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INVITED REVIEW

Subarachnoid haemorrhage: diagnosis, causes and management

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Summary

The incidence of subarachnoid haemorrhage (SAH) is stable, at around six cases per 100 000 patient years. Any apparent decrease is attributable to a higher rate of CT scanning, by which other haemorrhagic conditions are excluded. Most patients are <60 years of age. Risk factors are the same as for stroke in general; genetic factors operate in only a minority. Case fatality is ~50% overall (including pre-hospital deaths) and one-third of survivors remain dependent. Sudden, explosive headache is a cardinal but non-specific feature in the diagnosis of SAH: in general practice, the cause is innocuous in nine out of 10 patients in whom this is the only symptom. CT scanning is mandatory in all, to be followed by (delayed) lumbar puncture if CT is negative. The cause of SAH is a ruptured aneurysm in 85% of cases, non-aneurysmal perimesencephalic haemorrhage (with excellent prog nosis) in 10%, and a variety of rare conditions in 5%. Catheter angiography for detecting aneurysms is gradually being replaced by CT angiography. A poor clinical condition on admission may be caused by a remediable complication of the initial bleed or a recurrent haemorrhage in the form of intracranial haematoma, acute hydrocephalus or global brain ischaemia. Occlusion of the aneurysm effectively prevents rebleeding, but there is a dearth of controlled trials assessing the relative benefits of early operation (within 3 days) versus late operation (day 10–12), or that of endovascular treatment versus any operation. Antifibrinolytic drugs reduce the risk of rebleeding, but do not improve overall outcome. Measures of proven value in decreasing the risk of delayed cerebral ischaemia are a liberal supply of fluids, avoidance of antihypertensive drugs and administration of nimodipine. Once ischaemia has occurred, treatment regimens such as a combination of induced hypertension and hypervolaemia, or transluminal angioplasty, are plausible, but of unproven benefit.

Keywords: aneurysm; epidemiology; outcome; subarachnoid haemorrhage; treatment

Abbreviations: ADPKD = autosomal polycystic kidney disease; AVM = arteriovenous malformation; CI = confidence interval; CTA = CT angiography; GCS = Glasgow Coma Scale; MRA = MR angiography; SAH = subarachnoid haemorrhage; WFNS = World Federation of Neurological Surgeons

Introduction

Subarachnoid haemorrhage (SAH), mostly from aneurysms, accounts for only 3% of all strokes (Sudlow and Warlow, 1997), but for 5% of stroke deaths and for more than one-quarter of potential life years lost through stroke (Johnston *et al*., 1998*a*). The 20th century has seen great advances in diagnosis, starting with the ability to recognize the condition at all during life (Cushing, 1923; Symonds, 1923). Advances in treatment and prevention of complications have also occurred, but these have led to only modest improvement in overall outcome (Hop *et al*., 1997); hence there are still formidable challenges ahead for neurologists, neurosurgeons and radiologists.

Epidemiological aspects

The incidence of SAH has remained stable over the last 30 years. In a meta-analysis of relevant studies, the pooled

Table 1 *Epidemiological characteristics of SAH (Teunissen* et al.*, 1996; Linn* et al.*, 1996; Hop* et al., *1997)*

Incidence	*n*/100 000 patient years (95% CI)
Overall	10.5 (9.9–11.2)
Finland	22.0 (20.0–23.0)
Japan	23.0 (19.0–28.0)
Other regions	7.8 (7.2–8.4)
Virtual study with 100% CT	5.7
Women	7.1 (5.4–8.7)
Men	4.5 (3.1–5.8)
Risk factors	**Relative risk (95% CI)**
First degree relative with SAH	6.6 (2.0–21.0)
Hypertension	2.8 (2.1–3.6)
Smoking	1.9 (1.5–2.3)
>2 units alcohol/day	4.7 (2.1–10.5)
Outcome	***n*/100 (95% CI)**
Case fatality	51.0 (49.0–53.0)

incidence rate was 10.5 per 100 000 person years (Linn *et al*., 1996). There seemed to be a decline over time, but this was caused by diagnostic bias. That more recent studies reported lower incidence rates than older studies could be entirely explained by the increasing proportion of patients investigated with CT scanning. In a virtual study in which CT is applied to all patients, the incidence is calculated to be 5.6 per 100 000 patient years (Linn *et al*., 1996) (Table 1); this is only slightly lower than the incidence of 6.9 published later for a study spanning a 30-year period of the population in Olmsted, Minn., USA (Menghini *et al*., 1998). The average age of patients with SAH is substantially lower than for other types of stroke, peaking in the sixth decade (Longstreth *et al*., 1993; Lanzino *et al*., 1996).

Gender, race and region have a marked influence on the incidence of SAH. Women have a 1.6 times [95% confidence interval (CI) 1.5–2.3] higher risk than men (Linn *et al*., 1996), and black people a 2.1 times (95% CI 1.3–3.6) higher risk than whites (Broderick *et al*., 1992). In Finland and Japan, the incidence rates are much higher than in other parts of the world (Table 1).

Risk factors

An important, but non-modifiable risk factor is familial predisposition to SAH. Between five and 20% of patients with SAH have a positive family history (Schievink, 1997). First-degree relatives of patients with SAH have a 3- to 7-fold increased risk of being struck by the same disease (Bromberg *et al.*, 1995; Schievink *et al.*, 1995; Wang *et al.*, 1995; De Braekeleer *et al.*, 1996; Gaist *et al.*, 2000). In second-degree relatives, the incidence of SAH is similar to that found in the general population (Bromberg *et al.*, 1995).

The occurrence of SAH is also associated with specific heritable disorders of connective tissue, but these patients account for only a minority of all patients with SAH. Even though autosomal dominant polycystic kidney disease (ADPKD) is the most common heritable disorder associated with SAH, it is found in only 2% of all patients with SAH (Schievink *et al*., 1992). Other genetically determined disorders that have been associated with SAH are Ehlers–Danlos disease IV and neurofibromatosis type 1, but these associations are weaker than between ADPKD and aneurysms and these syndromes are seldom found in patients with SAH (Schievink *et al*., 1994; Pepin *et al*., 2000). Marfan's syndrome has often been associated with SAH, but in a clinical cohort of 129 patients with Marfan's syndrome, none had a history of SAH (Van den Berg *et al*., 1996).

Modifiable risk factors for SAH have been addressed in a systematic review of eight longitudinal and 10 case-control studies that fulfilled predefined methodological criteria; only smoking, hypertension and heavy drinking emerged as significant risk factors, with odds ratios in the order of two or three (Teunissen *et al*., 1996). In this study, the use of oral contraceptives did not present a significantly increased risk, but was found to do so in a meta-analysis published 2 years later (relative risk 1.42; 95% CI 1.12–1.80) (Johnston *et al*., 1998*b*). The risks were not clear for hormone replacement therapy or an increased level of plasma cholesterol (Teunissen *et al*., 1996).

Outcome

Case fatality ranged between 32 and 67% in a review of population-based studies from 1960 onward. The weighted average was 51%. Of patients who survive the haemorrhage, approximately one-third remain dependent (Hop *et al*., 1997). Recovery to an independent state does not necessarily mean that outcome is good. In a study on quality of life in patients after SAH, only nine of 48 (19%; 95% CI 9–33%) patients who were independent 4 months after the haemorrhage had no significant reduction in quality of life (Hop *et al*., 1998*a*). Re-evaluation of this cohort at 18 months after the haemorrhage showed that outcome had improved considerably in terms of handicap and quality of life, but that still only 15 of the 48 patients (31%; 95% CI 19–46%) had no reduction in the quality of life (J. W. Hop, G. J. E. Rinkel, A. Algra and J. van Gijn, unpublished data). The improvement in the first year and a half shows that long-term follow-up is essential in studies on effectiveness of new treatment strategies on functional outcome after SAH. All in all, only a small minority of all patients with SAH have a truly good outcome. The relatively young age at which SAH occurs and the poor outcome together explain why the loss of years of potential life before age 65 from SAH is comparable to that of ischaemic stroke (Johnston *et al*., 1998*a*).

Diagnosis of SAH

Clinical features

The clinical hallmark of SAH is a history of unusually severe headache that started suddenly. A period of unresponsiveness

of >1 h occurs in almost half the patients and focal signs develop at the same time as the headache or soon afterwards in one third of patients (Linn *et al*., 1998; Hop *et al*., 1999). In patients with such neurological deficits, it is straightforward that they should be referred for further investigation. In patients in whom headache is the only symptom, it is often more difficult to recognize the seriousness of the underlying condition. Classically, the headache from aneurysmal rupture develops in seconds. Therefore it is important to make specific enquiries about how quickly the headache developed; patients often complain only about the severity of the headache and do not know that the speed of onset is a pivotal piece of information. However, even an accurate history does not reliably distinguish between aneurysmal rupture and innocuous forms of headache, such as benign vascular headache or a muscle contraction headache. First, only half the patients with aneurysm rupture describe the onset as instantaneous, the other half describe it as coming on in seconds to even a few minutes (Linn *et al*., 1998). Secondly, in the group of patients whose headache came on within a split second, innocuous forms of headache outnumber SAH by 10 to one (Linn *et al*., 1994). Other features are equally unhelpful in making the distinction: the severity of headache is rated similar, vomiting occurs in 70% of patients with aneurysmal rupture, but also in 43% of patients with innocuous thunderclap headache. Also, preceding bouts of similar headaches are recalled in 20% of patients with aneurysmal rupture and 15% of patients with innocuous thunderclap headache (Linn *et al*., 1998). Neck stiffness is a common sign in SAH of any cause, but takes hours to develop and therefore cannot be used to exclude the diagnosis if a patient is seen soon after the sudden-onset headache. It does not occur if patients are in deep coma. Subhyaloid haemorrhages require experience with fundoscopy and occur in ~17% of patients, at least of those who reach hospital alive (Pfausler *et al*., 1996; Frizzell *et al*., 1997).

If explosive headache is the only symptom, the chance of SAH being the cause is only 10% (Linn *et al*., 1994). Nevertheless, the lack of clinical features that distinguish reliably and at an early stage between SAH and innocuous types of sudden headache necessitate a brief consultation in hospital for all patients with an episode of severe headache that comes on within minutes. Such an approach serves the patient's best interests and is also cost effective. The discomfort and cost of referring the 90% of patients with innocuous headache is outweighed by avoidance of the disaster in the other 10% so that a ruptured aneurysm is avoided (Tolias and Choksey, 1996).

It is even more difficult to suspect aneurysmal rupture if the patient does not report a history of sudden headache, or if other symptoms seem to prevail over the headache, such as in patients presenting with a seizure or a confusional state, or if there is an associated head trauma. Epileptic seizures at the onset of aneurysmal SAH occur in ~6–16% of patients (Sarner and Rose, 1967; Hart *et al*., 1981; Pinto *et al*., 1996). Of course the majority of patients with *de novo* epilepsy above age 25 years will have underlying conditions other than SAH, but the diagnosis should be suspected if the post-ictal headache is unusually severe. One to 2% of patients with SAH present with an acute confusional state and in most such patients a history of sudden headache is lacking (Reijneveld *et al*., 2000). The differential diagnosis of acute confusional state is extensive and SAH accounts for, at most, a few percent of all patients seen in an emergency ward because of an acute confusional state (Benbadis *et al*., 1994). In such patients, the diagnosis emerges only if the careful history of an eyewitness reveals the sudden onset of the symptoms; also detection of focal deficits or absence of a psychiatric history should raise the index of suspicion and lead to a brain imaging study.

Trauma and spontaneous SAH are sometimes difficult to disentangle. Patients may be found alone after having been beaten in a brawl or hit by a drunken driver who made away, without external wounds to indicate an accident, with a decreased level of consciousness or with retrograde amnesia, making it impossible to obtain a history and with neck stiffness, causing the patient to be worked up for SAH. Conversely, patients may cause an accident whilst riding a bicycle or driving a car at time of the aneurysmal rupture. The diagnostic conundrum is particularly difficult when patients sustain a skull fracture having fallen after aneurysm rupture (Sakas *et al*., 1995) or when head trauma causes an aneurysm to burst (Sahjpaul *et al*., 1998). Meticulous reconstruction of traffic or sports accidents may therefore be rewarding, especially in patients with disproportionate headache or neck stiffness.

Clinical clues to the cause of SAH

Past history may contain useful information. In patients with previous head injury, and particularly with a skull fracture, a dural arteriovenous malformation (AVM) should be suspected, since healing of the fracture may be accompanied by the development of such a malformation (Chaudhary *et al*., 1982). Although SAH from a septic aneurysm is a rare presentation of infective endocarditis in patients not known to have a disorder of the heart valves (Vincent *et al*., 1980; Salgado *et al*., 1987), this diagnosis should be considered in patients with a history of malaise in the days or weeks preceding the haemorrhage, even more so if the haemorrhage is located at the convexity of the brain. Usually it will not be hard for the physician to get acquainted with the existence of sickle cell disease, a history of cardiac myxoma, or coagulation disorders. Pain at onset in the lower part of the neck (upper neck pain is common also with ruptured intracranial aneurysms), or a sudden and stabbing pain between the shoulder blades (*coup de poignard* or dagger thrust), with or without radiation to the arms, suggests a spinal AVM or fistula as the source of SAH (Kinouchi *et al*., 1998). A history of even quite minor neck trauma or of sudden, unusual head movements before the onset of headache may provide a clue to the diagnosis of vertebral

artery dissection as a cause of SAH. Cocaine ingestion as a risk factor may not immediately be known in the case of an unconscious patient. Even if the family turns up in large numbers, one may find that not every relative is aware of illicit drugs being used or willing to volunteer this information even if they are. In cocaine-associated SAH there is often an underlying aneurysm (Levine *et al*., 1991; Nolte *et al*., 1996).

The physical examination can also provide an indication about the cause of SAH. Monocular blindness may result from anterior communicating artery aneurysms if it is exceptionally large (Chan *et al*., 1997). Complete or partial third nerve palsy is a well-recognized sign after rupture of an aneurysm of the internal carotid artery at the origin of the posterior communicating artery (Hyland and Barnett, 1954). The third nerve can also be involved with aneurysms of the basilar bifurcation or the superior cerebellar artery, but these are relatively infrequent sites (Vincent and Zimmerman, 1980). Sixth nerve palsies, often bilateral in the acute stage, usually result from a non-specific and sustained rise of cerebrospinal fluid pressure, either at the time of rupture or later. A combination of visual and oculomotor deficits should raise the suspicion of a pituitary apoplexy (McFadzean *et al*., 1991). Usually, the underlying adenoma has insidiously manifested itself before the dramatic occurrence of the haemorrhage by a dull retro-orbital pain, fatigue, a gradual decrease of visual acuity or a constriction of the temporal fields. Lower cranial nerve palsies point to dissection of the vertebral artery, through direct compression of the ninth or tenth nerve (Senter and Sarwar, 1982). Lower cranial nerve palsies (ninth to twelfth nerve) may also accompany dissection of the carotid artery in the neck, but this is an extremely uncommon cause of SAH (Sturzenegger and Huber, 1993). Deficits indicating lesions of the cerebellum or brainstem, such as dysmetria, scanning speech, rotatory nystagmus or Horner's syndrome, also strongly suggest vertebral artery dissection (Caplan *et al*., 1988). The presence or absence of hemiparesis does not contribute much to the diagnosis of uncommon causes, because the rare occurrence of hemiparesis with a ruptured aneurysm (mostly of the middle cerebral artery) will still outnumber all other potential causes of SAH, in which hemiparesis may be relatively common, for example with septic aneurysms.

Brain scanning (CT and MRI)

If SAH is suspected, CT scanning is the first line in investigation because of the characteristically hyperdense appearance of extravasated blood in the basal cisterns. The pattern of haemorrhage often suggests the location of any underlying aneurysm (van Gijn and van Dongen, 1980*a*), although with variable degrees of certainty (Van der Jagt *et al*., 1999). A false-positive diagnosis of SAH on CT is possible in the presence of generalized brain oedema, with or without brain death, which causes venous congestion in the subarachnoid space and in this way may mimic SAH (van Gijn and van Dongen, 1982; Avrahami *et al*., 1998). The CT scan should be carefully scrutinized because small amounts of subarachnoid blood may easily be overlooked (Fig. 1). If after a thorough review no blood is found, aneurysmal SAH cannot be excluded. Even if CT is performed within 12 h after the haemorrhage and with a modern CT machine, studies are negative in ~2% of patients with SAH (van der Wee *et al*., 1995).

Brain CT may also help in distinguishing primary SAH from traumatic brain injury, but the aneurysmal pattern of haemorrhage is not always immediately appreciated in patients admitted with a trauma (Vos *et al*., 2000). If trauma is the cause of SAH, the blood is usually confined to the superficial sulci at the convexity of the brain, adjacent to a fracture or to an intracerebral contusion; these findings dispel any lingering concern about the possibility of a ruptured aneurysm. Nevertheless, patients with basal-frontal contusions may show a pattern of haemorrhage resembling that of a ruptured anterior communicating artery aneurysm (Sakas *et al*., 1995), and in patients with blood confined to the sylvian fissure or ambient cistern it may also be difficult to distinguish trauma from aneurysmal rupture by the pattern of haemorrhage alone (Rinkel *et al*., 1993). In patients with direct trauma to the neck or with head injury associated with vigorous neck movement, the trauma can immediately be followed by massive haemorrhage into the basal cisterns resulting from a tear or even a complete rupture of one of the arteries of the posterior circulation, which is often rapidly fatal (Harland *et al*., 1983; Dowling and Curry, 1988).

MRI with FLAIR (fluid attenuated inversion recovery) techniques demonstrates SAH in the acute phase as reliably as CT (Noguchi *et al*., 1995), but MRI is impracticable because the facilities are less readily available than CT scanners, and restless patients cannot be studied unless anaesthesia is given. After a few days (up to 40), however, MRI is increasingly superior to CT in detecting extravasated blood (Ogawa *et al*., 1995; Noguchi *et al*., 1997). This makes MRI a unique method for identifying the site of the haemorrhage in patients with a negative CT scan but a positive lumbar puncture (see below), such as those who are not referred until 1 or 2 weeks after symptom onset (Renowden *et al*., 1994).

Lumbar puncture

Lumbar puncture is still an indispensable step in the exclusion of SAH in patients with a convincing history and negative brain imaging. Lumbar puncture should not be carried out rashly or without some background knowledge. The first rule is that at least 6 and preferably 12 h should have elapsed between the onset of headache and the spinal tap. The delay is essential, because if there are red cells in the CSF, sufficient lysis will have taken place during that time for bilirubin and oxyhaemoglobin to have formed (Vermeulen and van Gijn, 1990). The pigments give the CSF a yellow tinge after centrifugation (xanthochromia), a critical feature in the distinction from a traumatic tap, and are invariably detectable

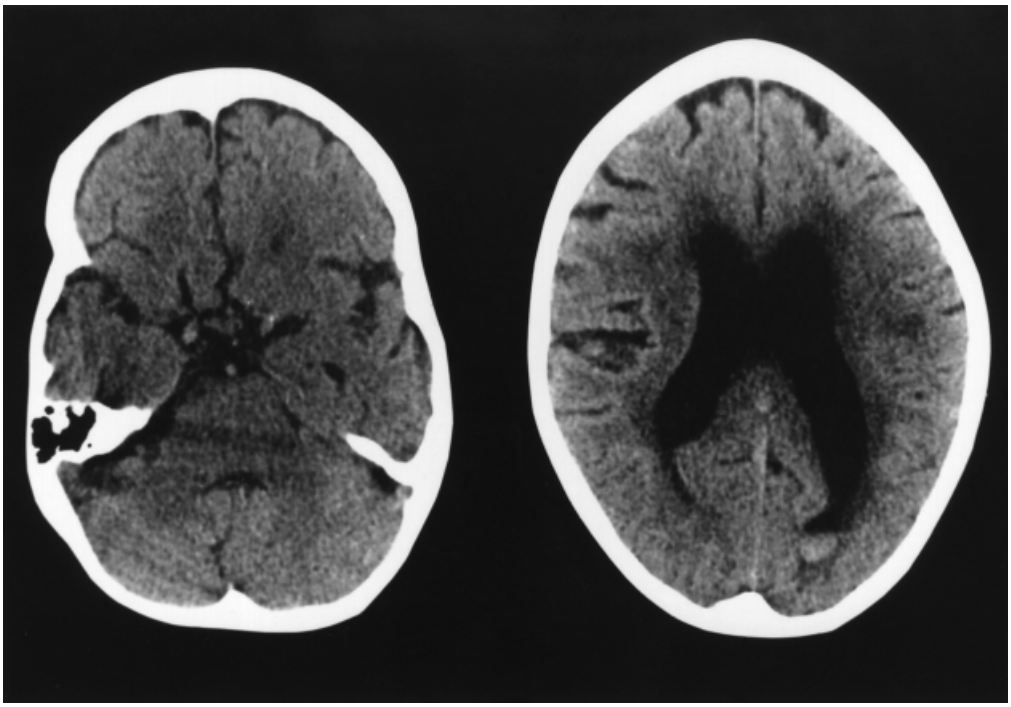

Fig. 1 Sedimentation in the left occipital horn as the only sign of SAH on CT.

until at least 2 weeks later (de Paepe *et al*., 1988). The 'three tube test' (a decrease in red cells in consecutive tubes) is notoriously unreliable, and a false-positive diagnosis of SAH can be almost as invalidating as a missed one. Spinning down the blood-stained CSF should be done immediately, otherwise oxyhaemoglobin will form *in vitro*. If the supernatant appears crystal-clear, the specimen should be stored in darkness until the absence of blood pigments is confirmed by spectrophotometry (Vermeulen and van Gijn, 1990). Although the sensitivity and specificity of spectrophotometry have not yet been confirmed in a series of patients with suspected SAH and a negative CT scan (Beetham *et al*., 1998), it is the best technique currently available.

Keeping patients in an emergency department or admitting them to hospital until 6–12 h after symptom onset may be a practical problem, yet we see no alternative until a scientifically sound method has been devised to distinguish reliably between blood caused by a traumatic tap from blood that was already present. Even the smoothest puncture can end in a vein. Immediately proceeding with CT or MR angiography in all patients with blood-stained CSF is not a good idea, because a small (<5 mm) aneurysm may well be coincidental and should be left untreated, while a negative study may still leave concerns, not only with the patients themselves but also with insurance company advisors.

The main cause: saccular aneurysms

Approximately 85% of all spontaneous haemorrhages into the subarachnoid space arise from rupture of saccular aneurysms at the base of the brain (van Gijn and van Dongen, 1980*b*; Kassell *et al*., 1990*a*; Velthuis *et al*., 1998). Such aneurysms are not congenital, but develop during the course of life. Cerebral aneurysms almost never occur in neonates and they are also rare in children (Heiskanen, 1986). In those exceptional cases, there is usually a specific underlying cause for the aneurysm, such as trauma, infection or connective-tissue disorder (Ferry *et al*., 1974; Stehbens, 1982). The frequency at which saccular aneurysms are found in the general population depends on the definition of size and the diligence with which the search for unruptured aneurysms has been performed. In a systematic overview of studies reporting the prevalence of intracranial aneurysms in patients studied for reasons other than SAH, 23 studies were identified, totalling 56 304 patients; 6685 (12%) of these were from 15 angiography studies (Rinkel *et al*., 1998). The prevalence was lowest in retrospective autopsy studies and highest in prospective angiography studies (Table 2). The prevalence of aneurysms was relatively high in patients with autosomal polycystic kidney disease, a familial predisposition or atherosclerosis.

It is largely unknown why only some adults develop aneurysms at arterial bifurcations and most do not. The once popular notion of a congenital defect in the muscle layer of the wall (tunica media) being a weak spot through which the inner layers of the arterial wall would bulge has been largely dispelled by a number of contradictory observations. First, gaps in the muscle layer of intracranial arteries are equally common in patients with and without aneurysms (Stehbens, 1989) and are usually strengthened by densely packed collagen fibrils (Fujimoto, 1996; Finlay *et al*., 1998).

Table 2 *Frequency of aneurysms and risk factors (Rinkel* et al.*, 1998)*

Frequency	*n*/100 (95% CI)
Retrospective autopsy studies	0.4 (0.4–0.5)
Prospective autopsy studies	3.6 (3.1–4.1)
Retrospective angiography studies	3.7 (3.0–4.4)
Prospective angiography studies	6.0 (5.3–6.8)
Age (years)	
<20	0.01 (0.00–0.03)
20–39	1.3 (0.8–2.1)
40–59	1.8 (1.4–2.2)
60–80	2.3 (1.9–2.6)
>80	2.1 (1.5–3.0)
Adult without risk factors	2.3 (1.7 – 3.1)
Risk factors	**Relative risk (95% CI)**
Women	1.3 (0.9–2.0)
Atherosclerotic diseases	2.3 (1.7–3.1)
Family history	4.0 (2.7–6.0)

Secondly, if an aneurysm has formed, any defect in the muscle layer is located not at the neck of the aneurysm, but somewhere in the wall of the aneurysmal sac (Stehbens, 1989).

A role of acquired changes in the arterial wall is likely because hypertension, smoking and alcohol abuse are risk factors for SAH in general (Teunissen *et al*., 1996). It may well be the influence of these factors that leads to local thickening of the intimal layer ('intimal pads') in the arterial wall, distal and proximal to a branching site, changes that some investigators regard as the earliest stage in the formation of aneurysms (Walker and Allegre, 1954; Hassler, 1962). The formation of these pads, in which the intimal layer is inelastic, may cause increased strain in the more elastic portions of the vessel wall (Crompton, 1966). Also, structural abnormalities in structural proteins of the extracellular matrix have been identified in the arterial wall at a distance from the aneurysm itself (Chyatte *et al.*, 1990).

Some neoplastic conditions may lead to the formation of aneurysms, i.e. cerebellar haemangioblastoma (Guzman and Grady, 1999) or metastasis from bronchial carcinoma (Gliemroth *et al*., 1999). Iatrogenic causes include radiation therapy (Jensen and Wagner, 1997), acrylate applied externally for microvascular decompression (Tokuda *et al*., 1998) and operation for a superficial temporal artery-middle cerebral artery bypass, with the aneurysm at the site of the anastomosis (Sasaki *et al*., 1996).

The search for the ruptured aneurysm: is catheter angiography still necessary?

The gold standard for detecting aneurysms is conventional angiography, but this procedure can be time consuming and it is not an innocuous procedure. A systematic review of three prospective studies in which patients with SAH were distinguished from other indications for catheter angiography found a complication rate (transient or permanent) of 1.8% (Cloft *et al*., 1999). At any rate, the aneurysm may re-rupture during the procedure, as occurs in 1–2% of cases overall (Hayakawa *et al*., 1978; Koenig *et al*., 1979; Saitoh *et al*., 1995). The rupture rate in the 6 h period following angiography has been estimated at 5% (Saitoh *et al*., 1995), which is higher than the expected rate.

Other imaging modalities are MR angiography (MRA) and CT angiography (CTA). MRA is safe, but less suitable in the acute stage, because in the acute stage patients are often restless or need extensive monitoring (Anzalone *et al*., 1995). A recent review of studies comparing MRA and intra-arterial angiography in patients with recent SAH, under blinded-reader conditions, showed a sensitivity in the range of 69–100% for detecting at least one aneurysm per patient. For the detection of all aneurysms the sensitivity is 70–97%, with specificity in the range 75–100% (Wardlaw and White, 2000). In a screening study for unruptured aneurysms in first-degree relatives of patients with SAH, the agreement between neuroradiologists about the presence of aneurysms was poor, not surprisingly, given the low prevalence (4%) of aneurysms (Raaymakers *et al*., 1999). Despite its limitations, but thanks to its non-invasive nature, MRA is a feasible tool for detecting aneurysms in relatives of patients with SAH (Ronkainen *et al*., 1995; Kojima *et al*., 1998; Raaymakers *et al*., 1999).

CT angiography is based on the technique of spiral CT. It can easily be obtained immediately after the non-contrast CT upon which the diagnosis is first made. It is minimally invasive because it does not require intra-arterial catheterization. Compared with MRA, it involves radiation and it requires injection of iodine-based contrast, but is much simpler to perform, especially in ill patients. After the data acquisition, which can be done within 1 min, post-processing techniques are needed to produce an angiogram-like display. The most practical procedure for daily routine is cine review of the axial source images combined with maximum intensity projection (MIP) of a limited volume of interest (Fig. 2) (Velthuis *et al.*, 1997). In addition, MIP images derived from CTA can be rotated and studied on a computer screen at every conceivable angle, which is a great advantage over the limited views with conventional angiography.

The sensitivity of CTA (compared with catheter angiography) is 85–98%, in the same range as that of MRA (Alberico *et al*., 1995; Hope *et al*., 1996; Wardlaw and White, 2000). On the other hand, with CTA aneurysms can be detected that were missed by conventional angiography (Hashimoto *et al*., 2000). In a study in which CTA and conventional angiography were compared in 80 patients with SAH, neurosurgeons assessed CT angiography as equal or superior to conventional angiography in 83% (95% CI 73–90%) of 87 aneurysms (Velthuis *et al*., 1998). It is not surprising, therefore, that an increasing proportion of patients with a ruptured aneurysm is successfully operated with CTA as the only imaging method (Anderson *et al*., 1999; Velthuis *et al*., 1999*a*). There is no doubt that catheter angiography is on its way out for the pre-treatment assessment of cerebral

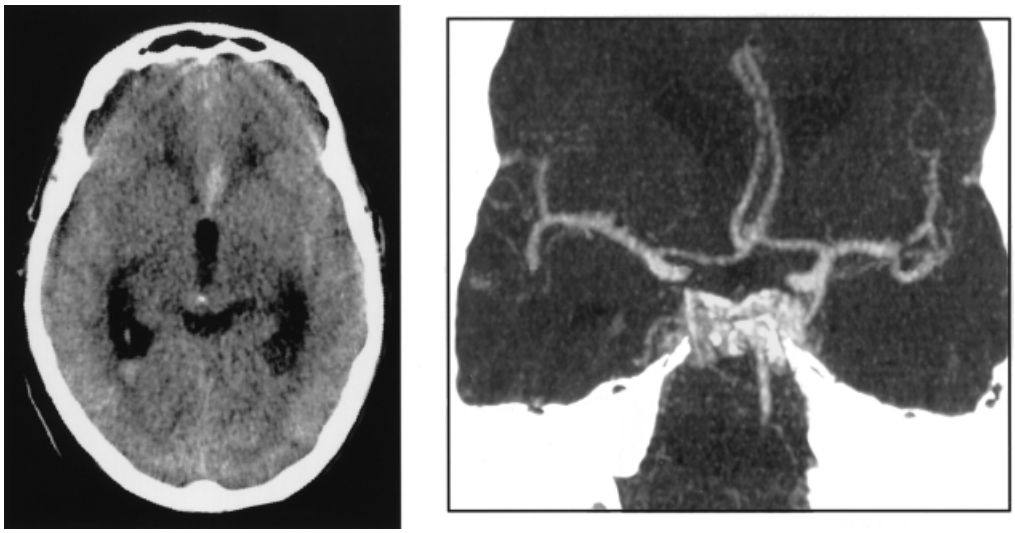

Fig. 2 CT scan with small amount of blood in the anterior interhemispheric fissure and some sedimentation in the right occipital horn. CT angiogram of the same patient shows a small aneurysm of the anterior communicating artery.

aneurysms, as the techniques of CTA and MRA are still improving and as neurosurgeons and interventional radiologists are growing familiar with them.

The technique of transcranial Doppler can be combined with echo imaging (duplex technique) and with colour coding (transcranial colour-coded duplex sonography). A recent modification of colour Doppler called Colour Doppler Energy or Power Doppler offers greater sensitivity to flowing blood than standard colour flow imaging (Wardlaw and Cannon, 1996). The sensitivity of power Doppler increases further by using an ultrasonic contrast agent, but even then the sensitivity is only 55% with a corresponding 83% specificity (Turner and Kirkpatrick, 2000). Another drawback of this technique is that ~15% of patients have no adequate bone window, which prevents adequate insonation (Seidel *et al*., 1995). Also, the technique is highly dependent on the skills of the operator.

Causes other than saccular aneurysms

Of the 15% of SAHs not attributable to saccular aneurysms, two-thirds (10% of the total) are caused by non-aneurysmal SAH and the remaining 5% by a variety of rare conditions (Table 3).

Non-aneurysmal perimesencephalic haemorrhage

Perimesencephalic haemorrhage constitutes ~10% of all episodes of SAH and two-thirds of those with a normal angiogram (van Gijn *et al*., 1985*a*; Farrés *et al*., 1992; Ferbert *et al*., 1992; Kitahara *et al*., 1993; Pinto *et al*., 1993; Vermeer *et al*., 1997). In this radiologically distinct and strikingly harmless variety of SAH, the extravasated blood is confined to the cisterns around the midbrain, and the centre of the bleeding is immediately anterior to the midbrain (Fig. 3) (van Gijn *et al.*, 1985*a*; Rinkel *et al.*, 1991*a*; Schwartz and Solomon, 1996). In some cases, the only evidence of blood is found anterior to the pons (Zentner *et al*., 1996). For this reason some have proposed the term pre-truncal haemorrhage (Schievink and Wijdicks, 1997), but in other patients the blood is found mainly in the ambient cistern (Fig. 4) or only in the quadrigeminal cistern (van Gijn *et al.*, 1985*a*; Rinkel and van Gijn, 1995; Schwartz and Mayer, 2000). There is no extension of the haemorrhage to the lateral sylvian fissures or to the anterior part of the interhemispheric fissure. Some sedimentation of blood in the posterior horns of the lateral ventricles may occur, but frank intraventricular haemorrhage or extension of the haemorrhage into the brain parenchyma indicates arterial haemorrhage and rules out this particular condition (Rinkel *et al*., 1991*a*). This disease entity is defined only by the characteristic distribution of the extravasated blood on brain CT, in combination with the absence of an aneurysm.

Perimesencephalic haemorrhage can occur in any patient over the age of 20 years, but most patients are in their sixth decade, as with aneurysmal haemorrhage. A history of hypertension was obtained more often than expected in a single study (Canhao *et al*., 1999), but not in another (Rinkel *et al*., 1991*b*). In one-third of the patients, strenuous activities immediately precede the onset of symptoms, a proportion similar to that found in aneurysmal haemorrhage (van Gijn *et al*., 1985*a*; Linn *et al*., 1998).

Clinically, there is little to distinguish idiopathic perimesencephalic haemorrhage from aneurysmal haemorrhage. The headache onset is more often gradual (minutes rather than seconds) than with aneurysmal haemorrhage (van Gijn *et al*., 1985*a*; Linn *et al*., 1998), but the predictive value of this feature is poor. Loss of consciousness and focal symptoms are exceptional and then

Table 3 *Causes of SAH*

Cause	Frequency (%)	Site of blood on CT	Characteristic features
Ruptured aneurysm	85	Basal cisterns or none	
Non-aneurysmal perimesencephalic haemorrhage	10	Basal cisterns	Pattern of haemorrhage on CT
Rare conditions	5		
Arterial dissection (transmural)		Basal cisterns	Preceding neck trauma or pain; lower cranial nerve palsy
Cerebral arteriovenous malformation		Superficial	Vascular lesion often visible on CT
Dural arteriovenous fistula		Basal cisterns	History of skull fracture
Vascular lesions around the spinal cord		Basal cisterns	Pain in lower part of neck or in back. Radicular pain or cord deficit
Septic aneurysm		Usually superficial	History; preceding fever or malaise
Pituitary apoplexy		Usually none	Visual or oculomotor deficits; adenoma on CT
Cocaine abuse		Basal cisterns or superficial	History
Trauma (without contusion)		Basal cisterns or superficial	History

only transient; a seizure at onset virtually rules out the diagnosis (Linn *et al*., 1998). On admission, all patients are, in fact, in perfect clinical condition, apart from their headache (van Gijn *et al*., 1985*a*; Rinkel *et al*., 1991*b*). Transient amnesia is found in about one-third and is associated with enlargement of the temporal horns on the initial CT scan (Hop *et al*., 1998*b*). Typically, the early course is uneventful: rebleeds and delayed cerebral ischaemia simply do not occur. Approximately 20% of patients have enlarged lateral ventricles on their admission brain CT scan, associated with extravasation of blood in all perimesencephalic cisterns, which probably causes blockage of the CSF circulation at the tentorial hiatus (Rinkel *et al*., 1992). Only few have symptoms from this ventricular dilatation and even then an excellent outcome can be anticipated (Rinkel *et al*., 1990*a*, *b*). The period of convalescence is short and almost invariably patients are able to resume their previous work and other activities (Rinkel *et al*., 1990*a*; Brilstra *et al*., 1997). Rebleeds after the hospital period have not been documented thus far (Rinkel *et al*., 1991*c*; Canhao *et al*., 1995) and the quality of life in the long term is excellent (Brilstra *et al*., 1997).

A perimesencephalic pattern of haemorrhage may occasionally (in 2.5–5% of cases) be caused by rupture of a posterior fossa aneurysm (Rinkel *et al*., 1991*a*; Pinto *et al*., 1993; Van Calenbergh *et al*., 1993). The chance of finding an aneurysm in 5% of patients has to be weighed against the risks of complications from angiography imposed upon the remaining 95% of patients. In recent years, CTA has been studied as a method to confirm or exclude the presence of an aneurysm in patients with a perimesencephalic pattern of haemorrhage on CT. In a prospectively collected series of 40 patients with either a perimesencephalic haemorrhage or a posterior circulation aneurysm in whom CTA and conventional angiography were performed, radiologists detected an aneurysm in 16 patients and no aneurysm in the remaining 24 patients. These findings were confirmed after reading the angiograms. (Velthuis *et al*., 1999*b*). A formal decision analysis based on these observations indicated that a strategy where CTA is performed and not followed by conventional angiography, if negative, results in a better utility than a strategy where CTA is followed by conventional angiography or if all patients are initially investigated by conventional angiography (Y. M. Ruigrok, G. J. E. Rinkel, E. Buskens, B. K. Velthuis and J. van Gijn, unpublished data).

Arterial dissection

Dissection, in general, tends to be recognized more often in the carotid than in the vertebral artery, but SAH from a dissected artery occurs mostly in the vertebral artery (Fig. 5) (Kaplan *et al*., 1993; Rinkel *et al*., 1993). It is unknown what precise proportion of all SAH cases arise from a dissected vertebral artery. All miscellaneous causes together account for only ~5%, against 85% for aneurysmal haemorrhages and 10% for idiopathic perimesencephalic haemorrhages. In a post-mortem study of fatal SAH, dissection was found in five of 110 patients (Sasaki *et al*., 1991*a*).

Neurological deficits that may accompany SAH from vertebral artery dissection are palsies of the ninth and tenth cranial nerves, by subadventitial dissection (Senter and Sarwar, 1982), or Wallenberg's syndrome (Caplan *et al*., 1988). Rebleeds occur in between 30 and 70% of cases (Caplan *et al*., 1988; Aoki and Sakai, 1990; Yamaura *et al*., 1990; Mizutani *et al*., 1995). The interval can be as short as a few hours or as long as a few weeks. The second episode is fatal in approximately half of the patients.

Dissection of the intracranial portion of the internal carotid artery or one of its branches as a cause of SAH is much less common than with the vertebral artery. Reported cases have affected the terminal portion of the internal carotid artery (Adams *et al*., 1982; Massoud *et al*., 1992), the middle cerebral artery (Kunze and Schiefer, 1971; Sasaki *et al*., 1991*b*; Piepgras *et al*., 1994) and the anterior cerebral artery (Guridi *et al*., 1993).

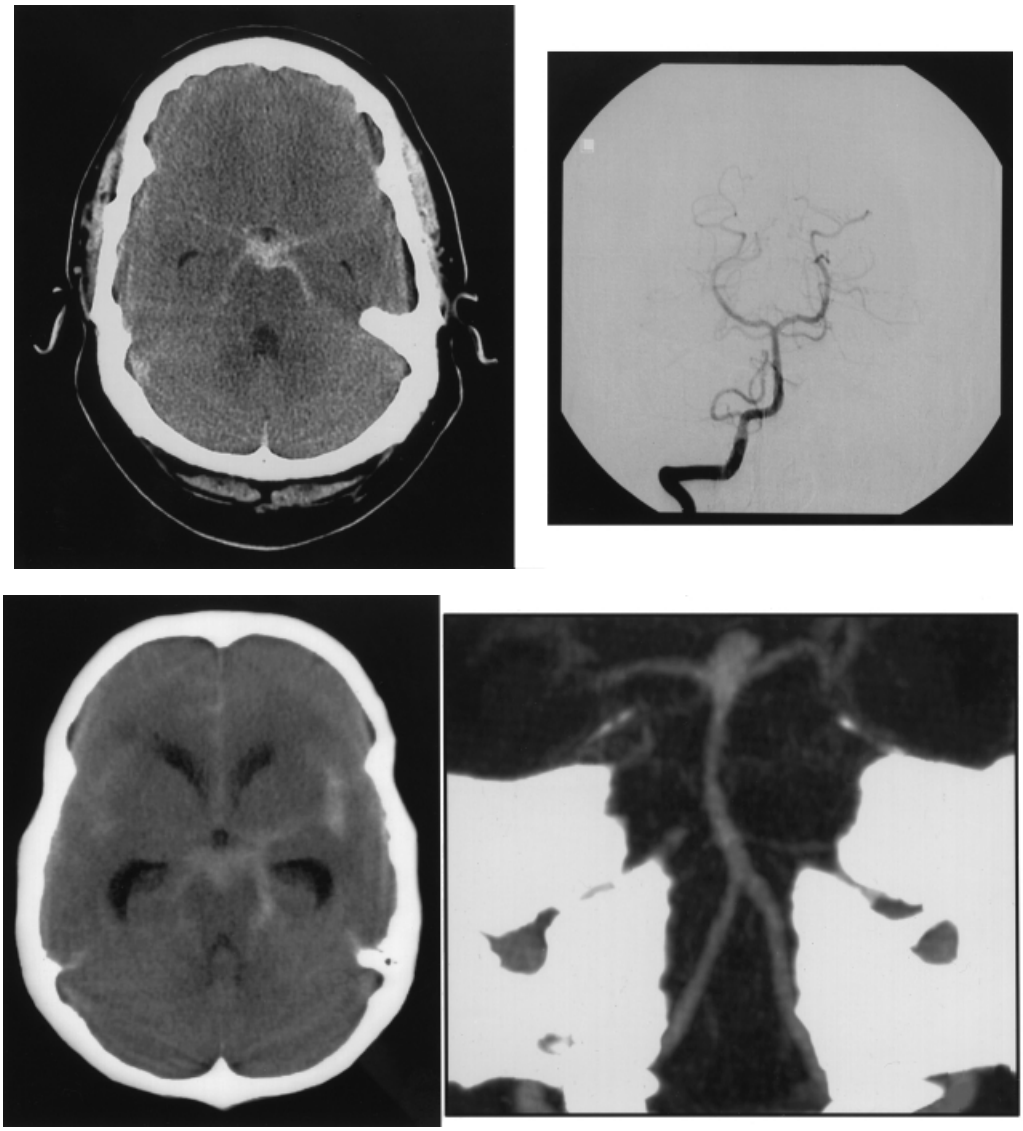

Fig. 3 *Upper panels*: a typical perimesencephalic pattern of haemorrhage. The centre of the bleeding is in the interpeduncular cistern; the haemorrhage extends into both ambient cisterns and the basal parts of the sylvian fissure, but not into the lateral parts of the sylvian fissures or the anterior interhemispheric fissure. The angiogram shows no basilar aneurysm, nor a vertebral artery aneurysm on the right. Angiography of the left vertebral artery was also normal (not shown). *Lower panels*: a patient with the centre of the haemorrhage in the interpeduncular cistern, but with extension into the lateral part of the sylvian fissures and into the anterior interhemispheric fissure. CT angiography shows a basilar tip aneurysm.

Cerebral AVMs

Subarachnoid bleeding at the convexity of the brain may occur from superficial AVMs, but only in <5% of all ruptured AVMs is the extravasation only in the subarachnoid space, without intracerebral haematoma (Fig. 6) (Aoki, 1991). Saccular aneurysms form on feeding arteries of 10–20% of AVMs, presumably because of the greatly increased flow and the attendant strain on the arterial wall. If bleeding occurs in these cases, it is more often from the aneurysm than from the malformation. In those cases the site of the aneurysms is different from the classical sites of saccular aneurysms on the circle of Willis and again the haemorrhage is more often into the brain itself than into the subarachnoid space (Brown *et al*., 1990; Marks *et al*., 1992).

Dural arteriovenous fistulae

Dural arteriovenous fistulae of the tentorium can give rise to a basal haemorrhage that is indistinguishable on CT from aneurysmal haemorrhage (Fig. 7) (Lasjaunias *et al*., 1986; Brown *et al*., 1994). The anomaly is rare and can be found from adolescence to old age. The risk of haemorrhage from dural AVMs depends on the pattern of venous drainage. Patients with direct cortical venous drainage have a relatively

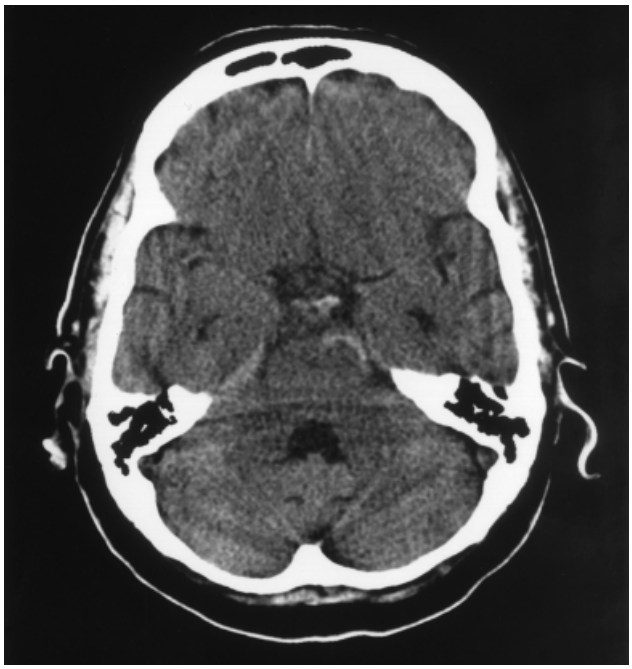

Fig. 4 Perimesencephalic haemorrhage, mainly in the ambient cistern.

high risk, which is further increased if a venous ectasia is present. Patients with drainage into a main sinus have a low risk of haemorrhage and if no reflux occurs into the smaller sinuses or cortical veins, it is negligible (Cognard *et al*., 1995). After a first rupture, rebleeding may occur; in a series of five patients presenting with SAH, three had one or more rebleeds (Halbach *et al*., 1987).

Cervical AVMs

Spinal AVMs present with SAH in ~10% of cases; in >50% of these patients, the first haemorrhage occurs before the age of 20 years (Caroscio *et al*., 1980; Kandel, 1980). Clues pointing to a cervical origin of the haemorrhage are onset with a sudden and excruciating pain in the lower part of the neck, or pain radiating from the neck to the shoulders or arms (Acciarri *et al*., 1992). In the absence of such symptoms, the true origin of the haemorrhage emerges only when spinal cord dysfunction develops, after a delay that may be as short as a few hours or as long as a few years (Kandel, 1980; Swann *et al*., 1984). Rebleeds may occur, even repeatedly (Aminoff and Logue, 1974). CT scanning of the brain in patients with a ruptured cervical AVM may show blood throughout the basal cisterns and ventricles (Acciarri *et al*., 1992). If a cervical origin of the haemorrhage is suspected, MRI or MRA angiography are the first line of investigation, because spinal angiography is impractical without localizing signs or symptoms.

Saccular aneurysms of spinal arteries

Saccular aneurysms of spinal arteries are extremely rare, with recorded incidents in ~12 patients (Handa *et al*., 1992; Mohsenipour *et al*., 1994). As with AVMs of the spinal cord, the clinical features of spinal SAH may be accompanied by those of a transverse lesion of the cord, either partial or complete.

Cardiac myxoma

Cardiac myxoma are uncommon to start with, and if present they may in exceptional cases metastasize to an intracranial artery, infiltrate the wall and thus cause an aneurysm to develop, even >1 year after operation on the primary tumour (Furuya *et al*., 1995).

Septic aneurysms

Infected tissue debris entering the blood stream may lodge in the wall of cerebral arteries and lead to aneurysmal dilatation. The traditional term 'mycotic aneurysms' refers only to fungi and should perhaps be discarded; after all, bacterial endocarditis is more common as an underlying condition than aspergillosis. Most strokes in the context of infective endocarditis are not SAH but (haemorrhagic) infarcts or intracerebral haemorrhages from pyogenic arteritis (Hart *et al*., 1990; Masuda *et al*., 1992; Krapf *et al*., 1999). Aneurysms associated with infective endocarditis are most often located on distal branches of the middle cerebral artery, but ~10% of the aneurysms develop at more proximal sites (Brust *et al*., 1990). Therefore, rupture of a septic aneurysm causes an intracerebral haematoma in most patients, but some have a basal pattern of haemorrhage on CT that is very similar to that of a ruptured saccular aneurysm (Fig. 8). CT-documented rebleeds have been reported (Steinberg *et al*., 1992). Usually patients present with clinical features of infected heart valves before SAH occurs, but sometimes rupture of a septic aneurysm is the initial manifestation of infective endocarditis (Hart *et al*., 1990; Salgado, 1991). Septic aneurysms can be obliterated by surgical or endovascular treatment (Steinberg *et al*., 1992; Frizzell *et al*., 1993), or they may resolve after adequate antibiotic therapy (Brust *et al*., 1990; Corr *et al*., 1995).

Septic aneurysms in patients with aspergillosis are usually located on the proximal part of the basilar or carotid artery (Lau *et al*., 1991). Rupture of such an aneurysm causes a massive SAH in the basal cisterns, indistinguishable from that of a saccular aneurysm (Kowall and Sobel, 1988). Aspergillosis is difficult to diagnose, but should particularly be suspected in patients undergoing long-term treatment with antibiotics or immunosuppressive agents. Most patients with haematogenous dissemination have pulmonary lesions, but X-ray films of the chest may be normal early in the course (Young *et al*., 1970; Kowall and Sobel, 1988).

Severely HIV-infected children may develop cerebral aneurysms secondary to generalized arteriopathy (Husson *et al*., 1992; Shah *et al*., 1996; Dubrovsky *et al*., 1998). In HIV-infected adults, aneurysmal SAH can also be coincidental (Maniker *et al*., 1996).

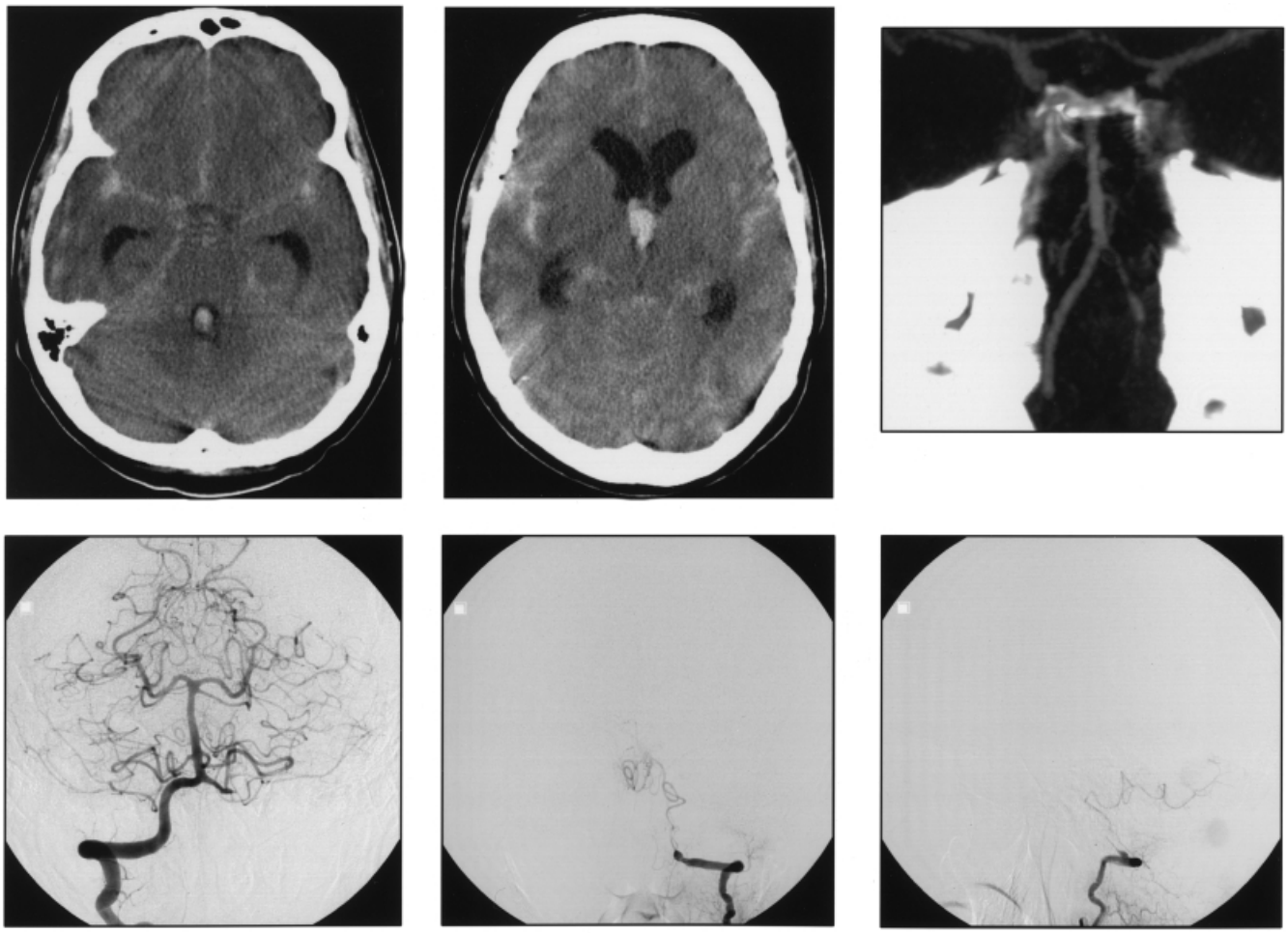

Fig. 5 Subarachnoid haemorrhage from dissection of a vertebral artery. CT angiogram on the day of admission shows irregular narrowing of the left vertebral artery. Intra-arterial angiography 1 week later shows absence of retrograde filling on injection of the right vertebral artery (lower left panel) and a string sign on injection of the left vertebral artery (lower centre and right panels).

Pituitary apoplexy

The precipitating event of arterial haemorrhage occurring in a pituitary tumour is thought to be tissue necrosis, involving one of the hypophyseal arteries. Several contributing factors may precipitate haemorrhagic infarction of a pituitary tumour, such as pregnancy, raised intracranial pressure, anticoagulant treatment, cerebral angiography or the administration of gonadotrophin-releasing hormone (Reid *et al*., 1985; Masson *et al*., 1993). The initial features are a sudden and severe headache (Dodick and Wijdicks, 1998), with or without nausea, vomiting, neck stiffness or a depressed level of consciousness (Reid *et al*., 1985). The hallmark of pituitary apoplexy is that most patients have a sudden decrease in visual acuity: in one series of 15 patients, only two had normal visual acuity. In most patients with pituitary apoplexy eye movements are disturbed as well, because the haemorrhage compresses the oculomotor, trochlear and abducens nerves in the adjacent cavernous sinus (McFadzean *et al*., 1991). Brain CT or MRI scanning indicate the pituitary fossa as the source of the haemorrhage and in most instances the adenoma itself is visible (Post *et al*., 1980; McFadzean *et al*., 1991).

Cocaine abuse

In patients with SAH related to the use of HCl ('crack') cocaine, ~70% have an underlying aneurysm, against 30–40% of those who used the alkaloid form (Levine *et al*., 1991). The pattern of haemorrhage on brain CT may be comparable to that of a ruptured saccular aneurysm (Wojak and Flamm, 1987) and the diagnosis rests on a confirmatory history or on the results of toxicological tests. Rebleeds do occur, even in patients with a normal angiogram, and the outcome is often poor (Mangiardi *et al*., 1988). The source of the haemorrhage in patients without an aneurysm is unknown. Although biopsy-proven vasculitis has been found (Krendel *et al*., 1990), changes suggestive of vasculitis often fail to show up on angiograms, admittedly a very insensitive test (Mangiardi *et al*., 1988; Levine *et al*., 1990).

Anticoagulants

Anticoagulant drugs are seldom the sole cause for SAH. In a series of 116 patients with intracranial, extracerebral haemorrhage while on anticoagulant treatment, seven had

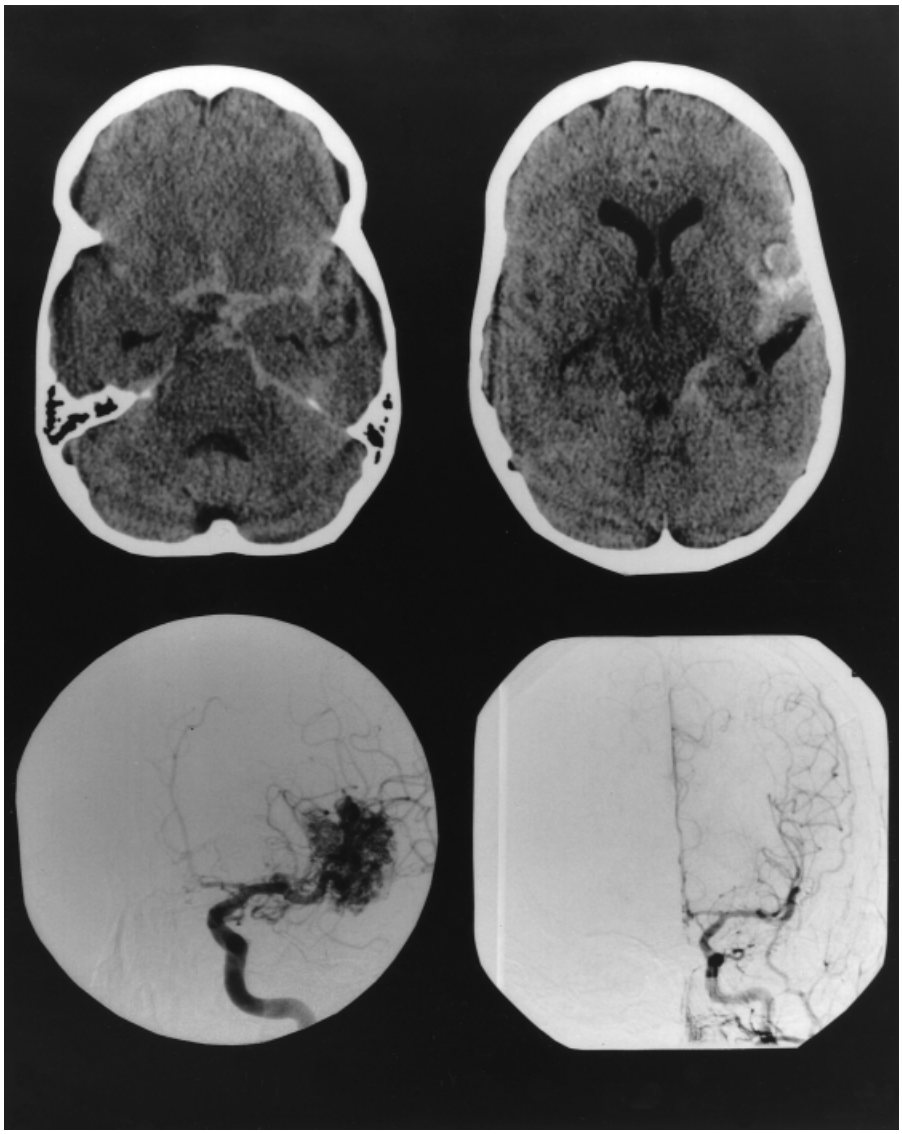

Fig. 6 Subarachnoid haemorrhage from an arteriovenous malformation on the left middle cerebral artery.

only SAH and in only three of these patients was there no cause for the haemorrhage other than anticoagulation (Mattle *et al*., 1989). Severe coagulopathy other than by anticoagulant drugs, e.g. congenital deficiency of factor VII, is also a rare cause of haemorrhage confined to the subarachnoid space (Papa *et al*., 1994). If aneurysmal haemorrhage occurs in a patient on anticoagulants, the outcome is relatively poor (Rinkel *et al*., 1997).

Sickle cell disease

Thirty per cent of patients with sickle cell disease and SAH are children (Carey *et al*., 1990). CT scans in these children show blood in the superficial cortical sulci; angiograms show no aneurysm, but often show multiple distal branch occlusions and a leptomeningeal collateral circulation. The SAH is attributed to rupture of these collaterals (Carey *et al*., 1990). The outcome is poor: only three of 11 recently reviewed children recovered in a good functional state (Carey *et al*., 1990). Most adult patients in whom sickle cell disease underlies SAH have a ruptured aneurysm at the base of the brain.

Superficial siderosis of the CNS

This condition is characterized by iron overload of the pial membranes, through chronic oozing of blood from any source in the subarachnoid space. It has been included in this review only for semantic reasons; the clinical picture is completely different from that with sudden haemorrhages and does not include sudden headache (Tomlinson and Walton, 1964; Bonito *et al*., 1994; Fearnley *et al*., 1995). The clinical syndrome is almost invariably characterized by sensorineural deafness (95%), furthermore by cerebellar ataxia (88%)

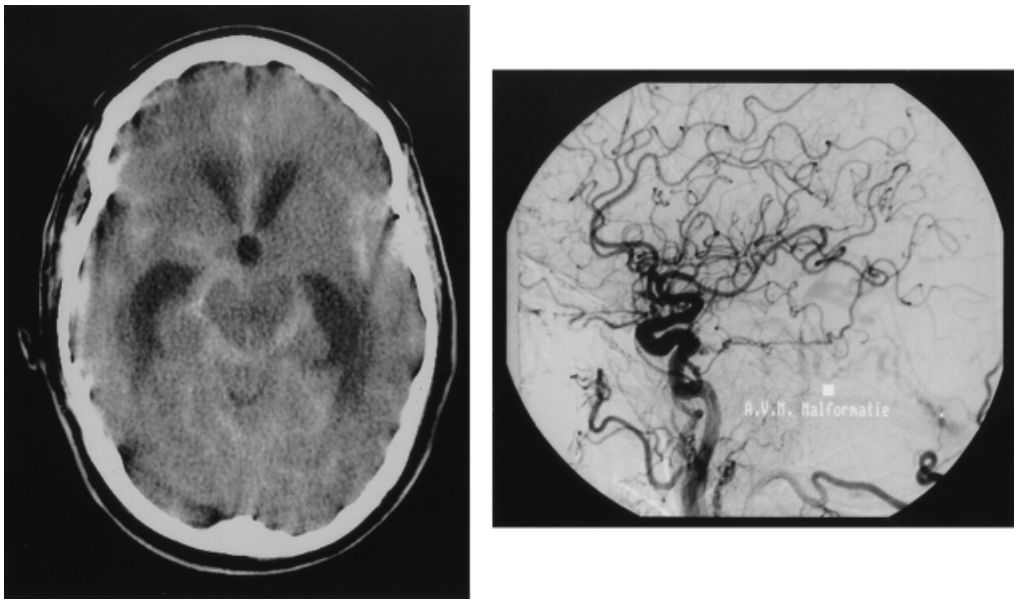

Fig. 7 Subarachnoid haemorrhage in a patient with a dural arteriovenous malformation. Apart from this malformation no aneurysm was found.

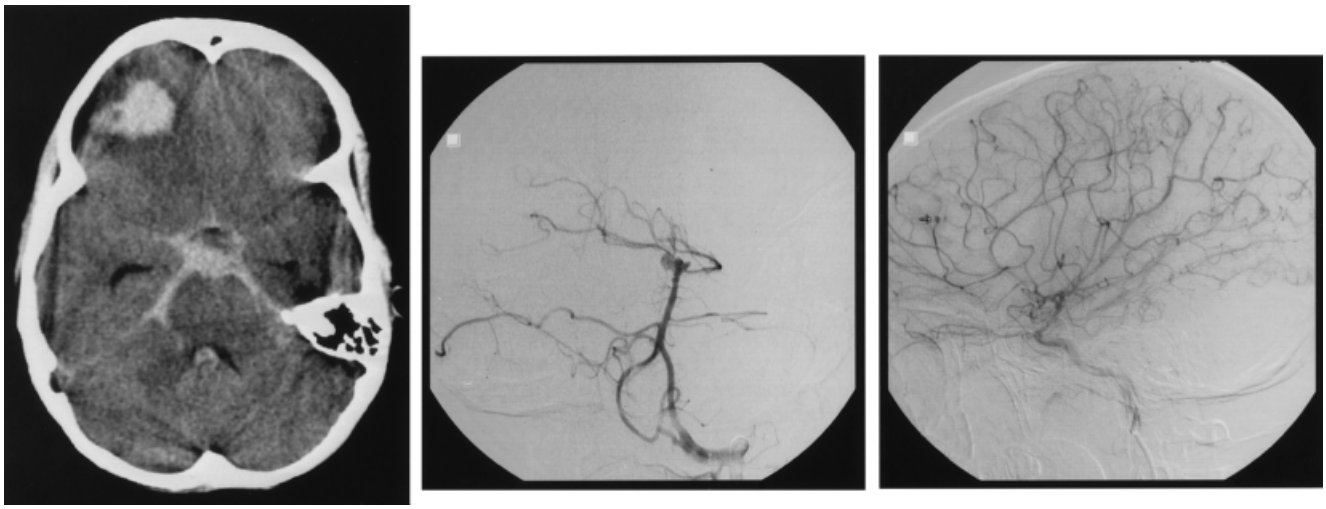

Fig. 8 Subarachnoid haemorrhage and an intracerebral haemorrhage in a patient with multiple septic aneurysms from infective endocarditis.

and pyramidal signs (76%). Possible other features include dementia, bladder disturbance and anosmia. Men are more often affected than women (3 : 1). A source of bleeding has been identified in a little more than half of the cases reported up to 1995 (Fearnley *et al*., 1995). Causes of chronic bleeding include a CSF cavity lesion or cervical root lesion, a vascular tumour (such as an ependymoma) or any other vascular abnormality. Probably the remaining cases are also caused by chronic haemorrhage. The high iron content of the pial membranes cause a characteristic signal on MRI scanning (Bonito *et al*., 1994; River *et al*., 1994; Uchino *et al*., 1997).

Patients without identifiable cause

If angiography is negative, it is essential to take account of the pattern of haemorrhage on the initial CT scan. If this pattern is perimesencephalic, the diagnosis of nonaneurysmal haemorrhage is established and no repeated studies are needed given the absence of rebleeds and the invariably good outcome. Such patients need no longer be on an intensive or medium care unit and can be transferred to a regular ward. Patients with a perimesencephalic haemorrhage can usually be discharged home after a few days and should be reassured that no complications will ensue and that they can take up their lives without any restrictions.

Patients with an aneurysmal pattern of haemorrhage on CT, but a negative angiography, can still develop secondary ischaemia and have a 10% risk of rebleeds (Rinkel *et al*., 1991*c*; Canhao *et al*., 1995). These patients should therefore remain on the intensive or medium care unit. The substantial risk of rebleeding in patients with an aneurysmal pattern of haemorrhage indicates that, at least in some patients, an

aneurysm escapes radiological detection. Apart from technical reasons, such as insufficient use of oblique projections, this phenomenon may have several explanations. Narrowing of blood vessels by vasospasm has been invoked in some cases (Spetzler *et al*., 1974; Bohmfalk and Story, 1980; Moritake *et al*., 1981). Thrombosis of the neck of the aneurysm or of the entire sac is another possible reason (Edner *et al*., 1978). Obliteration of the aneurysm by pressure of an adjacent haematoma may also prevent visualization, particularly with aneurysms of the anterior communicating artery (Spallone *et al*., 1986; Di Lorenzo and Guidetti, 1988; Iwanaga *et al*., 1990).

Given the risk of a later rebleed, it is in patients with an aneurysmal pattern of haemorrhage on CT that repeat angiography seems to be most clearly indicated. The combined yield of a second angiogram in eight reported series was 30 aneurysms in 177 patients (17%) (Ruelle *et al*., 1985; Juul *et al*., 1986; Spallone *et al*., 1986; Suzuki *et al*., 1987; Giombini *et al*., 1988; Cioffi *et al*., 1989; Iwanaga *et al*., 1990; Kaim *et al*., 1996). If it is taken into account that patients with perimesencephalic (non-aneurysmal) haemorrhage were not excluded from these series, the yield of repeat angiograms in patients with a diffuse or anteriorly located pattern of haemorrhage on CT scanning must be even higher. If a second angiogram again fails to demonstrate the suspected aneurysm, perhaps a third angiogram may be positive, after an interval of several months (Di Lorenzo and Guidetti, 1988; Rinkel *et al*., 1991*c*). In a unique, consecutive series of 14 such patients subjected to a third angiogram, one single aneurysm was found (Suzuki *et al*., 1987). MRI may, in exceptional cases, show the expected aneurysm, despite a normal angiogram (Pertuiset *et al*., 1989; Renowden *et al*., 1994).

Early assessment of prognosis in aneurysmal SAH

In the following sections it shall be assumed that the cause of SAH is an aneurysm, unless specifically indicated otherwise. The three baseline variables most closely related to poor outcome in aneurysmal SAH are the neurological condition of the patient on admission, age and the amount of subarachnoid blood on the initial CT scan (Hijdra *et al*., 1988; Kassell *et al*., 1990*b*). Of these three prognosticators, the neurological condition of the patient on admission, particularly the level of consciousness, is the most important determinant (Hijdra *et al*., 1988). Several grading systems have been developed for this initial assessment, in most cases consisting of approximately five categories of severity, in hierarchical order. No single system has gained world-wide acceptance, but until recently the most widely used scales were those of Hunt and Hess (1968) and of Botterell, either in the original version (Botterell *et al*., 1956) or in a modified version (Nishioka, 1966). The constituent features of these grading systems are not only the level of consciousness, but also headache, neck stiffness and focal neurological deficit. Unfortunately, these more or less traditional systems are neither valid nor reliable. Headache and neck stiffness are very poor predictors of outcome in their own right. The construction of these grading scales attributes equal weight to the presence of an impaired level of consciousness, focal deficit or both, the actual grade depending on the severity; and both these features are classified in vague terms. In view of the overlapping and equivocal terminology, it is not surprising that a formal study of observer variability demonstrated large inconsistencies when the same patients were graded by different physicians, on either the Hunt and Hess scale or the Nishioka–Botterell scale (Lindsay *et al*., 1982). Classification into a few levels of the sum score of the Glasgow Coma Scale, which consists of eye-opening, motor response and verbal response (Teasdale and Jennett, 1974), proved more reliable than any of the previous systems used to classify the degree of wakefulness (Lindsay *et al*., 1983). The prognostic value is not the same for all elements of the Glasgow Coma Scale (GCS); e.g. a patient being disoriented rather than alert has stronger implications for outcome than losing a point on the dimensions 'best motor response' or 'eye opening' (Hirai *et al*., 1996). A committee of the World Federation of Neurological Surgeons (WFNS) has proposed a new grading scale of five levels, essentially based on the GCS, with focal deficit making up one extra level for patients with a GCS score of 14 or 13 (Table 4). In other words, the WFNS Scale takes account of the fact that a focal neurological deficit in patients with SAH rarely occurs with a normal level of consciousness and assumes that the presence or absence of such a deficit does not add much to the prognosis in patients with a GCS score of 12 or less (Drake *et al*., 1988). No formal studies of the validity and reliability of the WFNS Scale have yet been undertaken, but at least its core is made up by the GCS.

Table 4 *World Federation of Neurological Surgeons (WFNS) grading scale for patients with SAH (Drake* et al.*, 1988)*

WFNS	Glasgow Coma Scale (sum score)
I	15
II	14 or 13 without focal deficit*
III	14 or 13 with focal deficit
IV	12 to 7
V	6 to 3

*Cranial nerve palsies are not considered a focal deficit.

It is often tacitly assumed that the initial clinical condition is related only to the impact of the first haemorrhage. This is incorrect, as some complications such as early rebleeding or acute hydrocephalus can occur within hours of the original rupture. Particularly, the presence of acute hydrocephalus may be sadly overlooked if the telltale history of increasing drowsiness in the first few hours after the bleed is not properly interpreted (van Gijn *et al*., 1985*b*), but should

Table 5 *General management of patients with aneurysmal SAH*

Nursing
Continuous observation (Glasgow Coma Scale, temperature, ECG monitoring, pupils, any focal deficits)
Nutrition
Oral route preferred, but only with intact cough and swallowing reflexes
If nasogastric tube is necessary:
Deflate endotracheal cuff (if present) on insertion
Confirm proper placement by X-ray
Begin with small test feeds of 5% dextrose
Prevent aspiration by feeding in sitting position and by checking gastric residue every hour
Tablets should be crushed and flushed down (phenytoin levels will not be adequate in conventional doses)
Total parenteral nutrition should be used only as a last resort
Keep stools soft by adequate fluid intake and by restriction of milk content; if necessary add laxatives
Blood pressure
Do not treat hypertension unless there is evidence of progressive organ damage
Fluids and electrolytes
Intravenous line mandatory
Give at least 3 l/day (normal saline)
Insert an indwelling bladder catheter if voiding is involuntary
Compensate for a negative fluid balance and for fever
Monitoring of electrolytes (and leucocyte count), at least every other day
Pain
Start with paracetamol and/or dextropropoxyphene; avoid aspirin
Midazolam can be used if pain is accompanied by anxiety (5 mg intramuscularly or infusion pump)
For severe pain, use codeine or, as a last resort, opiates
Prevention of deep vein thrombosis and pulmonary embolism
Before occlusion of aneurysm: apply compression stockings
After treatment of the aneurysm: fractionated heparin
Medical treatment to prevent secondary ischaemia
Nimodipine 60 mg orally every 4 h; to be continued for 3 weeks

instead be investigated and treated according to the problems that are identified.

Causes of poor clinical condition on admission

A decreased level of consciousness, with the initial haemorrhage or after early rebleeding, may be caused by intracerebral haematoma, subdural haematoma or hydrocephalus. Only by exclusion should it be assumed that the cause is global brain damage as a result of high pressure and subsequent ischaemia.

Early rebleeding

In the first few hours after admission for the initial haemorrhage, up to 15% of patients have a sudden episode of clinical deterioration that suggests rebleeding (Kassell and Torner, 1983; Hijdra *et al*., 1987; Fujii *et al*., 1996). As such sudden episodes often occur before the first CT scan, or even before admission to hospital, a firm diagnosis is difficult and the true frequency of rebleeding on the first day is invariably underestimated.

The question whether patients with a rebleed should be resuscitated and artificially ventilated if respiratory arrest occurs is not academic: in the series of 39 patients with a CT-confirmed rebleed mentioned earlier, 14 had initial respiratory abnormalities that required assisted ventilation. Spontaneous respiration returned within 1 h in eight of these 14 patients and in three more between 1 and 24 h (Hijdra *et al*., 1984).

In a study of episodes of respiratory arrest in which first bleeds were also included, the answer to the question of whether the patient would or would not regain spontaneous respiration could not be predicted from the anatomical site of haemorrhage on CT, the initial presence or absence of brainstem reflexes or the type of respiratory disorder (Hijdra *et al*., 1984). Many patients with initial apnoea who were successfully resuscitated later died from subsequent complications, but survival without brain damage is possible even after respiratory arrest. After resuscitation, it will usually become clear within a matter of hours whether the patient will indeed survive the episode or whether dysfunction of the brainstem will persist.

Intracerebral haematoma

Intraparenchymal haematomas occur in up to 30% of patients with ruptured aneurysms (van Gijn and van Dongen, 1982). Not surprisingly, the average outcome is worse than in patients with purely subarachnoid blood (Hauerberg *et al*., 1994). When a large haematoma is the most likely cause of the poor condition on admission, immediate evacuation of the haematoma should be seriously considered (with simultaneous clipping of the aneurysm if it can be identified), often with the aneurysm having been demonstrated only by MR angiography or CT angiography. Surgical treatment

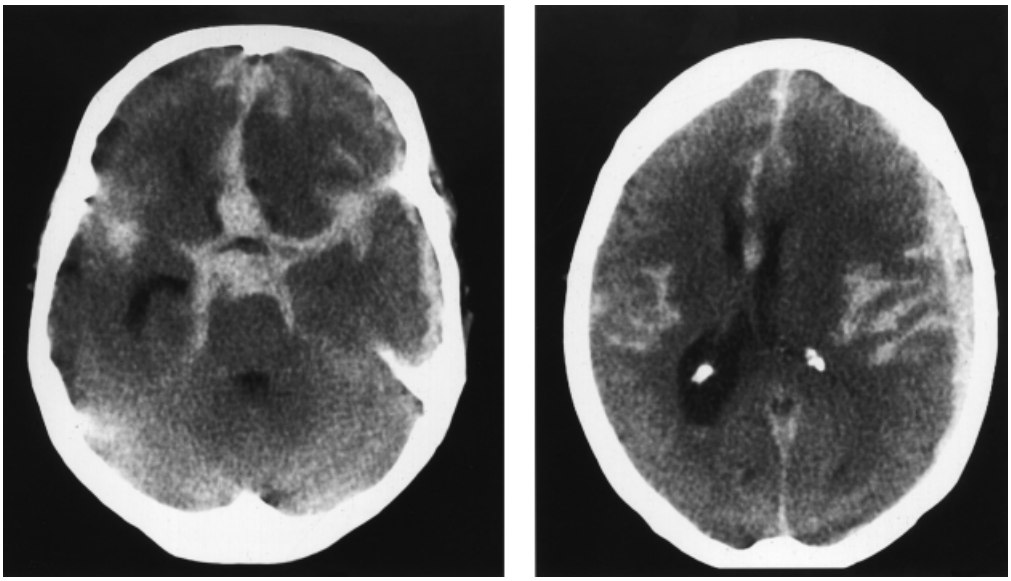

Fig. 9 A patient with SAH who was comatose from the outset. Apart from subarachnoid blood there is also a large subdural haematoma on the left.

may not only be life saving in patients with impending transtentorial herniation, particularly with temporal haematomas, but may even result in independent survival, according to uncontrolled reports (Brandt *et al*., 1987) as well as a small randomized study (Heiskanen *et al*., 1988).

Acute subdural haematoma

An acute subdural haematoma, which is usually associated with recurrent aneurysmal rupture but can also occur with the initial haemorrhage, may be life threatening; in these cases also, immediate evacuation is called for (Fig. 9) (O'Sullivan *et al*., 1994).

Acute hydrocephalus

Gradual obtundation within 24 h of haemorrhage, sometimes accompanied by slow pupillary responses to light and downward deviation of the eyes, is fairly characteristic of acute hydrocephalus (van Gijn *et al*., 1985*b*; Rinkel *et al*., 1990*b*). If the diagnosis is confirmed by CT this can be a reason for early ventricular drainage, although some patients improve spontaneously in the first 24 h.

Acute hydrocephalus with large amounts of intraventricular blood is often associated with a poor clinical condition from the outset (Fig. 10). If such patients are left untreated, >90% have a poor outcome. An indirect comparison of observational studies suggests that insertion of an external ventricular catheter is not very helpful in these patients, but that a strategy where such drainage is combined with fibrinolysis through the drain results in a good outcome in half the patients (Nieuwkamp *et al*., 2000). This needs to be confirmed in studies with concurrent, randomized controls.

Global cerebral ischaemia

Not all patients who arrive moribund can be saved, because irreversible brain damage may have occurred immediately after aneurysm rupture (Fig. 11). In a consecutive series of 31 patients who died on the first day, nine had a potentially treatable supratentorial haematoma and 16 showed dysfunction of the brainstem, associated with massive intraventricular haemorrhage on CT, including distension of the fourth ventricle with blood (in nine cases this occurred together with an intracerebral haematoma). In six patients, however, neither a supratentorial haematoma nor intraventricular haemorrhage could explain the progressive dysfunction of the brainstem and the fatal outcome, the CT scan showing no abnormality other than subarachnoid blood (Hijdra and van Gijn, 1982). The most likely explanation is a prolonged period of global cerebral ischaemia at the time of haemorrhage, as a result of the pressure in the cerebrospinal fluid spaces being elevated to the level of that in the arteries, for as long as a few minutes. This is quite distinct from delayed ischaemia, which is focal or multifocal (see below). Such an immediate and potentially lethal arrest of the circulation to the brain is indeed suggested by autopsy evidence and by the recording of intracranial pressure or transcranial Doppler sonography at the time of recurrent aneurysmal haemorrhage (Smith, 1963; Grote and Hassler, 1988).

Prevention of rebleeding

We mentioned above that early rebleeding, within hours of the initial haemorrhage, occurs in at least 15% of patients. At present it is virtually impossible to prevent this from happening, but medical or surgical intervention can prevent

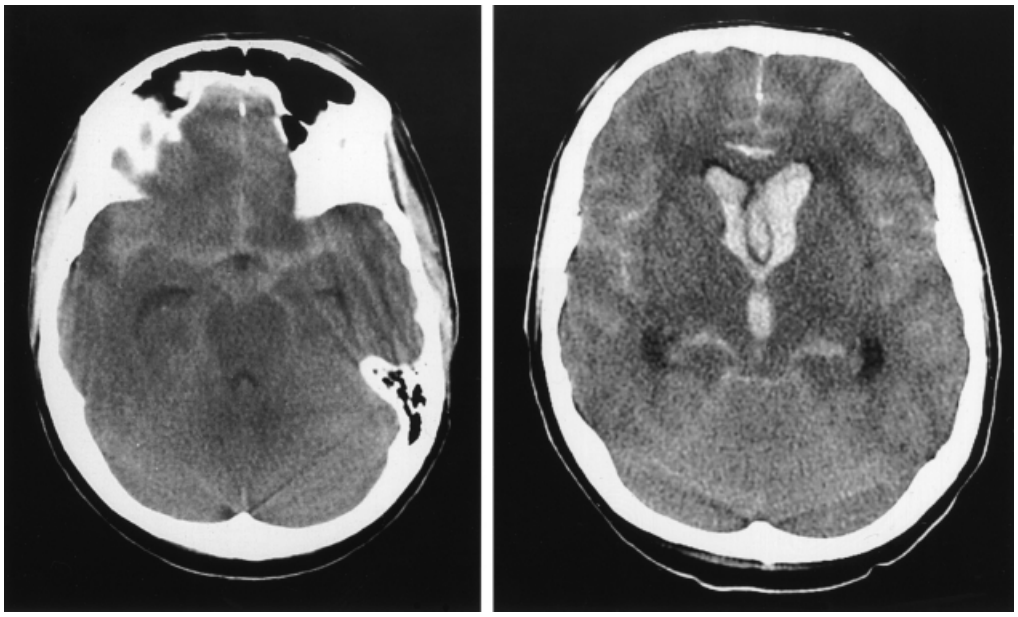

Fig. 10 A patient with SAH who was comatose from the outset. Apart from subarachnoid blood there is complete filling of the frontal horns and third ventricle.

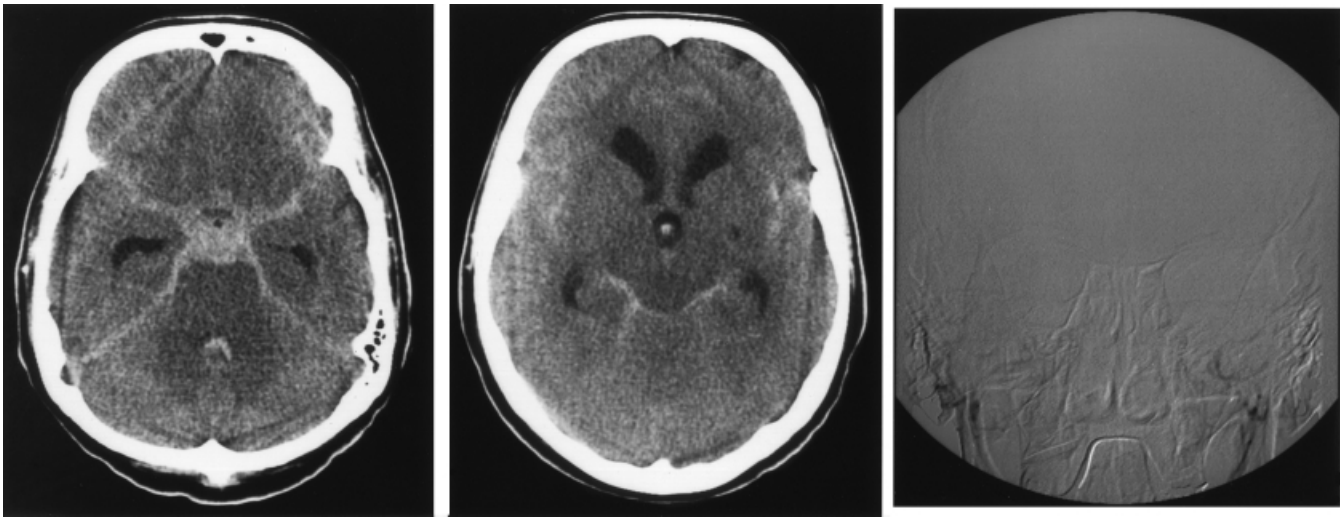

Fig. 11 A patient with SAH who was comatose from the outset. CT shows subarachnoid blood, but no other abnormalities. Angiography performed a few hours later proved absence of intracranial circulation.

recurrent haemorrhages occurring later. In patients who survive the first day, the risk of rebleeding is more or less evenly distributed over the next 4 weeks, although there may be a second peak early in the third week (Hijdra *et al*., 1987). Given that the proportion of patients who eventually rebled was 32% in a consecutive series of patients not treated with antifibrinolytic agents but in whom one-third of the patients had undergone aneurysm clipping around day 12, the total risk of rebleeding without medical or surgical intervention in the 4 weeks after the first day can be estimated at 35–40% (Hijdra *et al*., 1987). Between 4 weeks and 6 months after the haemorrhage, the risk of rebleeding gradually decreases from the initial level of 1–2% a day to a constant level of ~3% a year (Winn *et al*., 1977).

Antifibrinolytic drugs

Medical treatment for preventing rebleeding has not yet been successful; treatment with antifibrinolytic agents does reduce the rebleed rate, but fails to improve overall outcome.

A systematic review of antifibrinolytic agents included eight trials published before 2000 that met predefined inclusion criteria and totalled 937 patients (Roos *et al*., 2000). By far the largest study was a Dutch–Scottish trial (Vermeulen *et al*., 1984). In this meta-analysis, antifibrinolytic treatment did not provide any evidence of benefit on outcome. The risk of rebleeding was significantly reduced by antifibrinolytic therapy, but this was offset by a similar increase of the risk of secondary cerebral ischaemia. In other words, antifibrinolytic drugs work, but they do not help. However, because all trials

in this meta-analysis had been performed before the nineties, at a time when prevention or treatment of secondary cerebral ischaemia had yet to be developed, a new clinical trial on antifibrinolytic therapy has recently been completed in The Netherlands. In this trial, all 492 patients were maximally protected against ischaemia by means of calcium antagonists and normovolaemia. Tranexamic acid again significantly reduced the rate of rebleeding, yet the overall outcome was not different between the two groups, mainly because of cerebral ischaemia (Roos, 2000).

Operative clipping of the aneurysm

Surgical obliteration of the aneurysm has been the mainstay of treatment for decades. Until the 1980s this was deferred until day 10–12 because of the many complications with earlier operations. Since then, many neurosurgeons have adopted a policy of early clipping of the aneurysm, i.e. within 3 days of the initial bleed. The main rationale, of course, is optimal prevention of rebleeding. The theoretical advantages of early operation have not yet been proven by systematic studies, which is an uncomfortable reflection. In the only randomized trial of the timing of operation performed so far, 216 patients were allocated to operation within 3 days, after 7 days or in the intermediate period (Öhman and Heiskanen, 1989). The outcome tended to be better after early than after intermediate or late operation, but as the difference was not statistically significant, a disadvantage could not be excluded. The same result, i.e. no difference in outcome after early or late operation, emerged from the observational studies: a multi-centre study from North America (Kassell *et al*., 1990*a*), and a single-institution review in Cambridge, UK (Whitfield *et al*., 1996). The US study found the worst outcome in patients operated on between day 7 and 10 after the initial haemorrhage. This disadvantageous period for performing the operation in the second week after SAH coincides with the peak time of cerebral ischaemia (Hijdra *et al*., 1986) and of cerebral vasospasm (Weir *et al*., 1978), both phenomena being most common from day 4–12.

Endovascular treatment

Until a few years ago endovascular treatment was restricted to patients in whom the aneurysm was unsuitable for clipping because of the size or location of the aneurysm, or in whom surgical clipping was contraindicated because of the general medical condition of the patient. Since the introduction of controlled detachable coils for the endosaccular packing of aneurysms (Guglielmi *et al*., 1992), endovascular embolization is increasingly used. In some institutes, endovascular embolization is even proposed as the initial method of treatment (Cognard *et al*., 1997).

Numerous observational studies have published complication rates, occlusion rates and short-term follow-up results. These have been summarized, up to March 1997, in a systematic review of 48 eligible studies of ~1383 patients. In 900 of these, the aneurysm had ruptured (Brilstra *et al*., 1999). Permanent complications of the procedure occurred in 3.7% of 1256 patients in whom this was recorded (95% CI 2.7–4.9%). A >90% occlusion of the aneurysm was achieved in almost 90% of patients. The most frequent complication was procedure-related ischaemia, even if patients are treated with heparin. The second most frequent complication is aneurysm perforation, which occurs in 2% of patients. Most of the aneurysms treated with controlled detachable coils were located at the basilar artery, followed by the carotid and anterior communicating arteries. Pericallosal arteries are difficult to reach and these aneurysms constitute thus far only 2% of all aneurysms treated with controlled detachable coils. Another problematic site is the trifurcation of the middle cerebral artery (6% of all aneurysms treated with controlled detachable coils), because one or more of the branches often originate from the aneurysm.

Indirect comparisons between endovascular and surgical treatment are inappropriate, if only because there are so many differences in study design, patients and aneurysms. Moreover, rerupture of aneurysms may occur even months after apparently successful coiling (Manabe *et al*., 1998) and the long-term rates of rebleeding after endovascular coiling still need to be established. A first report from a single centre (Oxford, UK) in which >300 patients had been followed-up after aneurysm embolization for a median period of almost 2 years, showed rebleeding rates of 0.8% in the first year, 0.6% in the second year and 2.4% in the third year, with no rebleeding in subsequent years (Byrne *et al*., 1999). On the other hand, it should not be assumed that surgical treatment is always definitive: in a retrospective review of postoperative angiograms in a series of 66 patients with ruptured aneurysms and 12 additional aneurysms, all treated by surgical clipping, 8% of patients showed aneurysms with a residual lumen or aneurysms that were previously undetected (Macdonald *et al*., 1993). Controlled trials are urgently needed in patients with aneurysms for which it is uncertain whether surgical clipping or endovascular coiling should be the preferred treatment. The first such study, although a small one (109 patients), found no difference in outcome at 3 months between the surgical group and the endovascular group (Vanninen *et al*., 1999).

Prevention of secondary cerebral ischaemia

Delayed cerebral ischaemia occurs mainly in the first or second week after aneurysmal SAH, in up to one-third of patients, depending on case mix operative regimen (Hijdra *et al*., 1986). Despite many years of intensive research, the pathogenesis of secondary cerebral ischaemia following SAH has not been elucidated. It is a generally held belief that after the haemorrhage a thus far unidentified factor is released in the subarachnoid space, which induces vasoconstriction and thereby secondary ischaemia. Also, an often quoted study from Boston (of 41 patients in total) postulates a close relationship between the location of subarachnoid blood and

the 'thickness' of the clot on the one hand and the occurrence of vasospasm and delayed cerebral ischaemia on the other (Kistler *et al*., 1983). Several observations argue against this popular notion. First, the presence of subarachnoid blood, though a powerful predictor of delayed cerebral ischaemia, is not, in itself, a sufficient factor for the development of secondary ischaemia: secondary ischaemia does not occur in patients with a perimesencephalic (non-aneurysmal) SAH (Rinkel *et al*., 1991*b*) and it is rare in patients with SAH secondary to intracerebral haematoma or a ruptured arteriovenous malformation. Secondly, in larger series of patients than the Boston study, the site of delayed cerebral ischaemia does not correspond with the distribution or even the side of subarachnoid blood (Brouwers *et al*., 1992; Hop and Rinkel, 1996). The method of quantifying local amounts of subarachnoid blood in these later studies proved reliable between observers (Hijdra *et al*., 1990), whereas the Boston method (canonized as the Fisher Scale, after the last author), is associated with wide inter-observer variation (Svensson *et al*., 1996). Thirdly, many patients with vasospasm never develop secondary ischaemia. These observations collectively suggest that not only the presence of subarachnoid blood *per se*, but rather the combination with other factors such as the origin of the blood determines whether and where secondary ischaemia will develop.

Despite this lack of pathophysiological insight, some progress has been made in the prevention of secondary ischaemia after aneurysmal SAH by changes in general medical care (notably increased fluid intake and avoidance of antihypertensive drugs) as well as by specific drug treatment. Transcranial Doppler sonography may suggest impending cerebral ischaemia by means of the increased blood flow velocity from arterial narrowing in the middle cerebral artery or in the posterior circulation, but there is considerable overlap with patients who do not develop ischaemia (Sloan *et al*., 1989, 1994). One reason is that narrowing in distal branches of the middle cerebral artery often escapes detection (Okada *et al*., 1999). Only velocities $<$120 cm/s or $>$200 cm/s are reasonably accurate in excluding or predicting delayed ischaemia, respectively, but almost 60% of patients are in the intermediate range (Vora *et al*., 1999). Even then, demonstration of arterial narrowing does not prove, in itself, that clinical deterioration has been caused by ischaemia.

Management of blood pressure

Management of hypertension is a difficult issue in patients with SAH, especially if the blood pressure rises above 200/110 mmHg. Following intracranial haemorrhage, the range between the upper and lower limits of the autoregulation of cerebral blood flow becomes more narrow, which makes the perfusion of brain more dependent on arterial blood pressure (Kaneko *et al*., 1983). Consequently, aggressive treatment of surges of blood pressure entails a definite risk of ischaemia in areas with loss of autoregulation. The rationalistic approach is therefore to advise against treating hypertension following aneurysmal rupture. The empirical evidence for this advice is sparse, but tends to support the avoidance of antihypertensive drugs. In an American Cooperative Study conducted between 1963 and 1970, 1005 patients with ruptured aneurysms were randomized between four treatment modalities; one arm consisted of drug-induced lowering of the blood pressure, another of bed rest alone (the other two arms were surgical: carotid ligation and intracranial surgery). In the intention-to-treat analysis, antihypertensive drugs failed to reduce either case fatality or the rate of rebleeding within the first 6 months after the initial event. On-treatment analysis suggested that induced hypotension did decrease the rate of rebleeding in comparison with bed rest, but not the case fatality (Torner *et al*., 1981). It should be kept in mind, however, that the diagnosis of rebleeding had to be made in the pre-CT era and was therefore probably inaccurate. An observational study from the 1980s, in which all events had been documented by means of serial CT scanning, compared patients in whom hypertension had been newly treated with normotensive controls. The rate of rebleeding was lower but the rate of cerebral infarction was higher than in untreated patients, despite the blood pressures being, on average, still higher than in the controls (Wijdicks *et al*., 1990). All this suggests that hypertension after SAH is a compensatory phenomenon, at least to some extent, and one that should not be interfered with. In keeping with this, a further observational study suggested that the combined strategy of avoiding antihypertensive medication and increasing fluid intake may decrease the risk of cerebral infarction (Hasan *et al*., 1989).

It seems best to reserve antihypertensive drugs (other than those the patients were on already) for patients with extreme elevations of blood pressure as well as evidence of rapidly progressive end organ deterioration, diagnosed from either clinical signs (e.g. new retinopathy, heart failure, etc.) or laboratory evidence (e.g. signs of left ventricular failure on chest X-ray, proteinuria or oliguria with a rapid rise of creatinine levels).

Fluid balance and electrolytes

Fluid management in SAH is important to prevent a reduction in plasma volume, which may contribute to the development of cerebral ischaemia. Nevertheless, the arguments for a liberal (some might say aggressive) regimen of fluid administration are indirect. In approximately one-third of the patients, plasma volume drops by $>$10% within the preoperative period, which is significantly associated with a negative sodium balance; in other words, there is loss of sodium as well as of water (Wijdicks *et al*., 1985*a*; Hasan *et al*., 1990). Moreover, fluid restriction in patients with hyponatraemia is associated with an increased risk of cerebral ischaemia (Wijdicks *et al*., 1985*b*). Fluid restriction was applied in the past because hyponatraemia was erroneously attributed to water retention, via inappropriate secretion of antidiuretic hormone. Two non-randomized studies with

historical controls suggested that a daily intake of at least 3 l of saline (against 1.5–2.0 l in the past) was associated with a lower rate of delayed cerebral ischaemia and a better overall outcome (Hasan *et al*., 1989; Vermeij *et al*., 1998). The interpretation of these two studies is difficult not only because of their observational nature, but also because the liberal administration of saline in the second period was confounded by avoidance of antihypertensive drugs. The only randomized study of hypervolaemia that has been published included only 30 patients (Rosenwasser *et al*., 1983). Treatment allocation was not blinded (personal information obtained from the authors) and outcome was not assessed beyond the time of operation (day 7–10). At that time, the rate of delayed ischaemia had been reduced by two-thirds (67%; 95% CI 1–89%).

Despite the incomplete evidence, it seems reasonable to prevent hypovolaemia. We favour giving 2.5–3.5 l/day of normal saline, unless contraindicated by signs of impending cardiac failure. Nevertheless, it appears that many patients need a daily fluid intake of 4–6 l (sometimes as much as 10 l) to balance the production of urine plus estimated insensible losses (via perspiration and expired air). Fluid requirements may be guided by recording of central venous pressure (directly measured value should be >8 mmHg) or pulmonary wedge pressures (to be maintained at >7 mmHg), but frequent calculation of fluid balance (four times per day until approximately day 10) is the main measure for estimating how much fluid should be given. Fluid intake should be increased proportionally in patients with fever, whatever the cause.

Calcium antagonists

Initially, the rationale for the use of calcium antagonists in the prevention or treatment of secondary ischaemia was based on the assumption that these drugs reduce the frequency of vasospasm by counteracting the influx of calcium in the vascular smooth muscle cell. This anti-vasospastic effect of calcium antagonists was confirmed by many *in vitro* studies with intracranial arteries and also by *in vivo* assessments of arterial lumen changes after experimental SAH. Clinical trials have been undertaken with three types of calcium antagonists: nimodipine, nicardipine and AT877, of which nimodipine is the most extensively studied and used. A recent systematic review of all randomized controlled trials on calcium antagonists in patients with SAH showed a significant reduction in frequency of poor outcome, which resulted from a reduction in the frequency of secondary ischaemia (Feigin *et al*., 2000). When analysed separately, the nimodipine trials showed a significant reduction in the frequency of poor outcome, but the nicardipine and AT877 trials did not. On the other hand, nicardipine and AT877 significantly reduce the frequency of vasospasm, whereas the nimodipine trials showed only a trend towards reduction of vasospasm, despite a larger number of patients included. In brief, administration of nimodipine improves outcome in patients with SAH, but it is uncertain whether nimodipine acts through neuroprotection, through reducing the frequency of vasospasm, or both. Nicardipine and AT877 definitely reduce the frequency of vasospasm, but the effect on overall outcome remains unproved, which again underlines the weak relation between vasospasm and outcome.

The practical implications are that the regimen employed in the dominant nimodipine trial (60 mg orally every 4 h, to be continued for 3 weeks) is currently regarded as the standard treatment in patients with aneurysmal SAH. If the patient is unable to swallow, the tablets should be crushed and washed down a nasogastric tube with normal saline. Yet the entire evidence about efficacy and dosage of nimodipine hinges on a single, large clinical trial (Pickard *et al*., 1989). Because the results might be affected by unpublished negative trials, the benefits of nimodipine cannot be regarded as being beyond all reasonable doubt.

Neuroprotective drugs other than calcium antagonists

Tirilazad has been studied in four randomized, controlled trials, totalling >3500 patients (Kassell *et al*., 1996; Haley *et al*., 1997; Lanzino and Kassell, 1999; Lanzino *et al*., 1999). This drug belongs to the category of 21 amino steroids that inhibit iron-dependent lipid peroxidation. The only beneficial effect on overall outcome was seen in a single subgroup of a single trial, i.e. those treated with 6 mg/kg/day (two other groups received 0.2 or 2 mg/kg/day) (Kassell *et al*., 1996). This possible benefit could not be reproduced in the corresponding subgroup from a parallel trial (Haley *et al*., 1997), nor in two further trials with an even higher dose (15 mg/kg/day) in women (Lanzino and Kassell, 1999; Lanzino *et al*., 1999); the gender distinction was made because in the first two trials, women had seemed to respond less than men to tirilazad mesylate.

A single trial with another hydroxyl radical scavenger, *N′*-propylenedinicotinamide (nicaraven), in 162 patients showed a decreased rate of delayed cerebral ischaemia but not of poor outcome at 3 months after SAH (Asano *et al*., 1996). Curiously enough, the opposite was found in a trial of 286 patients with ebselen, a seleno-organic compound with antioxidant activity through a glutathione peroxidase-like action: improved outcome at 3 months after SAH, but without any reduction in the frequency of delayed ischaemia (Saito *et al*., 1998).

Aspirin and other antiplatelet agents

Several studies have found that blood platelets are activated from day three after SAH, mostly through increased levels of thromboxane B_2, the stable metabolite of thromboxane A_2, a substance that promotes platelet aggregation and vasoconstriction (Vinge *et al*., 1988; Juvela *et al*., 1990; Ohkuma *et al*., 1991). The practical question is whether

interventions aimed at counteracting platelet activation are therapeutically useful. A retrospective analysis of 242 patients who had survived the first 4 days after SAH showed that patients who had used salicylates before their haemorrhage (as detected by history and urine screening) had a significantly decreased risk of delayed cerebral ischaemia, with or without permanent deficits (relative risk 0.40; 95% CI 0.18–0.93) (Juvela, 1995). A first clinical trial was done in as early as 1982, which failed to show benefit from aspirin (Mendelow *et al*., 1982), but the number of patients was small (53), unoperated patients were also included and all were treated with tranexamic acid, which increases the risk of ischaemia (see above). There is a need for a prospective and randomized study of salicylates or other antiplatelet drugs as a preventive measure against delayed cerebral ischaemia, preferably after clipping of the aneurysm to avoid rebleeding being precipitated by the antiplatelet and so antihaemostatic action. A pilot study of aspirin after early operation in 50 patients has shown that this treatment is feasible and probably safe (Hop *et al*., 2000).

Four antiplatelet agents other than aspirin have been tested in separate trials of patients with SAH: dipyridamole (100 mg/day orally or 10 mg/day intravenously) in 320 patients (Shaw *et al*., 1985); the thromboxane A_2 synthetase inhibitor nizofenone (10 mg/day intravenously) in 77 patients (Saito *et al*., 1983); the thromboxane A_2 synthetase inhibitor cataclot (1 g/kg/min intravenously) in 24 patients (Tokiyoshi *et al*., 1991); and the experimental antiplatelet agent OKY-46 (160 or 800 mg orally) in 256 patients (Suzuki *et al*., 1989). In a systematic overview of these four trials and the two aspirin trials mentioned above, the rate of poor outcome was not significantly different between patients treated with antiplatelet agents and controls (S. Raup, J. W. Hop, G. J. E. Rinkel, A. Algra and J. van Gijn, unpublished review).

Other strategies to prevent delayed cerebral ischaemia

Prophylactic volume expansion in patients with aneurysmal SAH has been applied in three small randomized trials. In one of these, with only 30 patients, the treatment was started preoperatively; the rate of ischaemic episodes decreased significantly, but no information was given on long-term outcome (Rosenwasser *et al*., 1983). Two other studies randomized patients after aneurysm clipping, but reported only physiological surrogate measures and not functional outcome (Mayer *et al*., 1998; Lennihan *et al*., 2000).

Calcitonin-gene-related peptide is a potent vasodilatator, but in a randomized clinical trial, no effect of this drug was found (European CGRP in Subarachnoid Haemorrhage Study Group, 1992). Another strategy aimed at reducing the frequency of vasospasm is lysis of the intra-cisternal blood clot with intrathecally administered recombinant tissue plasminogen activator, but a clinical trial in 100 patients failed to show a reduction in the rate of secondary ischaemia or improvement in outcome (Findlay *et al*., 1995).

Prophylactic transluminal balloon angioplasty has been advocated (Muizelaar *et al*., 1999), but there are no controlled studies to support this.

Treatment of delayed cerebral ischaemia

Treatment with hypervolaemia, haemodilution and induced hypertension, the so-called triple H therapy, has become widely used, although evidence from clinical trials is still lacking.

Since the 1960s, induced hypertension has been used to combat ischaemic deficits in patients with SAH (Farhat and Schneider, 1967; Kosnik and Hunt, 1976). Later, induced hypertension was often combined with volume expansion. In a series of patients with progressive neurological deterioration and angiographically confirmed vasospasm, the deficits could be permanently reversed in 43 of 58 cases (Kassell *et al*., 1982). In 16 patients who had responded to this treatment, the neurological deficits recurred when the blood pressure transiently dropped, but again resolved when the pressure increased. The most plausible explanation for these phenomena is a defect of cerebral autoregulation that makes the perfusion of the brain passively dependent on the systemic blood pressure. The risks of deliberately increasing the arterial pressure and plasma volume include rebleeding of an unclipped aneurysm, increased cerebral oedema or haemorrhagic transformation in areas of infarction (Amin-Hanjani *et al*., 1999), myocardial infarction and congestive heart failure.

Few centres have experience with the endovascular approach in the treatment of symptomatic vasospasm after SAH (Higashida *et al*., 1989; Newell *et al*., 1989; Nichols *et al*., 1994; Firlik *et al*., 1997; Bejjani *et al*., 1998; Eskridge *et al*., 1998). These reports document sustained improvement in more than half of the cases (the total numbers were 10–20 in each of the first four studies and 31 and 50 in the two most recent ones), but the series were uncontrolled and evidently there must be publication bias. Rebleeding can be precipitated by this procedure, even after the aneurysm has been clipped (Newell *et al*., 1989; Linskey *et al*., 1991). Hyperperfusion injury has also been reported (Schoser *et al*., 1997). In view of the risks, the high costs and the lack of controlled trials, transluminal angioplasty should presently be regarded as a strictly experimental procedure. The same applies to uncontrolled reports of improvement of ischaemic deficits after intra-arterial infusion of papaverine, following super-selective catheterization (Kaku *et al*., 1992; Elliott *et al*., 1998; Fandino *et al*., 1998); moreover, not all these impressions are positive (Polin *et al*., 1998).

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