SECTION I

Preliminary Remarks on Subarachnoid Hemorrhage

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Preface

The subject of vascular disease is attracting greater and greater attention. Vascular disease of the brain ranks third in the causes of death in the United States at the present time. It has been estimated that hypertensive intracerebral hemorrhage accounts for 20 per cent, cerebral embolism 15 to 20 per cent, and cerebral thrombosis 50 per cent of all strokes. These figures will vary depending upon the population from which patients are derived and the nearness to hospital facilities. The remaining 5 to 10 per cent represents subarachnoid hemorrhage (Stevenson '28; Ohler and Hurwitz '32; Falconer '50, '51; Merritt '63).

In their excellent treatises, Dandy '44, Hamby '52, Walton '56, and later, Pool and Potts '65, reviewed the literature in detail and made important contributions to our understanding of subarachnoid hemorrhage, aneurysms and arteriovenous malformations. It is interesting and encouraging to note the many advances which have been made in this field in the past decade. These are covered in the publication by Fields and Saha '65. No apologies need be made for the fact that what appears to be a rather simple problem turns out to be an exceedingly intricate and difficult one, and that much work needs to be done to reduce the mortality and morbidity of this condition.

The authors hope that the review to follow will be a useful background for the material to be presented by the Central Registry of the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. The number of references must be limited in the interest of saving space for the large amount of data to be presented. Thus it is not possible to cover the literature in great detail, but pertinent references for the interested reader are provided.

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Introduction

Today's clinical approach to the problem of spontaneous subarachnoid hemorrhage is a product of the remarkable advancement of medical knowledge in recent years, but interest in this subject is not new. Gull, in 1859, wrote, "Whenever young persons die with symptoms of intransient apoplexy, and after death large effusion of blood is found, especially if the effusion be over the surface of the brain in the meshes of the pia mater, the presence of an aneurism is probable."

Fearnsides '16 reported that the first definite account of an intracranial aneurysm was published by Biumi of Milan 1763 and was reprinted by Sandifort at Leyden in 1778. Morgagni 1761 is also given credit as one of the first to describe an intracranial aneurysm. However, Walton '56 indicated that both of these authors were antedated by Pierre Dionis in 1718 who described in detail a Duke and a Prince, both of whom probably died from subarachnoid hemorrhage. Pool and Potts '65 suggested that intracranial aneurysms were recognized as a cause of cerebral hemorrhage by Wiseman 1696.

Incidence of Aneurysms

Richardson and Hyland '41 found the incidence of intracranial aneurysms to be 0.87 per cent in an autopsy series, in which slightly less than half the brains were removed. They indicated the actual incidence may be considerably higher. In a total of 2,030 cases of sudden and unexpected natural death necropsied between 1937 and 1943, Helpenr and Rabson '50 found 95 cases (4.7%) of spontaneous subarachnoid hemorrhage. This represented 23.7 per cent of the 450 fatalities from diseases of the nervous system. Housepian and Pool '58 reported an incidence of 2.1 per cent in the last portion of their autopsy series covering 1931 to 1958. Chason and Hindman '58 indicated that the incidence of aneurysms in their series was 4.9 per cent. This included 80 instances of unruptured aneurysms. The anterior portion of the circle of Willis was implicated nine times
more frequently than the posterior segment. The average size of the ruptured aneurysms was almost twice that of the unruptured ones. Stenbro '54 reported 182 cases of aneurysms in a large series of necropsies. He reported the incidence as 3.7 per cent.

Location of Intracranial Aneurysms

Bull '62 reviewed the 1,769 intracranial aneurysms collected by Mckissock in the 11 years from 1950–60, inclusive. The locations were as follows:

<table>
<thead>
<tr>
<th>Location</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral-anterior communicating</td>
<td>485</td>
<td>27.4</td>
</tr>
<tr>
<td>Internal carotid-posterior communicating</td>
<td>467</td>
<td>26.4</td>
</tr>
<tr>
<td>Middle cerebral artery (first bifurcation)</td>
<td>348</td>
<td>19.7</td>
</tr>
<tr>
<td>Bifurcation (termination) carotid</td>
<td>110</td>
<td>6.2</td>
</tr>
<tr>
<td>Distal anterior cerebral</td>
<td>48</td>
<td>2.7</td>
</tr>
<tr>
<td>Multiple</td>
<td>247</td>
<td>14.0</td>
</tr>
<tr>
<td>Vertebral artery tree</td>
<td>64</td>
<td>3.6</td>
</tr>
</tbody>
</table>

It should be noted that the percentage of intracranial aneurysms in the vertebral-basilar system is relatively low. Three- or four-vessel angiography would be expected to provide a higher yield of posterior fossa aneurysms.

Pathology

Pathologists have been making contributions to the study of aneurysms for many years. One of the pioneers in this field was Turnbull '18, who reported 33 examples of "medial degeneration following congenital developmental deficiency" in 29 cases. However, the classical work of Eppinger was published many years before, in 1887. He insisted that in the small and smallest arteries, like those forming the circle of Willis and its branches, many aneurysms have a congenital origin and are due to an inborn defect of the elastic properties of the vessel wall; in others, congenital defects with subsequent degeneration of atheromatous processes complicating the defect are the essential factors in causation. A major contribution was provided by Forbus '30, who emphasized the role of medial defects in the genesis of aneurysms. Since that time a great deal of controversy has developed as to whether saccular aneurysms of the circle of Willis are congenital, acquired or combinations of both. The role of atherosclerosis has been emphasized, especially by such investigators as Walker and Allègre, '53, '54.

Clinical Aspects

With the introduction of the spinal puncture by Quincke 1891, it became possible to establish the diagnosis of subarachnoid hemorrhage in life. It required many years, however, for physicians to develop the necessary sophistication to distinguish between bloody spinal fluid and the results of a traumatic puncture. Indeed, this differentiation is still an occasional problem.

The introduction of cerebral angiography by Egas Moniz in 1927 provided an important new diagnostic tool which is now an essential part of the work-up of patients with all types of subarachnoid hemorrhage. It is now possible to visualize the posterior part of the circle as well as the anterior portion of the circle of Willis. Unfortunately, angiography is not entirely without risk; skill is required in its performance and its possible dangers must be measured against the information to be sought.

Rupture of an aneurysm may occur into the subarachnoid space, brain substance, subdural space or cavernous sinus. Profound changes may take place in the intracranial circulation, especially in that portion distal to the aneurysm. The aneurysm will sometimes reach such a size that it will present as a space-occupying lesion. Finally, the extravasation of blood into the subarachnoid space will often result in obstruction of flow of the cerebrospinal fluid and impairment of absorption of cerebrospinal fluid.

The symptoms of intracranial aneurysms are variable and depend on the location of the aneurysm and the effect on the surrounding structures. An aneurysm may remain asymptomatic and be found incidentally at autopsy.

The symptoms of subarachnoid hemorrhage vary with the acuteness of the bleeding episode and the amount of blood extravasated into the subarachnoid space. In the classical case, the patient suddenly complains of a violent headache, with nausea, vomiting and prostration. Disturbance of consciousness is usually associated with the ictus, and the patient may have a convulsion. The neck becomes stiff and there is restriction of the leg-raising tests. In many instances there is little to be found in the way of focal neurological signs. More detailed accounts of the symptoms and signs can be found in textbooks by Merritt '63, Elliott...
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'64, Smith '65, Grinker and Sahs '66, and in the monographs of Walton '56, and Pool and Potts '65.

Aneurysms of the intracranial portion of the carotid artery may affect the II, III and IV cranial nerves (Walker '56). Cranial nerves V and VI may also be implicated. Aneurysms located in the anterior communicating-anterior cerebral region often produce visual disturbances and with rupture, sudden coma (Walker '56). Aneurysms situated on the middle cerebral artery are likely to produce hemiparesis, sensory changes and convulsions. When the lesion is on the dominant side, dysphasia is often present. Aneurysms of the vertebral-basilar system are accompanied by cranial nerve lesions (especially VII and VIII), other brain stem signs and cerebellar signs.

Prognosis (General)

The mortality rate varies somewhat, but there is no question that subarachnoid hemorrhage from various causes poses a serious threat to the life of the patient. Some published figures from a variety of causes are as follows:

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Patients</th>
<th>Mortality Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sands</td>
<td>1941</td>
<td>120</td>
<td>34</td>
</tr>
<tr>
<td>Magee</td>
<td>1943</td>
<td>150</td>
<td>56</td>
</tr>
<tr>
<td>Wolf et al.</td>
<td>1945</td>
<td>46</td>
<td>33</td>
</tr>
<tr>
<td>Richardson</td>
<td>1948</td>
<td>124</td>
<td>52</td>
</tr>
<tr>
<td>Hamby</td>
<td>1948</td>
<td>130</td>
<td>64</td>
</tr>
<tr>
<td>Ask-Upmark and Ingvar</td>
<td>1950</td>
<td>138</td>
<td>44</td>
</tr>
<tr>
<td>Wolfe</td>
<td>1953</td>
<td>93</td>
<td>56</td>
</tr>
<tr>
<td>Magladery</td>
<td>1955</td>
<td>255</td>
<td>49</td>
</tr>
<tr>
<td>Walton</td>
<td>1956</td>
<td>312</td>
<td>45</td>
</tr>
</tbody>
</table>

Many of these statistics were compiled in an era when routine angiography was not employed. Most of the patients in the earlier years were automatically relegated to the "conservatively" treated group, in which bed rest and supportive management were predominant.

Ask-Upmark and Ingvar '50 postulated that without operation one case in five of aneurysm can be expected to make a good recovery and take up his old occupation; one case out of five remains crippled; and three cases out of five die sooner or later from subarachnoid hemorrhage.

Abnormalities Associated With Aneurysms

GENERAL COMMENTS

The possible relationship of saccular aneurysms and congenital abnormalities has been discussed repeatedly in the literature. Stehbens '62 reviewed the prevalence of congenital anomalies, especially polycystic kidney disease, as well as coarctation of the aorta. He concluded that there was insufficient evidence to support the postulate that the association of cerebral aneurysms and developmental errors is significant. The coexistence of the lesions could be due to the concomitant hypertension and arterial degenerative disease rather than to hypothetical congenital factors.

COARCTATION OF THE AORTA

There are a number of reports indicating the association of coarctation of the aorta and intracranial aneurysms. Both conditions were confirmed at autopsy by Davies and Fisher '43 and by Bigelow '53. Walton '56 reported the case of a woman who had a verified coarctation of the aorta and a ruptured aneurysm of the left anterior cerebral artery. He indicated that of 22 reported cases of subarachnoid hemorrhage in patients with aortic coarctation, 14 died in the first attack. The average age of the patients was 25 years. These findings could possibly lend support to the view that intracranial aneurysms may develop early in such patients owing to associated congenital defects in the cerebral arteries. However, Walton indicated that the associated hypertension might promote aneurysmal formation, dilatation and rupture at a comparatively early age.

CONGENITAL POLYCYSTIC KIDNEY DISEASE

Up to 1955, Bigelow found 44 cases of associated congenital polycystic disease and intracranial aneurysm. In 1953, Bigelow suggested that polycystic kidney disease may represent one phase of a disseminated congenital disorder somewhat analogous to tuberous sclerosis, neurofibromatosis of von Recklinghausen, or Lindau-von Hippel's disease. Reports of the association of polycystic disease and intracranial aneurysm are to be found in the publications of Sahs '50 and Sahs and Meyers '51.

This subject has been reviewed recently by Ditlefsen and Tönjum '60, who reported that in a family consisting of 99 individuals, 88 grew up. Fifteen had verified and two suspected polycystic kidneys. Six had cerebral hemorrhage. Of these, three died of subarachnoid hemorrhage, one with a verified
raptured aneurysm on the middle cerebral artery. These are certainly not conclusive statistics.

**ARTERIOVENOUS MALFORMATIONS**

Saccular aneurysms have been reported in association with arteriovenous malformations by a number of authors, including Gould *et al.* '55, Vielen '55, Descuns *et al.* '56, Paterson and McKissock '56, Caram '59, and Reigh and Lemmen '60.

Reigh and Lemmen '60 reported that the congenital origin of arteriovenous aneurysm and cerebral berry aneurysm has long been suspected. They indicated that embryological and clinical studies have suggested that the arterial aneurysm commences in errors of fusion and absorption in the normal dynamics of the developing arterial system. Paterson and McKissock '56, however, pointed out that the coincidence of intracranial aneurysms and angiomias in four patients of 110 studied did not contribute to the current controversy as to whether intracranial aneurysms are congenital in origin or develop as a result of local pathological changes secondary to hypertension, atherosclerosis, and the like.

**MULTIPLE ANEURYSMS; SYMMETRICAL ANEURYSMS**

Bigelow '55 reviewed the literature comprehensively and reported that of a total of 2,237 cases of intracranial aneurysms, 228, or slightly over 10 per cent, had multiple lesions. Eppinger 1887 reported a case in which nine intracranial aneurysms were present. Stehbens '54 reported seven aneurysms on one circle of Willis. He found an incidence of 14.3 per cent of multiple aneurysms in a series of 182 cases containing 217 aneurysms. In 47 subjects inspected by him personally, the incidence of multiplicity was 25.5 per cent. Multiple aneurysms were reported by Walton '56 as amounting to 11.3 per cent of the total.

It is interesting that there have been a number of bilateral, symmetrical locations. Hamby '52 reported four instances in eight patients with multiple aneurysms. Bigelow '55 found eight instances of bilateral and symmetrical aneurysms among a group of 17 multiple aneurysms. He felt that bilateral symmetrical aneurysms of the berry type might well represent a fruitful source for investigation into the still unsettled subject concerning the etiology and pathogenesis of these lesions.

**Familial Aneurysms**

The occasional occurrence of familial cerebral aneurysms might lend support to their congenital origin. Cases have been recorded by O'Brien '42, Chambers *et al.* '54, Walton '56, Krayenhull and Yasargil '58, Ross '59, Ullrich and Sugar '60, and Phillips '63.

**Aneurysmal Rupture During Pregnancy**

A number of reports are available concerning ruptured aneurysms in pregnant patients (Sands '29, Richardson and Hyland '41, Rhoads '47, de Carle '49, Conley and Rand '51, Christensen and Larsen '54, Walton '56, Heiskanen and Nikki '63).

Pedowitz and Perell in 1957 collected a series of 79 cases of subarachnoid hemorrhage during pregnancy, thought to be caused by rupture of an intracranial aneurysm. Thirty-two of these were verified by angiography or autopsy. They reported that the mortality rate of subarachnoid hemorrhage during pregnancy does not differ materially from that in the nongravid state.

Heiskanen and Nikki '63 reported on seven cases of ruptured intracranial aneurysm during pregnancy treated at the University Central Hospital of Helsinki. The majority of aneurysms ruptured toward the end of pregnancy. Labor, as such, however, was not a significant factor in promoting the rupture of an aneurysm. They felt that termination of a pregnancy because of rupture of an aneurysm is not indicated; that if the aneurysm has been ligated, a normal vaginal delivery can take place, otherwise caesarean section should be considered. In surgically treated cases a future pregnancy is not contraindicated. If the aneurysm has not been ligated, it is advisable to avoid pregnancy for some years, according to Heiskanen and Nikki '63.

**Other Types of Intracranial Aneurysms**

Many authors such as Dandy '44, Hamby '52 and Bull '62 have indicated that other types of aneurysms may occur, but these are rather infrequent. They are: atherosclerotic aneurysms (especially of the carotid cavernous region, the intracranial portion of the internal carotid artery, and the basilar vertebral system); dissecting aneurysms;
mycotic aneurysms; syphilitic aneurysms; and traumatic aneurysms. Courville '62 has written on the morphology and pathogenesis of arteriosclerotic aneurysms. Dissecting aneurysms are uncommon, but they have been reported by Wolman '59, and by Scott et al. '60. The literature has been reviewed by these authors.

Mycotic aneurysms are somewhat of a rarity at the present time. Descriptions can be found infrequently in the literature (Stengel and Wolferth '23, Stein '44, Starrs '49, Walton '56).

Associated Lesions

The numerous, complex changes which take place in the brain after the rupture of an aneurysm need not be discussed in detail. These include: (1) massive subarachnoid hemorrhage; (2) intracerebral hematoma and intraventricular hematoma; (3) temporal (incisural) herniation; (4) cerebellar tonsillar herniation; (5) hemorrhagic lesions of the brain stem; (6) ischemic lesions; (7) hematomas between frontal lobes or in the sylvian fissure; (8) arachnoidal adhesions; (9) hydrocephalus; (10) compression of cranial nerves; (11) degeneration of the granular layer of the cerebellum.

With the increased interest in the field, the many ramifications of disease produced by aneurysms are becoming manifest. Some of these are as follows: (1) hypothalamic lesions following rupture of cerebral berry aneurysms (Crompton '63); (2) hypothalamic adhesions secondary to invasion of sella (Fine and Williams '63); (3) subdural hematoma (Boop et al. '61). Many of these changes were reviewed in the article by Tomlinson '59.

Treatment

The pioneer work of Dott '33, Jefferson '37, '38, and Dandy '38, '39 paved the way for many neurosurgical approaches to the problem of diagnosis and treatment of aneurysms. Walker '51 gives credit to Horsley '02 (citing Beadles '07) for exposing an intracranial aneurysm distal to the carotid canal, then ligating the carotid artery in the neck. Since then, many neurosurgeons have made contributions in the diagnosis and management of this condition.

In spite of the many advances in the diagnosis and management of patients with subarachnoid hemorrhage and intracranial aneurysms the mortality and morbidity rates remained high. The search continued for a better method of selection of patients for the various therapies. A statement concerning the management of intracranial aneurysms is summarized by Merritt '63, as follows: "The patient should be kept flat in bed and disturbed as little as possible. Analgesic can be administered for the relief of headache. Lumbar puncture should be performed to help in the establishment of the diagnosis. Surgical therapy is necessary when there is evidence of a large intracortical clot but there is still considerable disagreement as to whether patients with ruptured (or unruptured) aneurysm should be treated by bedrest and other supportive measures, or whether an attempt should be made to treat the lesion by surgical methods. Unfortunately there is insufficient evidence to make dogmatic statements with regard to this question. The high mortality rate with conservative treatment has convinced many neurosurgeons that operative therapy is essential. On basis of an extensive experience McKissock stated that the value of surgical treatment was still unproven. Other neurosurgeons have come to exactly opposite conclusions. Regardless of the controversy, the decision regarding conservative or operative therapy must be made by the physician who is responsible for the care of the patient. With modern neurosurgical techniques, including hypothermia and temporary control of the circulation, the risks of operative therapy are greatly reduced."

McKissock and his colleagues, '60, '62, reported on the results of a randomized study of treatment of intracranial aneurysms in an effort to determine which treatment or treatments were superior. A controlled comparative-treatment study was begun in the United States in June, 1963.

Indications for a Cooperative Study

In 1951, Mount assembled from the literature and from the cases at the Neurological Institute of New York a group of 752 cases treated conservatively. In this group the mortality rate was 48%. In the series of 469 cases treated surgically there was a mortality rate of 14%. In compiling this material it was obvious to the author that these two series of cases were not matching, and that a cooperative study would be necessary in order to obtain statistically valid conclusions. In an attempt to establish an aneurysm registry an IBM form was compiled and all certified neurosurgeons were written to at that time,
requesting them to cooperate in the study. It soon became apparent that financial, medical and secretarial help would be necessary in each cooperating center. In 1956, Dr. A. E. Walker requested the National Institute of Neurological Diseases and Blindness to call a meeting of doctors interested in subarachnoid hemorrhage. It was from this meeting that the present study evolved.

In 1958, Mckissock et al. indicated, “At the present time there is no conclusive evidence indicating the natural death rate in a large series of unselected cases of ruptured intracranial aneurysm and so there can be no proof of the value of surgical treatment in this condition.”

After a careful survey of their cases, McKissock et al. ’60, came to the following conclusions, “there is no proof that surgical treatment of ruptured intracranial aneurysms has effectively lowered the mortality unless a large hematoma is present and can be evacuated.”

It appeared at that time that no single investigator or clinic in the United States at least, would be likely to accumulate a sufficient number of clinical cases to resolve definitively the rather unsatisfactory state of information regarding questions of management and therapy which arose so urgently in patients presenting with nontraumatic subarachnoid hemorrhage, particularly those caused by aneurysms and arteriovenous malformations.

**Value of Cooperative Studies**

The value of cooperative clinical research programs among medical institutions is covered in the following quotation (Howard ’61):

“During the past few years, institutions have begun to join in the pooling of their experiences in clinical research. The results have been encouraging, often producing answers in a surprisingly short time.

“Historically, individual surgeons have evaluated the natural history of a given disease or the effect of operation in altering its natural course. After a lapse of years, one might have summarized and reported his observations. Other surgeons might have reported various modifications with divergent results. As a result, after a generation can anyone tell whether postoperative irradiation influences the course of breast cancer? Can anyone outline with factual assurance the course and treatment of gastric ulcer, of thyroid malignancy, of pancreatitis or of recurring tonsillitis, contaminated wounds, or ruptured disc? The answer is NO. Prejudiced, incomplete, or noncomparable reports often fail to answer any single question.

“Currently, a revival and extension of inter-institutional clinical research has occurred which promises to provide some definite answers in a reasonably short period of time. Clinical protocols have been developed to answer specific questions, progress data being forwarded to a central statistical unit. Under the auspices of the United States Public Health Service, various cooperative programs have been organized in the area of chemotherapy of cancer. Veterans Administration programs currently include both malignant and benign diseases. The National Research Council has organized a cooperative study in the prevention of wound infections. Other studies are underway but the horizon is unlimited. The profession is accustomed to the concept of ‘reportable diseases’; it is not oriented to the concept of ‘reportable treatment’ or ‘reportable results.’

“Such research is not original research: it does not result in new ideas or striking advances. It does not replace the individual investigator. It should, however, answer many of the questions that flood our profession. Our better institutions should increase their cooperative clinical research. The United States Public Health Service might well expand its financial support of such efforts in all spheres of medicine. State or local health agencies might join, or the World Health Organization might develop such a program among qualified institutions. The military services might well adapt the method to an increased extent.

“Clinical impressions would give way to clinical facts.”

**The Cooperative Aneurysm Study**

The Cooperative Study was sponsored by the United States Public Health Service through the National Institute of Neurological Diseases and Blindness. It represents the combined efforts of a number of university neurological and neurosurgical centers in the United States and one in England to study pressing clinical and research questions relative to subarachnoid hemorrhage and certain related aspects of cerebrovascular disease. This Cooperative Study was conceived at a meeting of an ad hoc committee called together by the National Institute of Neuro-
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logical Diseases and Blindness in Bethesda in October, 1956. It was proposed by the committee that many of the inconsistencies, and even antitheses, evident in the literature might be resolved through a general agreement regarding terminology, criteria for evaluation of patients, characterization of indications for various modes of treatment and adoption of a uniform method of case reporting.

A general plan for a Cooperative Study was evolved at this meeting of the ad hoc committee. At subsequent planning sessions, a Study Group was organized, and in May, 1957 a Central Registry was established. As originally constituted, the participating centers were represented nearly equally by medical neurologists and neurosurgeons.

Operation of the Central Registry, which is located at the University of Iowa in Iowa City, is supervised by a committee known as the Central Registry Committee. These participants have been listed above, in the University of Iowa section of Centers and Contributors.

The statistical aspects of the Study are supervised by the Department of Mathematics and Biostatistics at the University of Iowa. Those responsible for this function have been:

Lloyd A. Knowler, Ph.D., Professor of Mathematics;
James C. Hickman, Ph.D., Associate Professor of Mathematics;
Waldo F. Geiger, Jr., M.S., Biostatistician;
Brian L. Harvey, M.S., Biostatistician; and
Carl J. Gochenour, Manager, Data Processing Service.

The encoding of data on IBM cards and machine analysis of the data are carried out by the University of Iowa Statistical Center. The Study addressed itself to attempting to answer a number of questions. Some of these are of broad interest:

(1) The causes of spontaneous subarachnoid hemorrhage (excluding trauma) and their relative incidence;
(2) The natural history of intracranial aneurysms and cerebral arteriovenous malformations;
(3) The prognosis after subarachnoid hemorrhage of nonsurgically treated aneurysms in the various principal locations, with calculations of survival probability at various periods after the initial bleeding episode;
(4) The clinical course and prognosis of patients with subarachnoid hemorrhage due to various other definable causes, as well as those in whom no specific lesion is demonstrable by angiography and in whom the cause of hemorrhage remains obscure; and
(5) The influence on prognosis of factors such as age, site of aneurysm, and clinical condition.

Other questions of immediate practical value were:

(1) The optimal time for performance of angiography;
(2) Evaluation of various types of surgical therapy;
(3) The optimal time for surgery;
(4) The influence of age and site of lesion on the results of surgical therapy; and
(5) The value of various adjuncts to surgery, such as hypothermia, hypotensive agents, and temporary vascular occlusion.

A need for long-term follow-up data, with evaluation of patients' functional disability as well as the incidence of survival following the various types of therapies, was recognized.

Finally, the Study offered the participants an opportunity to investigate independently cerebrovascular dynamics under a variety of conditions, and it is conceivable that these ancillary studies will have yielded information quite as valuable as that in the main clinical study (Gurdjian et al. '65, Tourtellotte et al. '65, Wright and Sweet '65).

The first task undertaken was to prepare a set of protocol forms to be used by the participants for case reporting and follow-up studies. The protocol was, in a sense, the heart of the study. It attempted to incorporate in codable form all available data which might be needed to answer pertinent questions and represented much critical thought and discussion by sub-committees and individuals of the group. The protocol consisted of 6 fascicles dealing separately with (1) history and physical findings, (2) angiographic findings, (3) surgical treatment, (4) nonsurgical treatment, (5) pathologic findings, and (6) follow-up information. Completed protocols began arriving at the Central Registry in January, 1958, and as of June 1, 1965, totalled 6,368 cases. These 6,368 cases provide the basis for extensive studies to be reported in subsequent issues.