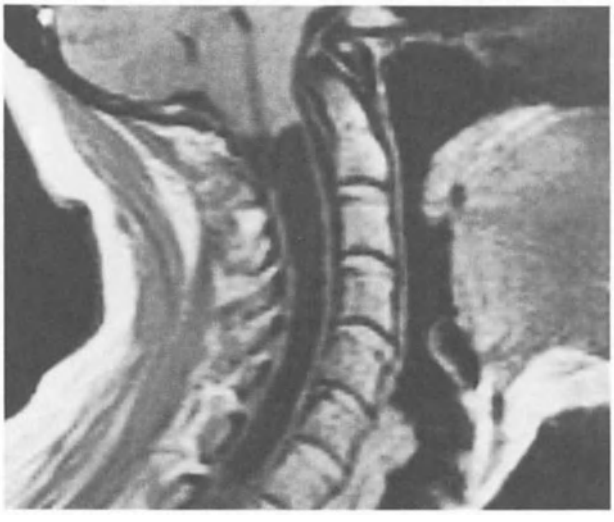

Fig. 40. Pre-operative appearances in a 48 year-old woman who refused surgery for nine years

may be long and uneventful. It is so easy to produce good results by any operation, in the short term, that prolonged follow-up is necessary above everything else in assessing these cases. The improvements are seldom so great that they can be registered on a gross grading such as the Karnovsky or Frankel scales. Careful attention to the patients complaints and func-

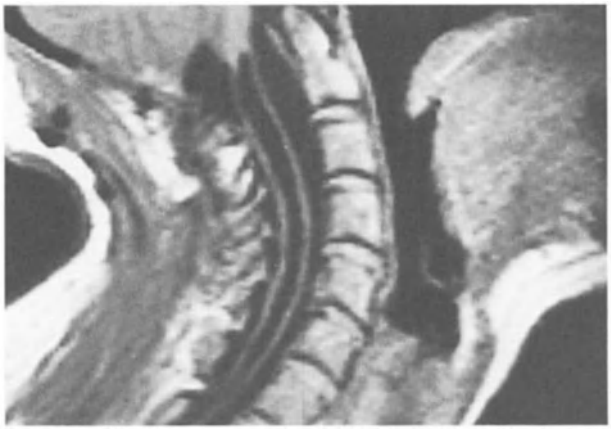

Fig. 41. Post-operative appearances in the same case as Fig. 40, the patient was symptomatically only slightly improved but seemed stable. The syrinx is still noticeably full, the hindbrain appearances are not relaxed. Whether anything more should be done about this lady's problems remains unclear, a waiting policy seems justifiable

tional abilities leaves the author in no doubt about the usefulness of the measures proposed in this chapter.

The results of hindbrain hernia decompression are often pleasing. The symptoms which do best are those of the long tracts, pain, especially neck pain and headache; and also stem or bulbar features[9, 10, 11, 12, 18, 19, 26, 27, 28, 31, 32, 33, 35, 41, 48, 51, 57]. Signs related to the cavity are not so favourably influenced; loss of tendon reflexes, muscle wasting and sensory loss seldom improve.

The results of hindbrain hernia decompression in patients with bulbar or hindbrain compression features are pleasing. Morgan and Williams[27] reviewing 54 such patients with follow-up of over three years found that 31 of the patients graded themselves as having "great improvement", 14 claimed "some improvement" 5 claimed to be unchanged and four patients thought that they were worse (Table 2).

Byrne and Williams reviewed 100 consecutive hindbrain hernia decompressions with a follow-up of over three years. The types of presentation are shown in Table 3, it should be noted that only two thirds of the cases had associated syringomyelia demonstrated. There was no mortality. The results are given in Table 4. It has to be noted that in both Table 2 and 4 the method of classifying the results is highly subjective. The assessors have tried to be fair but when several features are worse and several others are better than before operation then it is possible to classify the patients in

Table 4. *Signs at Presentation in 100 Cases of Symptomatic Hindbrain Herniation*

	Presenting signs	
Sign groupings	Signs	Number
Motor signs	weakness	40
(76%)	wasting	24
	spasticity	31
	reflex changes	54
	Babinski reflex	29
	fasciculation	6
	gait abnormality	20
Sensory signs	dissociated loss	31
(48%)	posterior column	15
Stem signs	nystagmus	28
(43%)	ptosis	2
	Horner's syndrome	5
	trigeminal loss	9
	tongue	4
	palate	3
Others	kyphoscoliosis	26
(41%)	trophic changes	25

From Byrne and Williams, unpublished.

any outcome group. Pain for example is not uncommonly better in the head but worse in an arm. Almost all the syrinxes were smaller, many of them almost disappearing (Figs. 1 and 2). Four of the patients had persistent syringomyelia cavities of such size that a later syringopleural drainage was thought justifiable[9].

Changes in the MRI scans may provide the best objective measure of success. The desirable objectives are the rounding off of the lower border of the tonsils, the opening up of the midline fourth ventricular drainage canal, the avoidance of slump and improvements in the appearance of the syrinx. Duddy and Williams analysed 17 cases of hindbrain decompression, eleven of whom had syringomyelia. These cases were chosen because comparable quality MRI scans were available before and after surgery. It was found that the tip of the odontoid peg was difficult to see accurately and measurements were therefore taken from a line drawn from the palate touching the top of the anterior arch of the atlas. Measurement showed that downward movement of the hindbrain was usual. The cerebellum

Table 5. *Results by Symptom Groupings After 100 Hindbrain Operations.* Minimum follow-up 3 years, no deaths

Symptom Grouping	Results	Percentages
Pain	improved	67
	stable	32
	worse	1
Motor	improved	29
	stable	67
	worse	4
Sensory	improved	34
	stable	63
	worse	3
Stem	improved	25
	stable	74
	worse	1
Other	improved	21
	stable	76
	worse	3

Note that all patients who did not have any features in a particular symptom grouping are recorded as "stable". By comparison with Tables 3 and 4 it can be seen that 59% of patients in the "other group" had no "other" features. Thus the improvement of 21% should be doubled to reflect the percentage improvement in patients who had such features.

came down more that the stem, five of their cases had a descent of more than 6 mm as measured from the fastigium or medial dorsal recess of the fourth ventricle, there were five cases with a descent of 4 mm or more of the pons. All 17 patients showed reduction in either the width or the length of the syrinx, usually both (Fig. 42). Clinically two patients were transiently worse, seven remained stable and the remainder were improved[10].

Follow-up

Prolonged out-patient surveillance commonly discloses slow progression of symptoms over many years[1, 26]. Most of them stabilise in a convincing way. Re-investigation to establish the state of the ventricles is sometimes rewarding and MRI is helpful[6, 10, 16, 25]. Imaging of the operation site and the cord is often inconclusive. It is sometimes tempting, on reviewing a patient with a persisting cord cavity and tonsils still jammed in an inad-

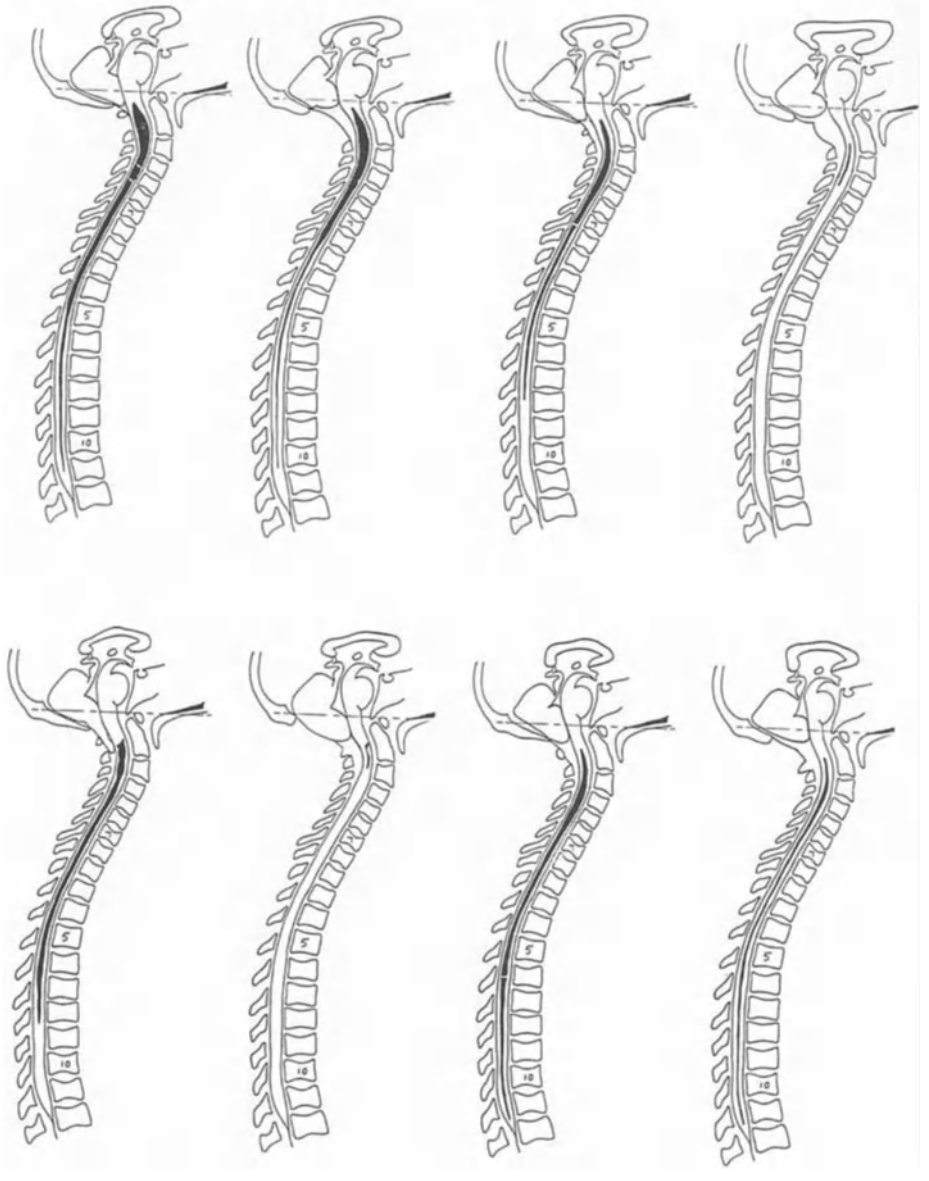

Fig. 42. Reproduction of drawings of typical cases before and after creation of an artificial cisterna magna (reproduced from Duddy and Williams, with permission). It was observed that the bigger the cisterna magna the less was the slump

equately decompressed foramen magnum, to recommence surgery even years after an earlier attempt, but the clinical progression may be equal in cases with a surgically perfect result and enthusiasm may need to be checked.

Counselling and Support

Patients with syringomyelia of all kinds have to anticipate the problems of chronic and slowly progressive neurological disease, even if operation may have produced improvement. They may need psychological and social support. A self-help group may be helpful for some patients**.

Future Developments

The problems of syringomyelia would be better prevented than cured; early diagnosis is best. Children with "idiopathic" scoliosis[17] and all forms of dysraphism constitute a high risk group for which early surgery may be helpful. Magnetic resonance imaging is the investigation of choice and may turn up hindbrain related syringomyelia unexpectedly.

The discovery that in hindbrain related cases there is an association with difficult birth[47] is interesting. It seems that a high proportion of cases without such an association being noted probably came on at birth. There is a need to study the infantile hindbrain during labour and immediately afterwards. The moulding of the infant skull during normal birth suggests that the hindbrain is commonly forced into the foramen magnum. Crying and suckling may tend to hold this in place by suck. This area is little explored, the tool most likely to advance understanding is real-time ultrasound imaging. It may be that prophylactic measures against dysraphism, screening of infants at risk from birth trauma and early surgery may almost eliminate hindbrain related syringomyelia from developed societies in the future.

Acknowledgements

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Medulloblastoma

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With 4 Figures

Contents

Medulloblastoma is a highly malignant cerebellar tumour which was identified as an entity by Bailey and Cushing in 1925[5]. They reported the clinical and pathological features of 29 patients, most of them children, who had a cerebellar tumour, usually located in the cerebellar vermis. Actually the paper prepared by Bailey and Cushing for presentation to the 50th annual meeting of the American Neurological Association in June 1924 was entitled "spongioblastoma". However Globus and Strauss had already submitted a paper in which they described another type of tumour that they called "spongioblastoma multiforme"[45]. After discussion between

the four authors, it was decided that the cerebellar tumour described by Bailey and Cushing would be called medulloblastoma. The medulloblast was considered as an embryonic cell which, different from spongioblasts and neuroblasts, was however able to differentiate along both lines. The authors considered the tumour as a glioma and thought that most of its cells were potential glia although some of them were potential neurons. Controversies surrounding the histogenesis of the tumour date back to this original concept and are reflected to day in the discussions about nomenclature: should medulloblastomas be considered as primitive neuroectodermal tumours?

The tumour was considered as sensitive to irradiation but incurable. Three years after surgery, only one of the 61 patients operated on by Cushing[25], was alive. Most authors in the past considered that treatment could produce only temporary palliation. Things began to change with the publications of Richmond in 1953[48] of Paterson the same year[91] and of Lampe[64], when the principle of associating surgery with irradiation of the whole central nervous system (CNS) was applied. In the series published between 1960 and 1970, most five year actuarial survival rates were around 30%[19]. In more recent series, five year actuarial survival rates vary between 50 and 60%[51, 83, 90]. These results are the consequence of the progress in neurosurgery during these past twenty years: improvement of diagnostic tools, air studies being replaced by CT scan and MRI; surgical progress due to the introduction of bipolar coagulation, the operative microscope and the ultrasonic aspirator; progress in anesthesiology and in radiotherapy, megavoltage replacing the orthovoltage techniques. Thus the history of the treatment of medulloblastomas reflects the progress observed during these past two decades. The post-operative mortality decreases from 30%[19] to 10%[78, 51] and is now nearly nil in the most recent publications[53]. About half of the patients are alive ten years after surgery.

Numerous publications have appeared since the original description of the medulloblastoma. Among these the monograph published by Crue[24], the well documented paper of Bloom in 1971[15] and the general review presented by Choux and Lena in 1982[19] to the "Societé de Neurochirurgie de Langue Française" are the most important.

In spite of the recent progress, several problems remain controversial:

1) Controversies surrounding nomenclature and histogenesis are well expressed in the publications of Rorke[100] and Rubinstein[101].

2) Progress in molecular biology and modern theories on the development of malignant tumours have led recently to an important number of experimental studies concerning the etiology and the growth of medulloblastomas.

3) Several cooperative studies have not yet precisely determined the usefulness of chemotherapy.

4) The last but probably the most important controversy concerns the quality of life of the survivors. We had shown in 1978[51] that if 70% of the patients who completed radiotherapy could be cured, an important proportion of them had relatively low IQs, behavioral disorders and school problems. More recently we have shown[53], that these disturbances worsen with time so that most survivors do not have a normal social life. This is especially true when the CNS irradiation is delivered before three years of age. A new therapeutic strategy should therefore be found in infants. In children, a reduction of the dosage to the cerebral hemispheres is under trial.

I. Epidemiology

Medulloblastomas constitute about 4% of all brain tumours. Adding the series of Cushing[26], Zulch[124], Berger and Elvidge[8], the precise incidence is 4.1%, a result close to that found in these different series taken separately.

However, most medulloblastomas occur in children so that their incidence in children is much higher: medulloblastomas represent 18.2% of all pediatric brain tumours[19] and roughly 30% of the posterior fossa tumours observed in children. In a recent study performed in Japan[85], the incidence of medulloblastomas was about the same in all pediatric age groups (17%) and in infants under 12 months (16.5%); 8.3% of the medulloblastomas were observed under 4 weeks of age.

Evans[35] estimated that 250 new medulloblastomas were observed in the United States each year. Bloom[15] found that there were 60 new cases of this tumour each year in England and Wales among a population of 10.7 million children under the age of 15. Indirect and approximate calculations give the same results for France.

In most series, there is a male prevalence: 2 to 1[15], 6 to 4[19, 51]. The explanation of this prevalence is not clear. It has been shown[79] that sex hormones could have a protective effect on the carcinogenic action of Dimethylbenzanthracene, but this effect was observed on the uterus and in mice. This experimental situation is so far from the posterior fossa medulloblastoma that no conclusion can be drawn.

II. Pathology

A) At surgery, most medulloblastomas appear as a friable, vascular tumour developing in the vermis, on the roof of the IVth ventricle, invading more or less laterally the cerebellar hemispheres on both sides. It often reaches upwards and blocks the aqueduct of Sylvius. In one third of the cases, it invades the brain stem. Sometimes tumoural seeding is observed in the subarachnoid spaces of the posterior fossa. The center of the tumour is more or less necrotic. Its most important vascular supply is by vermian

branches of the PICA. The cerebellar tonsils are practically always pushed downwards in the spinal canal.

In adults the localization of the tumour may be different. About one third of the tumours are purely hemispheric and one fifth develop in the cerebellar hemisphere and in the vermis[22].

B) The main characteristic of medulloblastomas is their capacity to transplant malignant cells on to the central nervous system. This seeding occurs mainly on the spinal cord, i.e., lower than the posterior fossa, but is also observed on the cerebral hemispheres. The proximity of the tumour to the IVth ventricle explains partially this spread through the CSF. The characteristics of the tumour should also be taken into consideration since other tumours in a similar location do not have the same capacity. In most cases, metastases develop in the subarachnoid spaces: however very rare cases of intramedullary metastases, probably transported through the central canal of the spinal cord, have been described[7, 125].

C) Extra neurogenic metastases are rare, but probably more frequent now than in the past[9, 105]. In most cases, they involve the bones, but they can also reach the lung or the liver. Ventriculo peritoneal or ventriculo atrial shunts are responsible for approximately one third of these deposits outside the central nervous system[9]. Shunt insertions in the treatment of medulloblastomas should be strictly reserved to these cases in which tumour removal is not sufficient to cure hydrocephalus. The practice of shunt insertion and the longer survival of these patients who however are not definitively cured explain the increased frequency of these extra neurogenic metastases of medulloblastomas.

D) Under the microscope, medulloblastomas appear as dense tumours composed of uniform, small angular cells with scanty cytoplasm and a chromatin rich nucleus. Neuroblastic rosettes can be observed as well as cells showing neuronal astrocytic or oligodendrocycitc differentiation. There are usually many thin walled blood vessels.

The traditional features used to grade neoplasms of the CNS vary from one case to the other. Thus there are lesions with conspicuous nuclear pleomorphism, chromatin coarseness, necrosis and high mitotic activity whereas others show uniform nuclei and scant mitotic activity[17].

Medulloblastomas sometimes contain a prominent mesenchymal component characterized by parenchymal desmoplasia, increased vascularity and prominent endothelial proliferation. The mechanism by which primitive neuroectodermal cells influence the growth and metabolism of neighboring stromal cells has been studied by Rutka[102]. He found in short term cell cultures an acid and heat stable protein that stimulates the proliferation of leptomeningeal cells and induces a shift in collagen synthesis (type III instead of type I). This shift might be equivalent to the desmoplastic process, as it occurs in vivo.

As already stated, the undifferentiated nature of the tumour was obvious to the earliest investigators. Most pathologists to day agree that the neuroepithelium is the progenitor, but the debate focuses beyond the "stem cell". Numerous observations have shown that the medulloblastoma is capable of differentiation along neuronal and glial lines, and sometimes of divergent differentiation to both. Electromicroscopic and immunohistological studies[50, 68, 72, 99] demonstrate this bipotentiality.

Glial fibrillary acid protein (GFAP) is a protein specific for astrocytes and ependymal cells. Its immunohistochemical localization in medulloblastomas[28, 34, 89] is one of the arguments which favors the possible astrocytic differentiation. Moreover it has been shown[76] that the glial fibrillary acidic protein mRNA could be expressed at significant levels in medulloblastomas. However it has been argued that GFAP positivity could be due to reactive astrocytes, not to neoplastic astrocytes[20].

Other data demonstrate the possible neuronal and glial differentiation of medulloblastomas. Gottfries[46] analysing the ganglioside composition of medulloblastomas was able to detect neuronal gangliosides (gangliotetraose series) – as well as astroglial gangliosides (ganglioside 3′-isoLM1). The phenotypic analysis of four continuous, karyotypically distinct medulloblastoma cell lines and transplantable xenografts[49] demonstrated that two cell lines were rather glial (TE 671 et Daoy) whereas the two others were close to the neuronal type (D 283–D 341).

Recently Maria[69, 70] showed that GFAP negative cells may represent astrocyte progenitors in maturation arrest. Retinoic acid treatment of a medulloblastoma cell culture with astrocytic differentiation decreased GFAP whereas dibutyryl cyclic AMP induced fine cytoplasmic processes containing GFAP in 85% of the cells. The maturation arrest could occur at the proastroblast, or even earlier, at the glioblast stage of normal astrocyte development.

Thus, the bipotentiality of medulloblastomas is now a well recognized feature. Another problem is to detect the localization in the cerebellum of the cell of origin. Since the cerebellar medulloblastoma is one of the most common embryonal tumour of the CNS, it is reasonable to assume that the window of vulnerability for the cells at risk is wider than for other tumours[101]. It is therefore understandable that the fetal granular layer of the cerebellar cortex, which maintains its mitotic activity up to the end of the 1st year of postnatal life, has been considered as the source of the tumour. However the cells of that layer give rise only to neurons.

The bipotentiality of medulloblastoma cells implies therefore that the transformation occurs at an earlier stage, probably from these cells located in the posterior tip of the fourth ventricle where they constitute the germinal bud. These cells normally migrate laterally to form the external granular layer but can sometimes persist after birth on the roof of the IVth ventricle[94].

The internal granular neurons have also been postulated as the site of origin[123], but it is possible that the transformed cells in Zimmerman's experiment were those of the fetal granular lyer.

Hart and Earle in 1973[48] individualized some supratentorial tumours that they called primitive neuroectodermal tumours (PNET). Palmer[89] considered that medulloblastomas, being developed from the primitive neuroepithelium, were analogous to other PNET developed in other sites, but the debate about nomenclature began really when Rorke[100], in her Presidential Address to the American Association of Neuropathologists, proposed a new classification of these tumours composed of neuroepithelial round cells occuring primarily in infancy and childhood. The new classification did not take into account the site of origin of the tumour and was based on the assumption that transformation of primitive neuroepithelial cells at all levels of the CNS could create tumours of similar appearance. In this classification, medulloblastoma is a PNET, histologically analogous to the other PNETS, but developed in the cerebellum. Rubinstein[101] argued that this classification was an oversimplification ignoring the fact that cytogenesis of subependymal primitive cells is not in the same time at the same stage at different anatomic sites. Therefore the classification fails to consider the possibility of restrictions in the differentiating potential of specific tumours at different locations and Rubinstein states that, in his experience, the bipotentiality of medulloblastomas separates them from other embryonal CNS tumours, especially from most supratentorial neoplasms.

This controversy, although of great interest to neuropathologists is of little help to neurosurgeons to whom a medulloblastoma, by any other name, remains a clinical and therapeutic specific entity.

III. Etiology and Patho-Physiology of the Tumour's Development

It has been known for a long time that the application of carcinogens such as methyl-cholanthrene on the cerebellum[122] could induce the development of a tumour or that the administration of ethylnitrosourea to pregnant rats could produce neurogenic tumours in the offspring[120]. In this case, it was clear that the carcinogen could pass through both the placental and the blood brain barrier and that the tumours were induced in the embryo, but no unequivocal medulloblastoma was reported.

It has also been shown that the intracerebral inoculation of simian adenovirus SA 7 in newborn hamsters could produce tumours that looked like medulloblastomas[96]. Varakis and Rhein were able to induce pineocytomas in hamsters with a human papovavirus and medulloblastomas with a human polyoma virus[116, 126]. Ogawa[84] induced embryonal neuroepithelial tumours by human adenovirus type 12 in rodents. Transgenic mice

are animals that have integrated foreign DNA into their genome as a result of experimental introduction of DNA. Recently Korf[52] used such transgenic mice expressing the large T-antigen of the simian virus 40 (SV 40) under the control of the Moloney murine sarcoma virus enhancer and the SV 40 promoter. These animals developed brain tumours that are comparable to the subtype of medulloblastoma displaying photo-receptor like features and to pineal cell tumours.

Oncogenic properties for CNS tissue have been associated with eight DNA-containing viruses (4 papovaviruses and 4 adenoviruses) and 4 RNA-containing retroviruses[117]. Medulloblastomas have been produced in the syrian hamster with the JC papovavirus or the simian SA 7 adenovirus. Other tumours have been obtained with other papovaviruses, adenoviruses or retroviruses, but it is possible that the type of tumour is related to the place where the virus diffuses and that, in most cases, an intracerebral injection of a virus ends up in an intraventricular diffusion of the virus. This would explain the frequency of ependymomas and of choroid plexus papillomas[81] after intracerebral injection of viruses.

Moreover most tumours, thus produced look like PNETS. It is very likely that their histological features reflect nothing but their site of origin[117].

Infection of cells in tissue culture with a tumour inducing virus produces a neoplastic transformation of the cells. However in cell culture the transformed cells do not have to contend with an immunological response of the host nor do they have to invade and disseminate through a three-dimensional tissue architecture[33, 109]. These cultures are therefore a good model for the initial stages of tumour induction, but not for the late stages.

The first indication that human tumours may result from an infection with papovavirus was a study by Farwel[36] which showed that the administration of Salk polio vaccine that had been accidentally contaminated with live, infectious papovavirus (SV 40) was associated with an increased incidence of certain childhood intracranial tumours. Medulloblastoma was the type of tumour found in half of these children who had been exposed to SV 40.

Thus there are now many arguments which favor the hypothesis that certain viruses may produce CNS tumours. However this evidence relies mainly on experiments in laboratory animals. The indisputable demonstration of this hypothesis in humans has yet to be given.

There is practically no evidence that hereditary factors play a role in the development of medulloblastomas. Hung[55] recently reported two siblings presenting with a medulloblastoma. He found seven similar reports in the literature. In our series of 120 medulloblastomas, we have one familial history: a 3 year-old boy with a medulloblastoma and a few months later his 10 year-old sister with an occipital malignant astrocytoma. These cases are too rare to demonstrate that heredity is responsible. An exposure to

similar carcinogens is more likely to be the cause of these rare familial cases.

There is no doubt that chemical agents, viruses and probably other physical agents can induce brain tumours and eventually medulloblastomas. The cerebellar medulloblastoma is an embryonal tumour. If we accept the view that malignant transformation results from a sequence of multiple mutational events and that the first hit should be given to cells that are still cycling, then the window of vulnerability for medulloblastomas should extend from fetal life to the end of the first year of post natal life, i.e., to the end of the mitotic activity of the fetal granular layer.

Most recent studies try to determine what mutational events occur in the genome and are responsible for the development of medulloblastomas. These studies are performed on biopsies, short term cell cultures and continuous cell lines. The first cell line, TE 671 was established by McAllister[75], but it was shown recently that it was actually a derivative of a rhabdomyosarcoma[106]. There are to day seven medulloblastoma cell lines[42] Daoy, D 283 Med, D 341 Med, D 384 Med, D 425 Med, ONS-76 and ONS-81. The five D lines grow in suspension whereas Daoy, the only tetraploid cell line, grows as an adherent monolayer. Daoy expresses a glial phenotype whereas the other D lines and the ONS lines[110] express a neuronal phenotype.

The early cytogenetic studies described the karyotypes of medulloblastomas. It was found that most tumours had near-diploid stem lines and occasionally near tetraploid stem lines[23, 71]. More precise analysis came from the routine incorporation of banding and from molecular biology. Bigner *et al.*[11] concluded from their observations that the primary karyotypic deviations of human medulloblastomas were gains of whole chromosomes, which were then deleted or involved in unbalanced translocations, resulting in partial trisomies. Cogen[21] performed a restriction fragment length polymorphism investigation in medulloblastoma and found a loss of 17p sequences in 45% of these tumours. The precise region involved was 17p 12–p 13.1, the same chromosomal region involved in colon cancer and the same region to which the p 53 gene has been mapped. This study suggested that medulloblastomas could be associated with the absence of a tumour suppressor oncogene. The same loss of 17p was found in one third of the PNETS studied by Thomas and Raffel[111]. The granulocyte colony stimulating factor (G-CSF) has been found in one medulloblastoma and in the Daoy cell line; the gene of this G-CSF is known to be located on 17q 11.2–q 21[92]. Gene amplification has been studied by Bigner[12]: C-myc amplification was found in cell lines and xenografts derived from 7 medulloblastomas. C-myc amplification was observed in the cell lines or xenografts when there were double minute chromosomes in the original biopsies. This study suggested that the C-myc gene could be amplified and/

or rearranged in human medulloblastomas, providing a growth advantage to those medulloblastoma cells which showed this amplification.

Fujimoto[43] found in one medulloblastoma and Valery[115] in 4 out of 18 medulloblastomas an accumulation of mRNA coding for C-myc gene without amplification. For Wasson[119] oncogene amplification is relatively uncommon in primary medulloblastomas but the frequency of gene amplification is greater in tumours that can be established as cell lines. Although medulloblastoma and neuroblastoma share many common features, they differ as far as N-myc amplification is concerned. N-myc amplification is frequent in neuroblastomas, but is not found in medulloblastomas[44]. In contrast, over expression of the gene was found in about half of the cases. A trend toward longer disease free survival was observed when the N-myc protein level was low.

Undoubtedly, in the near future, these basic studies will provide a better understanding of the malignant transformation that leads to medulloblastoma growth, but most of the research has yet to be done.

IV. Clinical Features

The main clinical features of medulloblastomas are due to raised intracranial pressure, a consequence of CSF blockage and of hydrocephalus; they also result from the cerebellar vermian involvement. In some cases, they express extension of the tumour into the brain stem.

In most cases, the evolution is characteristic of a malignant tumour: the delay between onset and diagnosis is short, usually around three months.

Headache and vomiting are the first symptoms in most children. In our series, headache and vomiting were associated in seven cases out of ten. Vomiting can also be a first isolated symptom which for a certain time misguides the clinician towards an abdominal pathology. Coma is extremely rare (1% of the cases in our series). The state of consciousness is normal in 80% of the cases; obnubilation is observed in two children out of ten. Non-specific complaints such as lethargy, irritability, behavioral changes are possible. Torticollis or abnormal postures of the head were found in 7% of our patients. Their presence indicates a compression of the spinal root of the accessorius nerve by a downward tonsillar herniation. A VIth nerve palsy, consequence of intracranial hypertension, was found in 20% of the children.

In infants macrocrania with bulging fontanel may be the first sign. Developmental regressions are sometimes claimed (for example regression of the gait in an infant who was beginning to walk).

On examination, cerebellar signs were observed in 75% of the cases. Dysmetria, adiadochokinesia were less frequent than truncal ataxia except in adults in whom medulloblastomas are more often developed in the cerebellar hemispheres than in the vermis.

Cranial nerve palsies (VI excepted) were found in 15% of our cases and pyramidal syndrome in 10%. In these medulloblastomas, the brain stem was usually invaded.

In our series, papilloedema was found in 75% of the children. Thus the fundus being normal in one case out of four, the absence of a papilloedema cannot rule out the diagnosis.

V. Radiology

Until approximately 1975, different investigations were necessary or at least useful to make the diagnosis of posterior fossa tumour. Among the non-invasive investigations, a normal EEG had the advantage to rule out a supratentorial tumour developed in a non-eloquent area such as the right frontal or temporal lobe; the isotope scan could localize the lesion in the posterior fossa but was not considered as sufficient to decide surgery and was not always positive. Pneumoencephalography was not recommended in acute intracranial hypertension. Ventriculography with water soluble contrast was the most important radiological investigation. Vertebral angiography was also recommended by some authors. These different investigations were time consuming and some were dangerous.

CT scan and more recently MRI allow a rapid and precise diagnosis so that all other investigations are now obsolete. CT scan and MRI give excellent information about the localization of the tumour; these examinations however cannot give with certitude an histological diagnosis.

CT Scan

Medulloblastomas appear usually as a midline vermian, hyperdense tumour on the CT scan. After contrast injection, the enhancement is positive, homogenous or non-homogenous. The heterogenous aspect of the tumour may reflect necrosis. Sometimes the image of the tumour is surrounded by an hypodense circle. Before injection, medulloblastomas are rarely calcified or isodense; large cysts are hardly ever observed. Thus they can be distinguished from cerebellar astrocytomas which are usually developed on the wall of a cyst and from ependymomas which are isodense before injection and show in most cases a downward extension towards the foramen magnum and the spinal canal. The CT scan detects metastases when their diameter is larger than 5 mm. It allows also a precise assessment of the degree of hydrocephalus.

MRI

On the T1 images (Fig. 1), the signal of the tumour is weak whereas it is intense on the T2 weighted sequences. Necrotic areas show a different signal which changes as the CSF signal on the different sequences. But the

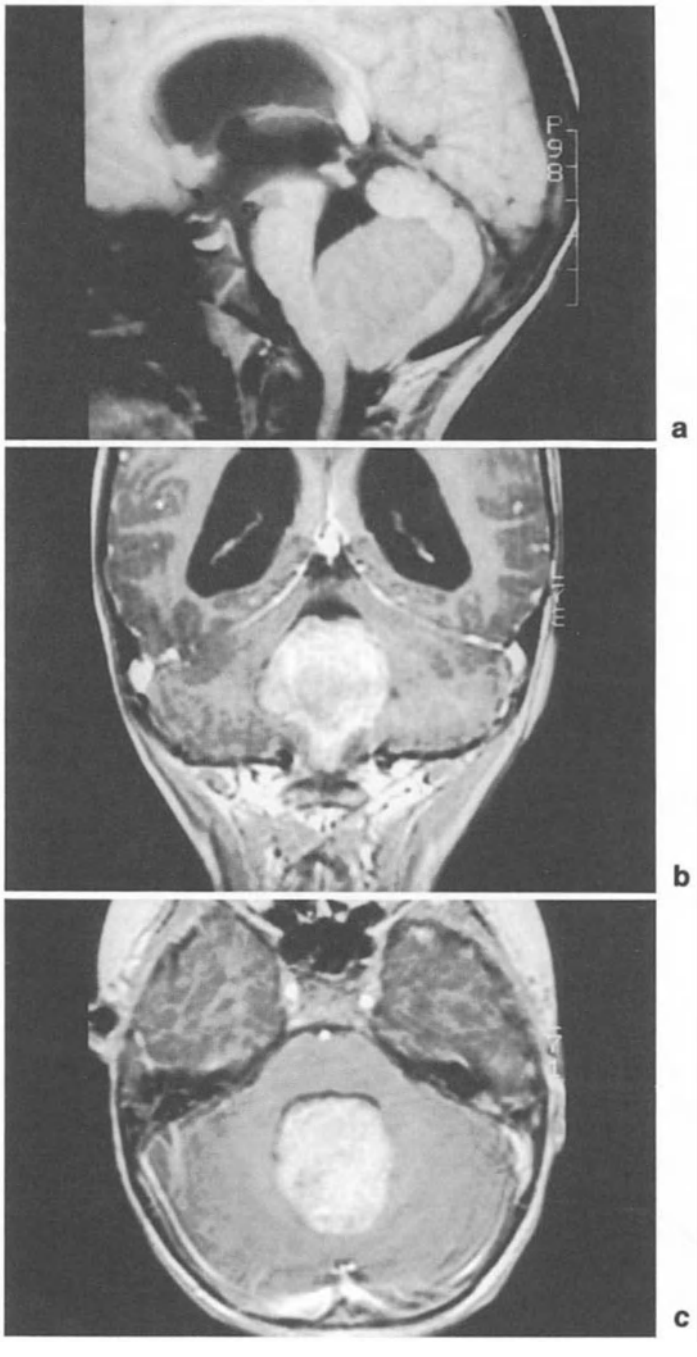

Fig. 1. MRI of a medulloblastoma. a) Sagittal cut of the T1 weighted sequence, b) frontal cut of the T1 weighted sequence with gadolinium, c) axial cut of the T1 weighted sequence with gadolinium

most important image for the neurosurgeon is the T1 image after injection of gadolinium. The contrast enhancement is the same as on the CT scan; the size, the localization, the extension, the aspect of the tumour are better evaluated on this image than on the T2 image which does not show the

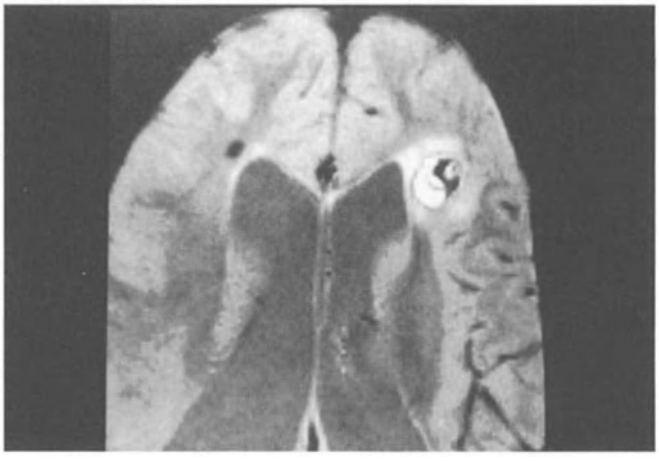

Fig. 2. Metastasis of a medulloblastoma. Axial cut of the T1 weighted sequence (60–1700)

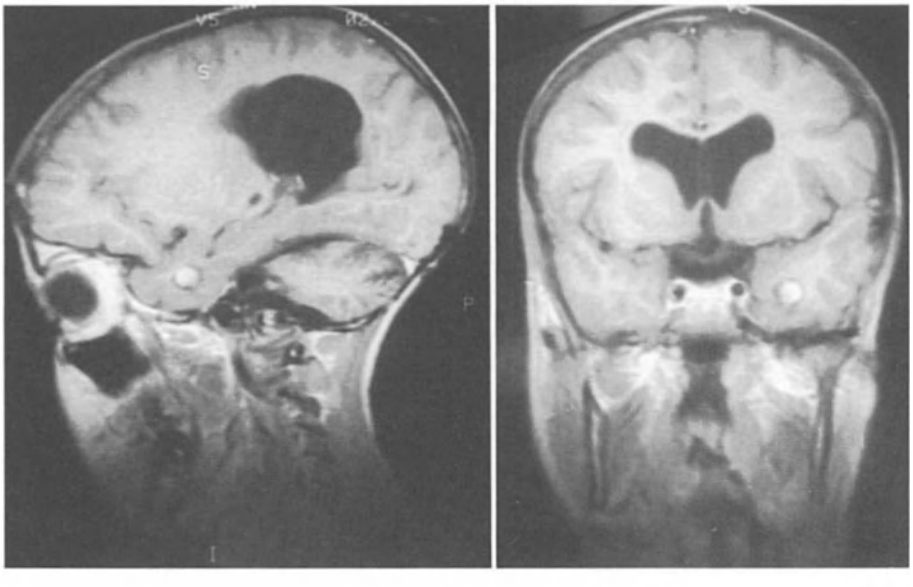

Fig. 3. Temporal metastasis of a medulloblastoma. T1 weighted sequence with gadolinium. a) Sagittal cut, b) frontal cut

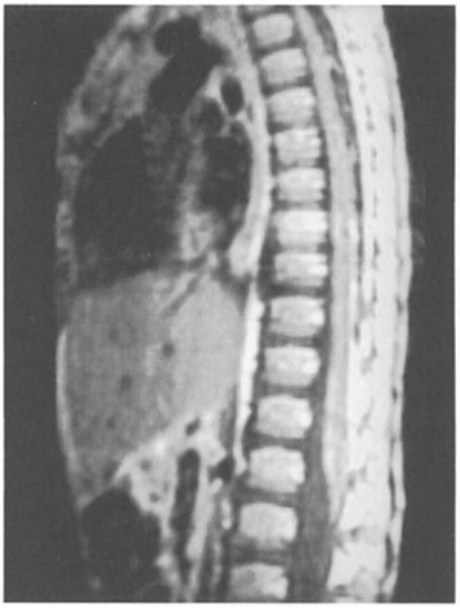

Fig. 4. Spinal cord metastases of a medulloblastoma

border between the tumour and the surrounding edema (Fig. 2). These characteristics are also better assessed than on the CT scan because they are given in three planes. Moreover gadolinium injection is the best way to detect metastases and extensions to the brain stem (Fig. 3).

A MRI study of the spinal cord (Fig. 4), with gadolinium injection, is mandatory after surgery. A pre-operative study of the spinal cord would not be useful since the presence of metastases on the cord would not contraindicate posterior fossa surgery. In contrast, however, the knowledge of such metastases after surgery would modify the technique of spinal cord irradiation.

MRI is also the best investigation to follow-up children after surgery. It can be repeated as often as necessary without any danger for the patient.

VI. Treatment

Without treatment, all children presenting with a medulloblastoma die within a few months[25]. With surgery alone, the result is the same although later. When radiotherapy is associated and given only to the posterior fossa, the survival time is lengthened, showing that the tumour is radiosensitive, but the final evolution is equally bad. As already stated, better outcome in children was obtained when it was realized that these malig-

nancies had a high likelihood of disseminating to the central nervous system and that irradiation had to be delivered to the entire neuroaxis.

Therefore, treatment to day associates surgery with radiotherapy of the whole CNS. Chemotherapy is usually given although its usefulness is not yet completely demonstrated.

A. Surgery

1) Once the diagnosis is made, surgery should be performed as early as possible since any wave of increased intracranial pressure can complete the cerebellar tonsil herniation and induce an abrupt and irreversible clinical worsening.

Most surgeons have abandoned pre-operative shunting or pre-operative external drainage of the ventricles. The practice was justified two decades ago when the progression of hydrocephalus and intracranial hypertension were life threatening, at a time when several days were often necessary to make the diagnosis. CT scan and MRI now allow rapid diagnosis; shunting has been proven to be dangerous, being sometimes responsible for tumour dissemination, intratumoural hemorrhage or upward herniation of the cerebellum through the incisura tentorii[77]. Therefore, after the routine pre-operative check, surgery should not be delayed since tumour removal is the best treatment of hydrocephalus and of tonsil herniation. In developed countries children are rarely referred very late when repeated vomiting has induced severe dehydration: only in these cases should surgery be postponed until after medical preparation.

Surgery is performed in either the sitting position or the prone position, both have their supporters. We have always used the sitting position because bleeding is reduced, the blood does not accumulate in the operative cavity and the upward extension of the tumour towards the incisura tentorii is more easily reached. However there are two drawbacks. When using the microscope, the surgeon is not in a comfortable operating position, his arms being usually stretched because of the focal length of the objective. The second drawback is more serious; air embolism is possible in this position, the pressure of the intracranial veins being negative. To avoid this complication, the surgeon should repeatedly ask the anesthetist to compress the jugular veins in order to increase the pressure in the intracranial veins and to detect those that might be open. A more elegant solution has proven to be effective, at least in children; the use of a g-suit[80]. With this technique, we have never observed any air embolism in spite of the fact that capnographs allow their precise detection even when they are small.

There is a general agreement as to the approach that should be used: incision of the skin on the midline, resection of the occipital squama and

of the posterior arch of the atlas. It is only exceptionaly necessary to resect the tuberosity or the laminae of the axis; it is better not to do so in children to avoid the risk of post-operative vertebral instability[97].

Before opening the dura, intra-operative ultrasonography is useful, but not mandatory: it shows the tumour, its extension and allows its measurement. It is usually not necessary to tap the lateral ventricle before opening the dura, modern anesthetic techniques reducing sufficiently ICP. The dura is cut along a Y-shaped incision; the occipital sinus and its branches are ligated or coagulated.

In some cases, the tumour is immediately visible in the midline; sometimes tumoural spots can be seen on the cerebellar hemispheres, indicating subarachnoidal extension of the disease. In most children however, it is necessary to make a vertical incision in the vermis before being able to see the tumour.

The surgical procedure should always begin with the incision of the cisterna magna and the placement of a cotton pad between the two amygdalae; this cotton pad should be pushed into the IVth ventricle, unless the tumour is adherent to its floor. The pad will prevent diffusion of malignant cells in the subarachnoid spaces. All through the surgical procedure it will also remain the main anatomical landmark to which the surgeon should return each time he has difficulty assessing the relationship of the medulloblastoma to the brain stem.

After incision of the vermis the next step should be to find the superficial limits of the tumour within the cerebellar hemispheres. While initiating this plane of dissection, a vermian branch of the PICA is usually found on both sides; this branch should be coagulated and divided at its point of entry into the medulloblastoma. The upper limits of the tumour with the vermis should also be detected. The tumour should then be debulked with the ultrasonic aspirator, the arterial blood vessels being progressively coagulated. When the volume of the tumour is sufficiently reduced, the dissection that had been initiated can be continued. The last portion of the tumour to be removed is that which is developed on the roof of the IVth ventricle. The tumoural fragment that blocks the aqueduct is easily aspirated. In most patients, it is easy to separate the tumour from the floor and from the edges of the IVth ventricle so that finally a macroscopic total removal is obtained. In other children, the medulloblastoma adheres to the floor of the IVth ventricle or even extends within the brain stem. Often when the surgeon works near the normal brain stem, cardiovascular reactions occur. In those cases, it is better to accept a subtotal removal rather than to increase the morbidity or the post-operative mortality rate since it is not proven that the risk of recurrence is significantly higher after subtotal than after total removal (if subtotal means "a few cubic millimeters left").

In those rare patients, mainly adolescents or adults, in whom the tumour is developed in the cerebellar hemispheres, the surgical procedure is easier since the tumour is not developed against the brain stem.

Once the tumour is removed and a perfect hemostasis obtained, the dura is closed in order to avoid any post-operative epidural CSF collection. It is our practice to insert, at the end of the surgical procedure, an external ventricular drain (the bag at the level of the ventricles) in order to avoid the risk of increased ICP during the first post-operative days. The bag of the external drainage is elevated 30 cm above the ventricles on the 4th post-operative day. The external drain is removed the next day if the patient remains well and without any headache in spite of elevation of the bag.

After surgery, the patient is made comfortable in his bed in a semi-sitting position. Intubation will be maintained during the three first post-operative days. During this period the drugs do not allow a precise assessment of the child's level of consciousness. He should therefore be followed up not only clinically but also with CT scans. A first CT scan performed in the 24 hours following surgery checks the absence of post-operative bleeding; moreover contrast injection shows whether or not the whole tumour has been removed, the post-operative inflammatory reactions that might simulate tumour remnants being seen only later on the CT scan. CT scans however do not diminish the importance of post-operative monitoring, especially of the arterial blood pressure which increases when the pressure in the posterior fossa rises.

Progress in anesthesiology and in surgery, bipolar coagulation, ultrasonic aspiration optical magnification have progressively decreased the risk of surgery. In the series published before 1970[19], most post-operative mortality rates were included, between 20% and 30%. This rate, in our series reviewed in 1978, was 10.5%[51]; it was 11% in the series of Mealey[78]. This post-operative mortality rate was further decreased to 6% in our series in 1988[53]. Moreover, in our last 35 children, all operated on with the cavitron, the post-operative mortality was nil. Although progress in intensive care has often postponed deaths related to surgery beyond the first month, thus artificially reducing the post-operative mortality rates, it can be concluded that surgical removal of a medulloblastoma is now a benign procedure.

Post-operative complications are however possible. Bleeding is very rare. Brain stem lesions, either through direct surgical trauma or through the coagulation of vascular supply are possible. In such cases, motor deficits, cardiovascular reactions or even coma are often observed while the clinical worsening usually takes place around the 3rd post-operative day.

Due to surgical progress and to the systematic use of oral sucralfate in the post-operative period, stress ulcers are now very rare.

Meningitis is still a serious complication, especially since the increased number of instruments used to operate renders perfect asepsis more and

more difficult. The diagnosis between infection and simple post-operative subarachnoid bleeding is often difficult.

Subdural CSF collections may be observed after tumour removal, particularly in the sitting position. Sometimes these have to be drained through a subdural external drainage; at other times they disappear spontaneously. The persistance of hydrocephalus in spite of the tumour removal is a possibility; it occurred in 16% of the cases in our series[51]. In this case an internal shunt should be inserted after surgery. Such shunts increase the risk of dissemination in case of recurrence; millipore filters do not prevent systemic relapse in shunted children[9].

When a child is referred with a shunt inserted before surgery, the removal of that shunt after surgery should always be undertaken with great care since often the child has become shunt dependant.

2) Immediate Post-Surgical Follow-up

Most authors agree that, after surgery, high and low risk groups should be defined. The Chang system of staging[18] is based on one hand on the size of the tumour (T1-T2-T3a and b-T4) and on the other hand on the extent of dissemination (M0 to M4). While the T-staging has been disappointing, the predictive value of the M-staging is obvious. Therefore other localizations of the tumour should be looked for.

There is now general agreement that post-operative myelography should be performed[2, 29, 30, 31, 39] after surgery in order to detect any tumour site on the spinal cord, especially at the bottom of the dural sac. However the frequency of these metastases varies from 3%[53], 10%[39] to 30%[30]. False positives certainly do exist. We have observed two such cases in our series probably due to the blood poured from the operative cavity into the subarachnoid space of the cord during surgery. Flannery[39] used a combination of computed tomography and of myelography. To day MRI studies of the cord, with gadolinium injection, increasingly replaces myelography. These investigations are performed from one to four weeks after surgery.

CSF cytology should also be studied. Some authors[39] find neoplastic cells in the CSF only when the metastases are visible on myelograms. For others[29], there is no such correlation. A bone marrow study is also advocated by Allen and Epstein[2].

Although the staging systems differ with different authors[2, 18, 31, 39, 56], the high risk group is essentially defined in different articles by the presence either of tumoural remnants after surgery or of metastases on the brain, the spinal cord or outside the C.N.S.

Other prognostic factors are, at the present time, under experimental evaluation. Marton[73, 74] has pointed out the predictive value of CSF polyamines (putrescine, spermidine and spermine) to detect metastases or recurrences. However the test is not specific. Deckert[27] tried the monoclonal antibody Ki-67 which recognizes a proliferation-associated nuclear antigen,

absent in the GO phase, in nine medulloblastomas. Ki-67 labelling reached maximal values of 42%, i.e., very high, but there were also values around 5%, close to the highest values observed in benign astrocytomas.

Yasue[121] and Tomita[113] have shown through flow cytometric analysis that about half medulloblastomas were aneuploid, the other half being diploid. Tetraploid tumours were very rare. Both studies concluded that aneuploid tumours were less aggressive and disseminated less than the diploid. Finding that medulloblastomas express N-CAM under a high sialylated isoform, Figarella-Branger[38] has set up an immunodot assay that allows titration of the presence of polysialic acid units in the CSF in order to detect metastases. Finally since C-myc amplification is observed in medulloblastoma cell lines and xenografts[12, 115] but usually not in medulloblastomas, the detection of a clone of cells that amplifies C-myc in the tumour might be a factor that would indicate the high aggressiveness of the tumour. Unfortunately this technique is not routinely feasible to day. Fujimoto[43] and Valery[115] have shown that there was an accumulation of RNA without C-myc gene amplification in medulloblastomas. This accumulation should be studied in correlation with tumorigenesis and long term results.

All these studies will certainly result in a better evaluation of prognosis. The post-operative assessment of the disease is however to day limited to the CT scan and/or the MRI, to the CSF cytology and to the MRI study of the cord. It is demonstrated that when the tumour is disseminated or when it is only partially removed the prognosis is worse. In these children, the treatment might eventually be more aggressive.

B. Radiotherapy

The absolute necessity of irradiation of the entire CNS is not any more a matter for discussion at the present time and although orthovoltage techniques can theoretically be used, megavoltage irradiation is preferred because of its skin sparing effect, reduced bone absorption and larger treatment portals which enable spinal irradiation to be carried out with one or at most two fields, thereby reducing the number of junction zones[15].

The principles of treatment are as follows; irradiation of the entire CNS down to S2, reduction of the field junction zones to a minimum in order to avoid any over or underdosage at their level. It is preferable to treat the head before dealing with the spine because of the risk of leucopenia which may cause treatment to be suspended. The extension of irradiation down to S2, where the theca ends, is of utmost importance because recurrences are often observed at that site. For the same reason, the lower half of the frontal lobes should be correctly irradiated, a result difficult to achieve since the eyes have to be protected in order to avoid the risk of

cataract. In a recent survey, Jereb *et al.*[57] found that 15% of all recurrences were in the region of the cribriform plate and therefore proposed a modification of the technique of irradiation of that site.

There is general agreement regarding the dose that should be delivered to the posterior fossa. It should be equal or superior to 50 gy[15]. Such a dose delivered in six to seven weeks is safe. On the contrary increasing the dose above 55 gy results in a diminution of the survival rate. Controversies begin with the dose that should be delivered to the spinal cord and to the brain. Radiotherapy to the vertebral column results in a reduction of growth. Irradiation of the brain is totally or partially responsible for endocrinological and neuropsychological consequences[51, 52, 95]. Therefore the dose of 35–45 gy which was considered as necessary until recently has been reduced down to 24–25 gy in different trials. Tomita and McLone[112], Brand *et al.*[16], Halberg *et al.*[47] conclude that craniospinal axis irradiation at a lower dose than conventionally used does not compromise local control or survival in patients with medulloblastoma, and may reduce toxicity. However the final results of a Children's cancer study group (CCSG) and Pediatric Oncology Group trial are not yet available so that Kun and Constine[63] advocate caution before limiting radiation therapy. The same conclusion can be drawn from the SIOP trial n° 2, the results of which are for the moment not conclusive.

When patients are under three years of age, doses are reduced, usually by one fourth. However this solution is illogical and inefficient. It is illogical because there is no reason to think that the tumour would be more radiosensitive in infants and it is inefficient because, in spite of this dose reduction, the neuropsychological consequences are, in these cases, catastrophic[53]. Therefore the solution of this problem should be looked for elsewhere. The general trend is to try to replace radiotherapy after surgery by chemotherapy and to postpone radiotherapy as much as possible. It is too early for the moment to draw any conclusion from these trials[6, 59].

C. Chemotherapy

Concerning chemotherapy, three problems should be discussed; is chemotherapy useful; when should it be given; what agents should be used? These questions are obviously linked. However since the drug that will cure 100% of medulloblastomas is not yet available, they can be discussed separately.

1) The usefulness of chemotherapy has been studied in two cooperative studies, one of the CCSG group[35] and one of the International Society of Paediatric Oncology (SIOP)[108]. In both trials CCNU and vincristine were given; prednisone was added in the North American trial. The results were similar; there were no statistically significant differences between the children who received chemotherapy after surgery and radiotherapy and those

who did not receive any chemotherapeutic agent. However in both studies a benefit of chemotherapy was observed in children with advanced stages of disease, with brain stem involvement or with partial surgery[35, 108]. These studies are thus rather pessimistic, but their results are only valid for CCNU and vincristine. Actually Packer *et al.* 1991[88] reach a slightly different conclusion with chemotherapy composed of CCNU, vincristine and cisplatin.

At the present time, numerous phase II trials with total or partial response have shown that many drugs were active on medulloblastomas. However there is a difference between reducing the volume of a malignant tumour and curing the disease. Cure probably implies the destruction of these isolated cells that are beyond the visible limits of the tumour. It is not yet proven that the chemotherapeutic agents at our disposal are able to destroy these cells which are in a different environment and which are protected by a normal blood brain barrier. However more research should be done because it is known from the treatment of children presenting a tumour outside the CNS that chemotherapy does not have any bad neuropsychological side effects. Therefore improving the post-operative quality of life of children with medulloblastoma will probably require in the future a limited irradiation associated with an efficient chemotherapy.

2) A second question about chemotherapy concerns the moment at which it should be given: before or after radiotherapy. Most authors have chosen to give chemotherapy after radiotherapy at least for one reason: they were not sufficiently sure of their chemotherapeutic agents and were afraid to leave the patients without any efficient treatment for a long period between surgery and radiotherapy.

However chemotherapy administrated prior to irradiation offers certain advantages. It allows evaluation of response rates for patients with radiographically measurable disease following surgery; treatment with myelosuppressive drugs is better tolerated when given before irradiation of the spinal axis; potential toxicity from the drugs is sometimes less important before irradiation; chemotherapy delivery to the tumour tissue may be optimized in the post-operative period when the blood brain barrier is disrupted[62]. Another reason is the necessity in infants to postpone irradiation as much as possible. Such trials have been started in infants with MOPP (methylchlorethamine, vincristine, procarbazine, and prednisone[6]), with vincristine and cisplatin[62] and in high risk medulloblastomas with cisplatin and Etoposide[61]. The SIOP trial n° 2 has extended this preirradiation chemotherapy technique to all patients, but its results are not yet available. The CCSG study includes a sandwich treatment protocol of eight drugs in one day therapy.

3) Since the blood brain barrier is usually intact at the level of these tumoural cells that are scattered beyond the visible limits of medulloblastomas, chemotherapeutic agents should be able to cross that barrier. There-

fore the molecules should be small and lipophilic. They should show a limited toxicity for the bone marrow, the liver or the nervous system. For instance the intrathecal administration of methotrexate has been abandoned because of the risk of encephalopathy[82, 104].

Many drugs have been tried; vincristine[65, 66] methotrexate, nitrosourea derivatives such as BCNU or CCNU[37, 118] procarbazine, epipodophyllotoxine[114], cyclophosphamide[40]. Other drugs such as melphalan[41] are presently under trial. However the most interesting molecule introduced recently in the treatment of the malignant CNS tumours is certainly cisplatin. Several studies have shown its efficiency, but unfortunately also its ototoxicity[4, 10, 32, 58, 61, 88, 103]. Carboplatin, a cisplatin analogue, is now preferred in most studies because of its low potential for auditory, renal and emetic toxicity, ease of administration and high disease specific activity[3].

To increase efficiency and to diminish the risk of drug resistance, these chemotherapeutic agents are usually associated. Two regimens have been often used, the MOPP (methylchlorethamine, vincristine, procarbazine and prednisone) and the 8 drugs-in-1-day therapy (CCNU-vincristine-prednisone-hydroxyurea-cis-platinum-procarbazine-cytosinearabinoside and cyclophosphamide). These associations are often more or less empirically chosen. Radiosensitizers such as bromouridine have been tried[54] but have not proven their efficiency. At any rate the drug that will cure medulloblastomas is not yet available and it is too early to know if immunotherapy will be of any help to solve the problem.

VII. Results

1) As already stated, modern surgical techniques have lowered the post-operative mortality rate nearly to zero, at least in the pediatric centers which have a large experience in the treatment of these children. However a small part of this improvement is artificial, due to the progress in intensive care that postpones, in bad cases, death beyond the first post-operative month. These children, because of their poor clinical condition, usually don't receive any radiotherapy so that, when they die, two or three months after surgery, it is often difficult to know if their death is the consequence of the post-operative complications, of recurrence or of both. Therefore the actuarial survival graphs should always indicate if all patients are included or only those who completed radiotherapy.

2) Five and ten year survival rates vary, in modern series, between 50 and 70% at least if the surgical resection has been macroscopically total. The series of "Les Enfants Malades"[51] was one of the first to show that such actuarial survival rates could be reached. The results of the "Sick Childrens' hospital" in Toronto[90] those of the childrens' hospital in Philadelphia[83] are similar. Unfortunately we found out, also in 1978 that our

enthusiasm had to be tempered; the improved survival rates had for a while overshadowed the late therapy-related effects: intellectual impairment and endocrine dysfunction.

3) The neuropsychological sequels are late occurring and difficult to recognize. Thus Bloom[14] stated that 82% of the survivors led an active life with a mild disability. Repeated neuropsychological tests are necessary as well as a sufficient number of long term survivors to detect these complications. Reviewing our series in 1978, we found that only 12% of the children had an IQ above 90: 70% were between 70 and 90, emotional and behavioral disorders were observed in 93% of the patients and specific types of retardation (spatial orientation, speech, writing, reading) in 82%. Academic failure was the consequence in 75% of the cases. However the functional results reported by Packer[86] were slightly better since the mean IQ, 4 years after treatment, was 97 even though children in most cases, showed significant learning disabilities. Reviewing our series[53] again, 10 years after the first study, we demonstrated that the intellectual deterioration was progressive over the years; at the 10 year evaluation only 7% of the children attended a normal school. No patient had normal employment whereas 64% worked in a protected environment. This progressive worsening was also demonstrated in a study of Packer[87]. This progressive decline, probably related to a serious impairment in the learning abilities of the child, is more important in infants.

Several arguments favor the hypothesis that radiotherapy is mainly responsible for these late complications. When surgery is restricted to the vermis or the cerebellar hemispheres, when there is no brain stem lesion and no radiotherapy, as is usually the case in cerebellar astrocytomas, there is no neuropsychological degradation[51]. Moreover when medulloblastomas are treated by surgery and radiotherapy, without any chemotherapy[95], the same IQ degradation is observed. Finally chemotherapy given for tumours outside the CNS, without any radiotherapy to the brain, does not induce any mental retardation, except perhaps when methotrexate is associated with radiotherapy[13]. The arm of the SIOP II study in which the dose of radiotherapy delivered to the cerebral hemispheres was reduced to 25 gy was justified by these data. However it has yet to be determined if the posterior fossa radiotherapy is not at least partly responsible for the IQ degradation. Should this be so, nothing could be done since it is well known that the X-ray dose delivered to the posterior fossa cannot be reduced. Abayomi *et al.*[1] have presented the hypothesis that the irradiation induced vasculopathy results in hypoxia, most pronounced in the hippocampus; they showed that hippocampal damage can manifest radiologically as calcification and clinically as memory and learning disabilities.

4) Growth retardation is another late effect of the treatment. It is related on one hand to the irradiation of the spine and on the other hand to growth

hormone deficiency due to cranial irradiation. The effects of the spinal irradiation are especially marked at the times of most active growth, under the age of six and at the time of puberty[93]. Growth hormone deficiency was observed in 60% of our cases[51]. It has been shown recently[107] that the final effect of growth hormone therapy on the final height of those children was small. It has been suggested that growth might be improved by higher doses of growth hormone and by delaying artificially puberty.

5) Tumours either malignant or benign have been observed in children treated for medulloblastoma. Thyroid carcinoma, bone sarcoma, intracranial sarcoma are rare. We have observed in our series two patients who developed a meningioma several years after the treatment of the medulloblastoma.

VIII. Recurrences

Considering the medulloblastomas to be embryonal tumours, Bloom[14] applied Collin's law to his series. This law is based on the assumption that the growth rate of any individual medulloblastoma is constant and equal to be growth rate of its recurrence, if it recurs. Therefore if the law is true and if the tumour has not recurred after a period of time equal to the age of the child at treatment plus nine months, the prognosis should be considered as excellent. With very few exceptions, the law was verified in Bloom's series as well as in ours[51]. However it should be pointed out that most recurrences occur within the two first post-operative years so that the assumption on which the law is based might not be true.

Posterior fossa recurrences are the most frequent. Their incidence varies from 30% in clinical series to more than 85% in the series in which the diagnosis is based upon post-mortem examinations[19]. CT scans or rather MRI studies should be systematically performed after surgery in order to detect them, every six months in the two first post-operative years, every year later until the fifth post-operative year.

The incidence of spinal metastases is extremely difficult to evaluate since their rate varies in the literature from 3.3% to 36.4%[19]. Nearly half of them are located in the lumbo-sacral region. An MRI study should be performed as soon as there is a clinical suspicion of such a metastasis. CSF cytology may also be of some help.

Supratentorial metastases are far less frequent and are often located in the region of the cribriform plate. Their clinical features as well as their radiological characteristics on the CT scan or the MRI allow an easy diagnosis.

Metastases outside the CNS are found in 5.6% of the cases[19]. They are located in the bones in more than 80% of the cases. The bone marrow is often invaded and anemia is then observed. Pelvis, femur and vertebra are the more frequent localizations.

Visceral metastases are in most cases located in the lungs or the liver. Lymph nodes may also be invaded.

This possible systemic dissemination of the disease explains that patients dead from medulloblastoma should never be chosen as donors for organ transplant. When this was done in one case[67], a tumour developed in the patients who received the organs (two kidneys, one pancreas and one heart).

The treatment of recurrences or CNS metastases associates an extra dose of radiotherapy (usually 15 gy) with chemotherapy. Most drug phase II trials are performed in recurrences or metastases. Surgery is not indicated, except in the patients who have not yet received any radiotherapy (as in infants treated by surgery and chemotherapy). Except in these cases, treatments may postpone the final result for months or even years, but death is unavoidable. However since these treatments lengthen survival, overall results in medulloblastomas should be assessed with survival rate actuarial graphs as well as with disease-free actuarial graphs.

Medulloblastoma, in 1991, remains a serious disease. However the progress is impressive: this malignant tumour was incurable when it was described in 1925; 60% of the children presenting with this lesion can now be cured.

Unfortunately the treatment, likely for the main part the radiotherapy, destroying the tumour but in the same time injuring normal cells, prevents the normal development of the brain. Therefore long term results are bad; school problems are usual; social integration is difficult. Much has yet to be done to improve the quality of life of these children. The general hypothesis underlying most trials at the present time is that radiotherapy doses might be reduced with the help of chemotherapy, but this remains to be demonstrated.

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Haemangioblastoma, Haemangioblastomatosis, and von Hippel-Lindau Disease

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Abbreviations

CNS: Central nervous system
CT: X-Ray computed tomography
MRI: Magnetic resonance imaging
RBC: red blood cells
VHL: von Hippel-Lindau
WBC: white blood cells

1. Introduction

1.1. Preface

Haemangioblastoma is the archetypal vascular neoplasm of the central nervous system (CNS). Cytologically benign, it may occur either as a single lesions or as a multicentric tumour, as a sporadic case or as a familial disease. It constitutes the retinal and neuraxial component of von Hippel-Lindau (VHL) phakomatosis.

The classical controversies surrounding this relatively uncommon tumour concern its uncertain histogenesis, factors predictive of local or distant recurrence and of multifocal disease, and the cumulative morbidity of the visual and central nervous system lesions.

Interest in haemangioblastoma has increased recently with the development of research in molecular biology and cytogenetics. Reasonable hopes are growing that cloning of the responsible gene will be realized soon.

This presentation is based on the review of more than one thousand familial and non-familial cases from previously studied[358, 360, 361] and currently updated data found in the English and non-English language literature and personal experience (FR) in 51 patients with CNS haemangioblastomas and related lesions.

Although an extensive bibliographical review is provided, corresponding to authors cited in text, all available references are not reported. The aim of this work is to describe past and current well-known data with a citation of a few characteristic examples, and to outline the most recent advances in knowledge of haemangioblastoma, especially in the fields of histopathology, genetics and therapy.

1.2. Definition

In 1928, Cushing and Bailey coined the word haemangioblastoma to describe all vascular tumours of the central nervous system, and to clearly separate them from CNS vascular malformations (telangiectasias, venous angiomas, arterial angiomas). They defined distinct pathological criteria for each group; within vascular malformations always remain glial tissue areas between vascular channels; the former are absent in haemangioblastomas, which are true neoplasms made up of vascular and intervascular (stromal) cell proliferation included in a reticular network[86]. Before to and after the Cushing and Bailey's paper, a few other CNS vascular tumours were described: haemangioendothelioma[133] at infratentorial and spinal cord levels, angioblastic meningioma[10] and haemangiopericytoma[416] above the tentorium. Although the initial ultrastructural studies gave some hope that all CNS vascular tumours might be included within a single group[52], haemangioblastomas in fact have their own anatomical, pathological, clinical and epidemiological characteristics that clearly separate them from other vascular tumours of the neuraxis:

- preferential location in the cerebellum though they may grow anywhere in the neuraxis;
- high frequency of simultaneous or subsequent multiple tumours (haemangioblastomatosis);
- possible production and release of an erythropoietic factor leading to secondary erythrocytosis;
- potential association with retinal haemangioblastoma (von Hippel's tumour) and/or lesions situated out with the CNS including malformative, dystrophic or tumoural forms (Lindau complex), giving to the disorder (VHL disease) a protean appearance;
- presence of inherited forms.

Strictly speaking, the term haemangioblastoma should be used for a single lesion, haemangioblastomatosis should be used for multifocal CNS

haemangioblastomas, and Lindau disease (or VHL disease if a retinal lesion is present) should be reserved for haemangioblastomatosis associated with lesions of the Lindau complex situated out with the neuraxis.

Currently, the term VHL disease is used in patients exhibiting more than one haemangioblastoma of the CNS, with or without visceral lesions of the Lindau complex, and in cases with a familial history.

2. Historical Sketch

Many contributors other than von Hippel and Lindau played an important part in the discovery of haemangioblastomas and related lesions.

Half a century passed between the first description of cerebellar (Jackson 1872)[206], retinal (Panas and Rémy 1879)[331] and visceral (Pye-Smith 1885)[354] lesions, and the comprehensive synthesis of Lindau in 1926–1927[273, 274], one year before the pathological definition given by Cushing and Bailey[86]. In retrospect, the earliest case of cerebellar haemangioblastoma was published by Jackson. In 1872 Hughlings Jackson reported autopsy findings of a 20 year old woman whose sister died of "seizures": "large cyst of the right cerebellar hemisphere containing a quantity of clear serous yellowish fluid ... on the outer part of this cyst was a tumour. It had a yellowish colour in the centre, and this yellow appearance merged into the adjoining highly vascular parts"[206].

The first retinal lesion was described as "décollement kystique de la rétine" (cystic retinal detachment)[331]. The patient was a 23 year old woman whose left eye was enucleated in 1876 for retinal detachment secondary to progression of an ocular tumour. The pathological pattern of this tumour included high vascularity, microcysts, and "embryoplastic" cells within a fascicular connective tissue. A few years later, this report was supplemented by Darier (1890): in 1886, he examined the patient who complained of progressive right ocular signs identical to those felt on the left side, ten years before. Fundoscopy showed a rounded tumour located in the inferior temporal quadrant of the retina, the diameter of the optic disc. Spontaneous development over four years ended in retinal detachment and total blindness[91]. Fuchs publishing a similar case in 1882 attributed to traumatic arteriovenous aneurysm[136].

The first description of both CNS and visceral lesions appeared in 1885: Pye-Smith reported autopsy findings in a 27 year old policeman who had a left cerebellar cystic tumour, several renal cysts and eight or nine pancreatic cysts "varying in size from a hempseed to a bean"[354]. In 1888 Turner reported similar autopsy data in a 44 year old man with two cerebellar "*vascular and reticular*" tumours, one of them being cystic and the other being solid, associated with a cystic tumour of the right adrenal gland, a cyst of the liver and a polycystic left kidney[430].

In 1889 Joseph reported the first two cases of angiomatous tumours of the brain stem[222].

In 1894 Collins reported the pathological findings in three enucleated eyes (characterized by the presence of "capillary naevus with cystic degeneratio") and stated on the familial inheritance of this new disease which had affected two siblings, brother and sister[73].

In 1895 the first contribution of Eugen von Hippel (1867–1939), a German ophthalmologist, was published. He described the fundoscopic appearance of the right eye of a 23 year old man named Otto M..., examined for the first time in 1893 for visual loss: both the superior temporal artery and vein were dilated and supplied a prominent rounded mass located at the periphery of retina and of a four disc diameter[445]. In 1904, von Hippel gave further details concerning his patient: in the superonasal quadrant of the same eye, three similar lesions had arisen, ending in 1897, after a short spontaneous course, in amaurosis. In the same report, von Hippel published a second case discovered in a 28 year old man. Unaware of the previous paper of Collins and because of tuberculous manifestations in his two patients, he concluded mistakenly that the aetiology of this ocular disease was presumably tuberculous[446].

This theory (just as Fuchs's previous one) was refuted in 1905 by Czermak[88] who reported the autopsy findings of a female patient of Goldzieher[152] that showed vascular tumours ("Gefässgeschwülste") of the retina (considered to be congenital lesions), a cyst of the left cerebellar hemisphere and cystadenomas of both ovaries. In 1911, von Hippel who had been aware of reports of Collins and Czermak and had studied the right eye of Otto M... was able to conclude that the retinal lesion was a cystic capillary angiomatosis of congenital origin[447].

The first case of intramedullary spinal cord vascular tumour (involving T 1 in a 29 year old man) was reported by Schultze in 1912[392].

In 1913 Koch reported the autopsy findings of a 47 year old male patient affected by cystic lymphangiomas of pancreas, liver cavernoma, renal cysts and angiomatous tumours of cerebellum and spinal cord[246]. Roman[368] and Wersilow[455] in 1913, and Pinner[344] in 1914 each reported a case of spinal cord vascular tumour. Wersilow's patient had vascular tumours of spinal nerve roots in addition.

In 1921 Brandt published the autopsy results of Otto M... who died in 1917 at the age of 47 years. The cause of death of von Hippel's first patient was pneumonia. During his last year the patient suffered from neurological disturbances compatible with a posterior fossa tumour. There were miscellaneous and surprising findings: a solid cherry-sized tumour within the left cerebellar hemisphere, a vascular tumour of the medullary conus, a few bone tumours, multiple renal pancreatic and epididymal cysts and bladder papillomas. Examining this case, Brandt stated that the cer-

ebellar and bone tumours might be metastases from hypernephroma; in the absence of such a tumour at kidney examination, he considered that the primary tumour might be the well-known retinal tumour; however delayed metastasis 7 years after enucleation and 23 years after the onset of ocular disturbances seemed unlikely to him. Thus he rightly concluded that these were primitive multiple tumours and included the disease in the group of dysontogenetic diseases[40].

In 1922 Berblinger published autopsy findings of a 27 year old female patient with a capillary haemangioma ("capilläres Hämangiom") of the medulla oblongata, a right retinal angioma, and pancreatic and renal cysts[16]. In the same year Friedrich and Stiehler reported the autopsy results of a 41 year old man who had a cystic angiomatous tumour of the medulla oblongata that they termed "hämangioendotheliom", a cervicothoracic intramedullary syringomyelic cavity and pancreatic cysts[133]. In 1924, Tannenberg described of the autopsy features of a 34 year old woman who had multiple medulla oblongata, thoracic and lumbar spinal cord and posterior spinal nerve roots capillary haemangiomas, pancreatic cysts and liver cavernomas[421].

Thus the way for synthesis was cleared. In 1926 Arvid Lindau (1892–1958) a Swedish pathologist in Lund, published his famous dissertation entitled "Studien über Kleinhirnzysten. Bau, Pathogenese und Beziehungen zur Angiomatosis retinae"[273]. In the first part, Lindau reported 16 cases of cerebellar cysts with vascular mural tumour of which 13 were his own. He compared their incidence with simple cysts (2 cases) and also with cysts having mural tumour of glial origin (8 cases); he pointed out that cerebellar vascular tumours appeared frequently associated with visceral lesions; in the second part, Lindau reviewed all the locations of tumours of identical nature in the CNS; he particularly described intramedullary spinal cord localizations and noted the frequency of associated syringomyelic cavities; he pointed out the possible familial inheritance and its rate, and characterized the disorder which he termed angiomatosis of the central nervous system. He suggested a misdevelopment during the third month of foetal life and stated that the disorder which appeared as a mesodermal dysplasia had some analogy with tuberous sclerosis and von Recklinghausen neurofibromatosis of ectodermal origin. All of them were included somewhat later by van der Hoeve in the framework of phakomatoses (term coined from the ancient Greek word φακος i.e. skin spot, strawberry mark), which constitute a group of congenital diseases, frequently inherited, and are the consequence of defective embryonic layer development[434, 435]. Lindau's monograph created a considerable stir in medical opinion: at the time of a congress held in Hamburg as soon as January 25th, 1927, Wohlwill introduced the term of Lindau's disease ("Lindausche Krankheit")[462]. In a second paper published in 1927, Lindau went deeper into the relationship between retinal and CNS angiomatosis and visceral lesions[274].

As stated above, Cushing and Bailey in 1928 recognized CNS vascular tumours that they termed haemangioblastomas: according to Cushing and Bailey haemangioblastomas are true neoplasms made of vascular and intervascular cell proliferation, originating from angioblastic remnants of mesodermal origin[86]. Two years later, another theory about histogenesis of stromal cells led Roussy and Oberling to propose the term "angioréticulome"[374]. A few other eponyms have been used in the past for haemangioblastoma: capillary haemangioma[16, 273], angioblastoma[481], angioblastic reticuloma[444]. Although created on the basis of currently unconfirmed histogenetic theory, the term haemangioblastoma has been hallowed by use and must be used exclusively.

Before ending this historical sketch, it should be pointed out that, in haemangioblastomas as in the majority of the fields of neurosurgery, the pioneer remains Harvey Cushing who, on September 14th 1908, successfully operated on a 28 year old man to remove a large solid microcystic tumour of the right cerebellar hemisphere (5 × 4 cm). 20 years later, when he wrote his monograph, Cushing examined his patient: he was healthy and well[86]. The tumour was a haemangioblastoma of cellular type. It is worth noting that this successful operation was performed by Cushing 3 years prior to the advent of vascular clips and 18 years before Bovie introduced electrocoagulation in neurosurgery. If the first case of intramedullary spinal cord vascular tumour was successfully removed in 1912[392], the second successful removal of a cerebellar haemangioblastoma only occurred in 1925[390]; this case was included by Lindau in his 1926 monograph[273].

3. Incidence – Location – Morphology

Haemangioblastomas are relatively uncommon tumours.

They account for about 2 to 3 per cent of all CNS tumours. Pooling of data from two series[347, 459] gives a total of 102 haemangioblastomas among 4356 CNS tumours (2.34 per cent).

The relative incidence varies with the different locations (Table 1).

Table 1

Series	Haemangioblastomas	CNS tumours
Poirier *et al.* (1988)	36	2000
Winkelmann (1978)	66	2356
	102	4356

3.1. Posterior Cranial Fossa Haemangioblastomas

3.1.1. Incidence

The most common location of haemangioblastoma is in the posterior cranial fossa.

Pooling of ten series[24, 212, 266, 300, 305, 315, 329, 332, 366, 406] reveals that 550 haemangioblastomas out of 594 haemangioblastomas of all CNS locations (92.6 per cent) were infratentorial (Table 2).

Despite this preferential location, *infratentorial haemangioblastomas account for less than 2 per cent of all intracranial tumours*, with an average rate of 1.35 per cent in four large neurosurgical series[42, 78, 87, 120] (Table 3).

Haemangioblastomas account for less than 8 per cent of all posterior cranial fossa tumours in adults.

Table 2

Series	Haemangioblastomas (infra-tentorial)	Haemangioblastomas (all CNS locations)
Böck and Brenner (1970)	39	42
Jeffreys (1975)	67	76
Leu and Rüttner (1973)	41	52
Mondkar *et al.* (1967)	112	119
Müller-Jansen *et al.* (1984)	44	46
Neller *et al.* (1969)	58	61
Palmer (1972)	80	81
Papo *et al.* (1961)	44	45
Robinson (1965)	23	25
Singounas (1978)	42	47
	550	594

Table 3

Series	Haemangioblastomas (infra-tentorial)	Intra-cranial tumours
Broager (1949)	33	2065
Cox and Trumble (1939)	6	300
Cushing (1937)	25	2000
Ferrante *et al.* (1988)	76	5991
	140	10356

Table 4

Series	Haemangioblastomas (infra-tentorial)	Infratentorial tumours
Börck and Tönnis (1955)	46	697
Krayenbuhl and Yasargil (1958)	45	508
Olivecrona (1952)	70	962
Tadros *et al.* (1963)	10	116
	171	2283

Table 5

Series	Cerebellar haemangiobl.	Brain stem haemangiobl.	Total
Bock and Brenner (1970)	38	1	39
Borck and Tönnis (1955)	43	3	46
Krayenbuhl and Yasargil (1958)	41	4	45
Leu and Rüttner (1973)	41	0	41
Müller-Jansen *et al.* (1984)	40	4	44
Olivecrona (1952)	65	5	70
Round table of the SFNC (1985)	230	9	239
Singounas (1978)	36	6	42
	534	32	566

Pooling of four series[35, 253, 325, 418] gives a total of 171 haemangioblastomas among 2283 tumours of the posterior cranial fossa (7.5 per cent) (Table 4).

Almost 95 per cent of posterior cranial fossa haemangioblastomas are located in the cerebellum.

Pooling of values reported in eight series[24, 35, 253, 266, 305, 325, 360, 406] gives a total of 534 cerebellar haemangioblastomas (94.3 per cent) among 566 infratentorial haemangioblastomas (Table 5).

The cumulative values cited above and originating from various medical sources have no statistical significance; all the biases due to the effect of selection are well known. Nevertheless, they clearly confirm that the *cerebellum constitutes, by far, the main location of this relatively uncommon tumour.*

3.1.2. Cerebellar Haemangioblastomas

3.1.2.1. Topography

In the cerebellum, haemangioblastomas may be located in the hemispheres, less frequently in the vermis and rarely in the tonsils.

For the "single" haemangioblastoma, the cerebellar hemispheres are four times more frequently involved than the vermis[358]. In a series of 224 cerebellar haemangioblastomas[360], topographical distribution was as follows:

- hemispheres: 177 cases, i.e. 79 per cent (right 78, left 99);
- vermis: 38 cases, i.e. 17 per cent (anterosuperior and middle: 23; posteroinferior: 15);
- cerebellar tonsils: 9 cases, i.e. 4 per cent.

3.1.2.2. Gross Aspect

Whatever their localization in the central nervous system and their macroscopic type may be, it has to be stressed that haemangioblastomas usually abut a pial surface. Despite the absence of a true capsule, their limits seem well defined from a macroscopical point of view.

Cerebellar haemangioblastomas may exhibit four macroscopic aspects[358]:

- Type 1: simple cyst
- Type 2: large cyst with mural nodule
- Type 3: solid tumour
- Type 4: solid tumour with internal small cysts

i.e. two predominantly cystic variants (types 1 and 2) and two predominantly solid variants (types 3 and 4).

Type 1 has the features of a simple cyst, containing xanthochromic fluid, with a smooth wall on which a few very thin vessels but no nodule can be seen. In spite of the lack of a visualized tumour, the authentic nature of this rare variant in the framework of haemangioblastoma (4.1 per cent in the literature[360]) has been clearly demonstrated[358, 360]. In this type the mural nodule that is responsible for the development of cyst is too small to be discovered. Such a difficulty had been underlined one century ago "the object of the present communication is to draw attention to the very great difficulty if not impossibility of excluding tumour as a cause of apparently simple cerebellar cysts. Until a most careful and minute microscopical examination of every part of the cyst-wall has been made, one is not justified in excluding tumour and describing the case as one of simple cyst"[458]. If the relative number of this variant has decreased since optical magnification methods have been used, a small proportion of such cases remains. In a review of 509 cases of infratentorial haemangioblastomas

from the literature prior to 1983[360], we listed 407 cases with 25 type 1 before 1973, and for the period 1973–1983, 102 cases with 2 type 1[161, 276]. In the literature there are some well-documented cases with, in a few instances autopsy findings, demonstrating association of purely cystic cerebellar tumour with retinal haemangioblastomas[439], visceral lesions[129, 339, 354], or both conditions[88, 150]. The rate of "recurrence" due to the in situ development either of a macrocystic haemangioblastoma (type 2), even less frequently of a solid haemangioblastoma (types 3 or 4) is 100 per cent[358]. It is not a true recurrence but simply the result of progression of the initially undiscovered mural tumour.

Macrocystic haemangioblastoma (type 2) is the most common macroscopic variant (60.6 per cent[360]). It appears as a spheroid or ovoid cyst, often large (30 to 50 mm in diameter), filled with a xanthochromic fluid. On its smooth wall, usually near a pial surface, is a reddish-orange colored mural nodule. Its size is smaller than the cyst (5 to 15 mm in diameter). The wall of the tumoural cyst is constituted by cerebellar tissue flattened by the transudation fluid gradually originating from the nodule. The nodule is the only cause of the formation of the cyst[86].

Solid haemangioblastoma (type 3) is less frequent (26.2 per cent[360]). It appears as a dense spheroid red-colored tumour. Its size may be 30 to 40 mm in diameter. It does not have a true capsule. Its limits are equally constituted by compressed cerebellar tissue. The blood supply of this variant is usually rich. Solid haemangioblastomas may be covered by large arteries and enlarged veins giving angiographic and macroscopic aspects which mimic an arteriovenous malformation[357].

Solid haemangioblastoma with internal small cysts (type 4) has a macroscopic external aspect identical to the precedent. It is rarer (9.1 per cent[360]). The difference comes from the presence of small internal cysts, 1 to 5 mm in diameter. Their size is less important than that of the dense part.

3.1.2.3. Gross Aspect and Topography

The distribution of 219 "single" cerebellar haemangioblastomas according to their location and macroscopic type was as follows[360] (Table 6).

This difference in distribution is statistically significant ($\chi^2 = 12.2$; $p = 0.01$). The disproportion affects hemispheric haemangioblastomas among which more than two-thirds are predominantly cystic.

3.1.3. Brain Stem Haemangioblastomas

In the brain stem, haemangioblastomas have been reported in all sites. However, ventral prepontine or premedullary tumours are exceptional[72, 97]. The main locations are the caudal part of the floor of the fourth ventricle

Table 6

Localization	Macroscopic appearance		Total number
	Cystic tumours	Solid tumours	
Vermis	19	26	45
Hemispheres	123	51	174
	142	77	219

particularly near the area postrema, the dorsolateral aspect of medulla oblongata and the cervicomedullary junction[22, 301].

The topographical distribution of 62 cases of single haemangioblastomas of the brain stem collected from the literature and a French multiinstitutional study[360], was as follows:

- pons: 2
- dorsal aspect of medulla oblongata: 17
- floor of the fourth ventricle: 16
- cervicomedullary junction: 17
- extensive tumour: 10

Macroscopically, brain stem haemangioblastomas are usually type 3 or 4 tumours, with a diameter smaller than 15 mm. A few cystic cases were reported[311].

3.1.4. Cerebellopontine Angle Haemangioblastomas

Exceptionally haemangioblastomas develop in the cerebellopontine angle and therefore may compress the brain stem as do schwannomas of the acoustic nerve at a late stage[377]. This location represents from 0.8[360] to 3.3 per cent[119] of all haemangioblastomas of the posterior cranial fossa. In such a localization almost the whole tumour exhibits itself as an subpial extraparenchymatous lesion.

3.2. Spinal Haemangioblastomas

3.2.1. Incidence

Spinal haemangioblastoma accounts for about 5 per cent of all spinal tumours.

Pooling of values reported in the eight subsequent series[66, 124, 162, 309, 408, 411, 459, 474] gives an average rate of 5.1 per cent (59 haemangioblastomas among 1156 spinal cord tumours) (Table 7).

Table 7

Series	Haemangioblastomas	Spinal cord tumours
Christiaens (1965)	1	30
Fornari *et al.* (1988)	5	81
Guidetti and Fortuna (1967)	6	74
Murota and Symon (1989)	18	310
Sloof *et al.* (1964)	10	301
Solomon and Stein (1988)	8	60
Winkelmann (1978)	4	278
Yasui *et al.* (1988)	7	22
	59	1156

3.2.2. Intradural Spinal Haemangioblastomas

Intradural spinal haemangioblastomas represent 87.7 per cent of all spinal haemangioblastomas and may be classified into intramedullary, subpial extramedullary and haemangioblastomas of spinal roots[192].

Intramedullary spinal cord haemangioblastomas commonly arise within the cord dorsal to the medullary canal in the neighbourhood of the dorsal septum and exhibit an subpial pole[470]. Wholly intraparenchymatous medullary spinal haemangioblastomas and haemangioblastomas located ventral to the medullary canal are exceptional[192]. In rostrocaudal situation, haemangioblastomas are most commonly found between C 3-D 1 and D 7-L 1 at the level of the cervical and lumbar enlargement[192, 358, 470]. This may have an embryological explanation[328].

Rare, *intradural extramedullary spinal cord haemangioblastomas* are in a retrolateralmedullary subpial location and appear easily separable from the spinal cord and roots[192, 460].

Most commonly but not exclusively originating from posterior roots[192] as do schwannomas, *spinal root haemangioblastomas* may exist at the spinal cord level or involve roots of the cauda equina[169, 192, 266, 287, 455, 464, 469, 470]. Cases of haemangioblastoma seeming to have originated from the filum terminale have also been reported[405, 463]. Usually spinal root haemangioblastoma lie within the spinal canal. Hour-glass spinal root haemangioblastomas are exceptional[71, 192].

3.2.3. Extradural Spinal Haemangioblastomas

Classically, from a pathophysiological point of view, extradural spinal haemangioblastomas have been separated from all other topographic forms

of haemangioblastomas insofar as all reported cases have been solitary and sporadic forms[192]. Some have considerated them as haemangioendothelioma rather than haemangioblastoma and proposed immunohistochemical analysis for diagnosis[25].

However two cases of extradural haemangioblastoma arising from vertebral body have been recently reported[309], one in association with cerebellar and retinal haemangioblastomas and bilateral renal clear cell carcinoma in addition to a positive familial history. Such a case clearly belongs to VHL disease.

3.2.4. Gross Aspects

Macroscopically intramedullary spinal cord haemangioblastomas may be solid (type 3 or 4), or more frequently cystic (in about two-thirds of cases)[44, 293, 473].

The association of intramedullary spinal cord haemangioblastomas with one or more intraspinal cysts is well documented[44, 113, 126, 127, 162, 192, 193, 241, 293, 470, 473]. Intramedullary spinal cord cavities contain high protein fluid. They may or may not be in juxtaposition to the haemangioblastoma. They may be multiple or extensive into the spinal cord in the presence of a single intramedullary tumour. Several different theories have been proposed to explain the origin of the intramedullary cystic cavities. Cavities were considered

– either as elongated cysts like those occurring in the cerebellum and likewise due to transudation of fluid from the tumour[273];

– or as hydromyelia secondary to circulatory disturbances and ischaemia or tumoural haemorrhage into the grey matter, followed by gliosis[375];

– or as a true syringomyelia of congenital dysraphic origin[470].

The variety of observed anatomical patterns seems to exclude a single origin and transudative, vascular or dysraphic theories must be considered in each individual case[192, 358, 361].

3.3. Supratentorial Haemangioblastomas

3.3.1. General Points

The relationship between haemangioblastomas situated above the tentorium and other cerebral vascular tumours, especially "angioblastic meningiomas" and/or tumours with a highly vascular pattern is a controversial and frequently debated subject. Inclusion of some tumours in the framework of haemangioblastoma, particularly the cases reported in the oldest papers, was discussed in the past. For example, the first case reported in 1902 by Bielskowski[19] was accepted by Cushing and Bailey[86] but rejected by others[303, 481].

The term "angioblastic meningioma" was coined by Bailey, Cushing and Eisenhardt[10] to define tumours that share identical histological patterns with cerebellar haemangioblastomas but that are located above the tentorium and the site of which is extraparenchymatous. They are distinguished from highly vascular meningiomas ("angiomatous meningiomas"): "by the term angioblastic meningioma, we do not mean meningiomas that merely happen to be highly vascular in the sense that "angioglioma" is sometimes used for a highly vascular glioma. What we do mean is that a meningeal tumour which possesses the unmistakable naked-eye appearance of the usual and familiar type of one of these lesions may prove histologically to have the same architectural features and reticular network that is possessed by the haemangioblastomas which originate within the brain itself, more frequently if not exclusively in the cerebellum"[10]. Therefore, according to that definition, supratentorial haemangioblastomas are comparable to angioblastic meningiomas. Light microscopic[9] and electron microscopic analysis[52] does not allow any differentiation.

3.3.2. Incidence

Haemangioblastomas located above the tentorium are exceptionally rare; they account for:

- 3 cases among 5991 intracranial tumours, i.e. 0.05 per cent[120];
- 2 cases among 1483 primitive supratentorial tumours, i.e. 0.13 per cent[303];
- 0.3 per cent of tumours of parietal localization[481].

In a recent review of the literature (1988), Ferrante *et al.* listed 71 cases[120].

We have to add ten additional cases[61, 299, 302, 310, 315, 362, 366, 465] that we personally collected in 1971[358] not included in the paper of Ferrante *et al.* and a few recent cases[2, 13, 369].

3.3.3. Sites

Supratentorial haemangioblastomas may develop in any cerebral site; however they are in a superficial lobar situation in 90 per cent of cases[358]. As with infratentorial haemangioblastomas, they abut a pial surface in the majority of cases. Sometimes they adhere to dura mater[12, 376].

A few cases of supratentorial intraventricular haemangioblastomas have been described, within a lateral ventricle[109, 307] and within the third ventricle[230, 277, 364].

Some cases of extracerebral supratentorial haemangioblastomas have been reported at the level of the parasellar region[412], the optochiasmatic cistern[326], the intracranial part of the optic nerve[415], the pituitary stalk[160, 241, 318] (personal case see Fig. 19), and the anterior hypophysis[57, 89, 364].

3.3.4. Gross Morphology

Types 2, 3, and 4 are seen with an approximately equal incidence[358].

3.4. Orbital Haemangioblastomas

3.4.1. Retinal Haemangioblastomas (von Hippel Tumours)

As indicated by Brandt[40] who named them "endotheliomas", retinal lesions known as von Hippel or von Hippel-Czermak tumours are true neoplasms, true haemangioblastomas: the term "retinal angiomatosis" ("angiomatosis retinae") is inappropriate and its use must be abandoned.

Retinal haemangioblastomas are typically located at the periphery of the retina, more frequently temporal than nasal. At ophthalmoscopic examination, the tumour appears as a rounded reddish-orange colored nodule, with a variable size from 0.1 to 6 disc diameters[33]. It is situated at the end of two supplying retinal vessels, both enlarged artery and vein, as an umbilical cord. When the tumour is discovered at an early stage, no vascular enlargement is seen. Other than the peripheral locations, some cases of unilateral parapapillary[335] optic disc[195] and bilateral papillary and parapapillary locations have been described[53, 92, 475]. Bifocal, even plurifocal tumours, in one or both eyes, may be seen[314].

Spontaneous progression is the rule. Four stages have been defined[131]:

- first stage: progressive vascular enlargement and tumoural growth;
- second stage: onset of haemorrhages and exudates;
- third stage: massive exudates and retinal detachment;
- last stage: secondary glaucoma and destruction of the eye.

Spontaneous evolution ends in visual loss. Sometimes enucleation is required because of refractory highly painful glaucomatous attacks.

According to the literature, retinal involvement appears more frequently unilateral, with an incidence slightly less than two-thirds of all cases[360, 432]. However it is important to point out that, if retinal haemangioblastomatosis may affect both eyes as early as the first examination, there are unilateral cases in which a delayed contralateral involvement also occurs. In an historical case the delay was 34 years (the son of Otto M..., the von Hippel's first patient, was enucleated on the right size in 1916[40] and affected on the opposite side in 1950[345]. Some incipient retinal haemangioblastomas may exist and be discovered as autopsy findings[218, 274, 293]. Therefore, involvement of both eyes is probably more frequent than evaluation of the literature might indicate.

3.4.2. Intraorbital Optic Nerve Haemangioblastomas

A few cases of haemangioblastoma involving the intraorbital part of the optic nerve have been reported[186, 196, 316].

3.5. Multifocal Localizations (Haemangioblastomatosis)

As already mentioned, multiple tumours may be present and evident at the first examination or appear in the course of the disease with a delay of variable duration, sometimes over 20 years.

No schema is possible: multifocal forms, either in the same region of the neuraxis, posterior cranial fossa[233], spinal cord[28], as well as above the tentorium in the cerebrum[201] or at many sites of the CNS at two, three even four different levels (i.e. cerebellum, brain stem, cerebrum, spinal cord[163]) have been described.

The most frequent association is cerebelloretinal haemangioblastomatosis. In a review of the literature prior to 1983, among a total of 624 cases of infratentorial haemangioblastoma[360] we listed 156 cases of associated retinal haemangioblastoma (i.e. 25 per cent of all cases). Retinal involvement was bilateral in 63 patients. The association of infratentorial haemangioblastoma with spinal cord haemangioblastoma is rarer: in the same series such an association was noticed in 69 cases (11.1 per cent); in further 11 cases, there was an apparently isolated intramedullary spinal cord cavity[360]. Spinal cord tumoural involvement was multifocal in 29 cases.

4. Pathology

4.1. Haemangioblastoma

4.1.1. Light Microscopy

Haemangioblastoma constitutes a singular neoplastic entity consisting of a double tissue, vascular and cellular intervascular proliferation. The characteristic pattern (see Figs. 1 and 2) is of vascular channels made up of capillaries of normal structure and intervascular spaces occupied by trabeculae of rounded or polygonal cells, with central spheroidal nucleus and a slightly stained, partly foamy cytoplasm ("stromal cells")[376].

In frozen sections, the so-called stromal cells are usually large and laden with small sudanophilic lipid droplets. Positive intracytoplasmic staining for glycogen is also frequent. A minor degree of nuclear pleomorphism is usually seen with sometimes uni- or multinucleated giant cells but mitotic activity is very inconspicuous and mitotic figures are absent. When lipid granules are not demonstrable, stromal cells are smaller, with a pale eosinophilic cytoplasm[376].

Silver impregnations well demonstrate the presence of the reticulin network that outlines the capillaries and aggregates of stromal cells but little pericellular reticulin is present. Deposits of haemosiderin may be found as a sequel of microhaemorrhage.

According to Cushing and Bailey the relative extent of capillaries and intervascular tissue leads to the recognition of three histological variants[86]:

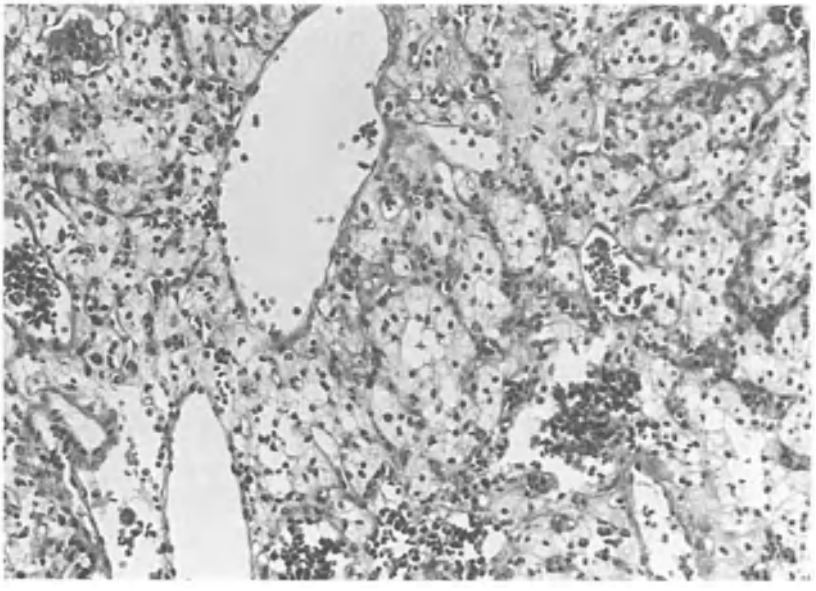

Fig. 1. Classical low-power appearance of cerebellar haemangioblastoma with vacuolated stromal cells interspersed between thin-walled blood vessels. Trichrome × 250

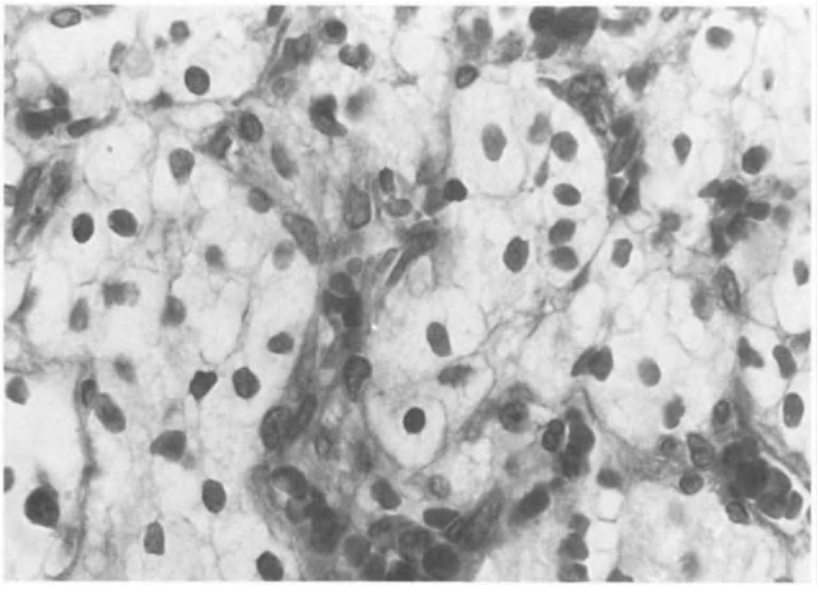

Fig. 2. Foamy stromal cells separated by small blood vessels. Trichrome × 400

– by far the most common one termed reticular or *capillary* haemangioblastoma is composed largely of a fine mesh of blood spaces and channels of capillary structure. In this type, intervascular tissue is hardly developed;

– the *cavernous* variant differs from the previous type by the presence of enlarged vascular channels: capillaries are dilated into large sinuses;

– the *cellular* haemangioblastoma in which intervascular tissue is the most developed and the architectural pattern of which may resemble that of a chemodectoma, is predominantly composed of compact lobules of pale eosinophilic stromal cells separated by compressed blood vessels.

These different patterns may be found in different fields of the same tumour[99].

The cellular variant defined by Cushing and Bailey may exhibit two patterns, with intermediate forms: a dense type, in which the intervascular proliferation is made up of regular round-shaped stromal cells clustered into islets outlined by an irregular reticulin network, and a loose type, with clear and enlarged lipid-filled stromal cells underlined by a mono or poorly cellular reticular network. These large and lipid swollen cells were labelled "pseudoxanthomzellen" by Lindau[273]. According to Bonnin *et al.*[34], the cellular variant of Cushing and Bailey is identical to "angioglioma" as defined by Roussy and Oberling[374].

Another histological classification was introduced by Silver and Hennigar, who suggested that the cytoplasmic storage of lipid in stromal cells is progressive, and therefore concluded that the lipid appearance of the stromal cells is an expression of the age of the lesion. Applying this theory to their series of 40 cases, they defined three histological types[402]:

– *juvenile* type, which they equated to capillary and cavernous variants of Cushing and Bailey; it contains sheets or columns of small cells coexistent with capillaries of various size, sometimes enlarged. There are a few or no xanthomatous cells. This type might be preferentially observed in the first three decades of life;

– *transitional* type, due to the development of intratumoural microhaemorrhages and transudation, with formation of microcysts; in reaction to haemorrhages, endothelial cells enlarge, using their phagocytic properties to capture erythrocytes and coagulated serum: they would become swollen with a xanthomatous appearance, while they fill with sudanophilic lipid material;

– *clear cell* type: in this type, the tumour is almost entirely made of xanthomatous cells; it might be preferentially observed at a late stage in the most advanced age-categories, corresponding to tumours seen in the elderly or to recurrent haemangioblastomas.

Such a correlation between the histological appearance and the evolutionary age of the tumour remains debatable. It was criticized by some[346], and accepted by other authors[132, 213].

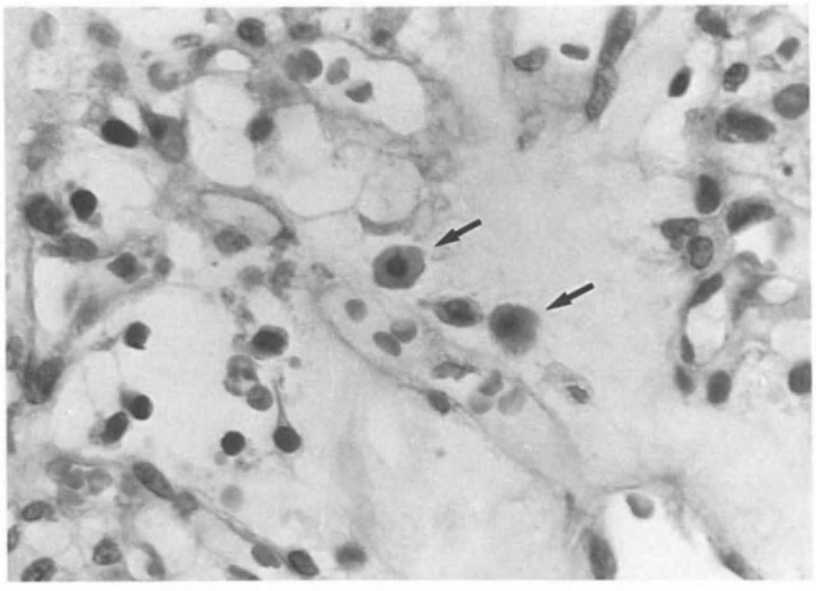

Fig. 3. Perivascular degranulated mast cells (arrows). Trichrome × 400

Some cytological and histological characteristics should be emphasized:

– firstly, borders of the tumour are less well defined than the macroscopic appearance suggests. Haemangioblastoma grows without any capsule within the nervous tissue: electron microscopic studies have provided confirmation of this lack of well-defined histological boundaries[263].

– secondly, reactive gliosis of the surrounding parenchyma is usually pronounced and associated with penetration of astrocytic processes into the tumour. The possible presence of a few astrocytes that might have accompanied vessels during the tumoural growth[86] has been confirmed[235]. Exceptionally astrocytes partipate into the neoplastic process and result in the development of true mixed capillary haemangioblastoma and glioma. The term "angioglioma" must be used only to designate such mixed tumours of both glial and vascular tissue origin[34].

– thirdly, foci of haematopoiesis are sometimes present within the tumour[157, 201, 277, 291, 358, 374]. They play no part in the genesis of secondary polycythaemia that may be encountered in haemangioblastoma.

– fourthly, a change with vacuolar clear stromal cell nuclei has been described[55, 278]. Its significance remains unclear.

– lastly, the presence of a large number of mast cells within the tumour[175, 273, 279, 291, 358] as compared to the adjacent cerebellar tissue constitutes a characteristic and significant histological feature (see Fig. 3). The

distribution of the mast cells in the tumour is uneven; however they are more abundant near the vessels, with up to 27 mast cells per high power field (× 400)[175].

Before ending this light microscopy section, a rare phenomenon, recently described in haemangioblastomatosis should be mentioned, i.e. the occurrence of haematogenous carcinomatous metastasis to a benign intracranial tumour. Such a metastasis, previously recorded in meningioma, acoustic schwannoma and pituitary adenoma, had been reported once in a recurrent cerebellar haemangioblastoma (metastatic carcinoma of prostatic origin)[82].

4.1.2. Electron Microscopy

Since the first analysis by Cancilla and Zimmerman in 1965[48], numerous studies on the ultrastructural morphology of haemangioblastoma have been published[52, 56, 60, 115, 135, 174–179, 208, 225, 226, 232, 254, 263, 358, 399, 401, 405, 413, 419, 453] cleary demonstrating the major components of the tumour: capillaries with endothelial cells and pericytes, stromal cells, mast cells and extracellular spaces:

– *Endothelial cells* of haemangioblastomas present frequent fenestrations[178, 419], and contain numerous Weibel-Palade bodies[174], crystalloid bodies[176], and an increased number of coated, both micropinocytic and megalopinocytic vesicles (large pinocytic vacuolar bodies[178, 248]), re-

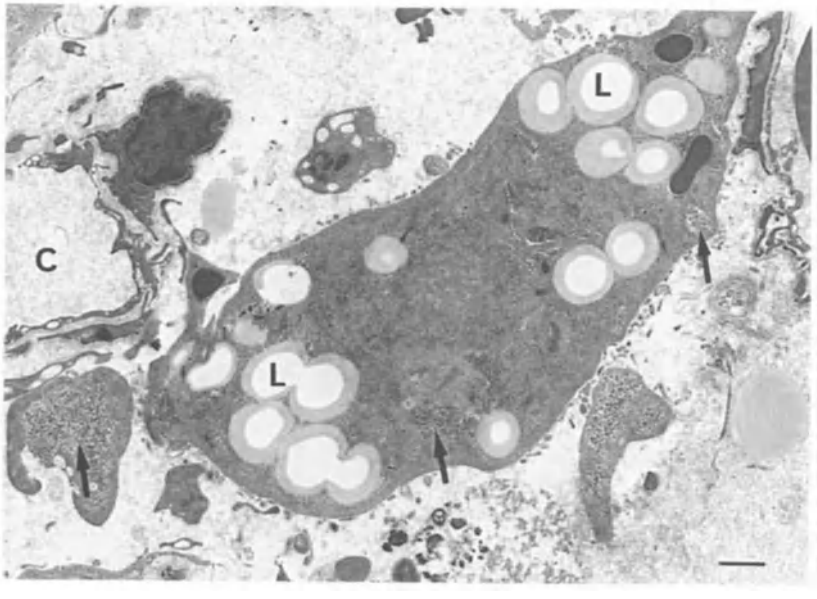

Fig. 4. Stromal cells with lipid inclusions (*L*) and glycogen (arrows) between capillaries (*C*). × 7500. Bar = 1 μm

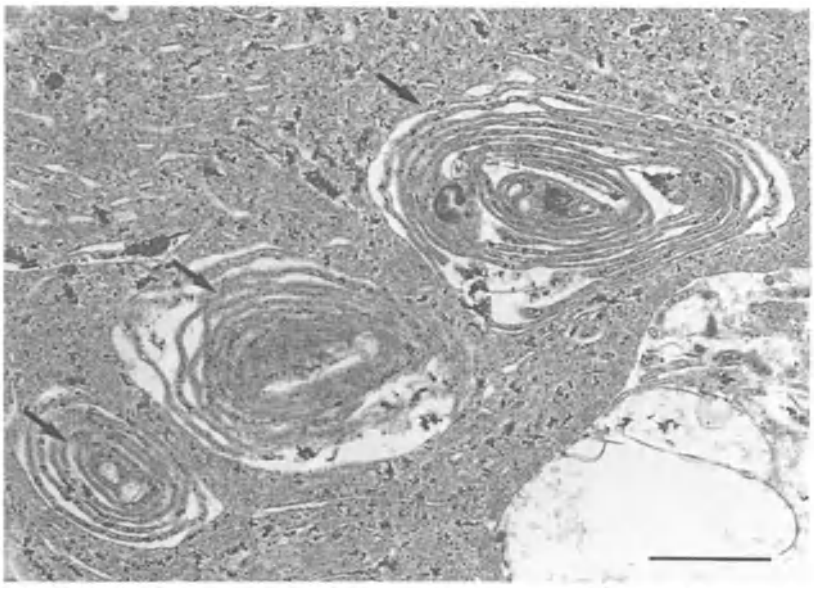

Fig. 5. Whorls of smooth endoplasmic reticulum (arrows) in cytoplasm of stromal cells. × 21000. Bar = 1 μm

flecting an active transendothelial transport and a high pathophysiological activity. Desmosomes are present at the junction zones.

– *Pericytes* lie immediately adjacent and external to the periendothelial basement membrane, being themselves completely surrounded by a basal lamina. Thus, capillaries are of continuous type with pericytes (Simon's classification equating to type A1α of Bennett, Luft and Hampton's classification)[52, 177].

– *Extracellular spaces* contain scattered collagen fibrils from 30 to 60 nm in diameter with 64 nm periodicity, cell debris, granulofibrillary material and some free-lipid droplets. Extravasated erythrocytes may also be observed.

– *Stromal cells* are interspersed as single cells or in group of a few cells in the loose intervascular space. They have a voluminous clear cytoplasm containing large lipid-membrane bound inclusions (see Fig. 4), 6–8 nm intermediate filaments and habitual organelles. Whorls of laminated smooth endoplasmic reticulum are common (see Fig. 5)[52, 56, 135, 232].

In some cases, rod-shaped concentric laminated and filamentous inclusions (Hirano's bodies) were reported[135, 453]. Junctions are zonula occludens and macula adherens[254]. The surface facing the perivascular collagen and cytoplasmic processes is frequently surrounded by basal lamina (see Fig. 6)[401] and those apposed plasma membranes have occasional desmosome-like junctions.

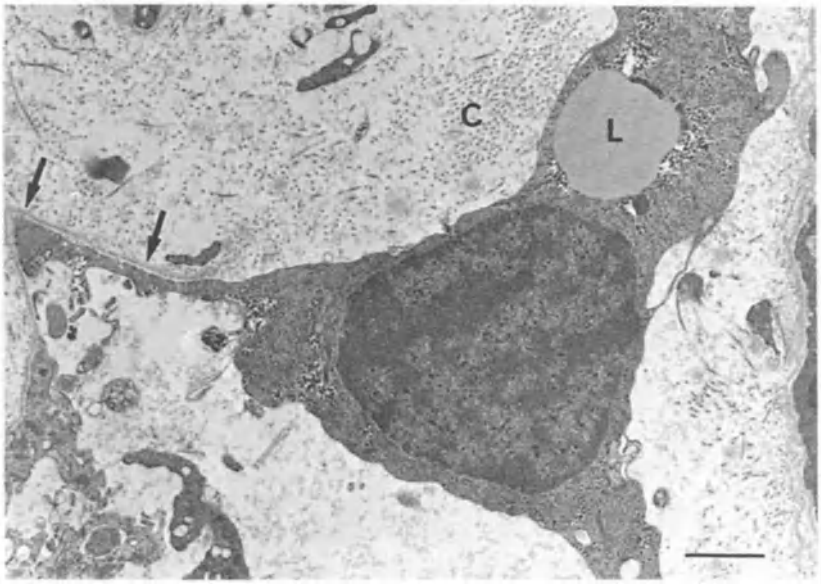

Fig. 6. A slender cytoplasmic process of stromal cell is surrounded by basal lamina (arrows). Lipid droplets (*L*). Collagen in the extra-vascular space (*C*). × 13800. Bar = 1 μm

Several reports pointed out the presence in the cytoplasm of stromal cells of membrane-bound electron dense bodies measuring 120–500 nm in diameter, suggesting secretory granules[6, 201, 203]. Some authors hypothesized that these granules might represent erythropoietin or a percursor substance[6, 201]; for others they might be neuropeptides[203]. Frequently glycogen is abundant in the cytoplasm of stromal cells[52]. In addition we recently observed large intranuclear glycogen deposits (see Fig. 7). Although invaginations of the nuclear envelope are not seen around these inclusions, we think that these deposits may be regarded as true inclusions. To the best of our knowledge, such intranuclear inclusions have not been reported previously. Further investigations appear necessary to determine their precise significance. Phagocytosis of red blood cells by the stromal cells, leading to constitution of erythrophagosomes, can be observed occasionally and probably reflects previous microhaemorrhage (see Fig. 8).

– Electron microscopy confirms the presence of *mast cells* and reveals the close relationship of mast cells to blood vessels and stromal cells[52, 54, 175, 225, 226, 232, 358]. They appear to be preferentially located at the site where the endothelial cytoplasm is attenuated and the vessel is devoid of pericyte covering[175]. Mast cells contain two types of granules: granules with electron-dense particulate appearance and granules with crystalline substructure,

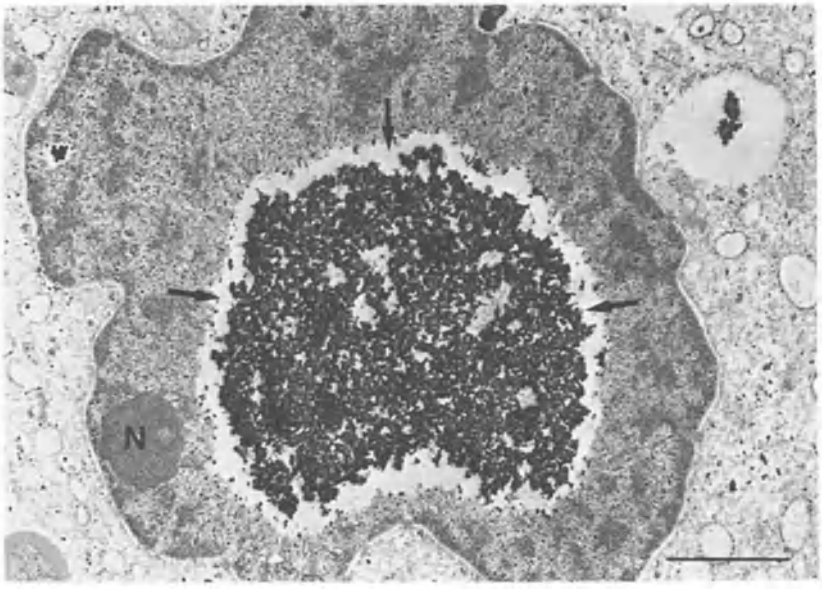

Fig. 7. Intranuclear inclusion of glycogen in stromal cell (arrows). Nucleolus (*N*). × 21000. Bar = 1 µm

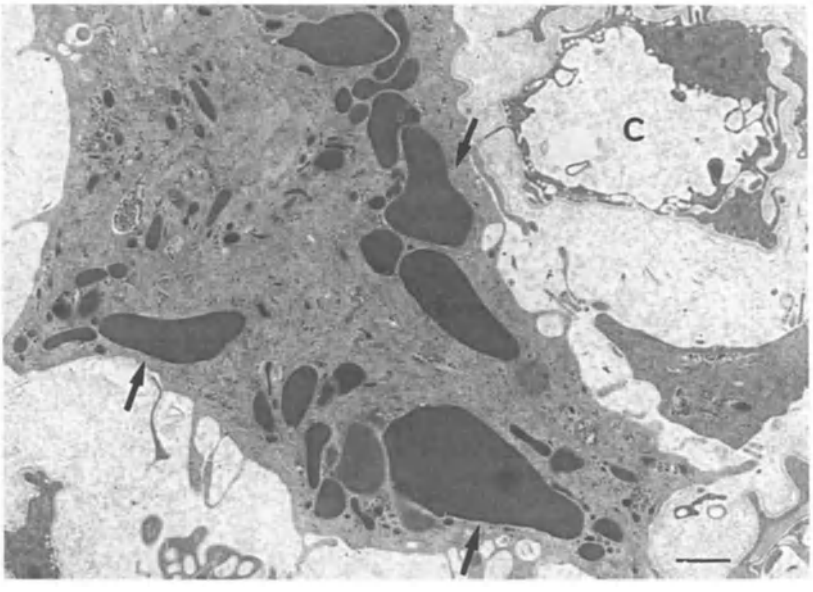

Fig. 8. Phagocytosis of red blood cells (arrows) by stromal cell. × 9000. Bar = 1 µm

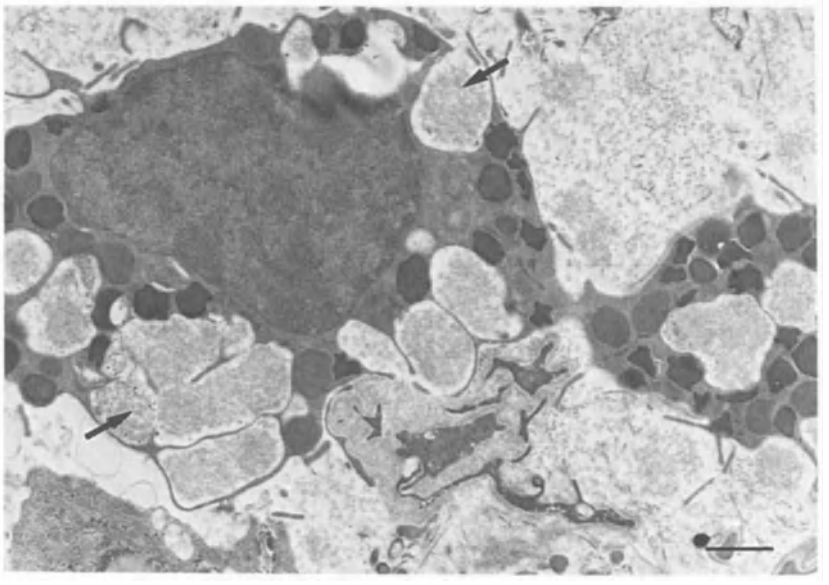

Fig. 9. Mast cells with features of degranulation (arrows). × 11000. Bar = 1 μm

such as scrolls, gratings and lattices. Degranulation of mast cells is sometimes observed (see Fig. 9). It occurs through a process of dissolution of granule substructures followed by extrusion of the contents into the extracellular space.

4.1.3. Immunocytochemistry

Numerous studies are currently being performed. Their greatest preoccupation is elucidating the nature of stromal cells. Unfortunately many previous studies using immunohistochemical methods have yielded conflicting results and published data must be interpreted with caution. Formalin-fixed, paraffin-embedded tissue is not the optimal material for demonstrating the presence of some antigens and the different reactivities could be methodological artefacts.

4.1.3.1. Studies Mainly Devoted to the Histogenetic Argumentation

– *Factor VIII-related antigen* (FVIII-RAg) is produced by endothelial cells. Immunocytochemical investigations utilizing the peroxidase-antiperoxidase technique with antiserum to FVIII-RAg showed that this endothelial cell marker reacted positively on endothelial cells lining capillary lumina of the neoplastic capillaries of the tumour[3, 25, 26, 54, 114, 118, 132, 154, 182, 188, 223, 226, 254, 281, 405, 420]. *Ulex europaeus agglutinin I* (UEA I) is a plant

lectin that reacts with the α-L-fucose moietics on the surface glycoproteins of endothelial cells. It is an highly specific endothelial cell marker and a more sensitive marker than FVIII-RAg. Immunocytochemical investigations using UEA I identically showed that it reacted positively only on endothelial cells of the neoplastic capillaries of the tumour[3, 25, 132, 182, 188, 388]. Study of the distribution of *laminin*, a basement membrane marker, showed that it was only found in the basement membrane of the capillaries, and not in the interstices of the neoplastic cells outside vessels lumina[25, 146]. *Fibronectin* which represents a family of structurally and immunologically related high molecular weight glycoproteins, was identified in endothelial cells, choroid epithelial cells and leptomeningeal cells. Within haemangioblastomas, immunofluorescence detection for fibronectin was positive for endothelial cells, and irregular for stromal cells, from poor to intermediate, as compared to that in the vessel wall[68, 247].

– Immunocytochemical investigations on the distribution of *glial fibrillary acidic protein* (GFAP), expressed in normal, reactive and neoplastic cells of astrocytic lineage, gave variable results: sometimes no evidence[68, 405], in other cases a variable rate, positivity at the level of glial processes or astrocytes particularly seen in the periphery[3, 26, 54, 99, 114, 132, 154, 155, 223, 226, 235, 247, 254, 281, 289, 333, 389a]. Some intervascular cells deeply located inside the tumour may exhibit a slight immunoreactivity: these cells are now considered to be entrapped astrocytes[182, 235, 281, 420], or atypical and lipidized astrocytes[208, 223], or stromal cells that took up extracellular GFAP derived from the adjacent reactive astrocytes[99, 223, 289]. Immunocytochemical detection of the S-100 *protein*, a neuroepithelial antigen, was positive for the glial processes of tumoural margin[3, 132, 182]. Immunohistochemical detection of S-100 protein gave variable results for stromal cells, sometimes negativity[3, 132, 182], sometimes positivity[420]. Immunohistochemical detection of S-100 protein gave variable results for stromal cells, sometimes negativity[3, 132, 182], sometimes positivity[420]. Immunohistochemical detection of *apolipoprotein E*, a marker of perikarya of astrocytes was negative[308].

– Immunocytochemical detection of *neuron-specific enolase* (NSE) was positive in one half of stromal cells[14, 118, 145, 155, 156, 203]. NSE, an isomer of the glycolytic enzyme enolase which was initially thought to be present exclusively in neurons, was later detected in neuroendocrine cells, reactive astrocytes and several non-neural CNS tumours and in other cells such as platelets or smooth muscle cells. Finally, its value in CNS tumours is poor.

– A weak cytoplasmic *synaptophysin* positivity of about 30 per cent of the stromal cells has been described. In the same study, approximately 25 per cent of the stromal cells reacted to antibodies against *substance P* and *neuropeptide YY*[14]. These results have not been confirmed[156]. This phenomenon might be due to antigen denaturation by the predigestion which was omitted in the former study. Immunohistochemical detection

of *chromogranin*, a neuroepithelial and neuroendocrine marker, was negative[132].

Immunocytochemical detection of *serotonin, vasoactive intestinal peptide* and *neurotensin* was negative in stromal cells[14].

– *Vimentin* is an intermediate filament present in fibroblasts and other cells of mesenchymal origin. It is a marker of antigens associated with mesenchymal tissue. Immunohistochemical detection of vimentin gave variable results for endothelial cells, sometimes negativity[405], sometimes positivity[132, 145, 389b]. Staining of a majority of intervascular cells was demonstrated[132, 145, 389b, 405] (and present study: see Fig. 10). However it was noticed that staining for vimentin was negative for large and lipid-filled stromal cells[389b].

– Stromal cells are negative for the detection of *myosin* and *desmin* which were demonstrated to be markers of smooth muscle cells and pericytes[182].

– Immunocytochemical detection of *leu-enkephalin* was negative in stromal cells and highly positive in mast cells[14].

– A granular cytoplasmic staining of 50 per cent of stromal cells with antisera to *somatostatin* and *bombesin* has been described[203] but not corroborated by others[145, 156].

Finally the components of the intercapillary space of haemangioblastoma appear antigenically polymorphous and express multiple antigens. Thus, as indicated above, stromal cells react positively to a large set of

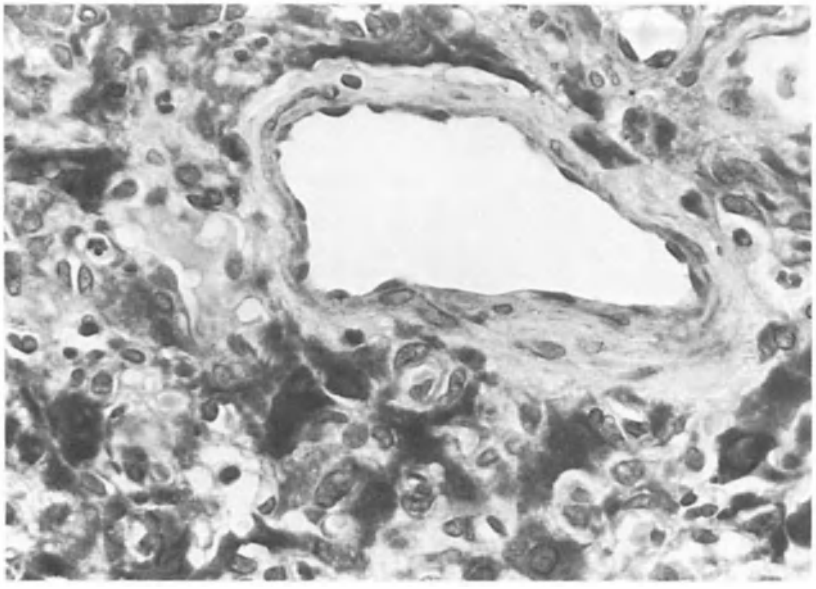

Fig. 10. Strong positivity of stromal cells with vimentin. Immunoperoxidase × 400

antigens. Possible interpretation includes a wide differentiation potential of the undetermined mesenchymal and multipotential primary cell line, or that of a monopotential reduplicating cell line sharing numerous antigenic determinants. Therefore the pattern of antigen expression by stromal cells does not permit the identification of a definite histogenesis.

4.1.3.2. Secretory Activity Study

"Small granular cells" scattered among stromal cells have been described, showing a positive-staining reaction with *alpha-1-anti-trypsin*[26, 288], *anti-erythropoietin*[26, 188] and *anti-renin* substrates[26] leading to the speculation that, in addition to the capillary endothelial cells, pericytes and stromal cells, haemangioblastomas harbour cells, the so-called "fourth cell type" containing and perhaps producing renin substrate and/or erythropoietin or a substance with similar antigenic determinant, that might explain the secondary polycythaemia associated with haemangioblastoma[26].

According to Böhling *et al.* these small granular cells that share a number of features with and on the other hand show differences in the immunocytochemical staining properties from skin mast cells (studied from patients with urticaria pigmentosa) would be different from mast cells and might have a relationship to macrophages[26]. For others, cells with abundant secreting granules observed within haemangioblastoma in the vicinity of capillaries are mast cells that might be capable of producing and releasing erythropoietin[225]. In the same way, we think that "small granular cells" are authentic mast cells. Our opinion is based on extensive ultrastructural examination of twelve cerebellar haemangioblastomas and agrees with previous studies[175]. Recent major advances in mast cell biology clearly demonstrated that mast cells constitute a morphologically, biochemically and functionally heterogeneous cell population[139]. We postulate that mast cells observed in haemangioblastomas may be somewhat different from mast cells that are present in the skin. Further investigations are of critical importance in order to determine the ascribed role of mast cell mediators in capillary migration and proliferation[175].

4.1.4. Cell Culture

Since the first presentation by Pomerat[348], a few studies concerning haemangioblastoma cell culture have been performed.

One of them used a supratentorial haemangioblastoma. Fibroblasts and epithelioid-like cells first appeared, followed by rounded or elongated hyperchromatic cells. After clarification, a capillary-like network could be seen, giving cords of endothelial cells and globulous lipid-filled histiocyte-like cells with an increase of their number with the ageing of the culture[41].

Another tissue culture showed outgrowths of cells arranged in loosely fenestrated patterns reminiscent of the tumoural tissue[238].

According to similar studies with ultrastructural analysis of cultivated cells, it seems that the three main cellular types (endothelial cells, pericytes, stromal cells) have a distinct evolution[413]. However stromal cells exhibit progressive changes (increase of the density of microfilaments and micropinocytotic vesicles, formation of segments of basement membrane and more numerous zonulae occludens) that give them some common features with endothelial cells, hence their designation as "transitional cells"[60].

In another study, transitional cells exhibiting abundant cytoplasmic microfilaments and cytoplasmic organelles similar to those of pericytes were present. They were considered as transitional cells between pericytes and leiomyoblastic differentiated cells[226].

4.1.5. Histogenesis

Despite numerous electron microscopic and immunocytochemical studies, the debate concerning the nature and origin of the stromal cells remains. The histogenesis of haemangioblastomas remains unclear and controversial. The main difficulty is the fact that stromal cells have no counterpart among mature or immature normal cells.

As indicated by its name, haemangioblastoma was historically believed to represent a neoplasm originating from primitive angiogenic elements that stromal cells might represent[86].

Since the first description of haemangioblastoma, various hypotheses about the origin of stromal cells have been expressed: blastemic angiogenic mesenchyma[60, 86, 232, 273], stromal cells possibly sharing with endothelial cells and pericytes a common, presumably angiogenic ancestry[376, 413], derivation from neuroglia[373], microglia[279], endothelial cells[48, 223], meningeal cells[198], modified astrocytes[208, 420]. For others, stromal cells would be undifferentiated mesenchymal cells originating in the pia or the vasculature[132, 281], or reticular cells[52, 374]. A relation to pericytes and smooth muscle cells was even expressed[226].

A reticular origin for stromal cells can be refuted on the basis of tumoural capillary type despite positivity of stromal cells to some of the histiocyte markers. There is no current evidence to support an histiocytic origin. Thus the significance of α-1 antichymotrypsin positivity in stromal cells[198] may be interpreted with caution since its lack of specificity has been demonstrated[260].

A possible pericytic or leiomyoblastic origin for stromal cells can be excluded because of the regular negativity for desmin and myosin[182].

Some years ago, a neuroectodermal origin was suggested[203] but immunocytological data was unconvincing because of a lack of specificity of

immunsera[254]. On the basis of positivity for several polypeptides, such a neuroectodermal origin theory was recently reiterated: it was proposed that haemangioblastomas might have a neuroendocrine component[14, 422]. On the basis of opposite results, other argued against such a neuroendocrine origin of stromal cells[156].

The most gratifying histogenetic hypothesis locates the origin of stromal cells in a proliferation of angiogenetic cells from an organogenetic defect affecting the vascular mesenchyma during the third month of foetal life; at this stage of development, a vascular mesenchyme is situated on the posterior medullary velum. Cerebellar hemispheres also begin to develop at this time. A part of the original vascular mesenchyma lying on the posterior medullary velum might be drawn into the cerebellar hemispheres[273] and might represent the germ of subsequent tumoural development. The terms "capillary haemangioma"[273] and "haemangioblastoma"[86] come from this theory. The presence of neoplasms in other organs might be explained upon the same basis. In the third month of foetal life, vascularization of retina and ingrowth of the mesodermal elements into the pancreas also occur. Contemporary vascular maldevelopment of the kidney might also explain the renal lesions. There are some elements supporting such an origin: "transitional cells" that appear in culture might suggest that endothelial cells and stromal cells have a common origin from angioblasts[60]. Moreover, using ultrastructural studies of tissue culture, Spence and Rubinstein demonstrated that stromal cells share features with both pericytes and endothelial cells and postulated that these three cell types derive from a common mesenchymal precursor[413]. This is in agreement with the results of the recent detailed immunocytochemical study of Frank *et al.*[132]. The consistent strong vimentin positivity of stromal cells in conjunction with the lack of reactivity for the other immunohistochemical markers led these authors to the conclusion that stromal cells are poorly differentiated cells of mesenchymal origin. This might explain the lack of common factors with endothelial cells: the presence in stromal cells of Weibel-Palade bodies that are specific for endothelial cells[51] was demonstrated exceptionally[174]; positive immunoreactivity to FVIII-RAg specific of endothelial cells was noted only twice in stromal cells[223, 405]; immunocytochemical investigations by UEA I, showed that this highly specific endothelial cell marker never reacted positively on stromal cells[3, 25, 132, 182, 188, 388]. Search for the presence of blood group A and B isoantigens, a marker of endothelial cell used to identify cells of endothelial origin in CNS tumours was positive for endothelial cells of infratentorial and supratentorial haemangioblastomas and negative for stromal cells[215]; similarly no positive reaction was observed with blood group antigen H[182].

The close association of mast cells with endothelial cells and stromal cells suggests, as stated above, that mast cells might play an important

pathophysiological part in the vascular proliferation and expansion of haemangioblastoma[175].

In summary, despite numerous studies the nature and origin of the stromal cells of haemangioblastoma remain enigmatic and unresolved. To date, the overwhelming view on the nature of stromal cells, essentially derived from ultrastructural studies, supports an angiogenic derivation from misplaced blastomatous vascular mesenchyma, as was suggested more than sixty years ago[86, 273]. Thus haemangioblastoma may be developmental in origin. Of course, additional immunocytochemical studies (especially at ultrastructural level) are required to elucidate the true origin of this fascinating tumour.

4.1.6. Differential Histopathological Diagnosis

It may be very difficult to distinguish the cerebellar or cerebral clear cell variant of haemangioblastoma from metastatic clear cell renal carcinoma. This diagnosis may be all the more difficult since both conditions are present in the Lindau's brain syndrome.

The problem of the differential diagnosis both of CNS haemangioblastoma and metastases of renal clear cell carcinomas was investigated by immunoperoxidase labelled antibody staining, using anticarcinoembryonic antigen, anti-brush border[5], anti-factor VIII-related antigen[5, 155], anti-keratin and anti-epithelial membrane antigen (EMA)[5, 70, 132, 155, 188]. Staining using the four former markers was unhelpful. On the other hand all the haemangioblastomas were negative and all the metastases (and primary clear cell renal carcinomas) were positive for EMA. This shows that epithelial membrane antigen is a useful discriminator to separate the two entities[5, 70, 132, 155, 188].

Another technique (AgNOR method) has been reported recently as a useful adjunct in the differential diagnosis of renal clear cell carcinoma metastasis and haemangioblastoma[83]. Nucleolar organizer regions (NORs) are segments of DNA encoding for ribosomal RNA present in human acrocentric chromosomes and can be demonstrated by the argyrophilia of their associated proteins. Mean nuclear AgNOR counts in the stromal cells exceed significantly the count in renal cell carcinoma. This attractive method is more rapid than immunocytochemistry but, since it seems well-established that mean nuclear profile AgNOR counts reflect cell proliferation, these data suggest a higher proliferation in haemangioblastoma than in renal carcinoma. Further investigations of this surprising phenomenon appear necessary.

4.2. Associated Extraneuraxial Lesions (Lindau Complex)

4.2.1. General Points

The lesions associated with CNS haemangioblastoma situated out of the neuraxis (Lindau complex) do not have the benign significance that was

still quoted recently "In von Hippel Lindau disease the prognosis depends entirely on the neurological lesions. Its visceral manifestations are really only curiosities, usually discovered incidentally during an operation or autopsy: they are of no significance in the evolution of the disorder"[391]. Such assertions must be denied strongly. Although Lindau initially stated that visceral lesions were benign[273], in fact the highly pathogenic even lethal nature of some extraneuraxial lesions, especially the renal ones, was well demonstrated, as early as 1931[236].

The general incidence of extraneuraxial lesions associated with CNS haemangioblastoma ranges in large series from 5[329] to 6.5 per cent[360]. The incidence obtained from reviews of the literature is higher, ranging from 22.5[358] to 26.4 per cent[360]. Because of asymptomatic lesions and perhaps insufficient (incomplete) screening in the former and probable overestimation in the latter with a bias due to the selective nature of data published in reports of one or a few cases, we think that the incidence may be more accurately evaluated at about 15 per cent.

Extraneuraxial lesions may be associated with all types and localizations of CNS haemangioblastoma. They have been observed in patients only affected with retinal haemangioblastoma[358].

Kidneys, pancreas, adrenals and epididymis are implicated in the main[358, 360].

4.2.2. Mainly Implicated Organs

4.2.2.1. Kidneys

Renal involvement is the first most frequent manifestation of Lindau complex. Several pathological types were described:

– *congenital malformations*: ureteropyelic duplicity[228, 375], horseshoe kidney[81];

– *dystrophic lesions*: arteriovenous malformation, cysts (solitary or multiple unilateral cyst, polycystic kidney disease with or without epithelial hyperplasia[18]);

– *tumours*: essentially *renal clear cell carcinoma*[227] (see Fig. 11). Some characteristics allow one to distinguish renal clear cell carcinoma belonging to Lindau complex and renal clear cell carcinoma not associated with the syndrome: renal clear cell carcinoma is bilateral and multicentric in more than 15 per cent of all cases in Lindau disease while renal clear cell carcinoma not associated with Lindau disease is bilateral in only about 1.8 per cent of all cases[438]; on the other hand the average age at detection of renal clear cell carcinoma in Lindau complex is significantly below the average age at detection of sporadic non-familial cancer (respectively fourth and sixth decade of life). Renal clear cell carcinoma has a malignant potential because it is both locally invasive and distantly metastasizing. Several

reports in the literature describe the lethal nature of renal clear cell carcinoma[67, 140, 184, 199, 227, 252, 285, 293, 325, 345]. From a clinical and pathological point of view, renal clear cell carcinoma associated with the Lindau syndrome appears probably as malignant a disease as renal clear cell carcinoma in the non Lindau-affected population[65, 184]. Single or multiple cysts, benign in appearance, may be lined by clear cells consistent with renal clear cell carcinoma[65]. In fact, in Lindau syndrome, it seems that renal cysts form a histopathological continuum ranging from benign cysts, atypical cysts (demonstrating epithelial hyperplasia with or without cytologic atypia), to malignant cysts with occult mural clear cell carcinoma[410].

In a few instances, some other renal tumours have been reported: cortical adenoma[67, 189, 285, 304]; vascular tumours termed as haemangioendothelioma[67, 270], angioepithelioma of von Hansemann[167] or haemangioblastoma[46, 466].

– associations as polycystic disease with tumours and malformations with tumours have been reported also[81].

4.2.2.2. Pancreas

Pancreas is in order of frequency the second organ involved in the Lindau complex. Several pathological types have been reported also:

– *dystrophic lesions*: simple cysts, single or more frequently multiple, producing a polycystic disease of the pancreas[273]. They may partially or completely deform and replace the pancreatic parenchyma.

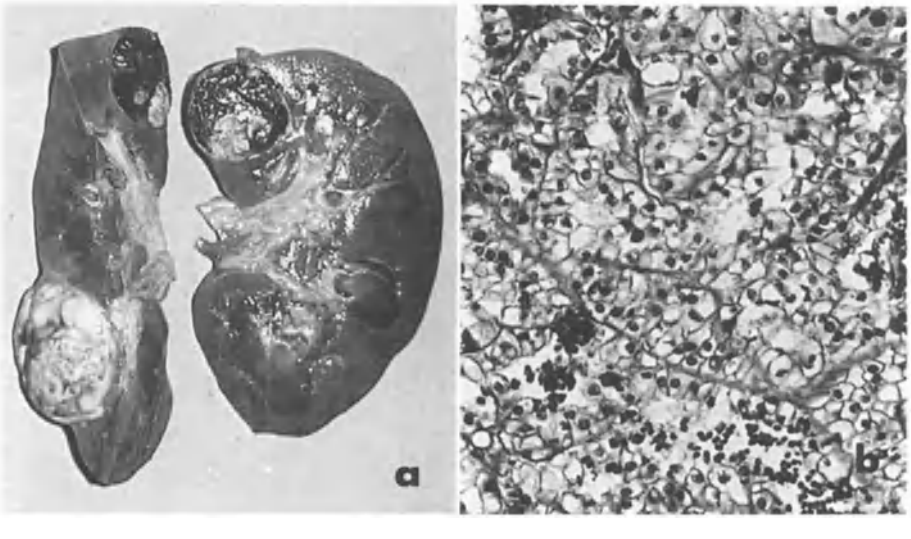

Fig. 11. Lindau complex: Renal clear cell carcinoma. Gross aspect (a) and microscopic appearance × 250 (b)

– *tumours of exocrine pancreas*: benign tumours such as cystadenomas, commonly *microcystic papillary cystadenomas*[15, 123] (see Fig. 12), vascular tumours termed as lymphangioma[246], lymphangioendothelioma[167], haemangioblastoma[387], haemangioendothelioma[255], and malignant tumours (adenocarcinoma[255]).

– *islet cell tumours*, benign tumours such as adenomas[264, 353], benign apudoma[306] (see Fig. 13), and malignant tumours named nesidioblastomas[190], islet cell carcinoma[77, 255]. Indeed in the latter metastases are possible[77]. Immunohistochemical stains may demonstrate insulin, glucagon, pancreatic polypeptide[353], calcitonin, or vasoactive intestinal polypeptide[77, 306]. Hormonal secretion has been described in a few cases, insulin[264] or ectopic secretion of calcitonin[77]. As with adrenal medullary cells, pancreatic islet cells embryologically derive from the neural crest[336] and make up part of the amine precursor uptake and decarboxylation (APUD) system.

4.2.2.3. Adrenals

Adrenals are the third organ affected by lesions of the Lindau complex.

The adrenal medulla is almost exclusively concerned:

– cyst[430];

– adrenal medullary hyperplasia (that might be a precursor of phaeochromocytoma);

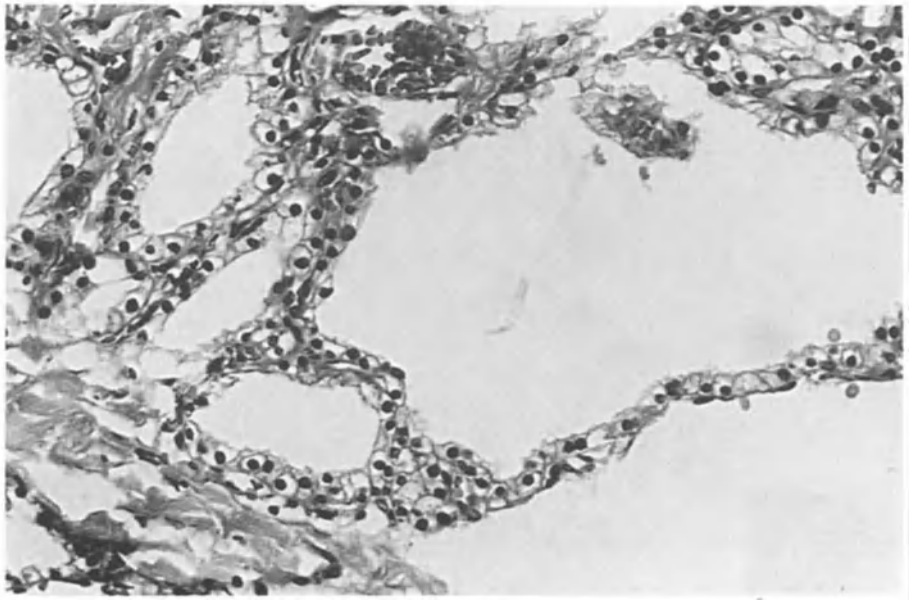

Fig. 12. Lindau complex: Microcystic papillary pancreatic cystadenoma. × 250

– *phaeochromocytoma*, initially described in the framework of the Lindau disease in 1934[464] (see Fig. 14). If it is present, phaeochromocytoma occurs bilaterally in more than one third of cases in patients with Lindau disease. Phaeochromocytoma and islet cell tumour may be a component of multiple endocrine neoplasia. As well as in Lindau disease, bilateral phaeochromocytoma has been reported in multiple endocrine neoplasia

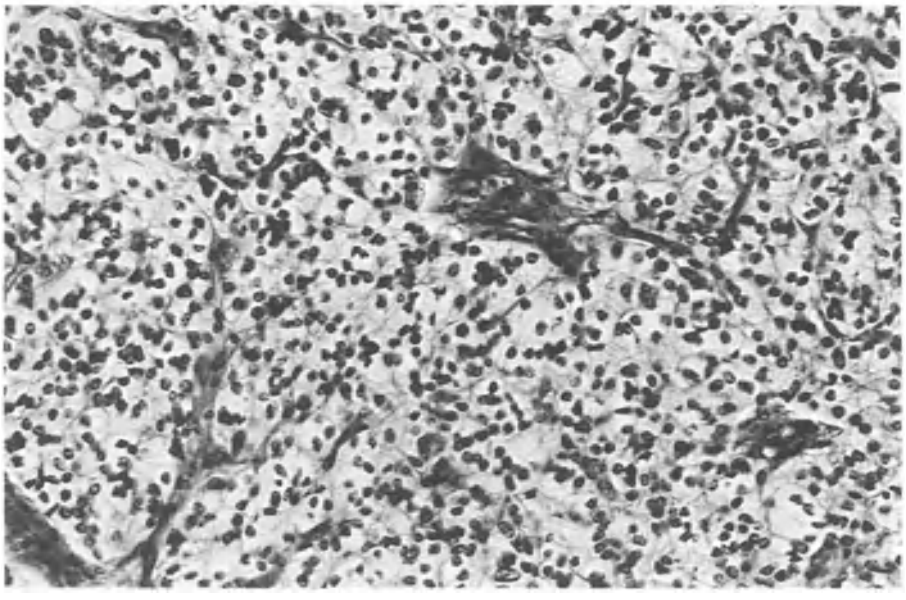

Fig. 13. Lindau complex: Islet cell tumour. × 250

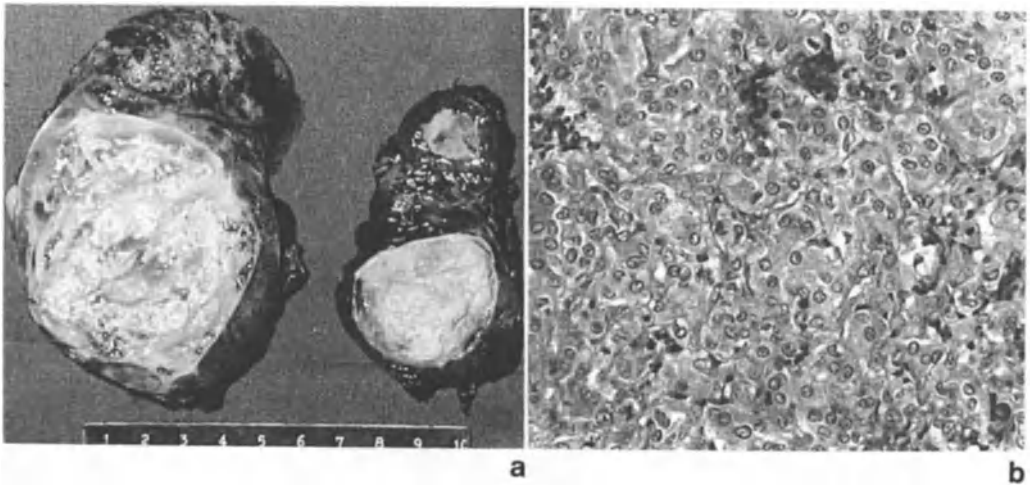

Fig. 14. Lindau complex: Both adrenals phaechromocytoma. Gross aspect (a) and microscopic appearance × 250 (b)

types 2 a and 2 b. Some cases of ectopic non-adrenal phaeochromocytoma (paraganglioma) were reported[180, 380].

The adrenal cortex is rarely affected: adenoma[273, 284, 387].

A few cases of adrenal haemangioblastoma have been described[45, 205].

4.2.2.4. Epididymis

Epididymal lesions are cysts or *papillary cystadenomas*[129, 273]. They are generally bilateral lesions. Incidence of epididymal lesions in Lindau disease is probably higher than demonstrated in the literature: a prospective study in an affected family have demonstrated a 28 per cent incidence[64].

4.2.3. Other Lesions

4.2.3.1. Liver

Liver involvement is the fifth in order of frequency.

Miscellaneous pathological types were described: cysts; adenoma[67]; vascular lesions termed cavernoma[246, 421], "superficial naevus"[72], "angioma-like structures adjacent to the portal triads"[387], multiple haemangiomas[479], angioreticuloma[431]; (suspected) hamartoma[47]; carcinoid tumour[372]; congenital hepatic fibrosis[448]; hepatocellular carcinoma[280].

4.2.3.2. Skin

Although rare, some interesting cases of patients exhibiting "café-au-lait" spots were reported illustrating (with phaeochromocytoma) the relationship between Lindau disease and von Recklinghausen neurofibromatosis[39, 293, 309, 338]. As will be noticed below, a few families affected by both dysgenetic disorders have been reported.

Some other skin lesions have been described in patients with CNS haemangioblastoma: small telangiectasias of trunk[98]; hemifacial "naevus flammeus"[128]; capillary naevus[148, 166]; pigmented naevus[253]; brown pigmented hairy hyperkeratotic naevi[470]; "spider" naevi[300]; tuberous angioma[358]; diffuse cutaneous angiomas[119]; capillary haemangioma[297].

One case of facial hemihypertrophy has been observed: despite being an extremely rare condition it has been reported previously both in Sturge-Weber syndrome and neurofibromatosis, and it was therefore suggested that facial hemihypertrophy in Lindau disease is not a chance association[138].

4.2.3.3. Ovaries and Annexes

Miscellaneous lesions have been described: polycystic disease of both ovaries[304, 338, 448]; ovarian cystadenoma[152]; ovarian serous adenofibromas[70]; ovarian vascular lesions: haemangioendothelioma[167], angioma[184]; multi-

locular cyst of fallopian tube[72]; leiomyoangioma of fallopian tube[448]; cysts of parametrium (in the daughter of Otto M..., the first patient of von Hippel)[243]; papillary cystadenoma of the broad ligament within the mesosalpinx, which is the female counterpart of papillary cystadenoma of the epididymis seen in men, both tumours having a mesonephric (Wolffian) origin[137, 144].

4.2.3.4. Lungs

A few lesions have been described: Cysts[241, 387]; focal aggregates of cavernous vascular channels adjacent to the bronchioles and pulmonary arterial branches[387]; undifferentiated carcinoma of the small cell type (oat cell carcinoma)[280].

4.2.3.5. Spleen

A few lesions have been described here also: Cysts[98, 123, 364]; endothelioma[40]; cavernous venous channels[387]; angioma[20].

4.2.4. Miscellanous Exceptional Lesions

A few other miscellaneous extraneuraxial lesions have been described exceptionally, some of them only once and thus of little interest, if not purely historical:

4.2.4.1. Omentum and Mesocolon

Serohaematic cysts[98].

4.2.4.2. Bladder

Bladder papillomas (in Otto M...)[40].

4.2.4.3. Prostate

Adenoma[41] but it is a sufficiently common condition for its presence to be fortuitous; cysts[364].

4.2.4.4. Parathyroid

Parathyroid adenoma with primary hyperparathyroidism[142, 256], leading to further discussion of the relationship of Lindau disease with multiple endocrine neoplasia.

4.2.4.5. Thyroid

Atypical thyroid adenoma[280]; mixed follicular papillary carcinoma[363].

4.2.4.6. Parotid

Parotid adenocarcinoma[313].

4.2.4.7. Carotid Body

Metastatic carotid body paraganglioma[191].

4.2.4.8. Skeleton

Temporal bone tumour[37, 40, 293], with in two cases, histopathological evidence of papillary adenoma[330, 352].

4.2.5. Comments

To date, skin, skeleton and fifteen organs have been implicated with one, a few or even several different lesions in the Lindau complex. More than fifteen different pathological types have also been described.

Among all these manifestations, some of them appear as a chance association and cannot be related aetiologically with absolute certainty to the primary genetic defect. For example, despite the well-known changes existing in chromosome 3 in small cell lung carcinoma, and its involvement in VHL disease as will be stated below, report of a metastatic small cell lung cancer and hepatocellular carcinoma described at autopsy in a both smoker and drinker patient[280] supports this view. Similarly, the reported pancreas and parotid adenocarcinomas were probably fortuitous.

From a pathological point of view, pecularly interesting as certain components of the Lindau disorder are the following:

- firstly, renal clear cell carcinoma,
- secondly, pancreas, epididymis, ovary and broad ligament, and temporal bone papillary cystadenomas,
- thirdly, the different tumours described as vascular lesions,
- and finally, the different-embryologically derived tumours, such as phaeochromocytoma, paraganglioma, and islet cell tumours, related to neural crest pathology.

5. Clinical and Biological Data

5.1. Epidemiological and Aetiological Factors

5.1.1. Exogenous Aetiological Factors

As with several other CNS tumours, some reports in the literature have indicated possible involvement of exogenous factors in the clinical appearance of haemangioblastoma.

5.1.1.1. Trauma and Haemangioblastoma

A head injury shortly before the onset of symptoms leading to the diagnosis of infratentorial haemangioblastoma has been present in a few cases[42, 62, 80, 130, 272, 341].

An ocular injury that revealed a retinal lesion[136] or a spinal injury prior to diagnosis of an intramedullary spinal cord haemangioblastoma[271] is quite exceptional.

Forensic discussions in such instances have to be individually considered.

5.1.1.2. Pregnancy and Haemangioblastoma

There has been frequent speculation that pregnancy might hasten the presentation of intracranial tumours.

There are some well-documented cases in the literature presenting symptoms during pregnancy leading to the diagnosis of retinal haemangioblastoma[8, 37], or infratentorial haemangioblastoma[24, 37, 42, 47, 58, 95, 96, 111, 212, 229, 273, 322, 329, 366, 386]. Symptomatology can appear immediately after delivery[183]. The majority of patients had two or even three successful previous pregnancies before[37, 47, 273].

Although increase in size of a haemangioblastoma during pregnancy is still controversial, the fact that some patients improve spontaneously after delivery supports the probable role of vascular engorgement as a cause of

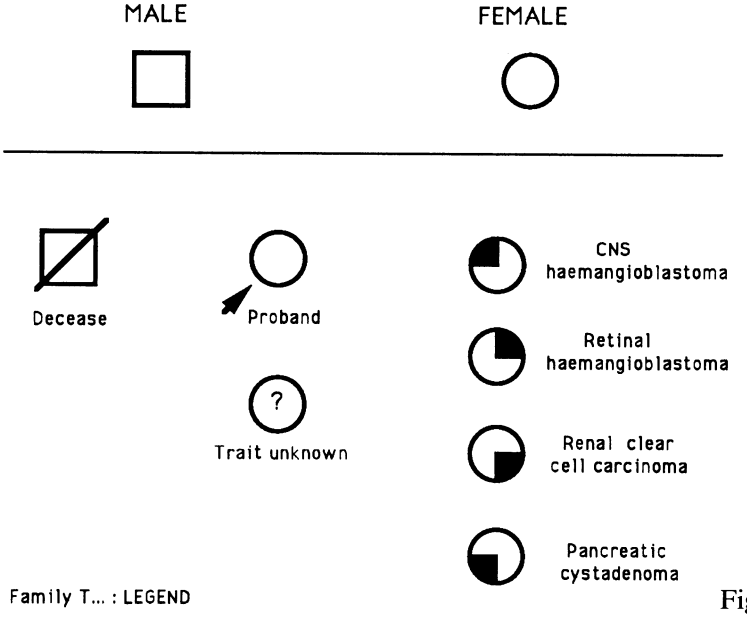

Fig. 15.1.

Fig. 15. Pedigree of a family affected with VHL disease

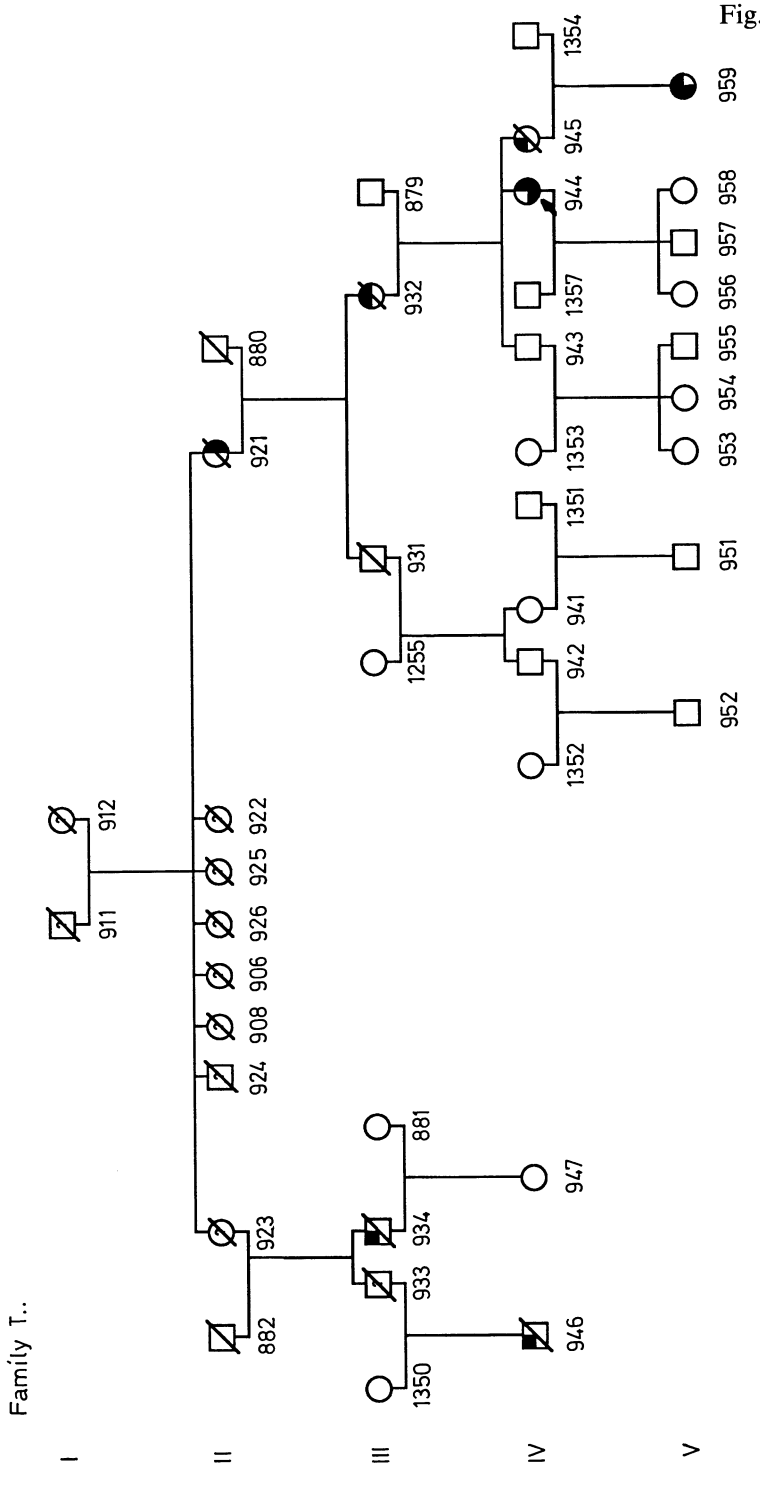
Family T..
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Fig. 15.2.

tumour enlargement and decompensation of symptoms by increased mass effect. Vascular engorgement has been shown by serial X-Ray computed tomography (CT) and magnetic resonance imaging (MRI) observations[229].

5.1.2. Endogenous Aetiological Factors: Familial Forms

The presence of an inherited factor was recognized as early as 1894 on the basis of observation of retinal tumours affecting two siblings[73]. In retrospect, the first case reported by Jackson probably had hereditary features. In 1913 Seidel described identical cerebellar tumours in two brothers[394]. In addition to the autopsy findings of Otto M..., Brandt in 1921 published the data of ocular examination of the Otto M... son[40]. Beside the M... family, of historical interest, followed for 70 years (1895–1965)[40, 224, 243, 345, 445, 447], several other families have been studied with pedigrees harbouring four[298], five[159, 283, 329, 387, 429] (and personal data: see Fig. 15), even six generations[255, 259, 285].

Familial forms are genopathies due to a gene or gene cluster harbouring a pleiotropic nature. This markedly pleiotropic genotype is evidenced by the wide range of dystrophic and neoplastic phenotypic manifestations as we have reported above.

Autosomally dominant inheritance was recognized as soon as 1929 with presentation of a pedigree with four generations[298].

Penetrance is incomplete but high, ranging from 70 to 80 per cent in most families. Penetrance ranges from 12[68] to 90 per cent[403] in both sexes. At the individual level the penetrance increases with age[149]. However the definition of penetrance is not unanimously agreed and from a strictly genetic point of view, it remains an inaccurate and uncertain notion as long as the causative gene has not been cloned.

The occurrence of the disease in identical twins has been reported[456].

The disease exhibits markedly variable expression, both within an affected family and between affected families:

– lesions exhibited by affected members within such a VHL disease family may vary: some members have isolated or associated lesions causing severe morbidity as multiple retinal, nervous and visceral tumours, whilst other members in the same family have a relatively mild expression of the disease (e.g. only unilateral retinal haemangioblastoma);

– review of the literature also shows an interfamily variability. Thus, phaechromocytoma seems confined usually to certain predisposed families[159, 184, 324, 380, 383, 400] in which there is a high incidence of association with retinal haemangioblastoma[159]; in some other families renal clear cell carcinoma appears as the main manifestation without phaeochromocytoma[149]; in some other families pancreatic involvement is the main trait[123]; in some other families there is a high rate of spinal haemangioblastoma[327].

Most of the familial cases exhibit CNS haemangioblastomatosis and extraneuraxial lesions of Lindau complex. In some instances familial forms have been reported with the presence of a solitary cerebellar haemangioblastoma in the lineage of an affected patient[31, 117]; however, because of the long duration that may be observed between the appearance of two lesions in the same patient and, in contrast, the frequent short duration of follow-up and the lack of well-performed screening for most of such cases, this entity must be considered as peculiarly doubtful.

Genetic antedating phenomenon is present. Although debated by some authors, its reality is clearly confirmed by the analysis of most families, whatever the origin and age of reports[20, 21, 323, 472]. In some families, presentation of the disease in children has even andetated that of their affected parent[216]. Neither the age of the mother at conception nor the order of birth influence the repartition of defect.

A few apparently "sporadic" forms might be the result of a mutation; the rate of mutation ranges from $1/2.8 \times 10^5$ [84] to $1/10^6$ [85]. In such instances, lineage is affected according to the autosomal Mandelian inheritance mechanisms.

The incidence of familial cases ranges in the literature from 5.3[300] to 11.8 per cent[360]. It must be stressed however that genetic inquiry is incomplete or absent in most series and therefore the real familial incidence is probably higher.

Lindau disease has been included in the framework of phakomatoses[434, 435]. In addition to rare skin lesions that may be present in patients with Lindau disease, remarkable kindreds have been reported in which Lindau disease and another dysgenetic syndrome were present in different members of the same family. In one kindred, patients exhibited concomitant lesions related to both Lindau disease and von Recklinghausen neurofibromatosis[423, 425]. In another family the coexistence of Bourneville tuberous sclerosis in a female newborn and her mother and Lindau disease in her maternal aunt was described[378]; the case of the aunt who exhibited "café-au-lait" spots had previously been published[338]; thus, in this kindred, lesions belonging to the three conditions, von Recklinghausen neurofibromatosis, tuberous sclerosis and Lindau disease were demonstrably coexistent.

5.1.3. Sex Incidence

Males are affected more frequently than females.

This male predominance is observed most notably in infratentorial and retinal localizations. Pooling of data from 15 reviewed series of infratentorial haemangioblastoma[35, 80, 119, 200, 209, 212, 253, 266, 325, 329, 332, 360, 366, 402, 472] indicates a sex ratio of 1.5 : 1 (Table 8).

Table 8

Series	Male	Female	Total
Borck and Tönnis (1955)	34	12	46
Cramer and Kimsey (1952)	34	19	53
Ferrante *et al.* (1984)	29	32	61
Isfort and Sunder-Plassmann (1965)	18	4	22
Jamieson *et al.* (1974)	14	4	18
Jeffreys (1975)	44	23	67
Krayenbuhl and Yaşargil (1958)	22	23	45
Leu and Rüttner (1973)	22	19	41
Olivecrona (1952)	41	29	70
Palmer (1972)	50	30	80
Papo *et al.* (1961)	27	17	44
Resche *et al.* (FSNC) (1985)	151	111	262
Robinson (1965)	11	12	23
Silver and Hennigar (1952)	24	16	40
Yamashita *et al.* (1982)	32	22	54
	553 (59.7%)	373 (40.3%)	926

5.1.4. Age at Diagnosis

5.1.4.1. General Points

Generally, haemangioblastoma of the CNS manifests itself in adult life. From a large review of the literature, the average age at diagnosis was calculated as 31.5 years for brain stem haemangioblastoma, 32.3 years for supratentorial haemangioblastoma, 34.9 years for cerebellar haemangioblastoma and 36.5 years for spinal haemangioblastoma[358].

Retinal haemangioblastoma appears earlier, in adolescents and young adults[358]. In a series of 147 cases of cerebelloretinal haemangioblastomatosis from the literature the first-revealed lesion was retinal in 62 cases (42.2%), 2–10 years prior to the cerebellar in 31, and more than 10 years before in 16[360].

Presentation before 10 and after 65 years is rare.

– In infancy and childhood, Ingraham and Matson[197], and Jeffreys[212] never observed a case before age 12, nor Olivecrona[325] before age 10. Mondkar *et al.* in a series of 112 cases described only one case diagnosed before age 10 (age 4)[300]. In the series of the French Society of Neurosurgery, of 262 cases, only 3 (i.e. 1.1 per cent) manifested themselves before age 10 (ages 2, 5, and 7)[360]. In a series of 700 children with brain tumours, only

0.9 per cent of haemangioblastomas[249] were seen. Only two reports indicate a slightly higher rate of infratentorial haemangioblastoma in childhood[200, 266]. In infancy, the earliest appearance was at the 8th month for cerebellar haemangioblastoma[119] and at the 6th month for spinal cord haemangioblastoma[297]. Three examples of congenital haemangioblastoma were reported, two with cerebellar localization responsible for the death of a newborn in the course of delivery[17] and of an infant at day 7[210], and one with a spinal location responsible for an upper cervical spinal cord section syndrome in an infant dead at the 6th week[367].

– In the elderly, haemangioblastomas are observed rarely. To date the reported oldest ages at diagnosis are 82 years for infratentorial haemangioblastoma[282], and 84 years in a case of supratentorial haemangioblastoma[364].

5.1.4.2. Variations

Haemangioblastomas present earlier in females than in males[325]. In addition to the probable role of vascular engorgement as a cause of increasing tumoural size and decompensation of symptoms during pregnancy, a hormonal factor may be implicated[358]. Progesterone receptors have been identified in all haemangioblastomas examined in patients of both sexes[262, 290, 437]; on the other hand, detection of oestrogen receptors gave variable results, positive in one case[262] and negative in another[290]. In the series of 262 cases of infratentorial haemangioblastoma (French Society of Neurosurgery), the mean age at diagnosis was 39.1 (± 14.8) years in 151 male and 36.5 (± 15.4) years in 111 female patients; the difference is not statistically significant (Student test: $t = 1.3$)[360]. On the other hand, in our series of 624 cases of infratentorial haemangioblastoma found in the literature prior to 1983, the difference was statistically significant [Male: $n = 397$; mean age 35.2 (± 12.6); Female: $n = 227$; mean age 32.1 (± 12.9); Student test: $t = 2.9$][360].

Haemangioblastomas present in VHL disease and familial forms earlier than in sporadic cases. There is a significant difference in the age at diagnosis between the group of patients with isolated and sporadic haemangioblastoma and the group of patients with a positive family history. In the same series of infratentorial haemangioblastomas, for both sexes, we calculated the mean age at diagnosis in familial cases as 5.6 years earlier than in sporadic cases:

– Male: $n = 397$ – sporadic cases: $n = 291$; mean age 36.7 (± 12.7) – familial cases: $n = 106$; mean age 31 (± 11.6) – statistically significant difference: Student test $t = 4.2$.

– Female: $n = 227$ – sporadic cases: $n = 134$; mean age 34.4 (± 13.6) – familial cases: $n = 93$; mean age 28.7 (± 11) – statistically significant difference: Student test $t = 3.5$)[360].

This could explain the two peaks that we noticed, the first at age 26–30, the second at age 36–40[358]. The existence of two peaks, noted slightly later (one in the third and the other in the fifth decade of life) has been confirmed by others[119, 329].

5.2. Clinical Data

5.2.1. Posterior Cranial Fossa Haemangioblastoma

5.2.1.1. Symptom Duration Prior to Diagnosis

In infratentorial haemangioblastomas the duration between the onset of symptomatology and diagnosis is relatively brief. In the literature some exceptional cases with a long duration of symptomatology previous to diagnosis have been reported (5 years[9], 10 years[440], even 28 years![366]). In most series, the prediagnosis mean durations are shorter than or equal to ten months (e.g. 7 months[119], 10 months[341]).

In female patients the mean length of symptoms prior to admission was calculated as 2.5 months shorter than in male patients[360].

5.2.1.2. Symptoms

Headache is the most common initial symptom present in incidence, ranged from 90.1[300] to 93.1 per cent[253] of all cases. Vomiting, giddiness, ataxia and gait disturbances are less frequent.

By the time of admission, increased intracranial pressure symptoms are manifest and may be the main if not the only component of the clinical presentation. They are present in almost 100 per cent of of all cases (98 per cent[119]). Spatiotemporal disorientation and behavioural disturbances accompanying symptoms of increased intracranial pressure were observed in 4.4 per cent of all cases, essentially in the oldest patients[360]. Giddiness and ataxia were present in 51.2 per cent and gait disturbances in 36.4 per cent of all cases[360].

Serious symptoms may be observed, such as the combination of occipital headache, neck stiffness and posterior and/or lateraldeviation of head[222] indicating a high risk of tonsillar herniation through the foramen magnum[441]. Incidence of abnormal head attitudes ranges from 6.4[360] to 25.8 per cent[300] of all cases. Jacksonian cerebellar fits are present in a variable proportion, from 5.2[360] to 20 per cent of all cases[325].

Brain stem haemangioblastomas may manifest themselves as postural hypotension[187, 360].

5.2.1.3. Signs

Papilloedema is present in various proportions ranging from 56[341] to 90 per cent[325] of all cases.

In the French Society of Neurosurgery series in which signs were specified 237 times out of 262 cases, we noticed[360]:

– a normal neurological examination in 34 cases (14.3 per cent);

– single or combined neurological disorders in 203 cases (87.7 per cent), a hemispheric cerebellar syndrome in 114 instances, a central vestibular syndrome in 97, a vermian syndrome in 68, a pyramidal syndrome in 29, a V^{th} and/or VII^{th} cranial nerves disorder in 24, a VIII cochlear to XII^{th} cranial nerves disturbance in 16, impaired consciousness in 13, a brain stem syndrome in 7 and apparent normal pressure hydrocephalus in 2 (64 and 71 year-old female patients).

Finally, infratentorial haemangioblastoma appears clinically with a paucity of symptoms and a rapid decompensation characterized by increased intracranial pressure and in contrast few cerebello-vestibular and cranial nerve signs. These criteria are non-specific.

5.2.2. Spinal Haemangioblastoma

Clinically, neither the duration of symptoms nor a peculiar sign-complex allows differentiation of intramedullary haemangioblastoma, intradural extramedullary haemangioblastoma or epidural haemangioblastoma from other intraspinal tumours of identical situation.

5.2.3. Supratentorial Haemangioblastoma

Similarly, supratentorial haemangioblastoma does not exhibit features different from other brain tumours located above the tentorium.

5.2.4. Retinal Haemangioblastoma

Symptoms such as progressive visual loss or ocular pain (exceptional at an early stage) lead to an ophthalmic examination. Diagnosis is based on funduscopy. If this examination is doubtful, fluorescein angiography has to be performed[165].

5.2.5. Extraneuraxial Lesions

5.2.5.1. Phaechromocytoma

The well-known symptoms of phaeochromocytoma may mark the onset of Lindau disease. Phaechromocytoma may manifest itself and be discovered a long time before the presentation of CNS haemangioblastoma: 7 months[364], 3 years[194], even up to 7 years[319]. In some instances a sudden presentation has occurred during general anaesthesia[350].

5.2.5.2. Kidneys

Growth of renal lesions is generally insidious and asymptomatic. At diagnosis, renal clear cell carcinoma has already metastasized in more than one half of all cases[184].

5.2.5.3. Pancreas

Large pancreatic cysts may be responsible for mild abdominal pain because of surrounding compression; in such cases, they are usually palpable. Exceptionally abdominal pain is the presenting feature of the disease[395]. Rarely extensive pancreatic involvement is responsible for steatorrhoea from exocrine pancreatic insufficiency[123] or even for islet destruction leading to insulin-dependent diabetes mellitus[20, 424]. Exceptionally microcystic papillary cystadenomas are responsible for pancreatic and common bile duct obstruction[15]. In one instance, an islet cell tumour was found fortuitously during a surgical procedure for another lesion[70].

5.2.5.4. Epididymis

In some instances an epididymal tumour has been the first clinical manifestation of Lindau disease[276, 293, 320, 352, 428, 461]. Papillary cystadenomas of the epididymis may be responsible for infertility[107, 276, 461]. Clinical examination is the easiest and main way leading to diagnosis of epididymal tumours ("it is important to examine the genitalia of male patients suspected of having Lindau's disease"[352]). Transillumination may be performed.

5.3. Are There Clinical Features Due to the Vascular Trait?

5.3.1. Haemorrhage

Despite the high vascularity of macroscopic types 3 and 4, haemorrhage (subarachnoid haemorrhage, intraaxial haematoma) as a primary symptom leading to the diagnosis is surprisingly rare: in the French Society of Neurosurgery series it accounted for 2 per cent of all cases[360].

There are a few reports indicating such a sudden onset of disease in infratentorial haemangioblastoma[58, 158, 202, 292, 294, 300, 357, 358, 407, 448, 449], supratentorial haemangioblastoma[2, 143, 449], and spinal cord haemangioblastoma[110, 250, 371, 436].

In a few cases such a sudden haemorrhage has proved fatal[2, 58, 202, 294].

5.3.2. Other Symptoms

Beside haemorrhage, the existence of other symptoms potentially linked to the vascular trait of haemangioblastoma, such as perception by the patient of pulsatile intracranial noises has been reported only rarely[93, 384, 394, 458].

5.4. A Biological Characteristic: Secondary Erythrocythaemia

The first report of secondary erythrocythaemia with cerebellar haemangioblastoma appeared in 1933: the report's author simply indicated the existence of erythrocytosis, without drawing any conclusion[439]. Ten years later, Carpenter *et al.* reported 2 cases of polycythaemia associated with an intracranial tumour and stated that in both cases, the tumour was a cerebellar haemangioblastoma; they considered this fact as surprising and suggested a diencephalic origin from stimulation (by increased intracranial pressure) of an erythropoietic center rather than an aetiological factor related to the tumoural type[50]. Later other hypotheses have been put forward: polycythaemia secondary to hypoxaemia due to respiratory intramedullary center involvement[181], or to hypoxaemia coming from an intratumoural arteriovenous shunt[451], and finally erythropoiesis of tumoural origin "it is theoretically conceivable that the cerebellar haemangioblastomas may be erythropietic"[80].

Only production by the tumour of an erythropoiesis stimulating factor, a hypothesis formulated by Ward *et al.* in 1956[452] can explain all the features that characterize the polycythaemia of haemangioblastoma. It is a secondary polycythaemia, only involving RBC (with in a parallel way increased values of haematocrit, haemoglobin level and blood mass), accompanied by bone marrow erythroblastosis at marrow examination if performed[480]. WBC and platelets counts are normal. There is no enlargement of the spleen. RBC counts return to normal after tumour removal. Haemangioblastoma represents the second aetiology of secondary polycythaemia of tumoural origin, after hypernephroma and before liver carcinoma and uterine fibromyoma.

Production by haemangioblastoma of an erythropoiesis stimulating factor, was demonstrated for the first time in 1961 by Waldmann *et al.*: successively they tested in vivo (in laboratory animals) the erythropoietic activity of urine, plasma, cerebrospinal fluid and cystic fluid of a patient with a recurring cerebellar haemangioblastoma; they observed an increased medullary bone erythropoietic activity after injection of haemangioblastomatous cyst fluid[450]. Erythropoietic -stimulating bioactivity was later confirmed in haemangioblastomatous cyst fluid[171, 214, 231, 355] and also demonstrated in tumour tissue homogenates[27, 214], plasma[27], and CSF[211]. No physicochemical difference exists between the erythropoiesis-stimulating factor of haemangioblastomatous origin and the erythropoiesis-stimulating factor (erythropoietin) of renal origin present in the serum of anemic patients[370]. It is not currently established whether the erythropoiesis-stimulating factor of haemangioblastomatous origin, found in tumour tissue homogenates, cystic fluid, CSF and plasma, is an ectopic erythropoietin identical to renal erythropoietin, a glycoproteic hormone having immu-

nological determinants in common with renin substrate, or is a precursor (proerythropoetin)[295].

From a clinical point of view, polycythaemia may be exceptionally the only factor leading to the diagnosis of haemangioblastoma[49]. Further, true secondary erythrocytosis (corresponding to following values: Male: RBC $\geqslant 6 \times 10^{12}$/l; Hb $\geqslant 180$ g/l; Haematocrit $\geqslant 54$ per cent; Total RBCVol = 28 ± 3 ml/kg – Female: RBC $\geqslant 5.5 \times 10^{12}$/l; Hb $\geqslant 160$ g/l; Haematocrit $\geqslant 47$ per cent; Total RBCVol = 25 ± 3 ml/kg) is rare[358]. Nevertheless, in a few cases, RBC counts superior to 8×10^{12}/l[38, 40, 440], even superior to 9×10^{12}/l[23,452], were reported. More frequently a polycythaemic trend (corresponding to $5.5 \times 10^{12}/l > RBC < 6 \times 10^{12}/l$ in male and $5 \times 10^{12}/l > RBC < 5.5 \times 10^{12}/l$ in female), may be observed especially in case of recurrence. The existence of such polycythaemia was seen in 18 per cent of all surgical cases observed for the first time and 63.6 per cent in cases of haemangioblastoma recurrence[80]. Most cases of secondary polycythaemia are observed more often in male patients than the sex-ratio would suggest. All reported instances of secondary polycythaemia were observed in cases of cerebellar haemangioblastoma or VHL disease with haemangioblastomatosis, except for one case of isolated supratentorial haemangioblastoma[340], one case of adrenal haemangioblastoma[45] and one recently reported case of extradural thoracic haemangioblastoma (in a male patient exhibiting "café-au-lait" spots[309]). Most cases of haemangioblastoma leading to secondary polycythaemia correspond to macroscopic types 3 and 4 (predominantly solid tumours)[80, 358].

The introduction of standardized erythropoietin radioimmunological assays represents a useful contribution to the follow-up of treated patients as results can be obtained rapidly in contrast to biological assay.

The electron microscopic and immunocytochemical studies indicate that modified mast cells might play an important part in the secretion and release of erythropoietic-stimulating-factor in haemangioblastoma.

6. Diagnosis – Disease Assessment and Prognosis

6.1. Imaging Data

6.1.1. Brain Haemangioblastomas

6.1.1.1. Plain Films and Nuclear Imaging

Plain film findings are not specific. Abnormalities are secondary to increased intracranial pressure in case of infratentorial tumour.

Currently, brain nuclear imaging provides no decisive diagnostic benefit.

6.1.1.2. X-Ray Computed Tomography (CT)

CT demonstrates hydrocephalus, if it exists, and the neoplasm.

The mural nodule of macrocystic cerebellar haemangioblastoma (type 2), the most common lesion, is isodense with the nervous tissue before contrast medium administration and is usually located on the part of the cyst closest to the pial surface of the cerebellum. After contrast enhancement, it appears markedly denser than the surrounding tissue and isodense with the venous sinus or denser than them. The tumoural cyst is hypodense. After contrast medium administration a layer of enhancement may be observed edging the cyst cavity.

Solid tumours (types 3 and 4) are isodense or slightly hyperdense before and strongly hyperdense after iodine intravenous injection (see Fig. 16). Sometimes, some vessels supplying the tumour can be seen as linear enhancing structures.

6.1.1.3. Magnetic Resonance Imaging (MRI)

Currently MRI appears as the imaging modality of choice for most intracranial tumours, especially for lesions located in the posterior cranial fossa in which the sensitivity and the accuracy of CT results are limited by beam-hardening artifacts induced by the petrous bone. MRI is particularly useful for the evaluation of brain stem tumours.

MRI demonstrates low signal on T 1-weighted images and high signal from the cyst or tumour on T 2-weighted images. This high signal may

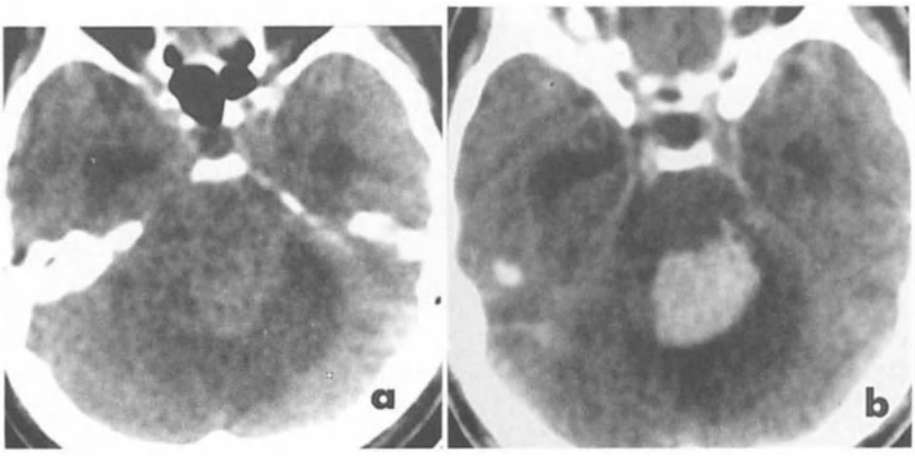

Fig. 16. Solid cerebellar haemangioblastoma (type 3): CT appearance before (a) and after (b) iodine contrast medium infusion. Tumour is surrounded by focal oedema and appears spontaneously slightly denser than cerebellar normal tissue. Note the enhancement after iodine administration

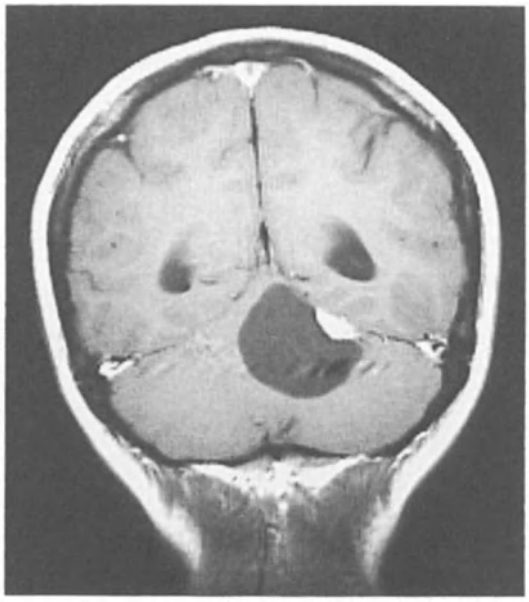

Fig. 17. Macrocystic cerebellar haemangioblastoma (type 2): T 1-weighted MRI (TR 60, TE 15, Gd-DTPA). Note the low-signal of the cyst and the enhanced signal of the solid part situated at the upper surface of the cerebellum, under the tentorium

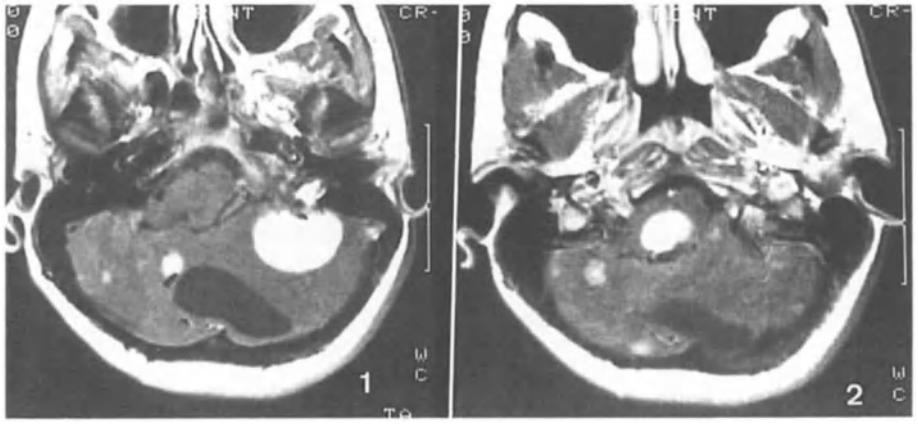

Fig. 18. CNS haemangioblastomatosis: T 1-weighted MRI (TR 60, TE 15, Gd-DTPA). Note the enhanced signal of the numerous tumoural nodules demonstrated at two levels (1 and 2) of the posterior cranial fossa and the low-signal of cystic components

exceed the limits of the tumour. Sometimes MRI may show the supplying vessels that appear hyperintense in fast imaging[102].

MRI improves the screening and the documentation of multifocal le-

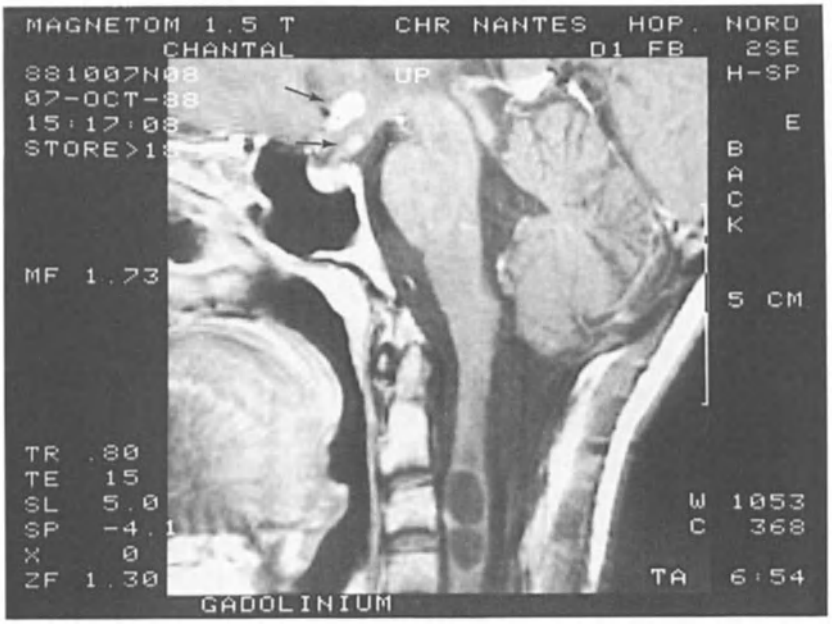

Fig. 19. CNS haemangioblastomatosis: T 1-weighted MRI (TR 80, TE 15, Gd-DTPA). Note the enhanced signal of the supraoptic and pituitary stalk tumoural nodules (arrows) and the low-signal of cystic formations located within the cervical spinal cord (in female patient operated two years before with excision of four haemangioblastomas, three into the cerebellum and one at the cervicomedullary junction)

sions. MRI, especially on T 1-weighted images after administration of paramagnetic contrast medium (Gadolinium-diethylene-triamine-pentaacetic acid or Gd-DTPA), is able to demonstrate nodules missed by CT. According to our own experience, in no instance was a lesion seen on CT missed by MRI (see Figs. 17–19).

Finally, although MRI and CT may provide complementary information to characterize intracranial haemangioblastoma, MRI, especially Gd-DTPA enhanced MRI, appears more sensitive than CT in detecting the lesions and delineating their exact extent. Currently MRI before and after Gd-DTPA administration appears necessary for accurate evaluation of brain haemangioblastoma.

6.1.1.4. Angiography

The first report of arteriographic demonstration of an infratentorial haemangioblastoma by angiography of the vertebral artery was by Lindgren[275].

Before the introduction of MRI, it had been demonstrated that angiography was far more sensitive than CT in detecting the vascular nodules and was usually more specific in characterizing the occult and multiple lesions[360, 393].

Currently angiography with a small focus X-ray tube, subtraction and enlargement remains essential to visualize both the vascular supply and confirm the nodules of a size smaller than 5 mm in diameter demonstrated by MRI. Bilateral vertebral angiography is necessary to visualize both posterior inferior cerebellar arteries (PICA) and provide a full evaluation of lesions in the posterior cranial fossa.

Images are characteristic: in the first stages, an inhomogeneous stain of contrast appears, and progressively expands up to delineate the whole neoplasm, while it becomes very homogeneous and dense at seriographic capillary-venous stages. In rare instances an early venous filling can be seen. It has no special significance (see Fig. 20).

Large solid tumours are supplied by enlarged and tortuous vessels which may mimic an arteriovenous malformation. Tumoural stain enables one to distinguish the two entities (see Fig. 21 and 22).

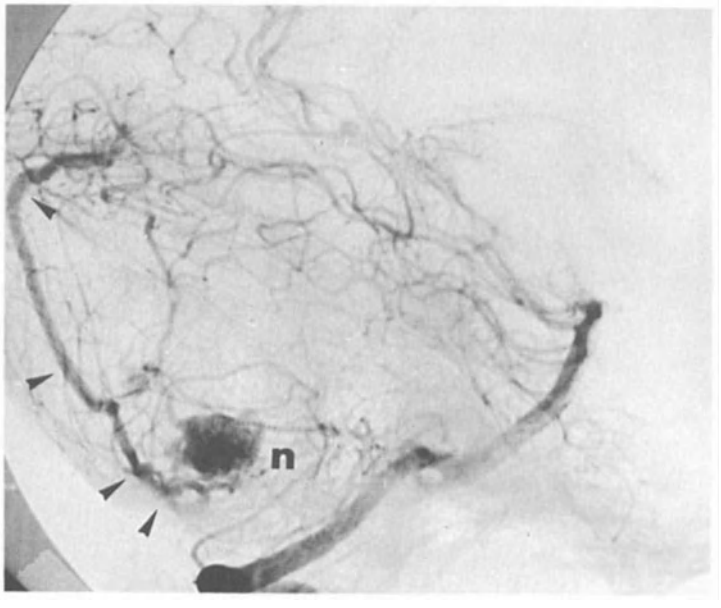

Fig. 20. Macrocystic cerebellar haemangioblastoma (type 2): Vertebral angiogram. Note the nodule (*n*) stain and an (unusual but not pejorative) early venous filling (arrows)

6.1.2. Spinal Haemangioblastoma

6.1.2.1. Plain Film

Plain film findings are non specific. Sometimes they are only able to demonstrate vertebral canal widening secondary to tumoural development and syringomyelia, if the latter exists.

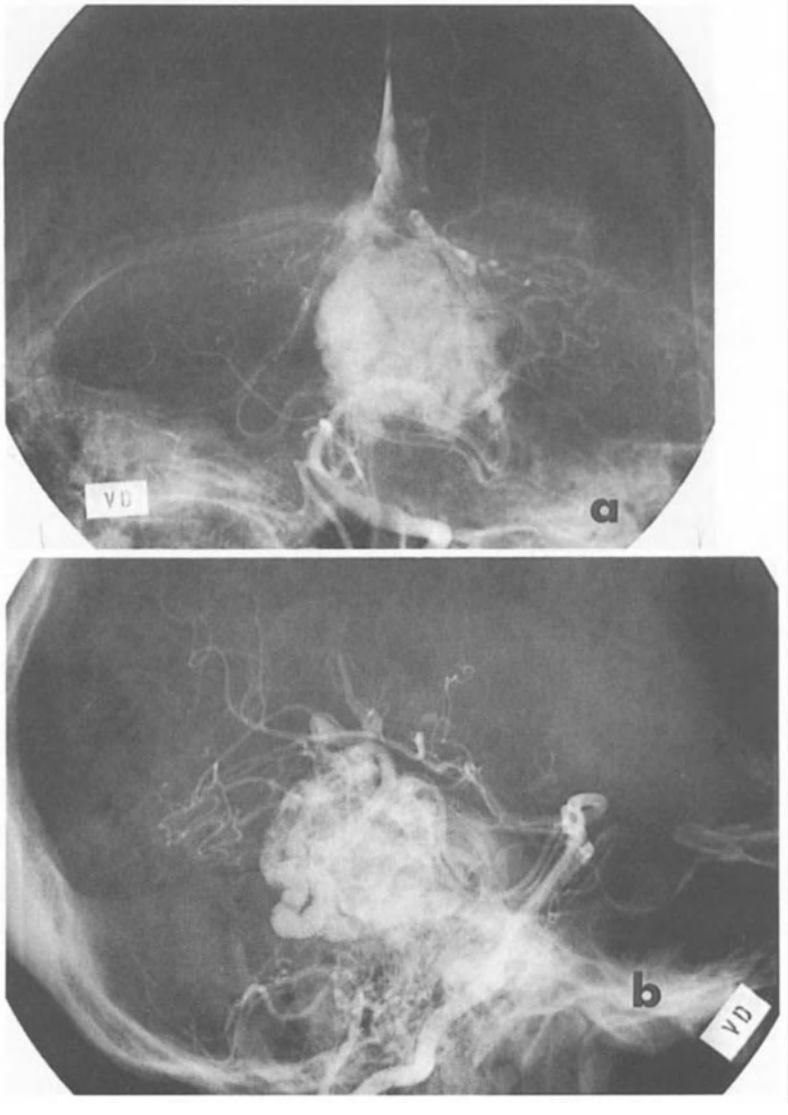

Fig. 21. Highly vascular solid cerebellar haemangioblastoma (type 3): Vertebral angiogram in anteroposterior (a) and lateral (b) views. Note the presence of large tortuous vessels mimicing an arteriovenous malformation

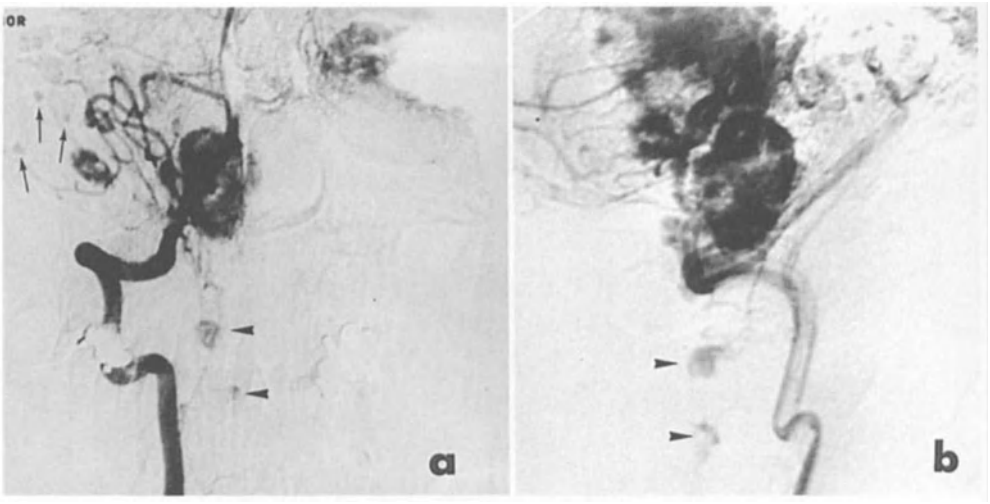

Fig. 22. CNS posterior cranial fossa and upper cervical spinal cord haemangioblastomatosis (same patient as Fig. 18): Vertebral angiogram in anteroposterior (a) and lateral (b) views. The smallest nodules are indicated (arrows)

6.1.2.2. Contrast Medium Myelography

Contrast medium myelography is non specific.

It shows either pial varices which may resemble a large arteriovenous malformation, or spinal cord widening secondary to tumour and syringomyelia if it exists, or a block of either extramedullary intradural or epidural type.

6.1.2.3. X-Ray Computed Tomography

CT with contrast infusion may demonstrate tumoural nodules.

Spontaneously isodense or slightly hyperdense, they are highly enhanced after iodine injection. CT allows one to locate spinal cord haemangioblastomas in the segmental plane (see Fig. 23). However, previous knowledge of the tumoural site is necessary. Therefore CT cannot be a screening method.

6.1.2.4. Magnetic Resonance Imaging

In contrast with CT, MRI is particularly useful to screen spinal cord expansive lesions, notably in case of a suspected multifocal trait. Rostrocaudal scanning is performed facilitating the diagnosis of multiple tumours the real rate of which was previously underestimated as suggested by some

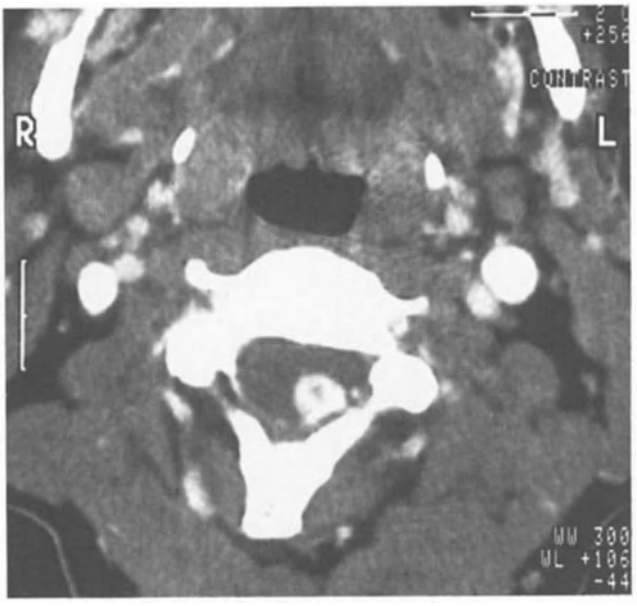

Fig. 23. Intramedullary cervical spinal cord haemangioblastoma: CT appearance after iodine contrast medium infusion. Note the enhanced nodule situated at the left posterolateral aspect of the spinal cord

autopsy findings[202, 267]. MRI criteria and advantages in spinal haemangioblastoma are identical to those described above in brain haemangioblastoma. MRI demonstrates low signal on T 1-weighted images and high cyst or tumour signal on T 2-weighted images. This high signal may extend beyond the tumoural volume. Gd-DTPA enhanced MRI is significantly superior to non paramagnetic enhanced MRI of the spine in tumour detection ($p < 0.001$)[122]. Use of Gd-DTPA is essential (see Fig. 24). Currently, MRI performed before and after Gd-DTPA administration appears the most useful tool to state precisely the number and accurate localization of spinal cord haemangioblastomas and the extent of their accompanying cysts. It also demonstrates spinal root haemangioblastomas.

6.1.2.5. Spinal Cord Angiography

The aims of spinal cord angiography are identical to those of cerebral angiography (vide supra). Using the same technical standards, it allows one to both visualize the vascular supply and confirm the presence of small nodules visualized by MRI. Exploration of the cervical spinal cord requires bilateral angiography of vertebral and cervical arteries.

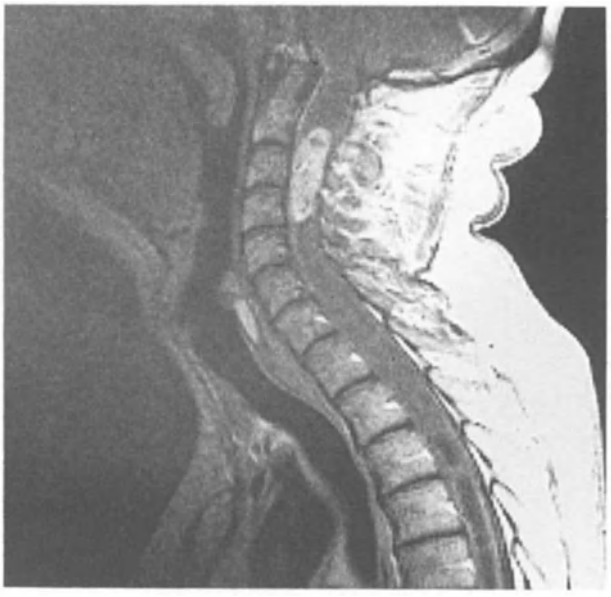

Fig. 24. Intramedullary cervical spinal cord haemangioblastoma: T 1-weighted MRI (TR 78, TE 22, Gd-DTPA). Note the high signal exhibited by the tumour at C 2–C 4 level, the low signal adjacent to it and the lower signal of cystic formations at the thoracic level

Tumoural patterns given by serial angiography are identical to those described above. Similarly intramedullary haemangioblastomas are sometimes supplied by enlarged and tortuous vessels that may mimic a medullary spinal cord arteriovenous malformation. The accurate diagnosis is based on tumoural stain.

Although an excellent anatomical demonstration of tumours is given by Gd-DTPA-enhanced MRI, visualization of supplying vessels by spinal angiography remains an essential investigation prior to any surgical procedure (see Figs. 25 and 26).

6.1.3. Extraaxial Visceral Lesions

Pancreas, adrenals and kidneys are the organs mainly involved in VHL disease. Screening is necessary.

6.1.3.1. Detection of Phaechromocytoma

Because of the well-known risk of severe, sometimes lethal vascular accidents occuring at the time of an anaesthetic induction, a surgical procedure,

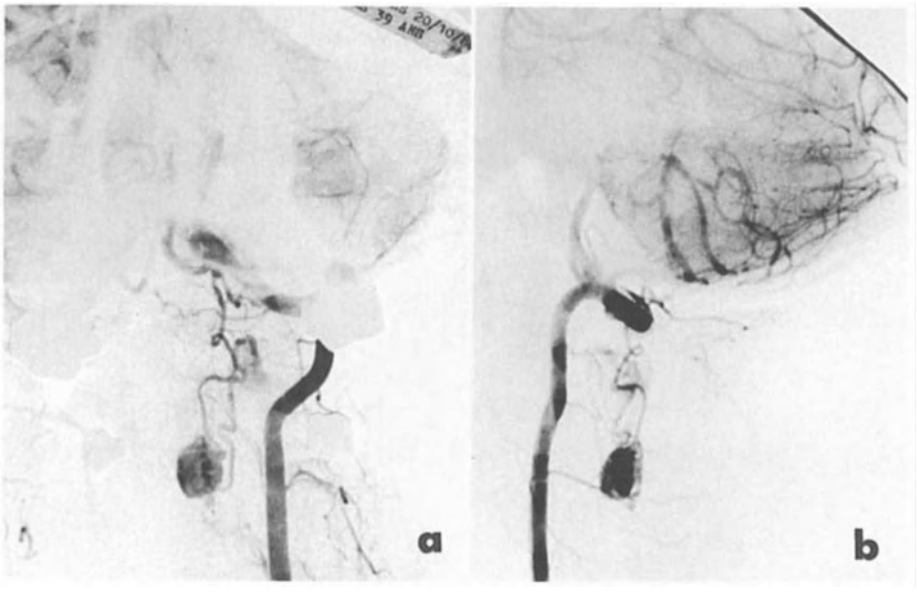

Fig. 25. Intramedullary cervical spinal cord haemangioblastoma (same patient as Fig. 23): Vertebral angiogram in anteroposterior (a) and lateral (b) views. Tumour and supplying vessels are well demonstrated

a delivery, even a simple iodine contrast medium infusion, screening of phaeochromocytoma is one of the first priorities. It depends on:

– Biological investigations: 24-hour urinary total catecholamine and vanillyl mandelic acid (VMA) levels, plasma and nor-adrenaline levels;

– Abdominal ultrasonography;

– Scintigraphy using metaiodobenzylguanidine (MIBG)[59]. Currently ^{123}I-MIBG is preferred to ^{131}I-MIBG[29].

– CT, MRI.

6.1.3.2. Detection of Other Visceral Lesions (Kidneys, Pancreas, Liver)

Detection of other visceral lesions of the Lindau complex is based on:

– Abdominal ultrasonography;

– If its results are doubtful or positive: Contrast enhanced abdominal CT[261, 268, 269] (see Figs. 27 and 28);

– If any doubt exists about the presence of a dense "fleshy" tumour

– Abdominal MRI, despite its relative insensitivity in the detection of renal and pancreatic lesions, and its tendancy for false-positive;

– Angiography (renal arteries, coeliac trunk, upper mesenteric artery). Sometimes, especially in cases of renal tumours, angiography remains an essential investigation[47].

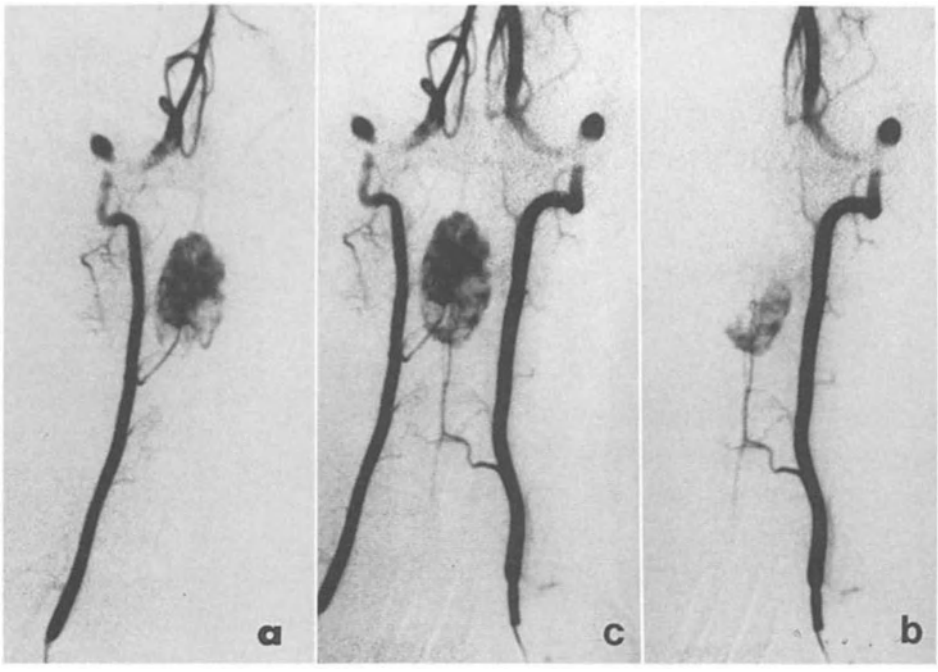

Fig. 26. Intramedullary cervical spinal cord haemangioblastoma (same patient as Fig. 24): Right (a), left (b) and both right and left (film superposition: c) vertebral angiogram in anteroposterior view. The double arterial feeding and area is clearly shown

6.1.3.3. Detection of Epididymal Lesions

Scrotal ultrasonography has been proposed to improve the diagnosis of epididymal lesions[106].

6.2. Disease Assessment

Given the high risk of multiple tumours in both sporadic and familial forms such screening is necessary.

Moreover in haemangioblastomatosis, removal of one tumour may lead to the development of other tumours that were in a quiescent state prior to surgery[263, 358]. The aetiology of such a phenomenon, sometimes also observed in von Recklinghausen neurofibromatosis, remains unknown. It might be due to the release of tumoural growth factors.

Except for emergency situations (e.g. severe increased intracranial pressure or poor medullary/spinal cord neurological condition) this potential risk must be weighed up before any surgical decision. Cerebellar tumours

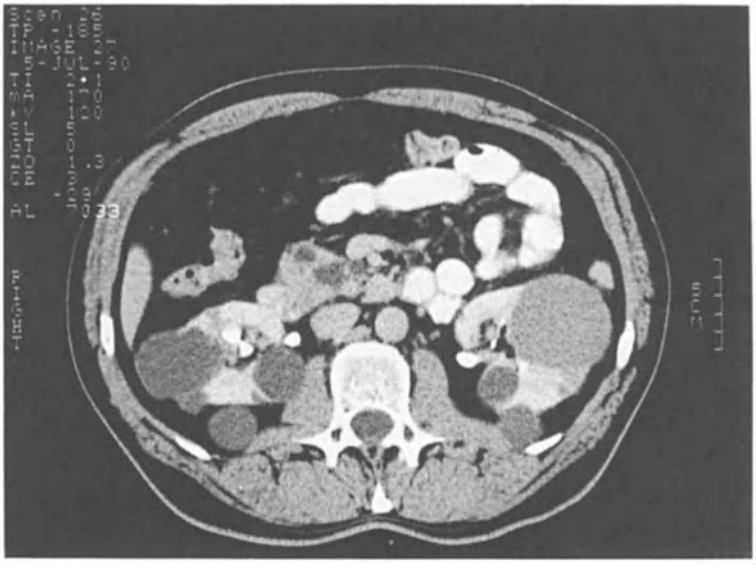

Fig. 27. Lindau complex: Abdominal CT demonstrating pancreas and both kidneys cystic formations

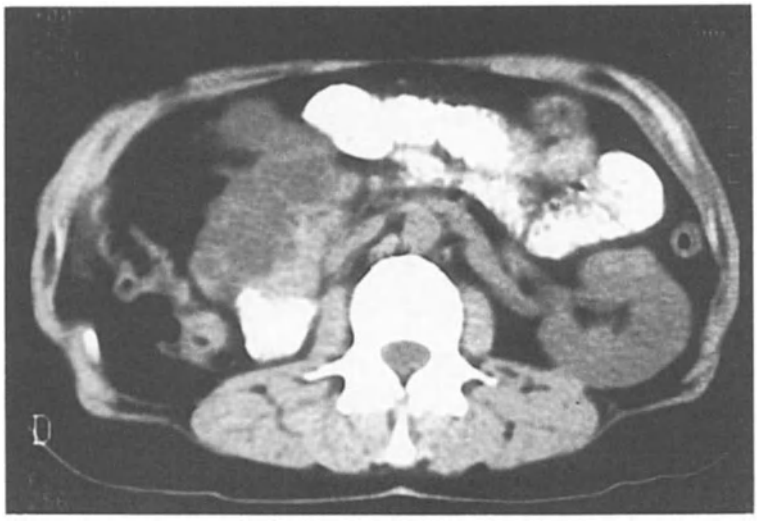

Fig. 28. Lindau complex: Abdominal CT demonstrating the large cystic changes of the pancreas head. Note the vacuity of the right renal area (the patient – 944 of family tree Fig. 15 – previously underwent right nephrectomy as treatment of a renal clear cell carcinoma)

leading to a CSF flow blockage with acute increased intracranial pressure or giving a risk of tonsillar herniation through their mass effect, clearly require an emergency treatment. On the other hand a spinal cord hae-

mangioblastoma with slight neurological signs will permit more prolonged analysis. Screening of an affected patient may be summarized as follows (Table 9):

Only such screening allows one to distinguish which form of the disease affects the patient: "solitary" haemangioblastoma, multiple haemangioblastomata at one location, disseminated CNS haemangioblastomatosis, retinal haemangioblastomata involving one or both eyes, presence of visceral lesions of various clinical significance, inherited or sporadic disease.

The most frequent association is that of cerebelloretinal haemangioblastomatosis. In a review of the literature prior to 1983, among a total of 624 cases of infratentorial haemangioblastoma, we listed 156 cases of associated retinal haemangioblastoma (i.e. in 25 per cent of all cases). Retinal involvement was bilateral in 63 patients[360].

Combined infratentorial haemangioblastoma with spinal cord haemangioblastoma is rarer: in the same series we noted such an association in 69

Table 9. *Screening of an Affected Patient*

Basis Check-up
- Neurological examination
- Fundus examination
- Somatic examination (abdomen, genitalia)
- Blood cell counts
- Biological investigations
  - 24-hour urinary total catecholamine and VMA levels
  - plasmatic epinephrin and nor-epinephrin levels
- Familial inquiry

Complementary Check-up
- Detection of retinal haemangioblastomas
  (if ophthalmoscopy is doubtful: fluorescein angiography)
- Detection of brain haemangioblastomas
  CT without and with contrast enhancement
  if doubtful or positive: Gd-DTPA enhanced MRI
  if positive: cerebral angiography (prior to surgery)
- Detection of spinal haemangioblastomas
  MRI before and after Gd-DTPA injection
  if positive: spinal cord angiography (prior to surgery)
- Detection of visceral lesions:
  Scintigraphy (^{123}I or ^{131}I-MIBG): phaechromocytoma
  Abdominal ultrasonography
  if doubtful or positive: contrast material abdominal CT; MRI
  if necessary: selective (especially renal) angiography

cases (i.e. in 11.1 per cent of all cases); in further 11 cases, there was an apparently isolated intramedullary spinal cord cavity. Spinal cord tumoural involvement was multifocal in 29 cases[360].

6.3. Prognostic Factors

At the time of diagnosis, the main factors that predict a bad prognosis in apparently sporadic cases are the presence of several or multiple CNS haemangioblastomas, the association of CNS haemangioblastoma with retinal haemangioblastoma, and/or the onset of the disease before the age of 30.

In most if not in all cases with a positive family history in an affected patient multifocal tumour scattering (even though not seen at the first screening), and future progression may be predicted.

7. Treatment

7.1. Methods

7.1.1. Central Nervous System Haemangioblastoma

7.1.1.1. Radiotherapy

In the past, radiotherapy was often advocated as a therapeutic modality, either as a palliative therapy when operation had been considered impracticable or in cases of multiple tumours[36, 170, 173] or as a preoperative treatment in cases of highly vascularized tumours[237, 339]. Radiotherapy was also proposed in brain haemangioblastomas as a postoperative treatment after simple biopsy or whenever the neoplasm had not been totally excised[256, 417], and in spinal cord haemangioblastomas if a decompressive laminectomy had only been performed[79]. Radiotherapy was also indicated as the only treatment after recurrence.

Radiation doses as indicated in literature ranged from 24[44] to 60 grays[170]. In case of postoperative treatment a 45 to 50 gray total dose administrated for a 4.5 to 5 week period was proposed[417].

The efficiency of conventional radiotherapy is controversial. The decrease in the tumoural volume evaluated on pre- and postradiotherapy angiograms ranges from 15[442] to 55 per cent[170] in size. In other reports no reduction in size or even a minimal enlargement of the tumour were noticed[256]. Analysis of the literature demonstrates the lack of any controlled trials that might establish that radiotherapy is really effective and useful for the treatment of CNS haemangioblastomas. To our knowledge, multibeam radiotherapy has not been evaluated in such indications on the basis of controlled trials.

7.1.1.2. Neurosurgery

The only efficient treatment of haemangioblastoma is the total surgical excision.

– *Posterior cranial fossa haemangioblastoma*

Anaesthetic and surgical techniques are those of infratentorial neurosurgery and have no special features related to haemangioblastomas.

– General measures

Operation is performed under general anaesthesia. During the operation and throughout most of the postoperative course, blood pressure is monitored by a radial arterial cannula. Central venous pressure monitoring is also performed by means of a central venous catheter introduced through a brachial vein into the right auricle and maintained peroperatively and for 12–18 hours postoperatively. This central venous catheter is used for air aspiration in case of air embolism. When the sitting position is used an anti-gravity suit may be wrapped around the lower trunk of patient to prevent of air embolism from veins opened during the surgical procedure. Heart rate and electrocardiographic monitoring, arterial and venous blood gas measurements are performed pre-, per- and postoperatively. During the immediate postoperative period it is our practice to maintain the patient on a ventilator. Extubation is undertaken at 18–24 hours postoperatively.

– Patient position and surgical approach

Removal of an infratentorial haemangioblastoma is achieved usually by a suboccipital approach. In such an approach, prone, lateral or sitting position may be employed. The choice depends on anatomical location and extent of the tumour and also on the neurosurgeon's habits. Advantages, disadvantages and complications of each of them are well-known. Prone position does not allow one to expose well lesions located at the superior part of the posterior cranial fossa under the tentorium particularly those situated near the middle line. Difficulties are most in patients with a short neck. In the prone position venous engorgement cannot be avoided. It may lead to problems with control of bleeding. The sitting position gives good exposure and on the other hand leads to a risk of air embolism from veins opened during the surgical procedure. This risk is potentially lethal because of systemic air embolism in case of patent foramen ovale. Currently despite the realization of systematic preoperative echocardiography with Valsava's test, in a few cases persistant interauricular foramen ovale cannot be detected. A safe method of detection of this high risk factor remains to be found. Beside air embolism, the sitting position has the danger of CSF depletion at supratentorial level with a risk of epidural or subdural haematoma and of excessive cerebellar displacement under the effect of gravity after tumoural excision. The latter is minimized by achieving the smallest craniotomy compatible with the intended surgical procedure.

The transoccipital transtentorial approach was proposed[325] and used[385] in case of haemangioblastoma of solid type, located at the superior surface of the cerebellum or adjacent to the midbrain and fed mainly by superior cerebellar artery. In such a case, it is easier with this approach to detect feeding and draining vessels of the tumour and to exclude them prior to removal. This approach requires the lateral decubitus position. Section of bridging temporal and occipital veins is necessary to permit the elevation of the occipital lobe.

– Techniques of excision

Currently surgery must be performed according to microsurgical standards. Except for microsurgery, the techniques of cerebellar haemangioblastoma removal were established as early as 1928[86, 90]. Excisional techniques depend on the macroscopic type.

In macrocystic haemangioblastoma (type 2), it may be useful, prior to dural opening, to puncture the cyst through the dura and aspirate part of the cyst fluid through a fine needle, using imaging data as a guide. It achieves a progressive decompression of the cerebellum and avoids a sudden decompression of the posterior fossa at the time of dural opening. After dural opening, exploration allows one to visualize the subpial tumoural nodule. Its supplying vessels are easily controlled before tumoural excision and cyst wall examination. If the nodule is not directly visible, the cystic cavity is opened by means of a short cerebellar corticectomy. Cyst wall examination leads to a mural tumour that is excised. In both instances the dissection plane must be 5–10 mm away from apparent tumoural margin. Thus excision must bring out a significant peritumoural cerebellar tissue ring. In case of macrocystic haemangioblastoma, once the mural nodule is excised and the cyst wall is meticulously inspected without discovery of another tumour, cyst wall excision is not required. On the other hand, if no mural nodule has been found outside or within the cyst in spite of careful exploration with optic magnification (type 1) excision of the cyst wall must be undertaken.

In solid haemangioblastoma (types 3 and 4) preoperative angiographic analysis is of particular interest. Excision must be carefully performed with progressive control of supplying vessels in the same way as in arteriovenous malformations i.e. first the arterial pedicles and then the enlarged veins. The dissection plane must remain a short distance from the tumour to allow one to circumscribe it and more easily control its supplying vessels. Haemangioblastoma must be removed as a single mass. It is very inadvisable to open the tumour for mass reduction. Torrential haemorrhage may occur if the tumour is transsected before being disconnected from its main supplying vessels.

– Problems specific to brain stem haemangioblastomas

To the best of our knowledge, the first successful removal of a medullary

haemangioblastoma was performed in 1936[94]. For a long time this case remained isolated since many authors in the past claimed that surgical removal was impossible in such a malignant location. Advances due to modern microsurgical and anaesthetic techniques have recently permitted total removal of haemangioblastomas of the brain stem, with an increasing proportion of success[63, 112, 312, 321, 356, 360, 382, 404, 426]. However surgical excision of some forms of brain stem haemangioblastomas currently remains technically challenging. Brain stem haemangioblastoma equally constitutes a challenge for anaesthesists not only at the time of surgery but also in the postoperative period[11].

From a surgical point of view it is necessary to distinguish topographically haemangioblastomas of the fourth ventricle, from haemangioblastomas located in the medulla and at the cervicomedullary junction[111, 112].

Haemangioblastomas involving the lumen of the fourth ventricle reach but do not invade its floor and can be more or less easily separated from it. In contrast, in spite of a cleavage plane, removal of the latter is far more difficult according to the degree to which the tumour is embedded into the medulla and the degree of vascularity.

Preoperative electrophysiological investigation of brain stem auditory evoked potentials are less informative than MRI data. On the other hand peroperative brain stem auditory evoked potential monitoring provides good functional control during the surgical procedure[164].

The exposure must be sufficient. It is generally necessary to divide the inferior vermis to obtain a good visualization of the tumour. Under high power magnification microsurgical techniques allow one to dissect the part of the tumour embedded within the medulla oblongata, after opening the pial layer. Dissection requires step by step bipolar microcoagulation of the supplying vessels. Their section, one by one, leads to progressive detachment before the removal of the tumour.

If the tumour is voluminous and highly vascular, it has been proposed to perform the operation under hypothermia and circulatory arrest, haemorrhage appearing as one of the main causes of death[404]. If such a method is used the main neurosurgical problem becomes postoperative haematoma into the operative site, the consequence of incomplete reversal of anticoagulation as the patient is rewarmed and taken off cardiopulmonary bypass.

Neurogenic pulmonary oedema may occur postoperatively[43]. It is clinically characterized by profound pulmonary vascular congestion, protein-rich oedema fluid, intra-alveolar haemorrhage and an often fulminant course. In a case of fulminant respiratory failure the successful use of a new technique was recently reported: low-frequency positive-pressure ventilation with extra-corporeal carbon dioxide removal[1]. An exceptional postoperative breathing disturbance was recently described after removal of a large haemangioblastoma of the fourth ventricle[116].

– *Spinal cord haemangioblastoma* (see Figs. 29 and 30)

Excision of intramedullary spinal cord haemangioblastomatomas requires the use of microsurgical techniques. Preoperative Gd-DTPA enhanced MRI and spinal cord angiography are necessary. Preoperative embolization has been advocated in some cases to make the surgical procedure easier[134].

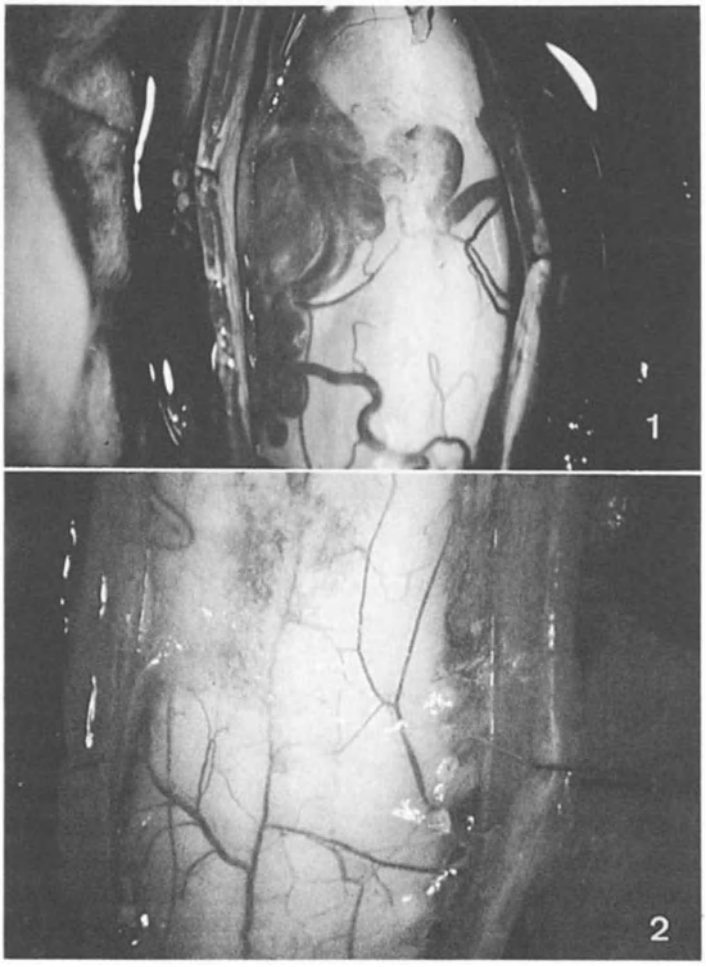

Fig. 29. Cervical spinal cord haemangioblastomas: Two different surgical views at the dura mater opening.
– case 1 (same patient as Fig. 23 and 25): from the dural opening the tumours and its supplying vessels exhibit themselves under the leptomeninges.
– case 2 (same patient as Fig. 24 and 26): at the dural opening no tumour is visible. The entirely intramedullary cervical spinal cord haemangioblastoma will be discovered at the myelotomy

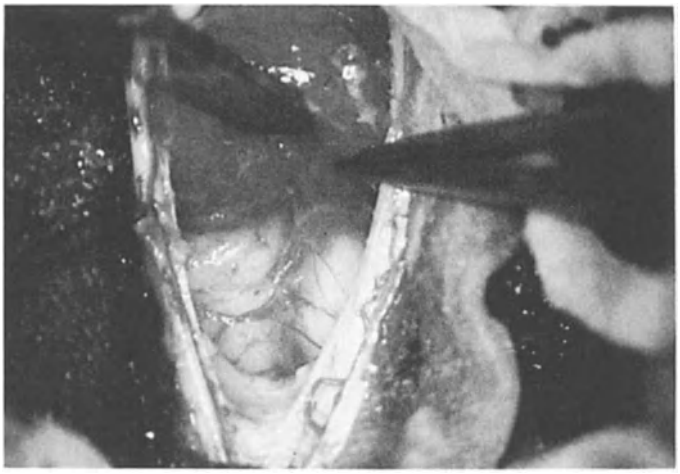

Fig. 30. Cervical spinal cord haemangioblastoma: Surgical view during the tumour excision (same patient as Figs. 24, 26, and 30, case 2). Progressive detachment of the tumour in a cleavage plane with step by step bipolar coagulation haemostasis of the anterior origin supplying vessels

Ultrasonosgraphy also has been recommended to improve the peroperative localization of the tumour[204, 381].

With an accurate microsurgical technique, under high power magnification, tumour dissection must remain outside the nodule with a progressive course in a loose cleavage plane created between the tumour and cord tissue. In this plane the small vessels supplying the tumour have to be isolated before step by step bipolar microcoagulation and section. Transsection of the tumour must be avoided. Resection of haemangioblastomas using carbon dioxide laser, as was recently reported[172] does not seem commendable, in our view.

– *Supratentorial haemangioblastoma*

Tumour excision techniques, as described above, have to be observed.

7.1.2. Retinal Haemangioblastoma

Several methods have been used to treat retinal haemangioblastomas: radiotherapy, curietherapy (radon), diathermocoagulation. The latter was suggested for the treatment of von Hippel tumour in 1931[74] and introduced in 1939[457]. All these techniques have been abandoned.

Photocoagulation with xenon arc was the first positive treatment[296]. Favourable results were reported[30, 217]. Nowadays two main methods are practized, argon laser photocoagulation[7, 151] that is better fitted than xenon

arc photocoagulation for the treatment of vascular tumours, and cryotherapy[4].

The latest methods are endocular surgery and eye wall resection[343].

7.2. Indications

7.2.1. Central Nervous System Haemangioblastoma

Considering the long term uncertainties and the risk of postoperative stimulation of previously quiescent lesions, only haemangioblastomas that present with symptoms have to be removed.

Asymptomatic haemangioblastomas are a matter for regular follow-up.

7.2.2. Retinal Haemangioblastoma

According to size, retinal haemangioblastomas are treated either by argon laser photocoagulation (if tumour size is smaller than 0.8–1 disc in diameter)[151] or by cryotherapy if tumour size is more than one disk in diameter. Cryotherapy is also indicated in the following cases: tumour associated with a serous retinal detachment, tumour associated with opaque media (cataract, vitreous haemorrhage)[33].

Endocular surgery is useful in advanced lesions that cannot be treated by cryotherapy, especially large juxtapapillary haemangioblastomas and in cases of exudative retinal detachment[33, 141]. Eye wall resection, although it is a difficult surgical procedure, was proposed as a radical treatment of large von Hippel tumours and a good alternative therapy to tumours resistant to photocoagulation or cryotherapy[343].

7.2.3. Visceral Lesions

Visceral lesions demanding treatment are renal clear cell carcinomas, islet cell carcinomas and phaechromocytomas.

Management of bilateral renal cell carcinoma remains controversial. Conservative therapy involving the ellipsing of well encapsulated solid lesions has been promulgated and used successfully[337]. Partial nephrectomy with or without nephrectomy of the opposite kidney was also used successfully[414]. A conservative therapeutic option requires meticulous follow-up with a yearly CT and arteriographic examination of any suspicious lesion. If conservative therapy is not feasible, patients have to undergo bilateral nephrectomy and be placed on haemodialysis[75, 108, 121] with or without subsequent transplantation[342, 414]. The risks of bilateral ablative surgery with dialysis and possible transplantation must be weighed against the risks of recurrence and metastases from renal tumours left behind in or subsequently arising from apparently normal tissue conserved at operation (foci or renal cell carcinoma may be microscopic in size and not detectable at surgery[65]).

7.3. Results

7.3.1. Direct Results

7.3.1.1. Cerebellar Haemangioblastoma

The postoperative mortality after total excision of a single cerebellar haemangioblastoma ranges from 8.3[80, 329] to 16.3 per cent[360]. It significantly increases with age. Mortality is higher with macroscopically solid forms (types 3 and 4) than with macrocystic haemangioblastomas (type 2)[360].

In the past partial removals and simple decompressive procedures were followed by a high postoperative mortality rate[253].

7.3.1.2. Spinal Cord Haemangioblastoma

In their large series, Hurth *et al.* reported 67 per cent of good results after surgical excision[192].

7.3.2. Delayed Results

7.3.2.1. Cerebellar Haemangioblastoma

Delayed results may only be assessed from rare series documenting a long follow-up.

– *Survival*

In a series of cerebellar haemangioblastomas with a follow-up duration ranging from 1 to 25 years (mean duration of follow-up: 7.9 years), survival rates were 90 per cent at 5 years, 80 per cent at 10 years and 40 per cent at 20 years[300].

– *Recurrences*

The relative frequency of infratentorial recurrences in posterior cranial fossa haemangioblastomas considered as the most favourable (single cerebellar haemangioblastoma – negative family history) mollifies the optimistic impression supplied by the two former data cited above. We must distinguish between real recurrences after total excision of the tumour and relapses that are due to a partial removal. Such recurrences correspond to the natural history of the disease with delayed symptomatic appearance of other tumours initially present at a quiescent state[359]. The recurrence rate ranges in the literature from 12[339] to 25 per cent[80]. In a review of single infratentorial haemangioblastoma in the literature the recurrence rate was 18.4 per cent[358]. Infratentorial recurrences may appear after a long delay, more than 20 years, e.g. 22 years[440], 24 years[300].

Delayed haemangioblastoma recurrence, the manifestation of an initially unrecognized haemangioblastomatosis, may involve another location in the neuraxis e.g. the recent case where a supratentorial haemangioblastoma appeared in a patient 23 years later than a cerebellar haemangio-

blastoma excision[13]. In the French Society of Neurosurgery series the rate of patients free of any lesion after total excision at postoperative follow-up (of a duration from 1 to 21 years) was 62 per cent at 5 years and 50 per cent at 10 years. None of 7 patients with a 21 year follow-up was healthy, because of infratentorial recurrences and/or the appearance of other localizations[360].

In a recent study, recurrence was correlated with younger age at the time of diagnosis ($p < 0.01$), VHL syndrome ($p < 0.001$), presence of multicentric tumours of the CNS at initial diagnosis ($p < 0.005$), and histopathologically with lower proportions of lipid-laden stromal cells ($p < 0.05$)[103]. In fact, some of these pieces of information are redundant: haemangioblastomatosis represents a form of VHL disease, and pathological criteria are those of "juvenile" type or "cellular" variant of haemangioblastoma, which is especially found in haemangioblastomas associated with Lindau disease[376].

– *Overall mortality related to haemangioblastoma*

The overall mortality rate was studied in a few series of infratentorial haemangioblastomas. It ranged from 26.3[360] to 35.1 per cent[459]. Such a result, about two to three times higher than the direct mortality rate, is explained by recurrences and the increased risks of repeated surgical procedures.

7.3.2.2. Spinal Cord Haemangioblastoma

Long-term good results were reported with follow-up durations from 11[125] to 18 years[328].

7.4. Follow-up

Thus the prognostic uncertainties after the treatment of a single lesion are due to the potential presence of latent haemangioblastomas located at one site or scattered in several CNS sites and eventually to the presence of visceral lesions that may also have a delayed presentation.

In the case of retinal haemangioblastoma the problem is somewhat different. In most instances the von Hippel tumour is the initial lesion of VHL disease or is discovered at the time of diagnosis of CNS haemangioblastoma. The most frequent tumoural association is cerebelloretinal haemangioblastomatosis. In our review of literature prior to 1983 in which we listed 156 cases of retinal haemangioblastoma associated with infratentorial haemangioblastoma, the chronology of the diagnosis of both localizations was specified in 147 cases: Diagnosis of both lesions was concomitant in 57 cases (38.8 per cent), and retinal haemangioblastoma was the initial manifestation of the disease in 62 cases (42.2 per cent), less than 2 years before infratentorial haemangioblastoma appearance in 15,

2–10 years in 31, and more than 10 years in 16[360]. To our knowledge, retinal haemangioblastoma remaining an isolated lesion throughout life does not exist. Therefore in the case of von Hippel tumour there is no uncertainty: a day will come when one or the other manifestation of the VHL disease appears.

Similarly, if haemangioblastoma in any CNS site or any related lesion manifests itself in a patient with a positive family history, there is no doubt: a day will come when another lesion appears.

The recurrent nature of haemangioblastoma and the multifocal tendency of CNS haemangioblastomatosis are the expression of one and the same affection in which multiple tumours are frequently if not usually present[359]. The solitary haemangioblastoma, sporadic forms included, is a fragile entity often shown false, sometimes after a short-term evolution[351], sometimes after a silent period of a long duration.

Regular follow-up of treated patients is therefore absolutely necessary. Postoperative screening has to be performed; its usefulness must be accurately explained to the patients. They must never be restricting and have to be understood and accepted. The important psychological repercussions affecting patients, especially in familial forms, must not be ignored. They have clearly been demonstrated in psychological studies in large kindreds[149, 293] that were the subject of genealogical inquiries and medical screening[257, 476]. Fear of disease, anxiety, depression, guilt of parents towards their children, blame of children directed at their parents, behavioural alterations have been reported. These psychological disorders seem to be exacerbated by repeated screening. A few cases of patients having attempting suicide have been reported[342]. All these psychological effects are well known in inherited disorders and are not particular to VHL disease.

In addition to affected patients and in spite of these psychological consequences, the screening of asymptomatic persons at risk of VHL disease i.e. primary relatives of patients and people with a positive family history, is necessary. It has to be performed in the same way that we described above for an affected patient. Genetic inquiry, clinical, biological, and imaging examinations have to be performed.

Although such investigations are expensive and time-consuming, they appear to be ethically justified firstly because the identification of affected patients permits accurate genetic counselling[476] and secondly because early detection of asymptomatic lesions may improve quality of life and long-term prognosis[159, 255, 269]. Ophthalmic screening, with funduscopy and if it is doubtful fluorescein angiography, has to be begun in the first decade of life and repeated every two years. It seems reasonable, according to our own experience and the literature, not to undertake either the CNS or visceral screening by means of noninvasive imaging investigations before the age of fifteen. Currently Gd-DTPA enhanced MRI of head and spine

is the best available method for the screening members of families affected with VHL disease. Early diagnosis of an asymptomatic lesion will lead either to direct therapeutic action e.g. in case of incipient retinal haemangioblastoma (that will be treated), or to an accurate follow-up planning, according to the discovered lesion. Demonstration of one or more lesions in a child, an adolescent or a young adult is evidence of a poor prognosis.

8. Current Status of Advances in Genetics Field

8.1. Advances in Cytogenetics

8.1.1. Karyotype of Peripheral Blood Lymphocytes

A few studies have been performed. No constant karyotypical abnormality was seen. In most cases, karyotype of peripheral blood lymphocytes was described as normal[69, 100, 149, 153, 240, 259, 293].

Nevertheless a few observations of miscellaneous chromosomal abnormalities were reported including chromatid breaks[207, 234, 245], C-, E-, G-monosomy[207], D-trisomy[234], and sex chromosomal mosaicism[317]. These changes might not be significant, and only correspond to "in vitro" modifications. However we recently observed, in a male patient with VHL disease, a translocation 1–12:

46,XY, t(1;12) (p31;q23)

(previously unreported data) (see Fig. 31).

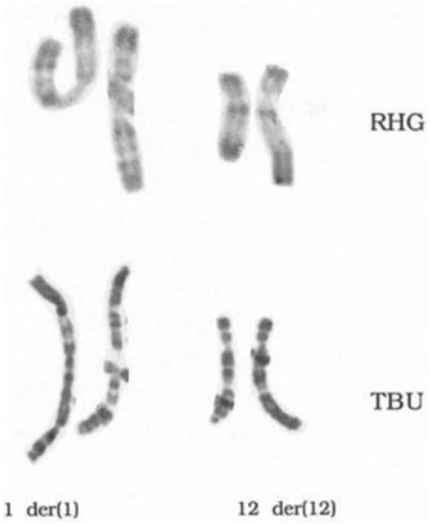

Fig. 31. VHL disease: peripheral blood lymphocytes karyotype. Translocation 1–12 (p 31; q 23)

8.1.2. Karyotype of Cultured Tumoural Cells

8.1.2.1. Cerebellar and Spinal Haemangioblastoma

No visible cytogenetic abnormalities were observed in studied cases of cerebellar haemangioblastomas[220, 221] and spinal haemangioblastomas[221].

8.1.2.2. Renal Clear Cell Carcinoma

In a renal clear cell carcinoma from a patient with VHL syndrome, a deletion of the short arm of chromosome 3 at band p 14 was described as the only change[240]. In another renal cell carcinoma from a patient with VHL syndrome, a dicentric chromosome evolving from an unbalanced translocation between the proximal part of the p arm of chromosome 3 (3p13 or 3p14) and the distal segment of the q arm of the X chromosome (Xq 25 or Xq 26) was reported[100]. In a third case, chromosomal analysis of the renal cell carcinoma showed a translocation that involved the short arm of chromosome 3 (3p14) and the long arm of chromosome 8 (8q22). Subsequent to this translocation the rearranged chromosome 8 carrying most of 3 p was lost[153]. In either patients peripheral lymphocytes showed a normal karyotype that indicated that there was not a constitutional chromosomal abnormality.

In another study, six of nine renal cell carcinomas studied from VHL patients showed cytogenetic abnormalities: monosomy 3 or a deletion of 3 p, in five cases, trisomy 7 in four, an abnormal 14 in three[220, 221].

3p14 was reported as a very common fragile site, but a significantly higher expression was seen in affected subjects in families with VHL disease[219].

8.1.2.3. Phaeochromocytoma

To date, nine cases of phaeochromocytoma from patients with Lindau disease in three reports[220, 221, 239] were studied cytogenetically. No visible abnormalities were observed in six cases. Two phaeochromocytomas were found to exhibit a trisomy 7[220, 221, 239]. Trisomy 7 is a karyotypical abnormality which was described in tumours of neuroectodermal origin including, in addition to some cases of phaeochromocytomas not associated with VHL syndrome, malignant gliomas and melanomas. Trisomy 7 was also described in a few cases of non-neuroectodermal origin tumours (malignant histiocytomas, bladder cancers, bowel cancers, and renal carcinomas in patients not affected by VHL disease). In the last case of phaeochromocytoma with cytogenetic abnormality, a polyclonal chromosome constitution was detected, with four distinct abnormal cell lines: one revealing partial trisomy for the long arm of chromosome 1 and exhibiting the phenomenon of telomeric association, and three cell clones showing re-

arrangements of chromosome 3 resulting in a partial or total trisomy of 3 p, therefore including the region where the VHL gene has been mapped[239].

8.2. Advances in Molecular Genetics

Studies at the cytogenetic level were the first steps to the localization of a gene involved in VHL disease. The data are not fully clarified but alteration of the short arm of chromosome 3 is the most commonly observed phenomenon. This last result was a good indication to initiate studies of DNA polymorphic markers by molecular biology methods.

In 1987, Zbar *et al.*[477] showed, on studying alleles detected by DNA markers, loss of heterozygosity on the short arm of chromosome 3 in renal clear cell carcinoma. Such an observation was later confirmed[101, 251] and is in good agreement with cytogenetics, since it means deletion of the short arm of chromosome 3.

However the first clear localization of a gene involved in VHL disease was performed by two groups, in 1987 by Wells *et al.*[454] and in 1988 by Seizinger *et al.*[396]. On studying nine affected families and using a polymorphic DNA probe corresponding to the RAF-1 oncogene, the latter demonstrated a genetic linkage with a VHL locus. The RAF-1 oncogene

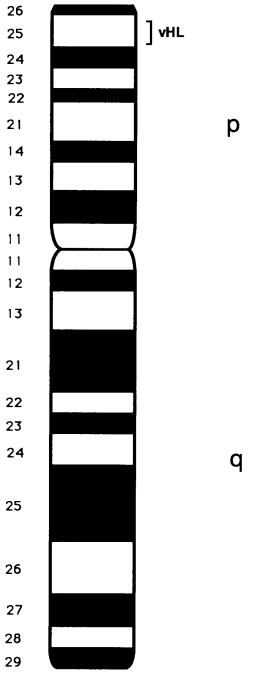

Fig. 32. Human chromosome 3 and localization at 3p25 of the gene involved in von Hippel-Lindau disease

is located on the short arm of chromosome 3 in p25[32] and the study estimated its distance at 11 centimorgans from the gene involved in VHL disease (see Fig. 32).

Since these first publications, data confirming the location of the VHL locus in 3p25 were published by Vance *et al.* [433] and Hosoe *et al.*[185], and also reported by several groups[242, 258, 286, 398, 478] at the 41th Annual Meeting of the American Society of Human Genetics recently held in Cincinnati (October 16–20th, 1990).

New polymorphic markers have also been characterized on chromosome 3, especially in the region 3p25, by these authors and by others[105, 147, 265, 334, 409, 467, 471]. Both Maher *et al.*[286] on studying 10 affected families and Hosoe *et al.*[185] on studying 25 affected families, estimated the genetic distance between the VHL locus and RAF-1 oncogene to be 6 centimorgans. The gene is now bracketed between several probes[185, 398] with the RAF-1 gene on its centromeric side[185, 286, 398].

All these data have several implications:

– firstly, it is already possible to offer genetic counselling to affected families using the genetic markers characterized by molecular biology. It will be particularly efficient and easy because we currently have markers flanking the VHL gene on both sides;

– secondly, the nearest probes are good start points for reverse genetics in order to reach the gene(s) involved in VHL disease. Indeed several teams are already working in that way. A short chromosomal walk was performed by one group[147] from a VHL linked probe (D3S18). Another group[409] isolated 90 cosmids of the chromosome 3p24 to 3pter region and is looking for candidate genes. Another group[468] constructed a chromosome 3 specific yeast artificial chromosome (YAC) bank, allowing the clonage of large DNA fragments of the VHL locus containing region. An interesting alternative to isolate this gene was proposed[76] by cloning the corresponding mouse chromosome region (on mouse chromosome 6) which seems to be shorter.

It is obvious that the gene(s) involved in the occurrence of tumours of the VHL disease will be cloned and characterized in the near future. This will provide new developments in diagnosis, e.g. of isolated tumours in sporadic cases, in genetic counselling and in the knowledge of the molecular mechanisms of the disease.

The first step will be to understand the function of the protein encoded by the gene. Seizinger *et al.*[396] postulated that a tumour suppressor gene could be involved in the genesis of the tumours observed in VHL disease, as described or suspected in some cancers such as retinoblastoma, Wilms tumour, familial adenomatous polyposis (see for review:[168, 349, 379, 397]).

VHL disease is inherited as an autosomal dominant. Nevertheless, development of tumours in this disorder might occur through a recessive

mechanism at the cellular level analogous to the retinoblastoma model[427]. The hypothesis involving a tumour suppressor gene in genesis of some cancers was proposed by Knudson[244]: To develop a tumour, the two alleles of a tumour suppressor gene must be defective (see Fig. 33):

– in familial forms, the first genetic event (germ line) might be an alteration (mutation) of one allele of the gene (or gene cluster) involved

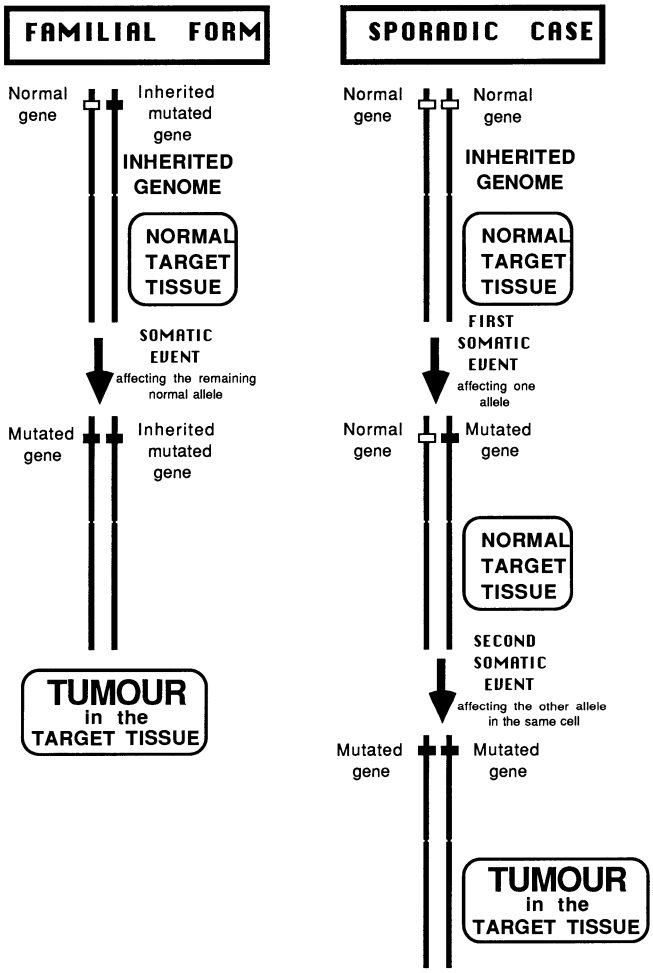

Fig. 33. Involvement of a Tumour Suppressor Gene in tumour genesis.
In familial forms (left) the individual inherited a mutated tumour suppressor gene, the other allele remaining normal. A somatic mutation can affect this normal gene and therefore the cell cannot produce any normal protein in a target tissue, allowing the development of a tumour. In sporadic cases (right) the inherited genome is normal, but two different somatic events affect the two alleles of the tumour suppressor gene

in the disease; this mutated allele is genetically transmitted from generation to generation. One of the copies of the gene is still normal and it is sufficient to have a normal physiological activity. In a target tissue in which the gene is expressed, this remaining normal gene can be affected by a hazardous somatic event as a point mutation, a deletion or any chromosomal rearrangement. The cell in which this event occurs has no other functional copy of the tumour suppressor gene and engages itself in a tumoural evolution. The probability of such an event in one cell of the target tissue is very high. Therefore an individual, already bearing a defective gene, has a great risk of developing a tumour in this tissue. Thus the predisposition to such a cancer is considered a dominant trait. For example, in VHL disease the penetrance would increase with age and was estimated as 95 per cent at age 45[149];

– in sporadic cases the individual has no genetic prerequisite but is the victim in the same cell of two successive independant somatic alterations, affecting the two alleles of the tumour suppressor gene.

Another interesting clue will be to see what the alterations of the gene and of its flanking regions are in the different tumour types. As stated above, the cytogenetics data reported by Jordan *et al.*[220, 221] showed differences in chromosomal alterations depending on the tumour type. For example most renal clear cell carcinomas presented chromosome 3 abnormalities, whereas haemangioblastomas never did. The observation in two different individuals of chromosome 3 defects in renal clear cell carcinoma and no cytogenetic abnormalities in haemangioblastoma is a particularly good illustration of this heterogeneity. Haemangioblastoma might be due to a different alteration of chromosome 3 from renal clear cell carcinoma, e.g. point mutation or microdeletion. Studies of the different tumours of the same patient or in large families as we already characterized in France[365] will be of a great interest.

Such families will be useful also to check whether second events occuring on other chromosomal loci are important for the development of the tumours, as postulated by Jordan *et al.* on the basis of their cytogenetic results[220]. We ourself observed a translocation between chromosome 1 (p 31) and chromosome 12 (q 23) with no chromosome 3 abnormality in a male patient affected by VHL disease. By analogy with the different genetic defects that have been observed in the development of colorectal cancer[104, 443], second events could be important steps in the expression of the tumours in VHL disease.

9. Conclusions

The main points to remember can be summarized as follows:

Phakomatoses constitute a group of congenital diseases, frequently inherited, which are the consequence of a defective embryonic layer devel-

opment. These are characterized not only by dystrophic lesions of tissues originating from affected embryonic layer(s), but also by a blastomatous tendency inducing tumours. Most of these tumours are cytologically benign. However the neuraxial forms of phakomatoses, because of their frequent multiplicity and the potential to form new tumours, are severe affections with a high morbidity. They can even be lethal. VHL disease is one of the four cardinal phakomatoses (with von Recklinghausen neurofibromatosis, Bourneville tuberous sclerosis and Sturge-Weber-Krabbe angiomatosis). In VHL disease, haemangioblastoma is the basic neoplasm and represents what schwannoma (or meningioma) are in type 2 neurofibromatosis (NF 2).

Haemangioblastoma is a vascular tumour of a two proliferative tissue types: a vascular proliferation made up of capillaries with endothelial cells and pericytes of normal appearance, and cellular (the so-called "stromal" cells). Mast cells are present near the capillaries. Modified mast cells might play a part in the endocrine secretion and release of erythropoietic stimulating factor originating the secondary polycythaemia.

To date, despite numerous electron microscopic and immunohistochemical studies, the histogenesis of haemangioblastoma remains unclear. The best hypothesis locates the origin of stromal cells in a proliferation of angiogenous cells from an organogenetic defect involving the vascular mesenchyma during the third month of foetal life; a part of the original vascular mesenchyma lying on the posterior medullary velum might be included into the cerebellum and represent the germ of subsequent tumoural development. The name haemangioblastoma comes from this theory. The presence of neoplasms in other organs might be explained upon the same basis: during the third month of foetal life, vascularization of the retina and ingrowth of mesodermal elements into the pancreas occur; contemporary vascular maldevelopment of the kidney might also explain the renal lesions.

Haemangioblastoma is a rare tumours. It is preferentially located in the cerebellum. It can be an isolated lesion ("solitary" haemangioblastoma). Sometimes in sporadic cases, and in most if not in all affected patients with a positive family history, multiple haemangioblastomas (CNS haemangioblastomatosis) are observed, the multifocal tumoural trait being present at the time of diagnosis or appearing in the course of the disease. In addition to the cerebellum, CNS haemangioblastoma may involve the brain stem, the spinal cord, rarely the cerebrum. Retinal haemangioblastomas (von Hippel tumours), that affect one or both eyes, are often the initial manifestation in the case of both retina and CNS haemangioblastomatosis. Visceral lesions that may be observed in association with CNS and/or retinal haemangioblastomas have a protean pathological appearance: pancreatic and epididymal papillary cystadenomas, renal clear cell carcinomas, phaeochromocytomas, islet cell tumours are the main lesions of the Lindau complex.

Whatever its location, CNS haemangioblastoma exhibits no clinically distinctive feature permitting it to be distinguished from the other space occupying lesions of the same location. Screening of the affected patients, and in case of familial disease screening of persons at risk, has to be performed. MRI before and after Gd-DTPA administration, currently appears as the best diagnostic method in detecting CNS haemangioblastomas and delineating their exact extent. Biological investigations and radioiodine MIBG scintigraphy are the first steps in detecting phaeochromocytoma. Confirmation of visceral lesions is provided by CT. Brain or spinal cord angiography remains necessary prior to any surgical procedure.

From a surgical point of view, the following points must be recalled. In case of haemangioblastomatosis, surgical excision must be restricted to symptomatic tumours. In most cases, whatever the location is, the surgical procedure can be without major difficulty. However, brain stem haemangioblastoma excision remains challenging. In most cases, difficulties do not come from the surgical procedure itself providing that perfect surgical management is used. Per- and postoperative problems that may occur with the excision of medullary haemangioblastomas come from neurovegetative complications due to the location of the tumour.

The recurrent trait of haemangioblastomas and their multifocal characteristic are the expression of one and the same affection in which tumoural scattering is frequently if not usually present. The solitary haemangioblastoma, sporadic forms included, is a fragile concept. Does solitary haemangioblastoma exist? It can be answered in the affirmative. The symptomatic appearance of a single CNS haemangioblastoma after the age of 45, especially if it is located in spinal cord, with a negative screening, provides the best chance to recover from the condition a well-treated patient free of any family history. In all other instances, the entity of solitary haemangioblastoma is doubtful and patients must be the subject of a regular follow-up that one day may refute the initially diagnosed monofocal trait of the disorder.

VHL disease is inherited in an autosomal dominant. Nevertheless, development of tumours might occur through a recessive mechanism at the cellular level analogous to the retinoblastoma model that involves a tumour suppressor gene. The gene causing VHL disease maps to the short arm of chromosome 3, at 3p25 near the RAF-1 oncogene locus on its centromeric side. The gene(s) involved in the occurrence of tumours of the VHL disease will be cloned in the near future. When the gene is characterized, the distinction of isolated tumours in the framework of either sporadic or transmissible forms will become possible. The study of molecular mechanisms of the disease will develop, the first aim being to understand the function of the encoded protein. Knowledge of action mechanisms of the latter will direct further studies hopefully leading to therapeutic consequences.

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Addendum see p. 304.

Addendum

Since the galleys have been corrected, von Hippel-Lindau disease has attracted more attention than used to be, and contributions too numerous to be cited here have appeared on that subject. The most important ones are concerned with the genetics of the disease. Presymptomatic diagnosis is now possible, although not generally available, inasmuch flanking marker loci have been identified, D3S18 and RAF1, located respectively at 3p26 and 3p25, being most useful. Their distance to the VHL locus is not negligible, being themselves 6 to 8 cM apart, but their flanking location limit the errors to the rare events of double recombination*.

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