Progress in Cerebrovascular Disease

Management of Cerebral Aneurysm

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SUMMARY The primary effort of neurosurgery over the past two or three decades has been to deal effectively with cerebral aneurysms surgically. Concomitantly with aggressive medical treatment, considerable progress has occurred in the prevention of early rebleeding and the treatment of the ischemic syndrome, the most serious features of the natural history of a ruptured aneurysm. The major problem now becoming evident is that in spite of this progress, the majority of patients are not seen by physicians and there has been only a small impact on the overall morbidity. It is dismaying to realize that many patients go unrecognized, at least until a massive brain-destroying hemorrhage has occurred. Only a small fraction of the patients are seen after the initial bleed when the greatest therapeutic reward would occur.

The challenge for the future, then, will be the early recognition of the initial bleeding, the warning bleeding. It will require public education about the problem in a continuing fashion, as well as continuing emphasis on it for students and physicians. The potential for prevention of death or dreadful disability is large for thousands in the prime of life each year.

While delayed surgery is safe, a significant amount of rebleeding and ischemia with vasospasm still occur, resulting in an unsatisfactory overall morbidity. A collaborative study is desirable to determine with sufficient patients whether very early modern operation in many hands will reduce this morbidity.

The modern story of intracranial aneurysms began with Charles Symonds who, after suggesting that a diagnosis could be made in life, looked into the matter at the request of Dr. Cushing. In papers in 1923 and 1924, he not only coined the term "subarachnoid hemorrhage," recognizable by lumbar puncture, but also brought its relationship to rupture of an aneurysm to the attention of the English literature. It was nearly another 20 years before the Canadian neurologists, Richardson and Hyland of Toronto in 1941, provided a new stimulus for the recognition of the disorder and the need to define the problem further. Their study correlated clinical and pathological findings in order to show the diverse nature of cerebral aneurysms and the consequences of their rupture. At that time, as there had been only a few reports of surgical treatment — mostly the use of carotid ligation in the neck — they favored medical management.

Although Moniz had described angiography in 1927, it is remarkable how slowly its significance and utility were recognized. A few studies were done in the 1930s in Europe, but in North America it was not employed widely until after World War II.

Dott, in 1931, by packing the sac with muscle to reinforce the wall, was the first to operate intracranially on an aneurysm to prevent recurrent rupture. Walter Dandy, who in 1938 was the first to occlude an aneurysm by clipping its neck, recognized the potential of direct surgical treatment in his monograph of 1944.

These pioneer studies provided much interest in subarachnoid hemorrhage and the deadly nature of cerebral aneurysms became widely known, particularly their vicious characteristic of rebleeding, usually in a few days or a week or two after the initial bleed.

Modern Surgical History

The story of modern surgical treatment began after World War II when wider use of angiography made it possible for surgeons to take up this challenge in a more exact and knowing way. Initially, carotid ligation was most widely used but it soon became apparent that it was useful only for aneurysms arising from the intracranial portion of the carotid itself. It did not prevent all rebleeding and, further, was plagued with a considerable but unpredictable incidence of massive cerebral ischemia.

Encouraged by the intracranial operations of Dott and Dandy, surgeons began to approach aneurysms on the anterior circulation early after the first recognized bleeding to prevent the disaster of a second rupture. Very soon this proved not to be straightforward. All too often, the swollen, angry brain required deep, firm, retraction so the surgeon could reach the carotid or its...
major branches. Poor illumination and restricted vision complicated the operation. The fragile sac frequently burst. Once placed, the silver clips were unremoveable and the frantic applications of others to prevent the patient from bleeding to death sometimes occluded the parent artery or an important branch.

A new phenomenon was recognized, peculiar to early, direct operation on a ruptured aneurysm, especially when the operation was uncomplicated, as it often was, even in those days. This was deterioration of the patient, who, after being well for a few hours or days, then went through states of confusion, stupor and coma with major neurological deficit or death.

When postoperative angiography was done on these deteriorating patients the puzzling sequence of events was shown to be associated with severe arterial narrowing. The cerebral arteries were often found to be mere threads in caliber and usually were found in cerebral areas appropriate to the clinical syndrome. This change, believed to be arterial spasm, became dreaded and was blamed for many of the poor results of otherwise uncomplicated aneurysm surgery. This phenomenon is probably responsible for the wave of surgical conservatism which caused surgeons to shy away from early operation.

It was soon learned that operations done a week or two after the initial bleeding were safe and ordinarily uncomplicated by clinical deterioration. This resulted in a tendency to delay operation until the acute reaction of the brain and its vessels had subsided, as few instances, exceeded the risk of rebleeding. During the 1950s, some clinical observers were struck by the mortality and morbidity of early operation and then at the disasters from rebleeding while the surgeon waited for the patient to become a good risk. Many suggested that surgical treatment was no better than a few weeks of bed rest.

Surgical Accomplishments

What, then, has been accomplished from the surgical point of view from the late 1940s through the 1950s? First, because surgeons were delaying operations, if possible, they had to find a way to delay rebleeding for a week or two. Induced hypotension, a logical step, was proposed but proved difficult in the recumbent patient with the hypotensive drugs then available. Even now, with better drugs, there is still lingering concern about the possible aggravation of the ischemia by hypotension which often follows a hemorrhage.

Mullan* has been most aggressive in the use of this treatment using I.V. hypotensive medication and partial carotid clamping alone or in combination, although never simultaneously and often for several weeks. He now favors intravenous over oral medication because of its ease of reversal, using Arfonad or nitroprusside. The patient is titrated down to ischemic levels when symptoms, general or regional, appear. The pressure is then immediately elevated to a point 15 torr above this or to a point which is 30% short of the entering pressure, whichever is higher, and then is maintained there. It is stopped, of course, during a phase of spasm or deterioration but resumed as improvement occurs. In 72 patients using oral or I.V. medication, the treatment had to be stopped because of deteriorations in 8, but in the remainder he achieved a 25–30% reduction in mean systolic pressure.

For carotid aneurysms, Mullan has reintroduced the concept of immediate partial occlusion of the carotid artery by subtotal occlusion with a Selverstone clamp on the common carotid artery low in the neck. This has produced a 44% mean reduction in carotid pressure above the clamp. However, in 39 patients, with a mean duration of clamp application of 11 days, the clamp had to be reopened in 5 because of hemiparesis, but 2 recovered. Embolism occurred after opening the clamp in 2 others when the clamp had been inadvertently closed by inexperienced assistants. Thus, there were 5 serious complications (13%), 4 hemiplegias and 1 ambiopia as well as 2 infections after the clamp was in place for 3 weeks, which necessitated carotid ligation, although without deficit. None of these patients with a carotid or middle cerebral aneurysm rebled, although one, with an anterior communicating aneurysm, did have fatal rebleeding.

This concept of regional reduction of pressure is attractive but, because of the potentially high complication rate, has not been used widely. It is not improbable that ischemia with vasospasm was responsible in 3 patients who continued to deteriorate in spite of restoration of flow. This form of therapy needs more study because carotid aneurysms make up a third of all aneurysms and, if it could be made safe, it might be possible to eliminate most rebleeding in this group of patients with immediate subtotal carotid clipping.

Antifibrinolysins

Mullan† now claims virtual immunity from fatal rebleeding when hypotension or subtotal carotid clamping is used with antifibrinolysins. In his series so treated, no patient who was on antifibrinolytic medication and who had effective blood pressure control, rebled and died. Few clinicians are as aggressive as this; the lingering fear of precipitating ischemia with hypotension worries most but under the circumstances described by Mullan, it should be almost immediately reversible and not prohibitively dangerous although a 10% hemiplegia rate with partial carotid clamping is disturbing.

In 1967, Gibbs,10 followed by Mullan11 in 1968, and Norlen in 1969,12 introduced the concept of the use of an antifibrinolysin to prevent the natural lysis of the clot sealing the rent in the dome of the aneurysm. A NIH Cooperative Study completed in 197514 suggested that early rebleeding within 14 days was reduced by nearly half from a bed rest rebleed rate of 20.9% to 11%. This was considered a remarkable figure if it could be maintained and a real achievement in the alteration of the natural course of a critical human disorder. It then seemed possible, with medical and minor surgical measures, to delay sur-
surgery to a good risk period as the rate of rebleeding could be reduced to below 10% and its mortality to about 5%.

There have been other major advances in the surgical obliteration of aneurysms. Neuroanesthesia has become a rapidly advancing science and now patients can have anesthesia without rebleeding. In our early series, there was a 0.5% mortality from rebleeding at operation before the skull could be opened.

The brain can be made slack on nearly every occasion with dehydrating agents such as mannitol and Lasix, combined with controlled respiration and lumbar drainage of all the spinal fluid. Using induced hypotension during the dissection of the aneurysm at lower and lower levels, a fragile thin-walled aneurysm could be routinely dissected with safety, often at mean arterial pressures (MAP) of 40, or temporarily lower. Hypotension to these levels is usually necessary for only a few minutes but it has been used for hours. With these deeper levels of hypotension, the chance of rupture is reduced allowing accurate dissection and occlusion of the aneurysm at the origin of its neck.

Microsurgery

The greatest technical advance has come about with magnification of vision and illumination, at first with operating loupes and later with the operating microscope. This was just the right tool to allow surgeons to work in and around the brain, allowing easy visualization of tissue planes so that even the most minute structures and intimate connections of the aneurysmal sac could be identified and freed for clipping. Bipolar coagulation and replaceable spring clips have vastly improved precision and safety. Now, surgical treatment for patients in good risk periods carries an overall morbidity of less than 5% in experienced hands.

Aneurysms on the anterior and carotid circulation were the first to be associated with reduced mortality and morbidity with surgical treatment. As late as the period of the National Cooperative Study of Subarachnoid Hemorrhage and Aneurysm (1963-1970), in 19 centers, the operative mortality for these aneurysms was 36.8% and major complications occurred postoperatively in nearly half the patients. The mortality in this series was highest when the operation was performed in the first 14 days (44.5%) after bleeding and it was 29.2% even in patients in good condition. The problem was not the approach; it was the structures in the neighborhood of the aneurysm and the arterial relations that had to be worked out at every site with new tools.

Ventricular Basilar Circulation

The history of the surgical treatment of aneurysms on the ventricular basilar circulation is different, probably because of their lower incidence (± 10%), the later development of routine ventricular angiography and the belief that because of their hidden position in front of and embedding in the brain stem, little could be done about them. Experience with over 650 patients suggests that if they are of ordinary caliber, they can be as safely treated as those on the anterior circulation.

The surgical results for these aneurysms, when not of giant size, show that most morbidity has occurred with those at the basilar artery bifurcation, and that morbidity mostly occurred early in our series, before the significance of, and the means to save the perforating arterial branches were appreciated. Overall, there is a 5% mortality and a 12% morbidity, mostly from injury to perforating vessels, giving an 83% success rate. For aneurysms on the trunk of the basilar, the vertebral and posterior cerebral arteries, although the mortality is the same, 5.5%, the morbidity is halved, 6.5%. This is largely because of the paucity of hidden perforating arteries. Thus, there is an overall 88% success rate for surgical treatment of these aneurysms. (See table 1).

Giant Aneurysms

The technical problems of surgery for aneurysms of ordinary size is largely solved. A remaining problem is for those of much larger size, so-called "giant" aneurysms, which are defined as being over 2.5 cm or 1 inch in diameter. Except for those found on the carotid artery, where treatment with carotid ligation was possible, there was little recorded evidence for surgery for giant aneurysms elsewhere in the cerebral circulation. Because of a special interest, the neurosurgical service of The University of Western Ontario has now managed over 250 patients with giant aneurysms, 100 on the anterior circulation and 161 on the posterior circulation (table 1).

Certain features of their natural history and treatment deserve comment:

1) Contrary to popular opinion, over one-third of our patients with giant aneurysms have presented with bleeding and another 10% have a clear history of bleeding in the remote past, presumably when the aneurysm was smaller.

2) Giant aneurysms provide a particularly bleak outlook. All but 3 of 18 patients we have followed without definitive therapy are now dead or severely disabled.

3) In spite of their size, it has been remarkable how often the neck of one of these aneurysms is small enough or can be made so for clipping (about one-third of patients), which indicates that on this basis alone, many deserve exploration.

Where occlusion of the neck of the aneurysm is not feasible, occlusion of the feeding artery proximal to it has proved to be effective, resulting in obliteration of the sac by thrombosis in nearly all patients where the occlusion is tolerated.

Carotid ligation for therapy of giant aneurysms has a long and successful history. This principle of treat-
ment has been extended to all other major arteries of the brain which give rise to giant aneurysms where it has been just as effective. The following arteries have been ligated to treat giant aneurysms:

- Posterior Cerebral Artery 11
- Basilar Artery 32
  (23 near apex and 9 lower on trunk)
- Vertebral Artery 24
  (bilaterally in 7)

On the anterior circulation, the middle cerebral artery has been occluded uneventfully either at its origin or proximal to the bifurcation for treatment of giant aneurysm in 12 patients. This has been accomplished uneventfully in the presence of a functioning EC-IC bypass using a tourniquet or intracarotid detachable balloon so that collateral flow can be tested when the patient is awake.

Most giant aneurysms can now be treated with reasonable safety but technical problems remain for very large aneurysms not treatable by these means, especially when massive mural thrombosis is present.

**Aneurysms in the Older Patient**

Previous experience with aneurysm surgery in patients over 60\(^{18}\) showed that except for aneurysms at the basilar bifurcation, older patients tolerated surgery as well as younger patients, although they had a higher risk of earlier subsequent demise from associated cardiac and vascular disease. In the 5 years since an initial study,\(^1\) the data from another 35 patients, Grades I, II or III, over age 60, indicate no operative deaths and one poor result in 21 aneurysms on the anterior circulation and one death and one poor result in 14 aneurysms on the posterior circulation, giving an overall 91.5% success rate (table 2). One patient died at home from a massive pulmonary embolus one month after discharge. The 17 patients in
Grade I all had good results. Older patients with subarachnoid hemorrhage, therefore, deserve consideration for surgical treatment, particularly where they are well, physiologically younger, and have been leading active lives.

Multiple Aneurysms

Earlier experience supported the view that intact multiple aneurysms are not innocent and can be dealt with safely. In the University of Western Ontario study, 91 intact aneurysms were treated surgically in 88 patients who had another ruptured aneurysm with only 2 serious complications from the additional surgery. Since then, another 198 unruptured aneurysms found in 155 patients have been surgically treated with only 3 poor results which could be attributed to surgery on the intact aneurysm. These included two intra-operative ruptures and one ischemic syndrome (table 3). Surgical obliteration of 289 intact aneurysms in 246 patients with multiple aneurysms resulted in worsening only in 5 (1.7%). These data give little support for the idea that there is significant morbidity when there is surgery on more than the symptomatic aneurysm. This small risk seems significant in view of the fact that our original incomplete follow up showed that at least 17% of untreated intact aneurysms had ruptured.

Asymptomatic Aneurysms

Little is known of the natural history of intact asymptomatic aneurysms discovered incidentally in the investigation of another disorder. These cannot be considered benign and the safety of their treatment is such that they should probably be obliterated. The Ontario surgical experience with this problem includes 37 aneurysms in 20 patients (many were multiple), 28 were found on the anterior and 9 on the posterior circulations (table 4). All but one were surgically obliterated without significant morbidity. The exposure and clipping of an intact aneurysm is ordinarily straightforward and uncomplicated by ischemia. Experience with intact aneurysms supports the idea of treatment of the aneurysm before rupture, if a means to identify them early were to be developed. This may be possible, as Olinger has developed a computerized stethoscope by which the bruit in some aneurysms can be heard. Developments such as this, coupled with newer CT scan techniques, may result in a screening system to detect these vascular lesions.

Most surgeons have believed that considerable progress has been made in treatment of cerebral aneurysms. Means have been developed to prevent most rebleeding until a safe operative period is reached. Surgical approaches and techniques have been developed for obliteration of aneurysms at all sites whether on the carotid or the vertebral basilar systems. Size of the aneurysm is no longer a major deterrent to treatment and most giant aneurysms are treatable. When more than one aneurysm existed or, fortuitously, an incidental asymptomatic aneurysm was discovered, the safety of their surgical treatment was such that the opportunity to help make these patients safe from hemorrhage was reasonable as these aneurysms can no longer be considered entirely benign.

Epidemiology and Natural History of Aneurysm

The progress in surgical treatment, rosy as it seems, has not prevented questions as to whether modern delayed surgery had a significant impact on the natural history of aneurysms.

Most surgeons have reported their operative results on those patients reaching their hands and upon whom

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**TABLE 2: Ruptured Aneurysms - Age > 60 - (Since 1975)**

<table>
<thead>
<tr>
<th>Circulation</th>
<th>No. Patients</th>
<th>Good</th>
<th>Poor</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>21</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vertebro-basilar</td>
<td>14</td>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>32</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: All 17 Grade I patient* had good results.

**TABLE 3: Subarachnoid Hemorrhage Patients With Multiple Aneurysms**

<table>
<thead>
<tr>
<th>Period</th>
<th>Intact Aneurysms Treated Surgically</th>
<th>No. of Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952-1975</td>
<td>91</td>
<td>88</td>
<td>2 poor results</td>
</tr>
<tr>
<td>1975-1979</td>
<td>198</td>
<td>155</td>
<td>3 poor results</td>
</tr>
<tr>
<td>Total</td>
<td>289</td>
<td>246</td>
<td>5 poor results</td>
</tr>
</tbody>
</table>

Morbidity = 1.7%

**TABLE 4: Surgical Results - Intact Asymptomatic Aneurysms**

<table>
<thead>
<tr>
<th>Circulation</th>
<th>No. Patients</th>
<th>(No. Aneurysms)</th>
<th>Good</th>
<th>Poor</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>13</td>
<td>(29)</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Posterior</td>
<td>7</td>
<td>(9)</td>
<td>6</td>
<td>1**</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>(37)</td>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*7 Patients had associated symptomatic AVM.
**Patient hemiplegic with Moyamoya Disease.
a decision was made to operate. But physicians and epidemiologists are concerned with the whole picture, including all those individuals in whom an aneurysm ruptures.

A recent 30 year survey of the morbidity from subarachnoid hemorrhage in the Rochester, MN, area, from 1945 to 1975, is alarming. In each of the 3 decades examined, there has been no significant reduction of morbidity. In this community, the probability of survival 30 days from the onset of the first subarachnoid hemorrhage was only 42%; only 39% survived 6 months of whom 75% were in good condition. These bleak figures suggest that 30 years of surgical effort have had little impact on the total problem of ruptured aneurysm and subarachnoid hemorrhage.

Only 4 surgical series speak to the overall management problem and these relate only to those patients who survive to enter the hospital (table 5).

Comparison among these studies is difficult because of the many variations, especially in the time of admission following hemorrhage.

Although these reports of surgery suggest an overall favorable outcome from ruptured aneurysm varying between 43% and 84% in patients who survive to the hospital admission, the 43% figure for the Cooperative Study, where all cases were admitted within a week of bleeding, is the most realistic. This study reaffirms the impression that the earlier the admission after hemorrhage, the worse the overall management success — less than 50% of patients doing well.

During the course of the New York Study, a record was kept of the cases coming to the City Morgue as a result of unrecognized or untreated subarachnoid hemorrhage. The number found amounted to about one-third as many as were admitted to the N.Y.U. Center during the same period of time. However, in Rochester, MN, all but 8% of known cases had some medical attention. This mortality, ordinarily un-}

| Table 6: No. Aneurysms Annually/Neurosurgeon or Unit |
|----------------------------------|----------|---------|
| Japan 1974-76                     | 4758     | 3967    |
| Ontario 1977 (8,400,000)          | 305      | 3.6/100,000/year |
| Mayo 1970-74 (89,000)             | 30       | 13      | 3.0/100,000/year |

who reach their hands in good condition, it must be that the bulk of patients with aneurysmal hemorrhage are not seen by surgeons or not until it is too late. There are 3 other reports which support such an assumption (table 6):

1) In a little known study, 133 Japanese neurosurgical units participated in a cooperative study of surgical treatment of aneurysms during 1974 and 1975. This report was believed to cover the bulk of this kind of surgery for this country of 114,000,000 persons. During the 2 year period of the study, 4,750 patients with ruptured aneurysms were seen and 3,766 (or 79%) were treated surgically. This meant that Japanese neurosurgical units were seeing only 2 cases/100,000/year and operating only upon 1.6/100,000/year.

2) The work load of neurosurgeons in Ontario (population 8.4 million) in 1977 was obtained from the provincial insurance billings in that year. Three hundred and five aneurysms were treated surgically, an operative incidence of 3.6/100,000/year.

3) In the Rochester survey, operations were carried out on only 3/100,000/year in the last 5 years of the study which represented only 43% of the patients reaching medical attention, which was about 7/100,000/year (table 6).

It is known, from Pakarinen's detailed and critical study of subarachnoid hemorrhage in Finland, that the minimum incidence of ruptured aneurysm is about 12/100,000/year, and in Rochester, MN the annual incidence of ruptured aneurysm has remained remarkably constant over 30 years at 11/100,000/year. This means that surgeons are treating only a fraction of the
assumed probable cases of subarachnoid hemorrhage occurring yearly, at best, 30% in Ontario, 25% in Rochester, MN, but only 13% in Japan.

If it is true that the delayed surgical success rate for all those admitted early after a hemorrhage is no more than 50%, then surgeons are helping only about 1 in 6 patients with aneurysmal hemorrhage. These sobering figures lend support to the surveys that indicate no increasing significance of effect of surgery in cerebral aneurysm.

About 25,000 aneurysms rupture each year in the United States and 3,000 in Canada, and at best, about 8,500 of this group of 28,000 ruptured aneurysms occurring annually on our continent are operated upon and it would appear that less than 5,000 are made well.

The causes of mortality and morbidity after aneurysm rupture must be investigated and if possible, what can be done about them must be determined. These include rebleeding, ischemia with vasospasm, and medical and surgical complications.

Mortality from Ruptured Aneurysm

The mortality from the first recognized subarachnoid hemorrhage is horrendous. Most reviews of the natural history of SAH are uniform in reporting that about 50% of patients die as a result of this hemorrhage within the first hospitalization. Untreated, another 30% die from rebleeding in the next decade.

The Warning Leak

The question arises whether the catastrophic hemorrhage that brings most patients to medical attention or the city morgue is the first. The more care given to the history taken from these patients, the more often a story is obtained of an incident that, in retrospect, was almost certainly a hemorrhage of minor degree, occurring a few hours or days, or even weeks, before it was recognized. John Gillingham? was the first to bring attention to the fact that the initial bleeding from an aneurysm may commonly be of minor severity. In 70% of his patients? this consisted of sudden headache without coma, although there may be brief collapse in some patients. He called this the “warning leak” which, often, goes unrecognized by the patient and his relatives and even by physicians. Headache is so common that families tend to disregard it, especially when it subsides in a day or two. Physicians too, when consulted, frequently miss the significance of this headache, believing it to be benign and explain it away as an attack of migraine, tension headache, the flu, sinusitis, or a “sprained” neck. Such early symptoms offer the greatest opportunity for alteration of the natural history of this disorder. Recognition of the warning bleed is needed in the many patients in whom the ictus is not diagnostic. Students and physicians must become aware of these warning symptoms and when unsure of a suspicious headache, a lumbar puncture should be done. If the fluid is clear, the patient and physician can be reassured. If it is bloody, then there is a state of emergency and the patient should be transferred immediately to a neurosurgical unit where every means should be brought to bear to prevent rebleeding. Even though most physicians have been trained to be alarmed at a sudden, severe, otherwise unexplainable headache, they frequently miss the significance of many. A major problem will be to educate the public, as the “warning leak” is not always suddenly vicious and frightening head pain but frequently is vague and generalized or even just a stiff, sore neck.

Because headache is so common, some will be concerned about unnecessary lumbar punctures that might result. This need not occur if the character and circumstances of headache are investigated so that lumbar puncture can be reserved for those with suspicious headache where the clinical features leave doubt.

Since the future for surgical treatment of ruptured aneurysm depends on seeing patients in good condition after the initial minor bleeding, considerable effort is needed:

1) to take every opportunity to educate students and physicians about the common occurrence of aneurysm and its initial presentation;

2) to educate the public about these symptoms as is done for cancer and heart disease.

An incident occurred which shows that, once alerted, both physicians and the public can recognize the warning bleed. In London, Ontario, a first year resident in neurology was sued by a widow for missing a “warning leak” some 2 weeks before her husband’s fatal hemorrhage. A large judgment was rendered against him by the court and the story was featured in detail in the newspapers. During the next week, eight patients were referred to an emergency department by their physician for lumbar punctures, and in 5 the fluid was bloody. Of interest, too, was that they came not only at their physicians’ direction. Three had sought out their doctor to tell him that they thought they had had a hemorrhage.

Antifibrinolytic Therapy

Not all reports are favorable for the use of antifibrinolyins in the prevention of rebleeding. The results from a recent Cooperative study suggest that antifibrinolyins, in large doses, are effective during the first 2 weeks after bleeding (table 7).

This report covers 1,114 patients in 13 institutions who were given treatment with either epsilon amino caproic acid (EACA) or amino methyl cyclohexanecarboxylic acid (tranexamic acid) (AMCHA) within 7 days of bleeding. In the first 2 weeks from the last hemorrhage, 111 of the 1,114 patients rebled, giving a rebleeding rate of 10%, which is less than half that expected with bed rest. There were 3 conditions that were found important in the rebleeding incidence:
drug dose, preoperative condition of the patient, and timing of the treatment.

EACA at 36 gms/day in 363 patients resulted in 7.7% documented rebleeding but lower dose schedules resulted in 10-19% rebleed rates. The difference was not as marked in AMCHA perhaps because it has an antifibrinolytic potency 10 times that of EACA. In these patients 50% of the mortality was due to rebleeding and 50% due to a progressive decline without rebleeding, presumably mostly from the ischemic syndrome. The overall mortality rate also seemed clearly related to the dose schedule of the antifibrinolytic agent. For large doses, it was only 6.6% while for lower doses, it varied from 12 to 24%.

The study has also reaffirmed the importance of the preoperative condition of the patient. Both rebleeding and death were much less common in patients in good condition where only 9.2% rebled and 7% died compared to 25% rebleed rate and 28% mortality for those in poor condition. Only 5.1% of 733 patients with initial symptoms only of headache, cranial nerve palsies, or meningeal irritation, died by the 14th day.

Both rebleeding and mortality were highest among those patients admitted to treatment during the first 3 days after the hemorrhage where 13% rebled and 13% died, compared to those admitted to treatment on days 4 to 7, where 6% rebled and there was a 9% mortality rate.

This apparent selection is probably based on the severity of the initial hemorrhage. Those admitted early may have had brisk, easily recognized, often briefly coma-producing bleeds, alarming to all, from aneurysms with large rents and with more clot in the cisterns. In those with smaller aneurysmal tears and leaks and probably stronger-walled aneurysms, it may be several days before the significance of their headache is realized. Many wander from one emergency room to another before a lumbar puncture is done.

This study revealed 2 other results of interest:
1) The site of the ruptured aneurysm did not alter the results of therapy.
2) Antifibrinolytic therapy is not accompanied by a prohibitive number of severe neurological or medical complications. The use of either drug carries the possibility of some minor but only few major side effects.

### Cerebral Ischemia

Cerebral ischemia is a serious postoperative phenomenon. Most patients surviving the first critical week or two on medical management, seem to have many more ischemic calamities, even without operation. The progressive cerebral ischemic syndrome appears, ordinarily, toward the end of the first week after the initial bleed, beginning insidiously with a little confusion, a drifting arm or dysphasia, which forecasts the major ischemic events to follow. Its association with arterial spasm is not doubted by most neurosurgeons, and more than suggestive evidence of appropriate reduction of cerebral blood flow (CBF) is just emerging. It seems to occur naturally in about 15-20% of the patients who recover from the initial bleeding and about half of those who have spasm demonstrated on angiograms.

One of the factors which make linking ischemia to arterial spasm difficult, is the large range of cerebral blood flow compatible with normal neural function. Regional CBF in man is 50-60 milliliters per 100 grams of brain per minute. Electrical dysfunction of neurons begins at flows of 16-22 ml/100 gr/min and structural damage usually occurs with flow below 15 ml/100 gr/min. Thus, a hemisphere could have marginal flow yet the patient could be perfectly well. In this setting it is easy to understand how the volume depletion that frequently accompanies bed rest treatment, or even gentle operative manipulation, especially brain retractor pressure and the use of hypotension, etc., might be just enough to precipitate ischemia.

What is needed is a clinical means to identify in which patient, remaining well during the first week, the brain circulation is most adequate, so that operation can be delayed and anti-ischemic treatment instituted. Predictors such as differential EEG slowing and retarded flow in dynamic isotope scans have not been used widely enough to know their value. More sophisticated CBF studies may be rewarding and the new CT and PET scan flow techniques may be helpful. At the moment there is little diagnostic help available except a repeat angiogram just before surgery. If this shows arterial narrowing, it should suggest strongly that delaying the craniotomy is indicated and institution of techniques to improve perfusion should be carried out. Cooper et al. have documented these points in a study of 35 grade I patients. In 18, where no preoperative spasm existed at 7 or more days after bleeding, there was no operative morbidity, but of 8 patients operated on with spasm during this period, 2 died and 3 had neurological deficits. In 9 others, where surgery was delayed until spasm had subsided, only 1 developed a neurological deficit and that was due to an airway problem.

There is evidence coming from CT scanning studies of subarachnoid hemorrhage, that the amount of clot in the cerebral cisterns may be important as a predictor of spasm. A strong correlation has been found between the amount of cisternal clot and the condition of the patient, including a subsequent decline, a tenet first proposed by Mizukami et al. In a study of

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**Table 7** Antifibrinolytic Treatment (EACA, AMCHA) (Iowa Cooperative Aneurysm Study)

<table>
<thead>
<tr>
<th>No. Case</th>
<th>First 2 Weeks Rebleeding</th>
<th>Died</th>
<th>Rebleed Rate</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1114</td>
<td>111</td>
<td>119</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>High Dose (36 gm/day)</td>
<td>7.7%</td>
<td>6.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Dose (&lt;.36 gm/day)</td>
<td>10-19%</td>
<td>12-24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Condition</td>
<td>9.2%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor Condition</td>
<td>25%</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted to Treatment Days 1-3</td>
<td>1.3%</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted to Treatment Days 4-7</td>
<td>6%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Of 733 Grade I patients, only 9% died by the 14th day.
MANAGEMENT OF CEREBRAL ANEURYSM

56 patients by Eisentrou et al.,49 10 patients without demonstrable blood by CT scan and low clinical grade initially, showed no significant vasospasm and did well prior to and following aneurysm treatment or hospital discharge. Twenty-three patients with blood in the subarachnoid space or ventricles had a variable clinical course. These patients also with low clinical grade showed a tendency to deteriorate without rebleeding, most likely due to vasospasm. Seventeen patients with perichymal hematomas showed a much higher mortality and morbidity. The study emphasized that the absence of blood seen on the CT scan is a favorable prognostic factor, while the presence of diffuse blood in the subarachnoid spaces predisposes the patient to develop ischemia with vasospasm.

In Fisher's49 series of 47 patients, it was found that when subarachnoid blood was not detected or faintly and diffusely distributed, severe vasospasm was almost never encountered, while in the presence of large subarachnoid blood clots or thick layers in fissures and vertical cisterns, severe vasospasm followed almost invariably (23 of 24 patients). There was an almost exact correspondence between the site of subarachnoid blood clots and the location of the severe vasospasm.

If arterial spasm persists after the second week and the patient has tolerated even a severe degree of narrowing this long, it is unlikely that severe ischemia will develop afterwards, either naturally or post-operatively. A few patients become worse, even after surgery done at 16-17 days, but it is unusual. More often than not, worsening can be reversed with energetic measures such as blood volume expansion and increase of blood pressure.

Knowledge of the ischemic syndrome has been thwarted in that there is no animal model yet available which mimics the human events. Such a model should produce progressive cerebral ischemia with infarction. Despite experimentation and attempts to reverse the arterial narrowing with numerous and ingenious combinations of vasoactive drugs, we have failed to alter routinely either the caliber of the vessels or the ischemia. The only treatment that seems to have some credible effect is to improve the rheology of the circulation. This is done with mannitol, albumin or low molecular weight dextran with further volume expansion by transfusion of whole blood if the hemoglobin is low, and with cautious increase of systemic blood pressure. Reduction of intracranial pressure may further improve perfusion pressure.

Experience with blood volume expansion and induced hypertension in the management of severely progressive ischemic deficits in 34 patients has resulted in a 66% success rate in that 22, or two-thirds of the 34 patients, were permanently improved.41 However, in 5 others, early improvement could not be sustained and in 7 there was no response, a 33% failure rate.

Experience in the use of deep barbiturate coma to tide over the patient's brain during a period of severe ischemia and high intracranial pressure in 11 patients was not rewarding.42 This has been true of reports from other centers which have used this method.43-44

An additional approach to the patient with cerebral ischemia would be to obliterate the aneurysm so that volume expansion and hypertension might be used to control the ischemia without risk. Snyckers of Johannesburg46 has used this program in 3 patients, all drowsy or in coma with a major neurological deficit. In none was the clinical course affected beneficially.

Deliberate, early operation has been tried in good condition patients to prevent the development of ischemia by obliterating the aneurysm and flushing the subarachnoid spaces to remove the cisternal clots as the source of the vasoactive material. This treatment was first proposed by Johnson et al. in 1958,47-48 Pool in 1959,49 and, more recently, by Suzuki,48 Sano48 and Handa48 in Japan. Each of the Japanese surgeons proposed operations on either the first, second or third day respectively, but not after. Their results for surgery during the remainder of the first week have been very poor. They argue that removal of the clot after it has been incubating for 2 or 3 or more days is too late, as vasoactive substances are by then already formed and disseminating. Although based on a small number of patients, Handa's belief is that if there is no cisternal blood in the CT scan, one can operate at any time, but if blood is present, removing clots will be successful in only the first 3 days. It is questionable that clot removal can be complete through an ordinary craniotomy if the clot has spread diffusely. Only Suzuki routinely turns bilateral flaps to remove as much clot as possible. Formerly there has been only one indication for early surgery to prevent rebleeding; now another is being proposed to prevent arterial spasm and the ischemic syndrome.

As aggressive conservative measures can lower rebleeding to 10% and death to half that figure in the first week or two, early surgery will be best justified if it can be shown to lower mortality further, and to prevent, by clot removal from the subarachnoid spaces, the development of vasospasm and the ischemic syndrome which is taking the place of rebleeding as the disaster of consequence.

The 1979 Amsterdam Workshop on Spasm49 concluded:

1) There has been some gain in learning the nature and action of the vasoactive substances. Peerless48 believes their action is a cascade effect, and that perhaps most of the many factors that have been incriminated, act in some form of synchrony or sequentially, but that the final common path of action is the cation calcium. One of the future avenues for treatment at this level is to block the contraction of arterial smooth muscle. There is belief that this contraction is not solely physiologic but results from a pathologic architectural change in the vessel wall making it more rigid and narrow, and not responsive to even the most potent vasodilating agents.

2) No treatment for spasm other than that of volume expansion and improvement of blood rheology with concomitant reduction of intracranial pressure produces reasonably consistent benefit.
Early Surgery

It is doubtful if early operation can be done indiscriminately unless it can be shown that removal of large amounts of cisternal clot will prevent the ischemic syndrome or that it becomes possible to reverse the ischemia routinely by medical measures.

It is disappointing to learn that Saito has found in an initial study of Sano's early operations there was not a statistically significant reduction of vasospasm and ischemia following the removal of clot although the number of patients was small. Sano's recent review of 31 patients with pre- and postoperative CT scan evaluation revealed that where either study was largely clear of cisternal blood (16 patients), significant arterial narrowing and ischemia did not occur. However, in 16 patients where cisternal clot was present postoperatively, 13 showed arterial narrowing and 8 developed severe ischemia. The results from the Japanese Cooperative Study were disappointing.

The mortality figures for operations done within 24 hours of bleeding revealed an operative mortality in Hunt Grade I patients of 9% and in Grade II, 33%. During the second day, the respective mortality figures were 44 and 20%. In Hunt Grade III, the mortality was 34% for operations within 24 hours and 37% for those during 24–48 hours. Thus, the operative mortality for early operation within 48 hours in these good and reasonably good condition patients was 26%.

Another factor in early operation must be considered. According to Nishimoto, many of the surviving good condition patients deteriorated after an early operation and many were discharged as having poor or only fair results. When reviewed months later, many of these patients had improved and were considered good results. In Sampson's series of 79 early operations in well patients, 23% were discharged as poor or only fair results, yet at later follow up, only 8% were considered not good results. In Sampson's series, no patient was discharged as a poor result after delayed surgery. The question is whether such protracted recovery leaves a subtle dulling of brain function.

Although about one-half of those patients who remain seriously disabled with copious diffuse subarachnoid blood and ischemia will ultimately have a good recovery, surgery should be delayed until there is a degree of improvement that makes it likely the patient will ultimately make a worthwhile recovery for self, the family and the community.

Medical and Surgical Complications

Of 420 consecutive patients analyzed by Peerless, 64% had some medical or surgical complications; although this included rebleeding and ischemia, many were of minor degree and most were treatable. Overall, 86% of the operated patients did well including all grades and aneurysm sizes and complexities. In 52% the complications were primarily medical but in 12% they were the result of the surgery; many had both.

Massive pulmonary embolism or myocardial infarction produced a low but persistent post-operative mortality rate especially in older patients. Delayed hydrocephalus, which occurs in about 10% of patients, is now easily recognized and treatment is almost invariably rewarding.

This list of possible complications related to surgery is long. Most of the arterial occlusions are deliberate and most of the patients do well, including those with EC–IC bypass. Postoperative surface hemotoma is generally not fatal but an intracerebral hemorrhage can be. A little brain swelling is common but occasionally may be serious. It is often unanticipated and sometimes inexplicable, although brain retractor pressure may be more of a factor than recognized.

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