

# Acute Operation and Preventive Nimodipine Improve Outcome in Patients with Ruptured Cerebral Aneurysms

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Sixty-five patients with ruptured aneurysms were operated upon within 48 to 72 hours after subarachnoid hemorrhage (SAH) and were treated with a regimen of intra- and postoperative nimodipine for the prevention of symptomatic vasospasm. The clinical grading (Hunt and Hess) was I to III in 49 patients and IV or V in 16. The SAH was mild in 15 patients, moderate in 27, and severe in 23; 12 patients harbored an intracerebral hematoma, and 6 had intraventricular bleeding. Acute hydrocephalus was observed on preoperative computed tomography (CT) in 19 patients. On CT 3 days postoperatively (i.e., Day 3–4 after SAH), 30 of 65 patients still had subarachnoid blood; however, severe symptomatic vasospasm as the deciding threatening event during the delayed postoperative period was not encountered in this series. Transient symptoms of ischemia were noted in 2 patients (3%) and were accompanied by angiographic spasm in 1. Irreversible neurological deficit occurred in 2 patients (3%); in 1 of these, it was a complication of postoperative control angiography. Of the patients preoperatively graded I or II, 96% had an excellent to fair outcome 6 months postoperatively, and 1 patient (4%) had died because of a surgical complication. Among patients preoperatively graded III or IV, 86% had an excellent to fair outcome, and the remaining 14% had a poor outcome. Shunt-dependent hydrocephalus developed in 7% of the patients. Acute surgical repair of ruptured cerebral aneurysms and preventive topical and intravenous administration of nimodipine reduce management complications and improve outcome; above all, ischemic lesions from symptomatic vasospasm are reduced to a minimum. (*Neurosurgery* 15:57–66, 1984)

Key words: Angiography, Cerebral aneurysm rupture, Computed tomography, Outcome assessment, Subarachnoid hemorrhage, Transient ischemia, Vasospasm

## INTRODUCTION

During the early days of neurosurgery, the results from the operation of cerebral aneurysms were so discouraging that surgical treatment did not seem to improve the natural course of the disease once an aneurysm had ruptured (23, 42). Despite the introduction of the operating microscope and the perfection of microsurgical techniques, the management mortality after acute admission and delayed operation calculated from the day of subarachnoid hemorrhage (SAH) was still very high, ranging between 34 and 72% (34, 68). There was a high rate of complications occurring mostly before operation so as to jeopardize the potential benefit of technically perfect microsurgery (31, 49). Two main events are responsible for complications in patients who survive the initial SAH, namely, recurrent hemorrhage and delayed ischemic symptoms from cerebral vasospasm (2, 12, 14, 17, 19, 34, 43, 51, 65).

Vasospasm has been described as a biphasic process. There is a more or less unimportant acute phase. The late phase is often but not always clinically relevant. It usually appears 5 to 8 days but sometimes as late as 2 weeks after the first SAH (2, 34, 37, 38, 53, 55, 57, 65, 70). However, the late phase appears earlier after repeated SAH (38).

In our personal unpublished series of 55 patients, we planned to operate after Day 6 following SAH. The rebleeding rate was 22%, and the mortality among rebleeders was 50%. Symptomatic vasospasm occurred in 20% of the patients who survived the acute phase after SAH. Altogether, preoperative complications due to rebleeding or vasospasm occurred in 30% of the cases; 50% of these patients died before operation.

Earlier attempts to solve the problems of rebleeding and vasospasm by operation within the 1st week after the last SAH caused a "forbiddingly high" surgical mortality of more than 50% (52) and definitively introduced the era of delayed

operation performed on clinically stabilized patients. The overall management results have been improved little by microsurgical and anesthesiological techniques, and acute operation has again been advocated (29, 33, 39, 46, 55, 59, 60, 62, 65, 66, 68, 69) to prevent those secondary processes that influence outcome and prognosis (rebleeding and vasospasm) by repair of the aneurysm and evacuation of blood clots from the subarachnoid space. An interval of 48 to 72 hours from SAH to operation was proposed because the high surgical mortality after acute operation derived from interventions performed on Days 3 to 7, whereas the mortality was low on Days 1 and 2 (56, 59, 74).

These procedures seemed to improve the overall outcome of patients (34, 65), although the incidence of ischemic deficits from vasospasm was still not reduced substantially (34, 55, 57, 65, 72). In the first series of patients operated upon acutely, 20 to 30% deteriorated during a later postoperative stage concomitantly with severe angiographically demonstrated vasospasm (34, 48, 65, 72). Symptoms seemed to be less severe and more easily reversible. The major problem in the treatment of SAH from ruptured aneurysms remains the management of arterial spasm and cerebral ischemia (38, 44, 54, 57).

Several pharmacological approaches have been tried to prevent or treat vasospasm, but none of the clinical trials could prove a convincingly better outcome (for references, see Ref. 71). Recently, the cerebrovascular effect of calcium antagonists was studied both in animal experiments and in patients: thus, the lipophilic, predominantly cerebroarterial dilatory drug nimodipine was shown to have a long-lasting effect when administered locally or systemically (4–6, 8, 64) and to increase cerebral blood flow (18, 21, 25–27, 35). In a previous study, the aim was to treat vasospasm by the topical administration of nimodipine via a cisternal catheter as soon as spasm was proven on angiography. For several reasons, the

results were not as good as had been expected (6). Therefore, it seemed more promising to prevent vasospasm after acute operation by administering the calcium antagonist nimodipine both locally and systemically.

### SELECTION OF PATIENTS AND METHODS

Of 97 consecutive and unselected patients admitted between September 1981 and December 1983 and graded I to V following the scale of Hunt and Hess (30), 68 patients were admitted acutely after SAH to allow operation within 48 hours (patients graded III to V) to 72 hours (patients graded I or II). Three patients could not undergo the planned treatment protocol, 1 because of unclipped multiple aneurysms, 1 because of severe hepatic disease, and 1 for technical reasons. The remaining 65 patients are the subjects of this study.

The mean age of the 65 patients was 45 years (range, 13 to 80 years). Thirty-three were female, and 32 were male.

#### Perioperative evaluation

Preoperative neurological symptoms were classified according to the scale of Hunt and Hess (30). Preoperatively, all patients underwent four-vessel angiography performed with the Seldinger technique by transfemoral catheterization. The location of the aneurysms is indicated in Table 1.

Vasospasm on preoperative angiograms was described with the scale that is being used in the ongoing International Cooperative Study on the Timing of Aneurysm Surgery and Acute Subarachnoid Hemorrhage (Table 2). Postoperative angiography was performed because of transient ischemic symptoms in two patients and rebleeding in one and was also performed in one asymptomatic patient.

Preoperative computed tomography (CT) was performed in all except two patients. Postoperative CT was performed on Days 3, 7, 10, and 14 after operation and at 3 to 6 months. SAH shown by CT was classified in three groups as summarized in Table 3. The computed tomographic diagnoses were made by two investigators not informed about the clinical condition and course of the patients (7). If the extent of SAH

TABLE 1  
Location of Aneurysms

Location <sup>a</sup>	No. Patients
MCA	15
A-COM	28
ICA	12
ACA (A <sub>2</sub> )	4
BAS	2
2 aneurysms	4
Total	65

<sup>a</sup> Abbreviations: MCA, middle cerebral artery; A-COM, anterior communicating artery; ICA, internal carotid artery; ACA, anterior cerebral artery; BAS, basilar artery.

TABLE 2  
Vasospasm on Preoperative Angiogram

Grade	No. Patients
0 (none)	48
I (local < 50%)	12
II (local > 50%)	4
III (diffuse, severe)	1
Total	65

TABLE 3  
Extent of SAH as Diagnosed from Preoperative CT and Operation

SAH Grade	Description of SAH	No. Patients
1—mild	Thin, localized layer	15 (2) <sup>a</sup>
2—moderate	Thick layer in two of three subarachnoid compartments (basal cisterns, sylvian fissures, interhemispheric space) or one subarachnoid compartment and the cortical surface	27 (4)
3—severe	Severe, diffuse SAH with thick layers in all three subarachnoid compartments or subarachnoid compartments and the cortical surface	23 (12)
Total		65 (18)
	Other Lesions	No. Patients
	Intracerebral hematoma	11 (1)
	Intraventricular hemorrhage	6 (2)
	Subdural hematoma	1 (0)

<sup>a</sup> Numbers in parentheses, number of patients with preoperative acute hydrocephalus shown by CT.

as encountered during operation was essentially different from the diagnosis made by CT, this circumstance was considered in the description of preoperative SAH as shown in Table 3. A difference was observed in only eight patients: six with mild SAH intraoperatively and normal CT and two with normal CT and significant SAH intraoperatively, presumably due to rebleeding when anesthesia was induced.

#### Surgical procedures

In two-thirds of the cases, the operation was performed by the author; as acute operation became increasingly institutionalized as a routine procedure, three more neurosurgeons who specialize in microsurgery (Dr. G. Clarici, Dr. H. Tritthart, and Dr. P. W. Ascher) performed the interventions.

Anesthesia was induced with pentobarbital and was continued with a neuroleptanalgesic. The use of controlled hypotension was restricted to a few patients with complicated aneurysms and premature rupture. Temporary clipping was used only in a very few complicated cases; hypertension was not induced in these patients. Intravenous mannitol and hyperventilation for the reduction of brain volume were used in a few patients, but not regularly. Ventricular drainage via the right frontal horn was performed in all patients, and 50 to 70 ml of cerebrospinal fluid (CSF) were usually withdrawn during the intervention. In 60 patients, the tube was left in place for postoperative drainage for a maximal duration of 12 days (average, 6 days).

In five patients with an anterior communicating or pericallosal aneurysm and extensive accumulation of blood in the interhemispheric space, we performed an interhemispheric approach via a bifrontal craniotomy. In all other cases, a frontotemporal craniotomy was performed (73) and the aneurysm was attacked by the transsylvian or intrasylvian approach. As much as possible of the subarachnoid blood was removed atraumatically by suction and irrigation with Ringer's solution. In cases with thick clots in the interhemispheric space and in one or both sylvian fissures, blood could be evacuated from only one of these subarachnoid compartments and from the basal cisterns.

*Pharmacological treatment*

All patients were treated using the lipophilic calcium antagonist nimodipine intra- and postoperatively following the treatment protocol as elsewhere specified for an open multicenter study (5). After the ruptured aneurysm was clipped, a  $2.4 \times 10^{-5}$  M solution of nimodipine in Ringer's solution was applied locally around the vessels in the operating field for 10 minutes. Immediately thereafter, an intravenous infusion of 0.25 to 0.5  $\mu$ g of nimodipine per kg per minute was started; this was continued until Day 14 after SAH. Then 60 mg of nimodipine was given p.o. 4 times a day until Day 21 after SAH. In five patients, the plasma and CSF levels of nimodipine were estimated during i.v. and p.o. treatment.

*Follow-up examinations and assessment of outcome*

After the patients left the hospital, neurological follow-up examinations were performed 1, 3, and 6 months postoperatively. Six months after operation, the examination was performed by a neurologist not involved in the treatment of these patients and uninformed about their clinical course. The clinical outcome was assessed according to the scale shown in Table 4, which is used for the International Cooperative Study on the Timing of Aneurysm Surgery and Acute Subarachnoid Hemorrhage. Patient data from the period of hospitalization and from follow-up investigations were stored in and evaluated with the aid of a PDP 1134 computer (Digital Equipment Corp. Maynard, Massachusetts) and a software package developed by G. Gell (20).

## RESULTS

## Preoperative Findings

The findings on preoperative CT, the location of the aneurysms, the extent of vasospasm indicated by preoperative angiography, and the clinical grades are indicated on Tables 1 to 3 and 5.

## Surgical Procedure

Initial "brain swelling" after opening of the dura mater was noted in almost all cases, although to a varying extent. External ventricular drainage resulted in a prompt reduction of cerebral volume in all except five patients. Cerebral swelling

in these five patients did not hinder our reaching the surgical goal in three patients graded III or IV (Hunt and Hess). No immediate postoperative deterioration was noted in these three patients. Subarachnoid blood clots were left after operation in 30 patients, as documented by postoperative CT 3 days later (Table 6). Leakage or rupture of the aneurysm during preparation occurred in 21 of the 65 patients and was treated without complications in 16.

## Complications during Operation

Ten of the 65 patients experienced surgical complications followed by clinical deterioration on awakening from anesthesia (Table 7). In 5 patients, massive rupture of the aneurysm occurred before the preparation of surrounding arachnoid structures was completed. Consequently, massive hemorrhage induced hemorrhagic hypotension in 2 patients; a temporary clip was placed on the major feeding vessel in 4 cases. A small infarct was seen on postoperative CT in 5 patients.

Brain swelling despite ventricular drainage persisted in two of five patients. Increasing edema forced partial resection of

TABLE 5  
Preoperative Clinical Condition

Grade	Description	No. Patients
I	Minor headache and/or minor neck stiffness	11
II	Severe headache, severe neck stiffness, and/or cranial nerve sign and photophobia	17
III	Drowsiness, confusion, mild paresis, and/or mild dysphasia	21
IV	Stupor or sopor, moderate to severe hemiparesis, and/or dysphasia	8
V	Coma, decerebrate rigidity, symptoms of acute mid-brain syndrome	8
Total		65

TABLE 4  
6-Month Follow-up Results

Clinical Outcome Grade	Description of Clinical Outcome	No. Patients with Preoperative Hunt & Hess Grade:					
		I	II	III	IV	V	Total <sup>a</sup>
1—excellent	Full recovery: Patient can lead a full and independent life without neurological deficit.	10	13	13	3	0	39
2—good	Minimally disabled: Patient can lead a full and independent life with minimal neurological deficit.	0	4	4 (1) <sup>b</sup>	0	0 (1)	10
3—fair	Moderately disabled: Patient has neurological or intellectual impairment, but is independent and partly able to work.	0	0	2	2	0	4
4—poor	Severely disabled: Conscious patient is totally dependent on others to get through the activities of the day.	0	0	0 (1)	3	1	5
5—dead	Dead	0	1	0	0	6	7
Total		10	18	19 (2)	8	7 (1)	65

<sup>a</sup> Includes patients with only 1 month of follow-up.

<sup>b</sup> Numbers in parentheses, number of patients with 1 month of follow-up.

TABLE 6  
Extent of Subarachnoid Bleeding

Classification 3 d after Operation	No. Patients with Preoperative Grade:			
	1	2	3	Total
1	0	6	13	19
2	0	0	11	11
3	0	0	0	0
Total	0	6	24	30

TABLE 7  
Surgical Complications Followed by Immediate Postoperative Deterioration

Event	No. Patients	Preoperative Grade		Outcome Grade
		Hunt & Hess	SAH	
Hemorrhagic infarction (spatula pressure)	2	III IV	3 3	1 4
Ischemic infarction (premature rupture, occlusion of anterior perforator, spatula pressure, and/or temporary clipping of the internal carotid artery)	2	II I	1 1	5 1
Premature rupture of aneurysm before final preparation; massive bleeding and hemorrhagic hypotension, temporary clip; postoperative infarct	4	III I II II	3 2 3 2	1 2 2 2
Brain swelling requiring major resection, probably higher spatula pressure	2	III III	2+ICH <sup>a</sup> 3	3 4
Total	10			

<sup>a</sup> ICH, intracerebral hematoma.

the superior temporal gyrus during the approach to a middle cerebral aneurysm, and preoperatively diagnosed hemiparesis-dysphasia was worse immediately after operation.

Spatula pressure on the self-retaining retractor produced a hemorrhagic infarct and hematoma in the right frontal lobe of one patient and in the left temporal lobe of a second patient. In a patient with a giant aneurysm of the internal carotid bifurcation, temporary clipping of the internal carotid artery and spatula pressure led to the development of a small ischemic infarct of the internal capsule. After massive bleeding during premature rupture, ischemic infarction (diencephalic) occurred in a second patient, in whom occlusion of a small perforator might also have occurred. In one patient with a broad-necked middle cerebral aneurysm that widely involved the circumference of one M<sub>2</sub> branch, neck occlusion was possible only by stenosing the branch with the clip. The patient's postoperative course was uneventful, but a small frontotemporal infarct was seen on CT.

#### Postoperative Complications (Table 8)

##### Psychoorganic syndrome

In three patients preoperatively graded I or II, a severe psychoorganic syndrome developed postoperatively and

TABLE 8  
Causes of a Complicated Postoperative Course in 65 Acutely Operated Patients

Cause	No. Patients
Preoperative Grade V, no recovery	6
Surgical complication	10
Severe psychoorganic syndrome	3
Delayed ischemic symptoms, reversible	2
Delayed ischemic symptoms, irreversible	2
Shunt-dependent hydrocephalus	4
Postoperative rebleeding	1
Total	28

lasted as long as 2 to 5 weeks. The patients recovered fully after 5 weeks with no ischemic lesion shown by CT. A minor psychoorganic syndrome of 2 to 3 days' duration with some restlessness and excitation was noted in the majority of the Grade I-II patients.

##### Delayed ischemia

Late ischemic complications occurred in 4 of the 65 patients. Spontaneous vasospasm could not be isolated as the origin of symptoms in any of these cases (Table 9). Although vasospasm may have been in part a cause of the symptoms, it never became symptomatic as the only complication, but always occurred in combination with other events.

*Case 1.* A 39-year-old woman clinically graded I before operation suffered an episode of dyspraxia of one arm and hand for a few minutes on Day 11 after uncomplicated operation (i.e., Day 13 after SAH); immediate angiography showed no vasospasm, and CT was normal and remained so on serial follow-up. The patient recovered without any deficit. The cause of the transient ischemic attack (TIA) remained unidentified. Because the TIA occurred when the patient stood up from bed, orthostatic dysregulation together with disturbance of cerebrovascular autoregulation might have played a role.

*Case 2.* In a 64-year-old woman with a preoperative clinical grade of III and massive SAH (Class 3), a faint left hemiparesis was noted immediately after a complicated operation. Although CT showed right temporooccipital edema and extensive SAH (Class 2) 3 days postoperatively, the symptoms had almost completely disappeared. On Day 7, the faint left hemiparesis recurred and angiography was performed. During angiography, the patient was again free of symptoms; however, marked vasospasm was found. The patient remained asymptomatic, and the temporooccipital edema on CT became a circumscribed infarcted area.

*Case 3.* In an asymptomatic 35-year-old woman, the nimodipine infusion was stopped during transport for and the performance of postoperative angiography; during injection of the contrast medium, the patient became hemiplegic and aphasic. The angiograms showed severe spasm. In this case, a rebound effect due to the withdrawal of nimodipine may have caused the devastating development of spasm. CT showed the development of an infarct. The patient recovered with minor residual left hemiparesis and is again a fully active housewife.

*Case 4.* A 30-year-old woman suffered severe subarachnoid and 3rd ventricular hemorrhage from an anterior communicating aneurysm. Her preoperative clinical grade was IV. There was uncomplicated intraoperative brain swelling, and her condition was unchanged after operation. On Day 8 after operation, however, her consciousness deteriorated and she developed hemiplegia on the left side. Immediate CT showed no changes from the CT performed on Day 7; there were no



TABLE 9  
Findings in Patients with Postoperative Delayed Ischemic Symptoms<sup>a</sup>

Patient	Hunt & Hess Grade	SAH Class		Angiographic Spasm	Infarct	Surgical Complication	Interval after SAH (d)	Degree of Resocialization
		Preop.	Postop.					
1	I	2	1	No	No	No	13	1
2	III	3	2	Yes	Yes	Yes	9	1
3	II	3	1	Angiographic complic.	Yes	No	12	2
4	IV	3	1	Not done	Yes	No	8	4

<sup>a</sup> Abbreviations: complic., complication; Postop., postoperatively; Preop., preoperatively.

signs of infarction. On the following day, however, a massive hypodense lesion became apparent in the supply territory of the middle cerebral artery responsible for the neurological deficit. Symptomatic vasospasm was strongly suspected, although angiography was not performed. According to the complex morphological and clinical picture, a clear-cut distinction of postoperative pathophysiological events is not possible. The woman recovered with considerable deficit, hemiparesis, and incomplete aphasia, independent in self-care but unable to work.

*Postoperative subarachnoid blood.* On preoperative CT, all 4 patients with delayed ischemic symptoms (Table 9) had Class 3 or 2 SAH; of the total series, there were 50 patients (Table 3) with the same extent of preoperative SAH. Three of the 4 patients with delayed ischemia had Class 3 SAH; in the whole series, there were 23 patients with Class 3 SAH preoperatively. Three days postoperatively, only 1 of the 4 patients still harbored a significant (i.e., Class 2) accumulation of subarachnoid blood (11 patients in the whole series (Table 6)). Thus, delayed ischemic complications (2 of them reversible (3%) and 2 irreversible (3%)) were always combined with a significant preoperative blood accumulation, and none of these patients was free from subarachnoid blood 3 days postoperatively (Table 9).

#### Rebleeding

The condition of one patient deteriorated suddenly on Day 18 after the uncomplicated repair of a middle cerebral aneurysm. The patient developed hemiparesis and dysphasia. Immediate CT revealed a temporal hematoma on the operated side, and angiography showed a second small middle cerebral artery aneurysm not visible on the first angiogram and undetected during the first operation. After clipping of this second aneurysm, the patient recovered with minimal deficit; CT showed a small hypodense temporal lesion.

#### Silent infarction

Postoperative ischemic infarcts on CT (Table 10) without permanent delayed neurological deficit were seen in 16% of the patients who had preoperatively suffered only SAH but no intracerebral or intraventricular bleeding. There was no apparent correlation with the extent of pre- or postoperative SAH (see Table 10). Among patients without a primary brain lesion and with subarachnoid blood on postoperative CT, 13% had a silent postoperative infarct, as had 17% of the patients without subarachnoid blood on postoperative CT. In all patients, the infarct could be seen as a hypodense lesion on CT 3 days after operation.

#### Hydrocephalus

The condition of a 53-year-old man who had preoperatively been graded IV deteriorated immediately after operation. CT 3 days after operation showed an iatrogenic intra-

TABLE 10  
Patients with Silent Infarcts after SAH and Acute Operation without Surgical Complications<sup>a</sup>

Patient	Hunt & Hess Grade Preop.	SAH Grade		Location	Outcome Grade 1 mo after Operation
		Preop.	Postop.		
1	III	3	1	Caudate nucleus	1
2	I	1	0	Frontobasal	1
3	III	1	0	Frontal	1
4	II	2	0	External capsule	1

<sup>a</sup> Abbreviations: Postop., postoperative; Preop., preoperative.

cerebral hemorrhage and a hypodense lesion. The day after the external ventricular drainage system had been mistakenly withdrawn on the 5th postoperative day, the patient fell comatose and exhibited a decerebrate posture. CT showed massive hydrocephalus. A new external drain was placed to relieve the highly elevated intracranial pressure. However, the patient remained in a vegetative state.

Three patients developed delayed hydrocephalus and required a shunting procedure. One of these had intracerebral and intraventricular hemorrhage, and the second patient was preoperatively in Class 2 SAH; both were clinically graded IV preoperatively. The third patient was preoperatively graded V and harbored an aneurysm of the anterior communicating artery. The patient was in a "coma vigilé" 1 month after operation when CT showed an increase in ventricular size.

Twelve other patients showed transient ventricular enlargement on postoperative CT without clinical deterioration and did not require a shunt.

#### Outcome

Thirty-seven patients had a completely uneventful postoperative course (except for a slight transient psychoorganic syndrome) with gradual improvement of their preoperative state. The follow-up results of these 37 patients and the 28 patients with postoperative complications are summarized in Table 4.

After 1 month, 20 of 28 Grade I–II patients were free of any symptoms. Minimal deficit without surgical complication and no "silent infarct" was observed in 4 Grade I–II patients who still felt physically unable to work (1 also had an oculomotor palsy), but were fully normal at 3 months (except the oculomotor palsy). Three patients had moderate neurological deficits after complicated operation. One patient initially graded II who had a surgical complication (diencephalic infarct) (see Table 7) had an outcome grade of 4 at 1 month

(diabetes insipidus, anorexia) and died 3 months after operation from pneumonia. Of the 21 Grade III patients, 7 were asymptomatic, 9 had minimal deficit, 4 had moderate deficit, and 1 had severe deficit. One patient with an anterior communicating aneurysm preoperatively graded III had presented with Korsakoff's syndrome. The syndrome lasted abnormally long, until 1 month after operation, and then resolved fully during the following month. The patient, a medical doctor in general practice, returned to his profession without any further sequelae, and CT was normal. Of 8 Grade IV patients, 3 had minimal, 2 had moderate, and 3 had severe deficits. Six of the 8 Grade V patients did not survive the 1st postoperative week; 1 patient had a severe deficit, and the other had a moderate deficit. The latter patient was a 67-year-old woman who had suffered a Class 2 SAH and a massive subdural hematoma from a ruptured right internal carotid aneurysm. She was comatose and exhibiting a decerebrate posture preoperatively, was operated upon on the day of the hemorrhage, and was fully alert at the end of the 1st postoperative week, although she had a left-sided hemiparesis.

At 6 months (Table 4), there was minimal deficit in six patients with intra- or postoperative complication. Of two surgically uncomplicated cases, one patient developed oculomotor palsy and the other, preoperatively graded III, developed a deficit from initial bleeding into the corpus callosum. This blood was visible postoperatively as a small hypodense lesion.

There were 7 management fatalities among the whole series of 65 patients who were followed for 6 months. Six of these patients had been graded V preoperatively, and the 7th was a late mortality after a complicated operation (see Table 7). No Grade I-IV patient had died by the 1-month follow-up examination. The mortality after 6 months was 11%. A summary of the outcome vs. the preoperative condition is given in Table 11.

#### Nimodipine Treatment

No important side-effect such as arterial hypotension or increased intracranial pressure was noted. Transient systolic pressures as low as 80 mm Hg were recorded on several occasions in normotensive patients and were also observed in patients not receiving nimodipine. Headache was a frequent complaint in patients both receiving and not receiving nimodipine. The CSF levels of nimodipine during its i.v. infusion were always below the sensitivity range of the technique, i.e., below 2 ng/ml. The plasma levels during i.v. and p.o. administration are summarized in Table 12. The values varied considerably among different patients and at different times in individuals.

#### DISCUSSION

##### Timing of operation

The reasons given for acute operation are (a) to overcome the most severe complication, rebleeding; (b) to reduce the severity of symptomatic vasospasm by evacuating blood clots; (c) to treat symptomatic vasospasm more aggressively; and

TABLE 11  
Results at 6 Months Related to Preoperative Grade

6-mo Follow-up Results	No. Patients in Preoperative Grades:		
	I-II	III-IV	V
Excellent—fair	96%	86%	14%
Poor—dead	4%	14%	86%

TABLE 12  
Mean Plasma Nimodipine Levels in 15 Patients

Time of Measurement	Nimodipine Level	
	Mean	Range
During i.v. treatment	53	12-98
Six hours after i.v. treatment was stopped	17	2-33
One hour after 60 mg p.o.	22	7-48
Two hours after 60 mg p.o.	16	4-40
Four hours after 60 mg p.o.	15	3-32
Six hours after 60 mg p.o.	13	3-41

(d) to lower the complication rate by shortening the period of bedrest (34). A recent argument against acute operation is that the dysregulation of cerebral blood flow and blood volume (24, 32) may combine with the additional surgical trauma to cause massive brain swelling, the "angry swollen brain" that requires major tissue resection. Spatula pressure upon poorly perfused brain may cause more ischemic surgical lesions and thereby depress the overall results. Recently reported data (34) and the present study do not substantiate either concern; a severely swollen brain was encountered in only 2 of our 65 patients.

Infarction not related to the initial hemorrhagic brain lesion or to surgical complications other than spatula pressure was noted in 8 patients among the 59 survivors of the immediate postoperative period, 4 without accompanying neurological symptoms (see Table 10) and 4 with clinical deterioration (Table 7). This 14% incidence of probable surgical lesions causing reversible or irreversible morbidity or mortality in 7% is difficult to compare with other series because complete follow-up CT of patients operated upon during a later stage includes infarcts from symptomatic preoperative spasm and usually shows ischemic lesions in about 30%.

Patients with a low pre- or intraoperative cerebral blood flow (CBF) had a worse prognosis (2, 41). Preoperative studies of CBF and cerebral blood volume might be useful indicators to select candidates for delayed operation, improving results by preventing surgically induced ischemic lesions. The risk of rebleeding would be low in a group of patients with low CBF (2); however, the risk of delayed ischemic symptoms might be high, with a low CBF announcing the development of symptomatic vasospasm (36). Alternatively, pharmacologically induced normalization of CBF during acute operation in these patients should be considered together with intraoperative CBF studies. In this study, this pharmacological concept is exemplified by the local administration of nimodipine. However, intraoperative assessment of CBF was not performed. Patients with preoperative vasospasm did not have a worse outcome in this series.

Massive premature rupture of the aneurysm during operation in five patients caused a 1.5% mortality and a 5% surgical morbidity with minimal deficit. Acute operation does not, therefore, seem to increase the risk of deterioration due to aneurysm rupture. Aneurysm rupture correlated with poor prognosis in another study, where the combined management morbidity and mortality was 58% after intraoperative rupture, compared to 28% without rupture (52).

The present data show that acute operation in patients graded I-IV seems to improve the outcome (see Table 11), although it remains evident that prognosis correlates with the initial clinical condition and that management mortality and morbidity are higher in patients who are in poor condition preoperatively. Our results do not support the assumption that acute operation should be restricted to patients in good

preoperative condition. Patients graded IV or III before acute operation did not have a worse outcome when compared with patients treated with delayed operation, as is seen in Table 11.

Acute operation did not seem to influence the outcome of patients graded V except in the patient with additional massive subdural hematoma. This somewhat misleading impression was due to several deaths caused by unrelated problems such as thrombosis of the mesenteric artery or pneumonia, as occurred after an astonishingly rapid postoperative recovery. Comatose patients with massive SAH and hydrocephalus but no devastating intracerebral hemorrhage do have a chance to survive.

#### *Delayed ischemic deficit, vasospasm*

The incidence of angiographic vasospasm in patients after SAH has been reported as 24% (38) to 76% (28, 37, 38, 40, 48). Angiographically diagnosed vasospasm roughly doubles the incidence of delayed ischemic deficit (55), the latter being observed in about 30% of the published series (34, 37, 38, 53-55, 57, 65, 70); delayed ischemic deficit does not correlate well with the incidence of angiographic spasm per se or with decreased CBF unless compared with the extent of angiographic spasm (15, 24, 50, 54).

Postoperative angiographic vasospasm was less frequent and less severe after acute operation (55). However, the time course of the development of angiographic spasm was not influenced by surgical intervention (53, 55). Although angiographic asymptomatic vasospasm has not been excluded in this series because regular control angiography was not performed, delayed symptomatic vasospasm with permanent neurological deficit, although very likely in one patient (Table 9, Patient 4), did not clearly and unequivocally play a dominant role in any patient in this series. The incidence of permanent delayed ischemic deficit or death from vasospasm after acute operation in other recent series varied between 11% and 58% in Grade I-IV patients (34, 48, 65, 66, 72) and between 10% and 21% in Grade I-III patients (39, 40, 72).

Less severe ischemic symptoms due to vasospasm, reversible in 90% of the cases, were seen after acute operation and evacuation of as much subarachnoid blood as possible (34). With the aggressive evacuation of subarachnoid blood, the incidence of symptomatic vasospasm was reduced from 28 to 11% in Taneda's series (65, 66). The extent of preoperative SAH on CT has repeatedly been described as one of the deciding factors in the occurrence of a delayed permanent neurological deficit from symptomatic vasospasm (11, 13, 16, 45, 53-55, 58, 63). This observation was also made in the four patients with ischemic complications in the present series (Table 9).

The distinction between postoperative cerebral lesions due to vasospasm and those due to the surgical procedure (such as from the pressure of the self-retaining retractor) is very difficult, if not impossible. Especially in patients who were in an unfavorable condition preoperatively and who also suffered intracerebral hemorrhage, focal neurological deficit, and disturbance of consciousness, such differentiation during the postoperative period is frequently complicated because of the complexity of the pathophysiological events (57). If the patient was in a favorable condition preoperatively, it may be difficult to classify postoperative cerebral lesions on CT without postoperative deterioration of the clinical picture, especially if the typical clinical course known to occur with severe angiographic spasm is absent. "Silent" ischemic lesions on postoperative CT (i.e., those not accompanied by a preoperative lesion from bleeding or by postoperative deterioration of the

patient's condition) occurred in four of our patients. Basically, these clinically silent infarcts could be considered as sequelae of vasospasm. In all four patients, however, the ischemic lesion had been seen as edema (hypodense lesion) on CT 3 days after operation (i.e., 3 to 4 days after SAH). This suggests that the lesion was caused by operation (e.g., by spatula pressure) rather than by vasospasm. If vasospasm had caused the infarct, the hypodense lesions on CT would have appeared at a later stage, which is typical for the late type of spasm. It may be accurate to ascribe such lesions to the surgical procedure itself if the patient was in a good clinical condition both pre- and postoperatively and if the lesion was visible when CT was first performed 3 days postoperatively.

Besides iatrogenic trauma with the self-retaining retractor, a primary event during the initial SAH could explain such lesions: as a consequence of the sudden rise during SAH of intracranial pressure up to the level of arterial pressure, cerebral circulation stops for a period, the length of which might be one of the factors deciding prognosis. As the intracranial pressure slowly regresses and cerebral perfusion is continued, circumscribed areas of "no reflow" have been observed (67). These ischemic zones might well be missed on initial CT on the day of hemorrhage and then become apparent on the first postoperative scan. To distinguish clearly between postoperative sequelae from morphological changes caused by the aneurysmal hemorrhage and the onset of delayed ischemic deficit from severe arterial spasm alone, in 1981 researchers began an open multicenter study for the observation of a beneficial effect of nimodipine, which is being continued (5).

The better outcome of patients in the present series compared to acutely operated patients in other recent series suggests an effect of nimodipine. Excellent to fair results were obtained in 91% of the patients preoperatively graded I-IV, as opposed to 72% in a comparable series (72). The outcome was excellent to fair in 96% of our Grade I-III patients and in 83 to 87% of those in other studies (39, 40, 72). Above all, however, better outcomes were observed in Grade III and IV patients; there was a poor outcome or death in 14% in our series but in 38 to 47% in other series (33, 66, 72). It remains unclear to what extent so-called "asymptomatic vasospasm," as eventually seen on postoperative angiograms, may have played a role in the origination or aggravation of cerebral lesions. Several observations in our patients indicate that angiographic vasospasm is not suppressed fully by the treatment protocol of acute operation and nimodipine, but is mitigated so as to keep patients free of irreversible symptoms. Other studies have also suggested such an effect of nimodipine (3, 6).

The unfortunate development of an angiographic complication in one of our patients (Table 9, Patient 3) suggests that asymptomatic spasm could have been changed suddenly into severe spasm by the effect of the contrast medium. On the other hand, it seems dangerous to stop nimodipine treatment before Day 14 after SAH if the absence of vasospasm has not been proven; symptomatic vasospasm threatens only an unpredictable proportion of patients, and the final goal is to focus prophylactic measures on these cases. Our experience urges us to find an alternative to angiography, especially when vasospasm must be suspected either by the clinical course or by the interval from SAH and the extent of pre- and postoperative subarachnoid blood accumulation. Transmural Doppler sonography might be a valid new technique (22).

One of the reasons for the difficulty in treating severe late vasospasm successfully might be myonecrosis of the walls of the involved vessels, which may thus become unreactive to vasodilator drugs (1). Therefore, prevention rather than treatment of vasospasm is advocated, as was recently also suggested



by Wilkins (71), and this led to the development of the presently used protocol for the administration of nimodipine (5). It remains a matter for further investigation to determine the manner in which nimodipine is effective. One explanation for the prevention of ischemic symptoms by nimodipine despite angiographic narrowing or spasm of larger arteries of the circle of Willis was given by the authors of a controlled study in patients that indicated that the i.v. infusion of nimodipine dilates predominantly the small resistance vessels (8). Moreover, during topical perivascular treatment with nimodipine, there is a cross correlation between vessel size and the percentage of dilatation (6, 9). Thus, opening of the pial collateral circulation could prevent focal ischemia. In fact, nimodipine increases the CBF in animals and in humans (18, 21, 25-27, 35) without causing a steal mechanism from hypoperfused brain.

In contrast, the solvent used with nimodipine (ethanol, polyethylene glycol) had no effect on human pial vessels when administered intravenously (8). Moreover, all 49 analyses of the blood level of alcohol during the intravenous administration of nimodipine in 7 patients in the present series were negative. A recent experiment showing a greater effect of the solvent than of nimodipine is not relevant because much higher doses of solvent and lower doses of nimodipine were used (47). Rheological factors as well as an influence on neuronal calcium metabolism have also been suggested (61) to explain the effect of nimodipine.

The better outcome of the patients presented here compared to the outcome after p.o. nimodipine treatment alone (3) might well derive from three factors: (a) Intraoperative topical administration provides an immediate high concentration of the drug, which reaches the smooth muscle cells more easily from the perivascular space than through the blood-brain barrier (25). (b) Plasma levels of nimodipine seem to become 2 to 3 times higher with the indicated i.v. dosage rate than with oral administration (10). (CSF levels, however, did not become higher.) (c) Continuous infusion assures a permanent level of nimodipine compared to fluctuation produced by drug intake at 6-hour intervals.

### CONCLUSION

I am fully aware that the present study is another anecdotal report that does not prove the beneficial effect of acute operation or an effect of the calcium antagonist nimodipine when considered in the light of modern biostatistics, which do not allow methods other than a controlled study. These first observations might, however, show how to proceed in the development of a regimen that definitively improves the outcome of aneurysm treatment by controlling ischemia from vasospasm.

Higher numbers of patients will be necessary to show unequivocally an effect of nimodipine or to allow a controlled study as soon as unequivocally defined severe symptomatic vasospasm occurs in a significant number of patients despite the application of the present protocol.

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### REFERENCES

1. Alksne JF: Myonecrosis in chronic experimental vasospasm. *Surgery* 76:1-7, 1974.
2. Allcock JM, Drake CG: Ruptured intracranial aneurysms: The role of arterial spasm. *J Neurosurg* 21:21-29, 1965.
3. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB, Dorsey SC, Intram CR, Mellits VE, Bertsch LA, Voisyert DPJ, Huntley MB, Johnson RK, Strom JA, Transou CR: Cerebral arterial spasm—a controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med* 308:619-624, 1983.
4. Auer LM: Pial arterial vasodilatation by intravenous nimodipine in cats. *Arzneim Forsch* 31:1423-1425, 1981.
5. Auer LM: Acute surgery of cerebral aneurysms and prevention of symptomatic vasospasm. *Acta Neurochir (Wien)* 69:273-281, 1983.
6. Auer LM, Ito Z, Suzuki A, Ohta H: Prevention of symptomatic vasospasm by topically applied nimodipine, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:297-302, 1982.
7. Auer LM, Ladurner G, Schneider G: Vaskuläre Hirnläsionen nach akuter Aneurysmaoperation—eine computertomographische Follow-up Studie über 55 Patienten. Presented at the 5th Süd-Ost-Europäische Konferenz für Neurologie und Psychiatrie, Graz, Austria, September 1983.
8. Auer LM, Oberbauer RW, Schalk HV: Human pial vascular reactions to intravenous nimodipine-infusion during EC-IC bypass surgery. *Stroke* 14:210-213, 1983.
9. Auer LM, Suzuki A, Yasui N, Ito Z: Intraoperative topical nimodipine after aneurysm clipping. *Neurochirurgia (Stuttg)* 27:36-38, 1984.
10. Battye R: Plasma and cerebrospinal fluid levels after oral doses of nimodipine, in Bettie R (ed): *Calcium Antagonists: Possible Therapeutic Use in Neurosurgery (Proceedings of a Workshop Held in Dorado Beach, Puerto Rico, June 10-11, 1983)*. New York, Raven Health Care Communications, 1983, pp 62-64.
11. Bell BA, Kendall BE, Symon L: Computerized tomography in aneurysmal subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 43:522-524, 1980.
12. Boullin DJ: *Cerebral Vasospasm*. Chichester, J Wiley, 1980.
13. Davis JM, Davis KR, Crowell RM: Subarachnoid hemorrhage secondary to ruptured intracranial aneurysm. *AJR* 134:711-715, 1980.
14. Drake CG: Management of cerebral aneurysm. *Stroke* 12:273-283, 1981.
15. Ferguson GG, Harper AM, Fitch W, et al: Cerebral blood flow measurements after spontaneous subarachnoid haemorrhage. *Eur Neurol* 8:15-22, 1972.
16. Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 6:1-9, 1980.
17. French LA, Blake PS: Subarachnoid hemorrhage and intracranial aneurysms. *Lancet* 1:459-466, 1950.
18. Gaab MR, Brawanski A, Bockhorn J, Haubitz I, Rode CHP, Maximilian VA: Calcium antagonism: A new therapeutic principle in stroke and cerebral vasospasm? *rCBF Bull* 3:47-51, 1982.
19. Gallhofer B, Auer LM: Spontaneous course after subarachnoid haemorrhage: Evaluation of 109 patients, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:67-70, 1982.
20. Gell G: AURA: A clinical data bank based on free text, in O'Moore RR, Barber B, Reichertz PL, Roger F (eds): *Lecture Notes in Medical Informatics*. Berlin, Springer, 1982, vol 16, pp 850-856.
21. Gelmers HJ: Effect of nimodipine (BAY e 9736) on postis-



- chaemic cerebrovascular reactivity, as revealed by measuring regional cerebral blood flow (rCBF), in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:283-290, 1982.
22. Gilsbach JM: *Intraoperative Doppler Sonography in Neurosurgery*. Wien, Springer-Verlag (in press).
  23. Graf CJ: Results of direct attack on nonfistulous intracranial aneurysms with remarks on statistics. J Neurosurg 12:146-153, 1955.
  24. Grubb RL Jr, Raichle ME, Eichling JO, Gado MH: Effects of subarachnoid hemorrhage on cerebral blood volume, blood flow, and oxygen utilization in humans. J Neurosurg 46:446-463, 1977.
  25. Harper AM, Craigen L, Kazda S: Effect of the calcium antagonist, nimodipine, on cerebral blood flow in metabolism in the primate. J CBF Metab 1:349-356, 1981.
  26. Harris RJ, Branston NM, Symon L, Bayham M, Watson A: The effects of a calcium antagonist, nimodipine, upon physiological responses of the cerebral vasculature and its possible influence upon focal cerebral ischaemia. Stroke 13:759-766, 1982.
  27. Haws CW, Heistad DD: Effects of nimodipine on cerebral vessels: Role of extracellular calcium in vasoconstrictor responses. Stroke 14:122, 1983 (abstr).
  28. Heilbrun MP: The relationship of neurological status and the angiographical evidence of spasm to prognosis in patients with ruptured intracranial saccular aneurysms. Stroke 4:973-979, 1973.
  29. Hori S, Suzuki J: Early intracranial operations for ruptured aneurysms. Acta Neurochir (Wien) 46:93-104, 1979.
  30. Hunt WE, Hess RM: Surgical risk as related to time intervention in the repair of intracranial aneurysms. J Neurosurg 28:14-19, 1968.
  31. Hunt WE, Miller CA: Results of early aneurysmorrhaphy in good risk patients. Adv Neurosurg 7:76-80, 1980.
  32. Ishii R: Regional cerebral blood flow in patients with ruptured intracranial aneurysms. J Neurosurg 50:587-594, 1979.
  33. Ito Z: The microsurgical anterior interhemispheric approach suitably applied to ruptured aneurysms of the anterior communicating artery in the acute stage, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:85-99, 1982.
  34. Kassell NF, Boarini DJ, Adams HP Jr, Sahs AL, Graf CJ, Torner JC, Gerk MK: Overall management of ruptured aneurysm: Comparison of early and late operation. Neurosurgery 9:120-128, 1981.
  35. Kazda S, Towart R: Nimodipine: A new calcium antagonistic drug with a preferential cerebrovascular action, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:259-265, 1982.
  36. Kobayashi K, Ishii R, Koike T, Ihara I, Kameyama S: Cerebral blood flow and metabolism in patients with ruptured aneurysms. Acta Neurol Scand 60(suppl 72):492-493, 1979.
  37. Kraysenbühl HA, Yasargil MG, Flamm ES, Tew JM Jr: Microsurgical treatment of intracranial saccular aneurysms. J Neurosurg 37:678-686, 1972.
  38. Kwak R, Niizuma H, Ohi T, Suzuki J: Angiographic study of cerebral vasospasm following rupture of intracranial aneurysms: Part 1. Time of the appearance. Surg Neurol 11:257-262, 1979.
  39. Ljunggren B, Brandt L, Kagström E, Sundbärg G: Results of early operation for ruptured aneurysms. J Neurosurg 54:473-479, 1981.
  40. Ljunggren B, Brandt L, Sundbärg G, Säveland H, Cronqvist S, Stridbeck H: Early management of aneurysmal subarachnoid hemorrhage. Neurosurgery 11:412-418, 1982.
  41. Lovick AHJ, Pickard JD, Goddard BA: Prediction of late ischaemic complications after cerebral aneurysm study: Use of a mobile microcomputer system for the measurement of pre-, intra- and postoperative cerebral blood flow, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:37-42, 1982.
  42. McKissock W, Paine KWE: Subarachnoid haemorrhage. Brain 82:356-366, 1959.
  43. McKissock W, Paine KWE, Walsh LS: An analysis of the results of treatment of ruptured intracranial aneurysms: Report of 772 consecutive cases. J Neurosurg 17:762-776, 1960.
  44. Mizukami M, Kawase T, Tazawa T, Matata K, Yunoki K, Yoshiva Y: Hypothesis and clinical evidence for the mechanism of chronic cerebral vasospasm after subarachnoid hemorrhage, in Wilkins RH (ed): *Cerebral Arterial Spasm*. Baltimore, Williams & Wilkins, 1981, pp 97-106.
  45. Mizukami M, Takemae T, Tazawa T, Kawase T, Matsuzaki T: Value of computed tomography in the prediction of cerebral vasospasm after aneurysm rupture. Neurosurgery 7:583-586, 1980.
  46. Mizukami M, Usami T, Tazawa T, Kawase T: Prevention of vasospasm by removal of subarachnoid blood in early operation. Neurol Med Chir (Tokyo) 21:103-107, 1981.
  47. Moursi MM, Luyckx BA, D'Alcy LG: The role of ethanol in diluents of drugs that protect mice from hypoxia. Stroke 14:791-796, 1983.
  48. Ono H, Mizukami M, Kitamura K, Kikuchi H, and the Cooperative Study Group in Japan: Preventive effect of ticlopidine on cerebral ischemia due to cerebral vasospasm following ruptured aneurysm: A double-blind cooperative study. Presented at the 52nd Annual Meeting of the American Association of Neurological Surgeons, Washington, District of Columbia, April 24-28, 1983.
  49. Phillips LH, Whisnant JP, O'Fallon WM, Sundt TM Jr: The unchanging pattern of subarachnoid hemorrhage in a community. Neurology (NY) 30:1034-1040, 1980.
  50. Pitts LH, Macpherson P, Wyper DJ, Jennett WB: Cerebral blood flow, angiographic cerebral vasospasm, and subarachnoid hemorrhage, in Ingvar DH, Lassen NA (eds): *Cerebral Function, Metabolism and Circulation* (Acta Neurol Scand 56 (Suppl 64)). Copenhagen, Munksgaard, 1977, pp 334-335.
  51. Pool JL: Cerebral vasospasm. N Engl J Med 259:1259-1264, 1958.
  52. Pool JL: Timing and techniques in the intracranial surgery of ruptured aneurysms of the anterior communicating artery. J Neurosurg 19:378-388, 1962.
  53. Saito I, Sano K: Vasospasm following rupture of cerebral aneurysm. Neurol Med Chir (Tokyo) 19:103-107, 1979.
  54. Saito I, Shigeno T, Aritake K, Tanishima T, Sano K: Vasospasm assessed by angiography and computerized tomography. J Neurosurg 51:466-475, 1979.
  55. Saito I, Yasuichi U, Sano K: Significance of vasospasm in the treatment of ruptured intracranial aneurysms. J Neurosurg 47:412-429, 1977.
  56. Sano K, Saito I: Timing and indication of surgery for ruptured intracranial aneurysms with regard to cerebral vasospasm. Acta Neurochir (Wien) 41:49-60, 1978.
  57. Sundt TM Jr, Kobayashi S, Fode NC, Whisnant JP: Results and complications of surgical management of 809 intracranial aneurysms in 722 cases: Related and unrelated to grade of patient, type of aneurysm, and timing of surgery. J Neurosurg 56:753-765, 1982.
  58. Suzuki J, Komatsu S, Sato T, Sakurai Y: Correlation between CT findings and subsequent development of cerebral infarction due to vasospasm in subarachnoid hemorrhage. Acta Neurochir (Wien) 55:63-70, 1980.
  59. Suzuki J, Onuma T, Yoshimoto T: Results of early operations on cerebral aneurysm. Surg Neurol 11:407-412, 1979.
  60. Suzuki J, Yoshimoto T, Onuma T: Early operations for ruptured intracranial aneurysms: A study of 31 cases operated on within the first four days after ruptured aneurysm. Neurol Med Chir (Tokyo) 18:82-89, 1978.
  61. Symon L, Harris RJ, Branston NM: Calcium ions and calcium antagonists in ischaemia, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:267-275, 1982.
  62. Takahashi S, Sonobe M, Nagamine Y: Early operations for ruptured intracranial aneurysms. Acta Neurochir (Wien) 57:23-31, 1981.
  63. Takemae T, Mizukami M, Kim H, Kawase T, Araki G: Computed tomography of ruptured intracranial aneurysm in acute

- stage: Relationship between vasospasm and high density on CT scan. *Brain Nerve* (Tokyo) 30:861-866, 1978.
64. Tanaka K, Gotoh F, Muramatsu F, Fukuuchi Y, Amano T, Okayasu H, Suzuki N: Effects of nimodipine (Bay e 9736) on cerebral circulation in cats. *Arzneim Forsch* 30:1494-1497, 1980.
  65. Taneda M: The significance of early operation in the management of ruptured intracranial aneurysms—an analysis of 251 cases hospitalized within 24 hours after subarachnoid haemorrhage, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:201-208, 1982.
  66. Taneda M: Effect of early operation for ruptured aneurysms on prevention of delayed ischemic symptoms. *J Neurosurg* 57:622-627, 1982.
  67. Trojanowski T: Disturbances of regional cerebral blood flow after experimental arterial subarachnoid haemorrhage, in Brihaye J, Vigouroux R, Achslogh J, Calliauw L (eds): *Abstract-book of the 7th European Congress of Neurosurgery, Brussels, 1983*. Brussels, European Association of Neurological Societies, 1983, p 231 (abstr).
  68. Weir B, Aronyk K: Management mortality and the timing of surgery for supratentorial aneurysms. *J Neurosurg* 54:146-150, 1981.
  69. Weir B, Aronyk K: Management and postoperative mortality related to time of clipping for supratentorial aneurysms: A personal series, in Auer LM, Heppner F, Symon L (eds): *Proceedings of the Symposium on Aneurysm Surgery in the Acute Stage*. Acta Neurochir (Wien) 63:135-139, 1982.
  70. Weir B, Grace M, Hansen J, Rothdert C: Time course of vasospasm in man. *J Neurosurg* 48:173-178, 1978.
  71. Wilkins RH: Attempted prevention or treatment of intracranial arterial spasm: A survey. *Neurosurgery* 6:198-210, 1980.
  72. Yamamoto I, Hara M, Ogura K, Suzuki Y, Nakane T, Kageyama N: Early operation for ruptured intracranial aneurysms: Comparative study with computed tomography. *Neurosurgery* 12:169-174, 1983.
  73. Yasargil MG, Smith RE: Surgery on the carotid system in the treatment of hemorrhagic stroke, in Thompson RA, Green JR (eds): *Stroke*. Adv Neurol 16:181-209, 1977.
  74. Yoshimoto T, Uchida K, Kaneko U, Kayma T, Suzuki J: An analysis of follow-up results of 1000 intracranial saccular aneurysms with definitive surgical treatment. *J Neurosurg* 50:152-157, 1979.

#### COMMENT

This is a well-documented series of 65 patients admitted acutely after aneurysmal subarachnoid hemorrhage, all of

whom were treated with the calcium channel-blocking agent nimodipine and all of whom underwent operation within 72 hours of the ictus. The characteristics of the patients on admission were similar to those in other large series: 75% were in "good condition" (Hunt and Hess Grades I to III). Dr. Auer's results were quite gratifying. Six months after the hemorrhage, 75% of the entire group of patients had a favorable outcome (capable of leading a full and independent life, with or without neurological deficit). The favorable outcome related to preoperative neurological status was equally impressive: Grade I, 100%; Grade II, 94%; Grade III, 80%; Grade IV, 38%, Grade V, 0%. Particularly noteworthy is the observation that only 6% of the patients developed delayed ischemic neurological deficits presumably related to vasospasm. These deficits were permanent in only 3%. This is considerably better than the recent results from the International Cooperative Study on the Timing of Aneurysm Surgery, in which the rate of delayed ischemic neurological deficits was 30%, resulting in permanent impairments in 15% (2).

Data from the Cooperative Aneurysm Study have suggested that delayed operation will result in a favorable outcome in only 45 to 50% (1). Dr. Auer's results obviously seem superior. The question that remains, however, is whether his superior results are related to early operation, nimodipine, other unidentified factors, or a combination thereof. Other series of early operation without calcium channel-blocking agents have also yielded an overall favorable outcome of approximately 75%. Although further studies are required to determine precisely which factors are responsible for the improving results in the management of patients with ruptured aneurysms, the general sense is that the situation is improving markedly. Dr. Auer's report will serve as a standard that all of us must strive to meet.

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1. Kassell NF, Drake CG: Timing of aneurysm surgery. *Neurosurgery* 10:514-519, 1982.
2. Kassell NF, Torner JC: The International Cooperative Study on Timing of Aneurysm Surgery: An Update. *Stroke* (in press).