Unruptured intracranial aneurysms: a review

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Object. In this article, pathological, radiological, and clinical information regarding unruptured intracranial aneurysms is reviewed.

Methods. Treatment decisions require that surgeons and interventionists take into account information obtained in pathological, radiological, and clinical studies of unruptured aneurysms. The author has performed a detailed review of the literature and has compared, contrasted, and summarized his findings. Unruptured aneurysms may be classified as truly incidental, part of a multiple aneurysm constellation, or symptomatic by virtue of their mass, irritative, or embolic effects. Unruptured aneurysms with clinical pathological profiles resembling those of ruptured lesions should be considered for treatment at a smaller size than unruptured lesions with profiles typical of intact aneurysms, as has been determined at autopsy in patients who have died of other causes. The track record of the surgeon or interventionist and the institution in which treatment is to be performed should be considered while debating treatment options. In cases in which treatment is not performed immediately, ongoing periodic radiological assessment may be wise. Radiological investigations to detect unruptured aneurysms in asymptomatic patients should be restricted to high-prevalence groups such as adults with a strong family history of aneurysms or patients with autosomal dominant polycystic kidney disease. All patients with intact lesions should be strongly advised to discontinue cigarette smoking if they are addicted.

Conclusions. The current state of knowledge about unruptured aneurysms does not support the use of the largest diameter of the lesion as the sole criterion on which to base treatment decisions, although it is of undoubted importance.

KEY WORD • unruptured aneurysm

An aneurysm is a swelling along a blood vessel. The majority of aneurysms are saccular in shape and result from a combination of factors including degeneration and weakening of the internal elastic lamina and collagen fibers of the arterial wall, as well as hemodynamic effects of fluid pulsations, which can be adversely increased by certain anatomical variants. Only very rarely do aneurysms develop in utero or in childhood. For practical purposes, it can be assumed that the majority of these lesions develop in adults. Certain inherited factors can increase the likelihood of aneurysm formation, although the specific genetic defect responsible for so-called familial aneurysms is unknown. The most common medical condition associated with saccular aneurysm formation is ADPKD, but the associated condition that appears to increase the risk of aneurysm development and rupture to the greatest extent is cigarette smoking. Arterial hypertension may also play a role. The rate of aneurysm growth is highly variable. In my opinion, it is probable that a majority of subarachnoid aneurysms will rupture, although nearly as many will not; this issue is debatable.

It is essential that we preemptively treat patients deemed to be at high risk for aneurysm rupture to avoid both the
horrendous risks of morbidity and mortality associated with SAH but also to prevent the delivery of an iatrogenic insult to patients destined to coexist peacefully with their unruptured aneurysms before dying of some other cause.

**Classification of Unruptured Aneurysms**

Unruptured aneurysms are those lesions with no historical or pathological evidence of a complete breach through the artery walls. They can be classified by a variety of criteria (Table 1).

**Pathology of Aneurysms**

Crompton examined 79 unruptured aneurysms histologically. He found that 50% exhibited fibrin staining both at the apex and in the endothelial region adjacent to the lumen. In some cases the fibrin staining appeared on the luminal side of the endothelium. Numerous leukocytes were found in the aneurysm wall and occasionally permeated through the endothelium. Such permeation of the lesion wall by polymorphonuclear leukocytes occurred in 29% of the unruptured aneurysms. Crompton suggested that fibrin and leukocytes would be more commonly found in aneurysms that had reached the critical size for rupture.

Kataoka and colleagues reported on the histological findings in 57 tissue samples obtained in patients with ruptured aneurysms. Seventy percent of the aneurysms were smaller than 10 mm. In almost half of the small ruptured lesions, the entire specimen had been replaced by a hyaline-like structure lacking collagen layers and vascular smooth-muscle cells. Only one of 17 large ruptured aneurysms was observed to have similar extensive replacement by hyaline-like structures. Unruptured aneurysms can appear uniformly pink like adjacent normal arteries and may contain red portions in which blood can be visualized through almost transparent arterial walls, and their walls can often have thick yellow atheroma patches as well. In an autopsy series in which unruptured aneurysms were examined, no relationships could be found between patient age distribution and aneurysm location or between aneurysm size and the thickness of its walls. It was concluded that the low risk of rupture of small aneurysms could not be adequately explained by morphological examination alone.

In a pathological study of 34 brains, 23 unruptured lesions and 22 ruptured aneurysms were examined. Lesions smaller than 3 mm in diameter were composed mainly of endothelial cells and fibrous tissue. Ones larger than 4 mm contained collagen in their walls and had developed extremely thin portions in their domes, which were considered to be potential rupture points. At points where rupture had occurred, a clot and a new fibrin layer was found. This fibrin layer was reinforced by capillaries during the first 3 weeks after rupture. The domes of the aneurysms ranged from 100 to 350 μm in minimum thickness and from 100 to 400 μm in maximum thickness. The neck walls ranged from 30 to 50 μm in minimum thickness and from 50 to 150 μm in maximum thickness. The thickened walls contained endothelial cells, fibroblasts, and elastic fibers. All 22 ruptured aneurysms were larger than 4 mm in maximum diameter and contained ruptured points in their domes. Lesions located along the ACoA consisted of three of the 23 unruptured aneurysms and 12 of the 22 ruptured ones. The ratios were reversed for lesions of the MCA; 14 of the 23 unruptured aneurysms and one of the 22 ruptured ones were located on the MCA.

Signs of impending rupture were believed by Stenbren to include unusually thin areas in the wall, saclike pouches extending outward, patchy fibrin infiltration, layers of thrombus on the inner aspect of the sac, inflammatory cells in the sac wall, and blood pigment containing macrophages and erythrocytes within the wall. Preaneurysmal lesions according to Stehbens include funnel dilations, areas of vessel wall thinning, and microscopic evaginations. Differences in pathological characteristics between unruptured and ruptured aneurysms were studied histologically by examining excised aneurysm walls removed from 45 ruptured and 27 unruptured lesions during surgery. With the aid of immunohistochemical methods, the collagen and smooth muscle content, hyaline-like structure, and degree of inflammatory cell infiltration of the vessel wall were all scored. The patients in the ruptured aneurysm group exhibited more significant endothelial damage, inflammatory cell invasion, and structural changes in vessel walls. The walls of the ruptured aneurysms were considered to be more fragile; this was attributed to macrophage infiltration with a loss of smooth-muscle cells and degradation in matrix proteins. The activity of the elastase and collagenase in the vascular wall removed during surgery was significantly higher in cases of ruptured aneurysms than in those of unruptured lesions. The level of these metalloproteases in the plasma did not reflect levels in the aneurysm wall. It was suggested that local, rather than systemic, changes in these enzymes might be involved in aneurysm rupture.

**Diagnosis of Aneurysms**

The most common way to diagnose an unruptured aneurysm is retrospectively, that is, after it bleeds. It is a reasonable assumption that the majority of ruptured aneurysms were asymptomatic unruptured lesions right up to the moment of rupture. Because unruptured aneurysms are mainly found by serendipity, during evaluation of other conditions, the most common types of known unruptured lesions are those that are part of a multiple aneurysm constellation or those that are symptomatic. The database on asymptomatic unruptured aneurysms is actu-

<table>
<thead>
<tr>
<th>TABLE 1 Classification of unruptured aneurysms</th>
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<tbody>
<tr>
<td>Symptomatic or asymptomatic</td>
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<tr>
<td>Single or multiple</td>
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<tr>
<td>Previous or no history of SAH</td>
</tr>
<tr>
<td>Size in millimeters of the maximum diameter &amp; neck</td>
</tr>
<tr>
<td>Location by site of artery bearing the neck in extrasubarachnoid or subarachnoid space</td>
</tr>
<tr>
<td>Multilobular or unilobular shape; nipple-like loculation or none associated arterial anomaly, that is, asymmetrical circle of Willis, azygous artery, fenestration, agenesis, or occlusion of related vessel</td>
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</tbody>
</table>

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Unruptured aneurysms

ally quite small and this accounts for the widespread disagreement concerning how they should be managed. In their review of 3605 unruptured aneurysms, Rinkel and colleagues\textsuperscript{109} identified 32% that were asymptomatic, 55% that were part of a multiple constellation, and 13% that were symptomatic.

In the majority of asymptomatic unruptured aneurysms current diagnoses are made with the aid of MR imaging, MR angiography, and CT scanning, which are performed to investigate nonaneurysmal symptoms or events. Current technology is likely to visualize an unruptured aneurysm larger than 3 mm in diameter. The gold-standard test for diagnosis of aneurysms remains DS angiography. This is a relatively invasive procedure, however, and it may be replaced by other technologies such as CT angiography in the near future.\textsuperscript{86}

Evidence from the literature indicates that the sensitivity of CT scanning and MR angiography in demonstrating aneurysms is 76 to 98% and the specificity is 85 to 100%. Many of the patients in these studies harbored aneurysms or had experienced recent SAH, however, which could have led researchers to overestimate the accuracy of these modes of imaging. Both CT scanning and MR angiography are poorer methods than DS angiography for detection of aneurysms smaller than 5 mm, which account for up to one third of unruptured aneurysms.\textsuperscript{109} A case has been reported in which a false-negative finding on an MR angiogram was followed 3 years later by the finding of an SAH from a small ruptured MCA aneurysm.\textsuperscript{195}

Sixty-eight consecutive patients with aneurysms who had undergone coil embolization were studied using both MR and DS angiography. Magnetic resonance angiography was not possible in two patients. In 72 studies there was good correlation between the MR and DS angiograms. Both modalities revealed residual aneurysms in 18 patients. In one case the MR angiogram yielded false-positive findings. In seven cases aneurysm remnants smaller than 3 mm were not found using MR angiography, but did appear on DS angiograms. Magnetic resonance angiography was considered to be a good imaging option for follow up of intracranial aneurysms treated with coils.\textsuperscript{9}

Between 1974 and 1992, 1114 patients with ruptured aneurysms were treated at one institution in Japan. Among them were 78 patients examined before they suffered SAHs. Judged retrospectively, there were 35 patients in whom the aneurysm that subsequently ruptured might have been treated at an earlier stage. Most of these patients had presented with headache and minor signs and symptoms. In 26% of the patients, the unruptured aneurysm was missed, despite the fact that angiography was performed, principally because of the use of nonselective injections, poor contrast, and other technical factors.\textsuperscript{109} By definition, incidental unruptured aneurysms are not discovered by design; usually, the patient is under observation for some vague symptom or because a different aneurysm has ruptured. The modes of presentation for 882 patients with unruptured aneurysms were as follows: symptomatic unruptured aneurysm, SAH from a different aneurysm or a different neurologic disease (90% of cases), and truly asymptomatic unruptured aneurysm (10%). Two thirds of the patients displayed objective signs. Twenty-seven percent harbored unruptured aneurysms larger than 25 mm, and 29.7% of these lesions were located within the posterior circulation.\textsuperscript{14} In a large autopsy series there was a history of persistent headache in 36% of patients in whom aneurysms were found postmortem, compared with only 4% in matched control patients. In autopsy cases the OR was 15.3 for this symptom in patients with 131 ruptured aneurysms compared with patients with 39 unruptured ones.\textsuperscript{21}

### Prevalence and Incidence of Aneurysms

#### Prevalence of Aneurysms

The prevalence of unruptured aneurysms is measured by surveying a group of people. An example of this would be to study cadavers that have undergone complete autopsy; some will have ruptured aneurysms, some will have unruptured ones, and the remainder will have neither. The fraction or proportion of the entire group that underwent autopsy which is found to harbor aneurysms of either type constitutes the prevalence of aneurysms. All cases are counted during a single examination of the group at a single point in time. On the other hand, the incidence of unruptured aneurysms would be the number of new cases that occur during a certain time in a group that initially was free from these lesions. Incidence is measured in cohort studies and prevalence in cross-sectional studies. Although it is relatively easy to determine the incidence of SAH and aneurysm rupture, thus far it has been impossible to agree on the incidence of rupture among patients harboring asymptomatic unruptured lesions. The person-years approach is usually used to estimate the incidence of rupture in aneurysms that previously were unruptured. A disadvantage of this method is that patients in whom considerably different durations of follow-up data are available may be studied as a group. A small number of patients with long-term follow up contribute more heavily to the denominator than a large number of patients fol-
lowed up for a short time. If the short- and long-term follow-up groups differ systematically from the universe of patients with unruptured aneurysms, the resulting incidence is biased.39

There have been many thousands of autopsies in which brain examinations have been performed. Data from the majority of such studies have shown that ruptured aneurysms are present in 1% or more of adults who die in hospitals and that ruptured aneurysms outnumber unruptured ones in this patient population. Many such pathological reports suffer from a paucity of data regarding the age of these patients, the size and location of the aneurysms, and associated pathological findings such as intracerebral hematomas. The number of aneurysms uncovered is also influenced by the drawing card of a particular institution for patients suffering from cerebrovascular disease, as well as the experience and assiduousness of the pathologist in search of aneurysms.

Data from selected autopsy series are provided in Tables 2 23,27,60,116,149,180 and 3. 31,67 In Crompton’s series29 the ratio of unruptured to ruptured aneurysms was 1:2.58. Two hundred eighty-nine brains were examined following fatal aneurysm rupture. One hundred fifty-nine unruptured aneurysms measuring 2 mm or larger were present in 90% (31%) of these patients.29

In a review by Fox43 of 20 autopsy series published between 1926 and 1973, and each of which covered more than 5000 cases, there was a total of 164,764 autopsies during which 1289 aneurysms were found, for an aneurysm rate of occurrence of 0.8%. In nine studies published during which 1289 aneurysms were found, for an aneurysm rate of occurrence of 2%.43 In Stebbens’s180 personal series of 1364 autopsies conducted at a large hospital in Australia between 1952 and 1954, at least one cerebral aneurysm was found in 5.6% of cadavers. The patients in whom autopsy was performed were generally middle aged at the time of death; almost no autopsies were performed in young children or infants. The presence of a neurosurgical unit at this hospital might have produced some increase in the prevalence of ruptured aneurysms.180

In a review of pathological literature published between 1890 and 1966, Steibens181 found 14 references that together gave a prevalence of lesions at autopsy of 2.4% (range 0.2–9%). Expert neuropathologists with an interest in aneurysms tend to record higher rates of prevalence of lesions at autopsy. This may be due in part to their expertise in finding lesions that are present, but it may also reflect the fact that the institutions that these physicians serve attract more cases of aneurysms.180

When aneurysms rupture, 10 to 20% of patients die immediately; the remaining patients seek medical attention.199 In forensic series ruptured aneurysms have been noted in approximately 2 to 5% of autopsies because lesion ruptures are a relatively common cause of sudden death.199 In a forensic series10 of 583 cases of ruptured aneurysms, more than half of the deaths had occurred in patients between the ages of 50 and 80 years and the overall male/female ratio was 2:3. Most deaths occurred at home without precipitating factors, and in one fifth of the cases, death was sudden and unexpected.10

In the autopsy series conducted by McCormick and Nofzinger17 153 patients were identified as harboring saccular intracranial aneurysms among 7650 patients older than 10 years; this was a prevalence of 2%. Eighty-three percent of the patients harbored ruptured aneurysms and 17% did not. Unruptured aneurysms were found in older patients and were only approximately one third the size of the ruptured lesions. The mean age of patients with ruptured aneurysms was 46.3 years, whereas the mean age of those with unruptured lesions was 57.9 years. The ruptured aneurysms averaged 9.9 mm in diameter and the unruptured ones averaged 3.9 mm. The authors of this study rejected the hypothesis that aneurysm size is related to patient age.

The prevalence of saccular intracranial aneurysms in 11,696 autopsies was 1.2%. Ruptured lesions accounted for 50% of the total.154

Rosenorn and colleagues164 estimated a median prevalence of unruptured aneurysms of 0.6% (range 0.1–2.9%), based on a review of the literature available before their study was conducted in 1988. This prevalence was based on data from autopsy studies. On the basis of data from radiological studies, they estimated a prevalence of 0.4% (range 0.18–6.01%). The authors found that the prevalence of unruptured aneurysms varied by a factor of 90. The incidence of aneurysmal SAH, however, was much less uncertain and varied by a factor of only 2.7. The median incidence value was 10 cases per 100,000 population per year. The authors calculated that if the prevalence is 0.5% and the incidence of SAH is 10 in 100,000, then the minimal annual risk of rupture for an unruptured

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**Table 3**

**Findings of aneurysms in recent autopsy series**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Types of Patients</th>
<th>Percentage of Cases W/Aneurysms</th>
<th>Mean Age of Aneurysms (yrs)</th>
<th>Percent of Aneurysms Cases W/MAs</th>
<th>Percentage of Cases W/RAs</th>
<th>Mean Age of Ruptured Aneurysms (yrs)</th>
<th>Mean Ruptured Lesion Size (mm)</th>
<th>Cases of RAs</th>
<th>Cases of UAs</th>
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<tr>
<td>de la Monte, et al., 1985</td>
<td>9,142</td>
<td>&gt;30 yrs</td>
<td>2.1</td>
<td>24</td>
<td>1.7</td>
<td>11.4</td>
<td>49</td>
<td>0.4</td>
<td>7.6</td>
<td>63</td>
</tr>
<tr>
<td>Inagawa, 1990</td>
<td>10,259</td>
<td>all†</td>
<td>2.1</td>
<td>18</td>
<td>1.3</td>
<td>9.5</td>
<td>53</td>
<td>0.8</td>
<td>6.0</td>
<td>67</td>
</tr>
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</table>

* MA = multiple aneurysm; RA = ruptured aneurysm; UA = unruptured aneurysm.
† No age exclusion noted.
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The authors believed that a critical size for an unruptured aneurysm predisposing to rupture had not been demonstrated. They recommended surgery for an identified unruptured aneurysm because of the estimated mortality rate of 50 to 60% and the estimated morbidity rate of 20 to 25% following aneurysmal SAH, as well as because of the presumed absence of mortality and the very low morbidity rate (4%) after operative treatment of unruptured lesions.

A systematic review of the prevalence and risk of rupture of intracranial aneurysms was performed by Rinkel and colleagues150 and published in 1998. In this study the authors focused on 23 reports published between 1995 and 1996 that contained data on 56,304 patients. In a retrospective study of 43,676 autopsies, 191 aneurysms were found (prevalence 0.4%, 95% CI 0.4–0.5%). In a prospective study of 5493 autopsies, the prevalence was 3.6% (95% CI 3.4–3.8%). In a retrospective study of 2934 angiographic examinations, the prevalence was 3.7% (95% CI 3.4–4.4%). The highest rate of prevalence was 6% (95% CI 5.3–6.8%) for 3751 patients studied prospectively by using angiography. In angiographic studies the prevalence per 100 for male patients was 3.5 (95% CI 2.7–4.5) and for female patients it was 4.6 (95% CI 3.5–5.9). By indication for angiography the rates of prevalence per 100 in diminishing order were as follows: ADPKD 10 (95% CI 6.2–15), family history of aneurysms 9.5 (95% CI 7–12), atherosclerosis 5.3 (95% CI 4.6–6.1), and brain tumor and other indications 2.3 (95% CI 1.7–3.1). The rate in patients with brain tumors is probably the closest approximation to the entire universe of unruptured aneurysms cases. From these authors’ review of the literature since 1955, it was concluded that adults without risk factors for SAH would have a prevalence for aneurysms of approximately 2%.150

Among 1612 Japanese patients undergoing four-vessel angiography for suspected nonaneurysmal diseases, the prevalence of aneurysms was 2.7%; in 463 patients with ischemic stroke it was 2.8% and in 127 cases of intracerebral hematomas it was 7.8%.191 In a total of 375 presumably healthy people in Japan undergoing routine MR angiography, there were 10 cases (2.7%) in which an unruptured aneurysm was present.213 On the basis of a literature review, Sekhar and Heros176 concluded that at least 5% of the population might harbor an aneurysm. This figure is frequently quoted, but, in my opinion, it is a considerable exaggeration.

Incidence of Aneurysms

The incidence (number of aneurysm ruptures/100,000 population/year) varies depending on the following factors: the nature of the population (Finnish and Japanese persons may be particularly prone to develop aneurysms); the quality of diagnostic techniques (industrialized countries record higher rates of unruptured aneurysms than developing ones); the size of the population being studied (a small town with high autopsy rates had a higher incidence than the prefecture in which it was located); the diagnostic criteria (blood in the cerebrospinal fluid or evidence based on CT scans, MR images, DS angiograms, or clinical impressions); the age distribution of the population being studied (a younger population will have a lower incidence); the sophistication of data collection and analysis (the ability to differentiate spontaneous from aneurysmal intracerebral hematomas and the ability to capture these distinctions among hospital deaths); and the prevalence of cigarette addiction and hypertension.

In a literature review on SAH, the incidence of this event was found to have remained stable over the last three decades. In six studies the incidence in women was 1.6 times higher (95% CI 1–2.3) than that in men. The more frequently CT scanning was used, the lower the incidence of aneurysmal SAH. In 15 studies of non-Finnish populations, the incidence of SAH was 7.8 per 100,000 persons per year (95% CI 7.8–8.4). In three studies undertaken in Finland the pooled incidence was 21.4 per 100,000 persons per year (95% CI 19.5–23.4). In 13 studies performed in the 1980s or later, in which CT scanning was performed in some percentage of patients, the incidence was 10.4 per 100,000 persons per year. The studies reviewed were prospective and population-based. Computerized tomography scanning was considered to be the definitive diagnostic method for SAH because lumbar puncture can be traumatic or provide false-positive results in the presence of nonaneurysmal lesions such as intracerebral hematomas. Reliance on angiographic series can lead to underestimates of the incidence of aneurysmal SAH because angiography is not performed in patients who die outside of institutions or who are very old or moribund.105

Table 4 lists the incidence of patients admitted to hospitals for SAH, which approximates the incidence of aneurysm rupture, as well as the incidence of patient admissions for unruptured lesions and intracerebral hematomas in the US.129 Table 5 provides the average number of years of life remaining for different age groups. This information, of course, is essential for making judgments about the treatment for unruptured aneurysms. Patients 60 years of age have an estimated 20 years of life remaining on average for both sexes, whereas patients...
who are 85 years of age have only an estimated 6 years of life remaining.\textsuperscript{130}

Table 6 provides the latest available population breakdown for the USA. Of approximately 250 million people alive in 1990, almost 30\% were under the age of 20 years, an epoch during which the number of deaths from SAH is negligible.\textsuperscript{131}

The annual risk of rupture of an unruptured aneurysm has been calculated by multiple authors to be 0.1 to 0.5%.\textsuperscript{56,64,76,123,125,205–207}

In a classic study of 589 cases of SAH in Helsinki, which was published in 1967, Pakarinen\textsuperscript{138} listed the age-specific annual incidence of SAH between 1954 and 1961. In a more recent study of Helsinki (average population 439,751 persons) in the eighth decade of life from Izumo City was an extraordinary 92.3 per 100,000 population per year.\textsuperscript{69}

During a 5-year period in the early 1980s, Izumo City,
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Japan, which had a population of 79,026, contained 83 patients with aneurysmal SAH who survived until hospitalization. The hospital in that city has a designated emergency center to which all patients with verified or suspected SAH, regardless of condition, are transferred within 30 minutes. During the same time interval, the 789,712 population of the surrounding Shimane Prefecture contained 548 patients with SAH. Ruptured aneurysms were confirmed in 93% of cases in the smaller city and in 85% of cases in the Prefecture. Respective annual incidences were 21 and 13.9 per 100,000 population of all ages. The age-adjusted annual incidences were 18.3 and 11 per 100,000 population for all ages. It was suggested that larger population groupings probably have smaller rates, being 2.3 times higher for women than for men after adjusting for age. Interestingly, nine patients (35%) died 8 hours or sooner after onset of SAH and in none of these cases was the correct diagnosis listed on the death certificate. Four (44%) of the patients who died were given misdiagnoses of intracerebral hematoma. The results of this careful autopsy-based population study are likely generalizable: data provided on death certificates present an underestimate of the true incidence of SAH from aneurysmal rupture, and a diagnosis of intracerebral hematoma is often mistakenly applied to patients with aneurysmal rupture.26 In a later report based on a 30-year period preceding 1984 in Rochester, Minnesota, the average annual incidence of SAH remained approximately constant at 11 per 100,000 population per year. Age-specific incidence rates displayed increases with advanced age. The average annual mortality rate for patients with SAH fell from 6.8 per 100,000 population in the years from 1955 to 1964 to 4.3 per 100,000 population in the period from 1975 to 1984. The mortality rate, therefore, fell from approximately 60 to 40% during this time period.72

Assuming a mean frequency of intracranial aneurysms in large autopsy studies of approximately 5%, combined with the population-based incidence of aneurysmal SAH of approximately 10 per 100,000 population per year suggested to Easton and associates35 that the vast majority of aneurysms that form never rupture. I do not agree with this opinion. These authors also concluded that most aneurysms would tend to rupture at the time of or soon after formation. They believed that the only example of an accidentally discovered aneurysm smaller than 10 mm that subsequently ruptured was a 6-mm lesion that was located ipsilateral to a carotid endarterectomy, which may have predisposed it to rupture. They suggested that

### Table 7

<table>
<thead>
<tr>
<th>Site of Study</th>
<th>Authors &amp; Year</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>≥70</th>
<th>≥80</th>
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<td>Helsinki, Finland</td>
<td>Pakarinen, 1967</td>
<td>20.3</td>
<td>25.3†</td>
<td>16.2</td>
<td>13.1</td>
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<td>Greenland, Denmark</td>
<td>Ostergaard Kristensen, 1983</td>
<td>26.6</td>
<td>6.3</td>
<td>20.1†</td>
<td>0</td>
<td>—</td>
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<tr>
<td>Izumo City, Japan</td>
<td>Inagawa, et al., 1988</td>
<td>21.0</td>
<td>61.9†</td>
<td>59.0</td>
<td>51.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Shimane Prefecture, Japan</td>
<td>Inagawa, et al., 1988</td>
<td>18.1</td>
<td>30.4</td>
<td>38.3†</td>
<td>26.2</td>
<td>15.4</td>
</tr>
<tr>
<td>Framingham, MA</td>
<td>Sacco, et al., 1984</td>
<td>0.0</td>
<td>15.0</td>
<td>37.0</td>
<td>78.0†</td>
<td>—</td>
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<tr>
<td>Rochester, MN</td>
<td>Ingall, et al., 1989</td>
<td>16.1</td>
<td>22.3</td>
<td>31.7†</td>
<td>30.0</td>
<td>—</td>
</tr>
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</table>

* Incidence falls off with extreme old age. For all ages, the incidence reported in six studies—of which one conducted by Phillips, et al., in 1980 was used instead of the study by Ingall, et al., in 1989—was a mean of 11.9 per 100,000 persons per year (range 6–21/100,000/yr). — = not differentiated from patients 70 years and older.
† Age group with highest incidence found in study.
patients with unruptured aneurysms who have not undergone treatment could reasonably be studied at yearly intervals for 3 years, particularly those harboring lesions between 6 and 9 mm in diameter. In these authors’ opinion even if enlargement occurs and no symptoms develop after 3 years, it may be adequate to rely on follow-up examinations performed at 5-year intervals. They consider that a history of SAH from a different source increases the likelihood that a patient with an unruptured aneurysm will experience a later SAH from the untreated lesion. These authors have suggested that any recommendation should be less than dogmatic, especially given the relatively scant and nondefinitive nature of the available data; their study was written in 1993.35

In the study performed by Juvela, et al.,36 in 1993, the overall risk of rupture for an unruptured aneurysm was 1.4% annually; this figure was based on 27 first aneurysm ruptures during a follow-up period of 1944 patient years. Considering aneurysms rather than cases, the annual risk was 1.1% (27 events during 2434 aneurysm years). In patients with single aneurysms, it was 1.4% (22 events in 109 patients during 1538 aneurysm years and 1538 patient years). In patients with multiple unruptured lesions, the risk was only 0.56% (five events during 896 aneurysm years).

In their review of the literature, Rinkel and associates150 provided data on the sizes of aneurysms in 356 patients. Ninety-three percent of these patients harbored lesions that were 10 mm or smaller. Rinkel and associates assumed that, in a cohort of 100,000 persons, only the 75,000 persons older than 20 years would be at risk for aneurysm rupture. The majority of patients would not have a family history of aneurysm or ADPKD or other risk factors and, thus, the prevalence should be approximately 2.3%. This means that 1725 patients will harbor an aneurysm. Of these, 93% can be anticipated to harbor lesions smaller than 10 mm. Therefore, 1605 patients will harbor small aneurysms and 120 patients will harbor larger ones. The annual risk of rupture is assumed to be 0.7% in the cohort with small aneurysms and 4% in the group with larger ones. Rinkel and associates further assumed that in the general population, a ruptured aneurysm previously would have been asymptomatic and not additional to another ruptured lesion. The risk of rupture per 100 patient years in asymptomatic aneurysms is 0.8, whereas overall it is 1.9. This ratio (0.8/1.9) equals 0.4. In a single year, 0.4 times 0.7% of the 1605 patients with small aneurysms yields 4.5 ruptures, and 0.4 times 4% of the 120 patients with large aneurysms equals 1.9. The total number of SAHs within the cohort of 100,000 patients will therefore be 6.4. This calculated incidence is similar to the incidence of six per 100,000 patient years observed in the general population.150

Table 8 provides some estimates of ruptured and unruptured aneurysms in the US population.

### Associated Diseases

Certain disease states appear to be associated with an increased prevalence of both unruptured and ruptured aneurysms. These include familial intracranial aneurysms, ADPKD, fibrous dysplasia, and coarctation of the aorta. The evidence for other conditions—Marfan disease, tuberous sclerosis, neurofibromatosis, moyamoya disease, Ehlers–Danlos syndrome, and hereditary hemorrhagic telangiectasia—is less strong. It is likely that cigarette smoking and hypertension increase the risk for aneurysms not only to develop, but also to rupture. Pregnancy may also promote aneurysm formation and growth.

**Familial Aneurysms.** A prospective study of healthy persons with a family history of SAH in more than one family member revealed the presence of incidental unruptured aneurysms in 12%.156 Between 1977 and 1990, 1150 patients with proven aneurysms were evaluated from among 870,000 inhabitants of east Finland. Of all these patients with aneurysms, 10% had a proven familial occurrence of aneurysmal SAH (≥ two patients within the same family with proven SAH). Ninety-one families with histories of SAH produced 203 patients with aneurysms. Among the cases of familial aneurysms, 54% were female patients with a mean age of 49 years; the 46% who were male patients had a mean age of 44 years. Lesions along the MCA comprised 40% of the aneurysms.156 The prevalence of intracranial aneurysms among familial intracranial ones is possibly 10 times higher than the rate found in the average population.157 Also in east Finland,157 families with familial intracranial aneurysms were studied; 167 patients harbored 215 aneurysms. The patients tended to be younger and have smaller lesions than patients with incidental aneurysms. One half of the familial aneurysms were located along the MCA, one-third of the ruptured familial aneurysms were smaller than 6 mm, and more than 80% of the lesions were less than 14 mm in diameter. Among siblings with familial aneurysms, the frequency of pairs of siblings in whom the age at onset was within 10 years of each other was double that expected by chance, based on a comparison with randomly selected pairs of patients in a nonfamilial intracranial aneurysm group.158 Based on a new study of the population of east Finland, it was concluded that first-degree relatives of patients with familial

### Table 8

_Estimated annual rate of rupture of intact aneurysms using US population data_

<table>
<thead>
<tr>
<th>Line No.</th>
<th>Factor</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>total US population (1990)</td>
<td>248,000,000</td>
</tr>
<tr>
<td>b</td>
<td>US population ≥20 yrs of age</td>
<td>176,000,000</td>
</tr>
<tr>
<td>c</td>
<td>estimated hospital discharges from aneurysmal SAH during yr</td>
<td>30,000</td>
</tr>
<tr>
<td>d</td>
<td>prevalence of aneurysms in adults based on autopsy findings</td>
<td>0.02 (2%)</td>
</tr>
<tr>
<td>e</td>
<td>no. of aneurysms in US population</td>
<td>3,520,000</td>
</tr>
<tr>
<td>f</td>
<td>incidence of aneurysmal SAH</td>
<td>10/100,000 population/yr</td>
</tr>
<tr>
<td>g</td>
<td>estimated annual rate of rupture of unruptured aneurysms (c ÷ e)</td>
<td>0.0085 (0.85%)</td>
</tr>
<tr>
<td>h</td>
<td>estimated no. of aneurysm ruptures during yr (a × f)</td>
<td>24,800</td>
</tr>
</tbody>
</table>

* Mathematical functions shown in parentheses demonstrate the method by which the number in the last column was derived. Letters a through f represent the numerical values shown on those corresponding lines.
intracranial aneurysms were at a high risk for harboring incidental intracranial lesions and would benefit from screening studies. The RR for intracranial aneurysms among first-degree relatives in families in which there are familial intracranial aneurysms was 4.2 (95% CI 2.2-8) and among first-degree relatives in families with only one affected family member it was only 1.8 (95% CI 0.7-4.8) compared with the general population.159

Between 1988 and 1992, 400 volunteers from Japan underwent neurological examinations, which included DS angiography, CT scanning, and MR imaging and angiography.127 In this population 27 asymptomatic unruptured aneurysms were found in 26 volunteers for an incidence of 6.5%. The mean age of the patients was 55 years (range 39-71 years). Sites of aneurysms included the following: ICA in 48%, ACoA in 22%, MCA in 22%, and BA in 7%. The sizes of the lesions were as follows: 5 mm or smaller in 59%, 6 to 10 mm in 33%, and 11 mm and larger in 7%. Volunteers with a family history of SAH within the second degree of consanguinity demonstrated a 17.9% incidence of aneurysms. The relatively high incidence in this series may be explained partly by the fact that 45% of the volunteers had a family history of cerebrovascular disease and 24% complained of slight headaches or heavy sensations in the head. Hypertension was found in 40%, and 30% were smokers. Additionally, cerebral infarction was observed in 4% of the volunteers, and in one, a brain tumor was discovered.127

Another group of Japanese patients with no symptoms of SAH, but with a family history of SAH within the second degree of consanguinity was studied.128 Of 244 patients with a mean age of 50.9 years, 34 (13.9%) were found to harbor unruptured aneurysms. The screening tests used in this cohort included MR angiography in 96%, three-dimensional CT scanning in 7%, and intraarterial DS angiography in 15%. The locations of these aneurysms included MCA in 44%, ICA in 39%, ACoA in 7%, VBA in 7%, and PerA in 2%. The diameter of the aneurysm was approximately 4 mm in 51% of cases and 5 to 10 mm in 46%. Prevalence was no different in patients in whose families there was a history of aneurysms in parents alone, siblings alone, or more than one family member. The incidence of hypertension in the 244 cases was 30% and that of habitual smoking was 25%. Thirty-two percent of 25 patients who had more than one of the following conditions: hypertension, diabetes mellitus, hyperlipidemia, and smoking—also harbored aneurysms.

Thirteen Canadian families were identified in which two or more individuals harbored aneurysms.102 Among these families there were 38 aneurysms, of which 71% had ruptured. The male/female ratio in this group was 1:3.35. These patients had only a 17% prevalence of multiple aneurysms, which was low compared with the rate in patients with sporadic cases. Only 16% of aneurysms were located on the ACoA artery. The lesions tended to occur at the same sites or at mirror sites, and to rupture during the same decade at a higher rate than aneurysms found only sporadically. The average age of the patients at rupture was 47.2 years and 60% of patients were 50 years or younger. Among those patients in whom the aneurysm had ruptured, the mortality rate was 70%. Screening of 41 asymptomatic family members led to the identification of only one aneurysm.102

Within a prepaid medical care program in the USA during a 30-month period, 63 surgical candidates who had one or more first-degree relatives with an aneurysm were studied using MR angiography.15 Nine unruptured aneurysms were found in six patients. Eight of the nine aneurysms demonstrated on DS angiograms were also evident on MR angiograms. The mean treatment cost was 50% lower for an unruptured aneurysm than a ruptured one. No patient surgically treated for an unruptured lesion required rehabilitation. Magnetic resonance angiography, therefore, displayed a 9.5% prevalence of unruptured aneurysms among persons with one or more first-degree relatives with a cerebral lesion.15

Six hundred twenty-six first-degree relatives (parents, siblings, or children) of 193 consecutive patients with SAH were screened using MR angiography.144 Eighteen relatives underwent elective angiography and operation. Before the angiography was performed all patients were neurologically normal. Three months postoperatively, 28% of patients (95% CI 10-54%) displayed neurological impairments; in one patient the deficits were attributed to angiography. A decrease in the Barthel Index score occurred in 11% of the patients and 83% displayed suboptimal Rankin Scale scores, although no one was dependent on others to perform activities of daily living. One year postoperatively, 28% still displayed neurological impairment; all had an optimal Barthel Index score, but 47% had suboptimal Rankin Scale scores. Quality of life had returned to baseline levels in most domains. Although outcomes had improved markedly within 1 year following the operation, the neurological impairments were not completely resolved.

Twenty-four Americans who underwent surgery for intracranial aneurysms had at least two affected siblings.28 Affected family members with familial aneurysms exhibited prevalence rates of smoking (74%) and hypertension (43%), which were higher than rates in a population-based control group (52% and 36%, respectively). The comparable rates for patients harboring sporadic intracranial aneurysms were 64% and 40%. The difference in the percentage of patients with hypertension in the familial group and control patients was the only one that was statistically significantly (p < 0.005). Female patients comprised 71% of those with sporadic aneurysms, 59% of those with familial lesions; and 50% of control patients. Affected family members with aneurysms were statistically more likely than their unaffected siblings to smoke, have hypertension, and be female.28

Autosomal-Dominant Polycystic Kidney Disease. This disease is characterized by cyst formation and structural defects in the vascular tree, cardiac valves, gastrointestinal tract, and kidneys. There is a defect in the ECM.45 According to the author of a 1951 review,140 in 199 cases of ruptured aneurysms, the incidence of polycystic kidney disease was 3.5%. In a study of 144 patients with ruptured aneurysms treated in Glasgow before 1948, 6% had associated polycystic kidneys.145 Four-vessel angiography performed in 17 patients who had ADPKD but no neurological deficits or history of SAH revealed seven unruptured aneurysms (41.2%).146 Five of the unruptured aneurysms were treated surgically and there was no incidence of mortality or morbidity. Of the nine patients with hypertension,
22.2% harbored aneurysms. Of the eight patients who did not have hypertension, 62.5% harbored aneurysms, suggesting that hypertension was not the key causal factor for lesions in patients with ADPKD. Seventy-seven cases of ADPKD from among 64 families involved 71 ruptured aneurysms and six unruptured lesions. The mean age of these patients at the time of rupture was 39.5 years (range 15–69 years), and renal function was normal for one half the patients at the time of presentation. The ruptured aneurysms were most frequently located on the MCA. Surgical or endovascular treatment was performed in 76% of patients. At long-term follow-up review, 38% were severely disabled. A family history of aneurysm rupture was present in 18%. Ninety-six patients with ADPKD were studied using CT or MR imaging. No definite aneurysms were observed on any of the images obtained in these 96 patients, all of whom underwent imaging performed using equipment available before 1990.

In one review the authors concluded that the prevalence of patients with ADPKD who harbored intracranial aneurysms approaches 40% and that this rate is likely to be significantly higher in patients with a positive family history for cerebral aneurysm. Screening angiography was recommended for patients with a strong family history of cerebral aneurysm or SAH. In another review of the literature, Lozano and Leblanc analyzed the cases of 79 patients with ADPKD. These patients had a mean age of 39.8 years compared with 52.6 years in patients with sporadic aneurysms. The peak decennial age was 40 to 49 years, which is younger than the age of patients with more sporadic aneurysms (50–59 years). In the ADPKD group, MCA aneurysms were overrepresented (37%), as were male patients (72%). Seventy-seven percent of ADPKD-associated aneurysms had ruptured by the time the patient reached 50 years of age, compared with 42% in patients of similar age who harbored sporadic aneurysms.

Of 92 patients with ADPKD who had no symptoms or signs of neurological disorders, 60 underwent CT scanning, 21 underwent DS angiography, and 11 underwent both. Intracranial aneurysms were found in four (4%) of these patients (95% CI 0.1–9%). Three of the four patients harbored multiple lesions. Complications of angiography occurred in 25% of these patients, compared with only 10% in 220 patients with conditions other than ADPKD.

Between 1945 and 1984, 41 patients with SAH and ADPKD were diagnosed in Rochester, Minnesota. Eighty percent presented with SAH and 24% harbored multiple aneurysms. A family history of aneurysm and/or SAH was present in 22% of the patients. In 64% SAH occurred before the patient reached 50 years of age. Of 89 cases of ADPKD in which autopsies were performed, 23% were found to have intracranial aneurysms.

One hundred eighteen patients with ADPKD underwent MR angiography, and the incidence of saccular intradural aneurysms was 7% (unpublished data). Three patients underwent prophylactic clipping of six aneurysms without complications. The results of autopsy studies have demonstrated that the prevalence of intracranial aneurysms in ADPKD cases is 7.3 to 40%. In a prospective evaluation of 93 ADPKD cases in which MR angiography was performed, 9% were found to harbor intradural saccular aneurysms (unpublished data). A family history of aneurysms was a significant predictor for the presence of an aneurysm. In addition, the patient’s age, duration of known ADPKD disease, and duration of hypertension were each associated with the presence of an aneurysm. The authors concluded that the prevalence of aneurysms in patients with ADPKD is 10.5% (95% CI 4.3–16.8%). For patients with a family history of aneurysms, the corresponding prevalence was 24.7% (95% CI 8.4–41%). This was the first prospectively determined documentation of aneurysm prevalence during life (unpublished data).

Four hundred asymptomatic individuals in 68 families with a history of aneurysmal SAH underwent MR angiography. Six families also had a history of ADPKD. Intracranial aneurysms were detected in 37 individuals, 32 of whom later underwent DS angiography. The age-adjusted prevalence of incidental intracranial aneurysms among first-degree relatives of patients with SAH screened using MR angiography was 9.1%, which was the same as the crude assessment of prevalence in the ADPKD group. Only two of the 40 individuals found to have incidental aneurysms on MR angiograms, who were investigated because of a family history of SAH, were also found to have ADPKD.

Some researchers have developed a model that can be used to predict whether a screening strategy for 20-year-old patients with ADPKD would provide a 1 additional year of life without neurological disability. The suggested prevalence of asymptomatic unruptured aneurysms in patients with ADPKD was 15%. The annual incidence of aneurysm rupture was estimated to be 1.6%, and the morbidity and mortality rates associated with SAH were assumed to be 70% and 56%, respectively. The risk of permanent morbidity or mortality associated with transfemoral angiography was calculated to be 0.2%, and the morbidity and mortality rates associated with surgery for unruptured aneurysms were thought to be 4.1% and 1%, respectively.

Carotid Artery Stenosis. Solomon and Correll presented the case of a 50-year-old woman who underwent a left-sided carotid endarterectomy to treat TIAs. Two years later repeated angiography was performed to investigate the possible occurrence of new TIAs. Angiography revealed a 6-mm right ICA aneurysm at the PCoA site. An ipsilateral carotid endarterectomy was performed and the patient’s symptoms were resolved. Approximately 3 months later, the patient suffered an SAH from the previously noted incidental aneurysm.

Wieber and Whisnant mention 11 patients who underwent carotid endarterectomy for six ipsilateral and five contralateral aneurysms, which had not previously ruptured and did not rupture during a mean follow-up period of 13 months. Three of these patients underwent surgery on the aneurysms between 2 and 3 months after the endarterectomy. These authors also reviewed three cases in which SAH had previously occurred and in which contralateral carotid endarterectomies had resulted in rerupture of the intracranial aneurysms at 2 days, 1 week, and 10 months after endarterectomy. They mentioned two other cases of rupture occurring 1 and 3 months after ipsilateral carotid endarterectomy. These aneurysms had not previously ruptured. In six of eight patients with extracra-
Unruptured aneurysms

Of two patients in whom clipping was performed before the endarterectomy, transient morbidity occurred in one. Forty-four patients harboring unruptured aneurysms and concurrent ischemic cerebrovascular disease were studied. The mean age of these patients was 63 years. The associated ischemic diseases included TIA's in 22%, minor completed stroke in 52%, and major completed stroke in 25%. The 30-day postoperative mortality rate for the patient harboring these unruptured aneurysms was 6.8%. The rate of permanent morbidity was 4.5% and the rate of transient morbidity was 9.1%. New ischemic events occurred in 14% of patients. Forty patients with unruptured aneurysms who had no associated cerebrovascular disease recovered without morbidity or mortality. Clipping of unruptured aneurysms in patients with associated cerebrovascular disease should be undertaken with great caution—if at all.

Two hundred nine consecutive angiographic studies were performed for the investigation of symptomatic CA disease.90 Five patients harbored intracranial aneurysms that were smaller than 5 mm and five other patients harbored larger aneurysms. A giant ICA aneurysm was found in one patient. Angiography performed in a prospective series of 405 patients who underwent endarterectomy was 10% after endarterectomy and 23% with the best medical care. The researchers concluded that the decision to perform an endarterectomy should not be influenced by the presence of a small intracranial unruptured aneurysm.

The prevalence of unruptured aneurysms in elderly patients with CA stenosis is ipsilateral to an unruptured lesion, endarterectomy was performed before aneurysm clipping; all these patients had excellent postoperative outcomes.101 Of patients presenting with ruptured lesions, approximately one in 100 will harbor an AVM. The prevalence of AVMs does not increase progressively with age, as does that of aneurysms. There is a tendency for unruptured aneurysms to be located along feeding vessels leading to an AVM (approximately 85%), and some lesions have been observed to regress after removal of the AVM. The presence of an unruptured aneurysm probably increases the likelihood of bleeding in patients with an unruptured AVM. Intranidal aneurysms may be present in as many as one in eight cases of AVMs. Consideration should be given to treating a large unruptured aneurysm on a feeding vessel before undertaking the acute excision of a significant AVM.

An examination of 91 patients with unruptured AVMs showed that in 16 (18%), unruptured aneurysms were present. There was a total of 26 unruptured aneurysms in the 16 patients. An actuarial analysis showed that the risk of intracerebral hematoma among patients with AVMs and aneurysms was 7% per year at 5 years following diagnosis compared with 1.7% per year for patients with AVMs alone. Ninety-two percent of the aneurysms were located on enlarged feeding arteries to the AVM. Surprisingly, 21% of the 24 patients with low-flow AVMs harbored associated aneurysms, which was a higher percentage than the 16% of 67 patients with high-flow AVMs.16 In the ISUIA, 33 patients harbored both aneurysms and AVMs; SAH occurred in two cases, at 2 and 5.6 years after diagnosis.

Intracerebral Hematoma. Resulting from intrinsic small vessel disease, intracerebral hematoma is approximately twice as common as SAH caused by aneurysm rupture. Nevertheless, some aneurysms rupture directly into the brain parenchyma and may be overlooked during a cursory clinical, radiological, or even pathological examination. Approximately 40% (range 8–67%) of fatal aneurysm ruptures are associated with an intracerebral hematoma.199 In eight clinical series of 1670 cases of intracerebral hematomas, an aneurysm was found to be the cause in 21%.200 Among 67,930 autopsies there were 233 nonsurgically treated ruptured aneurysms (0.3%). Massive SAH was present in 77% of these cases and massive intracerebral hematomas were present in 35%. Only 14% of these patients had been given clinical diagnoses of ruptured intracranial aneurysm. In Stehbens' pathological series of 252 autopsies in patients with aneurysms, the lesions were ruptured in 74%. In cases of ruptured aneurysms, intracerebral hematoma was present in 24%, intracerebral hematoma and intraventricular hemorrhage in 37%, and intraventricular hemorrhage alone in 7%.

Table 4 is based on patients who survived to be admitted for a short stay in nonfederal hospitals in the USA. It indicates that patients with ruptured aneurysms are two or three times more likely to be admitted to the hospital than patients with unruptured ones. Currently, it is probable that approximately 30,000 patients with SAH are admitted to American hospitals each year. Female patients outnumber male patients by approximately 1.8 to 1. Admissions for patients with SAH are more than twice as common as admissions for patients with unruptured aneurysms. Al-
though approximately 10 to 20% of cases of SAH are not due to aneurysm rupture, it is likely that a comparable percentage of patients die before they can be admitted to a hospital and, thus, the figures given for SAH can reasonably be equated with the true number of ruptured lesions. There is probably also a significant number of patients in whom the correct diagnosis is not made. In approximately 40% of patients who die of aneurysm rupture, there is associated intracerebral hematoma. Because intracerebral hematoma is listed as a diagnosis more than twice as often as SAH in records of hospitalizations in the US, it is possible that in a significant number of such cases, ruptured aneurysms may actually be present but undiagnosed. In 1990, based on information on death certificates, which can be filled out by a variety of personnel including non-professionals, it was concluded that there were 6815 deaths from SAH in the USA. The number of deaths in male patients was 2379 and the number in female patients was 4436. During the same year, there were 17,852 deaths due to intracerebral hematoma. The death rate per 100,000 population for SAH was 2.7 for both sexes and 2 for male and 3.5 for female persons. The most deaths occurred in patients ranging in age from 65 to 69 years. Of all patients with cerebrovascular diseases, only 38% died in the hospital.

During 1988 among the nearly 1.3 million people in the greater Cincinnati area, there were 159 cases of intracerebral hematoma and 62 of SAH. The ratio of intracerebral hematoma to SAH was approximately 2.3:1.14 Between 1991 and 1996 in a Japanese city of 85,000, there were 267 patients with intracerebral hematoma and 123 with SAH. Surgery was performed in 22% of cases of intracerebral hematoma and 58% of cases of SAH. Overall 30-day mortality rates were 14% in cases of intracerebral hematoma and 34% in cases of SAH. The ratio of SAH to intracerebral hematoma was 1:2.17. Overall survival rates at 1 month and 2 years post-SAHD were 66% and 62%, respectively.

Anatomical Variants. Anatomical anomalies with hemodynamic consequences associated with an increased risk of aneurysm formation include the azygous ACA (PerA aneurysm), unbalanced ACAs (ACoA aneurysm), large PCoA or the CA origin of the PCA (PCoA aneurysm), lower BA fenestration (VBA aneurysm), and CA agenesis or occlusion (contralateral proximal CA aneurysm).

Clinicopathological Aspects of Unruptured Aneurysms

Numerous pathological studies have firmly established the following points: ruptured aneurysms are larger than unruptured ones, but the median size of ruptured lesions is smaller than 10 mm at the time of patient death; ruptured aneurysms are found more often than unruptured ones in younger patients; ruptured aneurysms outnumber unruptured ones in autopsy series; the ratio of ruptured aneurysms to the total number of lesions decreases progressively with increasing age of the patient; and the average size of ruptured and unruptured aneurysms does not increase with the increasing age of the patient. Aneurysms are rarely found in patients younger than 30 years of age, but their prevalence thereafter increases progressively with increasing age before decreasing when patients reach extreme old age. Midline aneurysms have been found more often in series of ruptured aneurysms than in series of unruptured ones, and midline aneurysms rupture at a smaller size than lateral ones. The distribution curve for patient age at rupture peaks around 50 years. Fatal aneurysm ruptures are associated with intracerebral hematoma in approximately 40% of cases. Approximately 25% of patients with aneurysms harbor multiple ones; in multiple aneurysm constellations the largest one is usually the one that ruptures, except in rare cases in which a smaller midline aneurysm may rupture before a larger lateral one. The proportion of total aneurysms in any size range that are ruptured increases with size, until the giant-sized range. In patients with systemic risk factors for aneurysm formation and rupture, bleeding takes place at an earlier average age than in those without these risk factors.

Patient Sex Distribution

In Stehbens’ review of 15 clinical and pathological series comprising 4826 cases, the male/female ratio for saccular aneurysms was 1:1.4. Given the data from Fox’s literature review and the first Cooperative Aneurysm Study, it seems that ICA aneurysms occur approximately twice as frequently in female patients, MCA lesions occur almost 1.5 times more frequently in female patients, and ACoA ones occur almost 1.5 times more frequently in male patients. In the autopsy series conducted by Iwamoto et al., the prevalence of aneurysms in male patients did not show an obvious trend of increasing with patient age. In female patients, the highest prevalence occurred in those in the 60 to 69 years age group. In the decades leading up to age 50 years, male patients predominate in ruptured aneurysm series; thereafter, women predominate. Female patients comprise 55 to 60% of all patients with ruptured aneurysms.

Patient Age Distribution

The number of cases of ruptured aneurysms that have been categorized by patient age form a bell-shaped curve between the ages of 30 and 70 years, with a peak between 50 and 60 years. In 278 cases of ruptured aneurysms the maximum external diameter of the lesion did not increase progressively with age. Crompton has suggested that there was evidence that aneurysms can begin at any age and enlarge rapidly. In 4518 MR imaging studies, the prevalence of aneurysms in men rose progressively from 0.26% in those younger than 50 years to 4.11% in those older than 80 years. The respective percentages in women were 0.87% and 5%. Age distribution by decade was analyzed for 3081 single aneurysms. The most common decades were the 41 to 50 years age group (28% of aneurysms) and the 51 to 60 years age group (24% of aneurysms).

In McCormick’s 1971 paper ruptured aneurysms constituted 40% and unruptured lesions 60% of his pathological series. The decennial age distribution displayed a bell-shaped curve for both ruptured and unruptured aneurysms, with the most common decades being 50 to 59 years for patients with ruptured aneurysms (29% of aneu-
Unruptured aneurysms

**Aneurysm Size Distribution**

Data from 1092 patients admitted to the Cooperative Aneurysm Study between 1970 and 1977 revealed a mean maximum angiographically measured diameter of 8.2 ± 3 mm (standard deviation) and a median diameter of 7 mm. Seventy-one percent of the aneurysm sacs were smaller than 10 mm and 13% were smaller than 5 mm. Aneurysms of the MCA were the largest and those of the ACoA were the smallest in this series of ruptured aneurysms. In patients harboring multiple aneurysms, the ACoA were the smallest in this series of ruptured aneurysms. In patients harboring unruptured aneurysms with no history of SAH, only 33% of the lesions were 2 to 5 mm and 26% were 6 to 9 mm. When there was a history of SAH from a treated aneurysm, the respective percentages were 61% and 28%. The presence of very small aneurysms was

In one series 13% of symptomatic unruptured aneurysms were giant, whereas only 3% of symptomatic ruptured lesions were giant. One of the asymptomatic unruptured lesions in the initial Cooperative Aneurysm Study was giant sized. In a forensic series of sudden fatal aneurysm ruptures, 62% of the lesions were smaller than 9 mm. In an aneurysm study conducted in Denmark, 948 patients underwent angiographic examinations. The average diameter of ruptured aneurysms according to the day of angiography postrupture did not differ significantly within the first 10 days. Seventeen percent of ruptured aneurysms were smaller than 5 mm and 50% were between 5 and 10 mm; therefore, more than two thirds of ruptured aneurysms were 10 mm or smaller.

In the Johns Hopkins series, 131 ruptured aneurysms ranged in size from 2 to 65 mm and 39 ruptured ones ranged in size from 2 to 25 mm. There was a significant increase in the occurrence and frequency of rupture associated with the increasing size of the aneurysm. The ruptured aneurysms had a mean size of 11.4 ± 1.2 mm and the unruptured aneurysms had a mean size of 7.6 ± 1.5 mm. A critical size at which aneurysms were more or less likely to rupture was not observed. Aneurysms as small as 2 mm ruptured and ones as large as 25 mm did not rupture or cause symptoms. In the review of 356 unruptured aneurysms reported on by Rinkel and colleagues, 72% were smaller than 6 mm, 21% were 6 to 10 mm, 6.5% were 11 to 20 mm, and 0.8% were larger than 20 mm.

In the pathological series conducted by Crompton and McCormick and Acosta-Rua, 96% and 98% of unruptured aneurysms found at autopsy were 10 mm or smaller, respectively. In a clinical series conducted at the University of Alberta, 84% of the unruptured aneurysms were smaller than 10 mm and approximately two thirds of the ruptured were smaller than 10 mm. The curve for the size distribution of unruptured ones was located to the left of the curve for the size distribution of ruptured ones; however, the most common size bracket for both was 4 to 10 mm.

In retrospectively studied groups in the ISUIA, in those patients harboring unruptured aneurysms with no history of SAH, only 33% of the lesions were 2 to 5 mm and 26% were 6 to 9 mm. When there was a history of SAH from a treated aneurysm, the respective percentages were 61% and 28%. The presence of very small aneurysms was

**TABLE 9**

Cooperative Aneurysm Study of 1966: type and location of aneurysms*

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidental Unruptured (73 aneurysms)</th>
<th>Symptomatic Unruptured (165 aneurysms)</th>
<th>Single Ruptured (3321 aneurysms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>37</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>MCA</td>
<td>27</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>ACoA</td>
<td>23</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>PerA</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>posterior circulation</td>
<td>10</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

* Based on data presented in Locksley.

**TABLE 10**

Cooperative Aneurysm Study of 1966: size and location of 160 symptomatic unruptured lesions*

<table>
<thead>
<tr>
<th>Location</th>
<th>&lt;3 mm</th>
<th>3–10 mm</th>
<th>11–24 mm</th>
<th>25–50 mm</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>OphA</td>
<td>0</td>
<td>28</td>
<td>24</td>
<td>48</td>
<td>19</td>
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<tr>
<td>PCoA</td>
<td>0</td>
<td>87</td>
<td>12</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>MCA</td>
<td>0</td>
<td>75</td>
<td>25</td>
<td>0</td>
<td>9</td>
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<tr>
<td>ACoA</td>
<td>0</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td>3</td>
</tr>
</tbody>
</table>

* Based on data presented in Locksley. The sizes of nine aneurysms were not recorded. Other sites 15%. 

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approximately twice as common in the group positive for a history of SAH.

Of the 1558 patients with aneurysms who underwent surgery at Shinshu University, 80% harbored ruptured lesions and 20% unruptured ones. Of the ruptured aneurysms, 38% were smaller than 6 mm in maximum diameter. Of the single ruptured aneurysms smaller than 6 mm, 36% were located along the ACoA. The percentage of single unruptured lesions in this size group was 12%. Among aneurysms located along the MCA, 23% were ruptured and 37% were unruptured. Among ruptured aneurysms of all sizes, 30% were located on the ACoA and 29% on the MCA. Among unruptured aneurysms of all sizes, 12% were located on the ACoA and 38% on the MCA. Of the 169 ACoA lesions smaller than 6 mm, 89% were ruptured. Of the 591 aneurysms of all types smaller than 6 mm, 71% had ruptured. Among those larger than 25 mm, 62% were unruptured and 31% were cavernous or ophthalmic ICA aneurysms. In the 34 patients who harbored medium or large lesions accompanied by small ones, the small aneurysm was ruptured in 27% and most of these were located on the ACoA.136

Kailasnath and colleagues89 hypothesized that a histogram of lesion sizes within a given population could provide insight into the fundamental nature of aneurysm evolution. They developed a mathematical model that incorporated the observation of erratic behavior in aneurysm growth into a physical scenario in which the ratio of successive sizes of an aneurysm could be considered a random multiplier function. This mathematical formulation was applied to data from the previous studies of Crompton29 and McCormick and Acosta-Rua,116 which Kailasnath and colleagues concluded were the only two studies in which average sizes of unruptured and ruptured aneurysms were measured rigorously in a relatively large population. Their model predicted that within a large population of aneurysms, a log normal histogram of lesion sizes would occur; that is, the logarithm of the aneurysm size would have a normal distribution. They found this to be demonstrated in the size data from the pathological series of Crompton and McCormick and Acosta-Rua.

### Aneurysm Site Distribution

Crompton29 found that in 88% of 90 cases of multiple aneurysms, rupture occurred in the lesion with the greatest maximum external diameter. In 36 cases in which two or more aneurysms occurred on the same side, the proximal lesion ruptured in 70%. In the 11 cases in which the distal aneurysm had ruptured, seven patients harbored ruptured ACoA and unruptured ICA aneurysms.29

In Fox’s review43 of 17 clinical series comprising 12,760 cases (presumably mainly ruptured aneurysms) published between 1952 and 1980, the locations of the aneurysms were the following: ICA in 40%, ACoA in 32%, MCA in 21%, and VBA and PCA in 10% of cases.

In 13 autopsy series comprising 2324 cases, which were published between 1941 and 1967, the locations of the aneurysms were the following: ICA in 24%, ACoA in 31%, MCA in 32%, and VBA and PCA in 13% of cases.

In the first Cooperative Aneurysm Study106 the site distribution of unruptured aneurysms was as follows: ICA in 72%, MCA in 13%, ACoA and ACA in 10%, and posterior circulation in 5.7% of cases. Also in the first Cooperative Aneurysm Study, among lesions discovered incidentally, MCA ones constituted 27%, whereas ACoA and ACA ones constituted 26%. The ratios were reversed in ruptured aneurysms, that is, ACoA and ACA aneurysms constituted 35.4% and MCA aneurysms 21%,106

Table 11 lists the sites of both ruptured and unruptured aneurysms in two large autopsy series undertaken by Inagawa and Hirano. Aneurysms located along the ACoA or the PerA were more likely to be ruptured than MCA lesions, but not more likely than ICA ones. In most series the mean size of ruptured aneurysms has been smallest at the ACoA site and largest at the proximal CA site. For example, in the ruptured aneurysm series of the Cooperative Aneurysm Study of 1983,24 the sizes and sites of lesions (in mm) were as follows: 11.4 in OphA, 9.1 in MCA, 8.8 in BA, 8.2 in PCoA, 7.6 in PerA, and 7.4 in ACoA 7.4. In the University of Alberta series, the sizes and sites (in mm) of ruptured aneurysms were as follows: OphA 15.3, MCA 12.7, BA 9.1, PCoA 9.3, PerA 7.6, and ACoA 9.6.290 In Suzuki’s surgical series of 636 ruptured aneurysms,121 the following sizes (in mm) and sites were recorded: ICA 8.6, MCA 8.3, VBA 10.7, ICA 8.6, PerA 6.7, and ACoA 7.6. The importance of these observations on the use of size as the sole criterion for deciding not to operate in a patient harboring an unruptured aneurysm smaller than 10 mm seems to me to be obvious.

### TABLE 11

**Summary of aneurysms identified in autopsy series**

<table>
<thead>
<tr>
<th>Aneurysm Site</th>
<th>RA†</th>
<th>UA†</th>
<th>RA‡</th>
<th>UA‡</th>
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<tr>
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<tr>
<td>VA</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>62</td>
</tr>
</tbody>
</table>

‡ Measurements were obtained for 109 ruptured and 93 unruptured aneurysms.

* Data obtained from two autopsy series by Inagawa and Hirano.57,66

Some patients with unruptured aneurysms harbored more than one. Abbreviation: VA = vertebral artery.

† Group refers to specific aneurysm site or size, or patient age for both ruptured and unruptured aneurysms.

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B. Weir

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<td>27</td>
<td>41</td>
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Unruptured aneurysms

The percentage of ruptured lesions in each size category among the 1088 ruptured aneurysms reviewed in the 1997 Shinshu series was highest in those located along the ACoA and PerA (46–63%), compared with those located along the MCA (31%) and those located along the PCoA (28%). In the Alberta clinical series, 86% of ACoA aneurysms and 86% of PerA aneurysms were ruptured, as were 77% of BA, 61% of MCA, 58% of PCoA, and 65% of OphA aneurysms. None of the cavernous ICA lesions were ruptured. This seems to provide further evidence that ACoA and PerA unruptured aneurysms should be viewed as relatively dangerous compared with aneurysms appearing at other sites.

In a series by Inagawa, 16 cavernous ICA unruptured aneurysms were followed for a mean of 4.7 years. These lesions had a mean initial diameter of 5 mm and none became symptomatic or ruptured. Although rupture of a cavernous ICA aneurysm has been reported, it is extremely rare and a relatively conservative approach should be used to treat lesions in this location, regardless of size. Surgical indications would be epistaxis, intractable pain, or severe visual compromise.

Morphological Characteristics

Lobulation. A multilobular aneurysm is probably at greater risk of rupture than a unilobular one. Subarachnoid hemorrhage occurred in seven of 20 cases of multilobular aneurysms and in two of 50 cases of unilobular ones. In another study, seven of 11 multilobular and three of 14 unilobular aneurysms ruptured. Forty patients with ruptured and 34 with unruptured aneurysms were referred for coil embolization. Sixty percent of the ruptured aneurysms were unilobular and 40% were multilobular. Ninety-one percent of unruptured aneurysms were unilobular and 9% were multilobular.

Loculation. In Crompton’s pathological series of 275 ruptured aneurysms, a distinct loculus or secondary bubble on the lesion surface was found in 57%. In contrast, only 16% of 112 unruptured aneurysms had a loculus. Loculations became more common with increasing size of the aneurysm. Three of four unruptured aneurysms with a daughter loculus ruptured between 1 month and 10 years of follow-up review, whereas only two of 10 unruptured lesions without a daughter loculus later ruptured.

Volume/Orifice Area Ratio. Synthetic rubber casts were made of aneurysms removed at autopsy. Seven aneurysms showed an orifice area ranging from 1.5 to 15.05 mm² and volumes ranging from 1.09 to 69.43 mm³. The volume/orifice area ratio ranged very widely, between 0.6 and 22.4.

Aspect Ratio. In an effort to find a more reliable basis for differentiation between ruptured and unruptured aneurysms, Ujie and colleagues looked at a ratio that they termed “aspect,” which consists of the ratio of the depth of the aneurysm to its neck width, rather than simply using the maximum diameter in any plane. These authors compared 129 ruptured aneurysms with 78 unruptured ones. The mean aspect ratio was significantly different at the PCoA, ACoA, MCA, and other sites. No ruptured aneurysms were found to have an aspect ratio below 1. Almost 80% of all ruptured aneurysms were found to have an aspect ratio greater than 1.6, whereas almost 90% of unruptured lesions were found to have an aspect ratio of less than 1.6. These authors had previously established that this ratio was a key factor in determining intraan- eurysm flow in an aortic bifurcation aneurysm model in rabbits. Aneurysms with a ratio greater than 1.6 exhibited very low flow near the dome, which may incite atherosclerotic inflammatory change and activate matrix metalloproteinase.

Rate of Growth. The rate of growth of aneurysms is not predictable and does not appear to progress steadily or inexorably. An angiographic study was performed in 67 patients who harbored 82 aneurysms. Studies were performed at intervals ranging from days to 10 years. There was no consistent rate of change in the size of these lesions. Four patients underwent at least four angiography sessions; in two of these patients the aneurysms remained stable for 4 years or more, in one patient the lesion grew slowly during this time, and in the third patient the lesion grew rapidly within a short time period. In 38 patients who underwent repeated angiography because of bleeding, 68% of the aneurysms were larger and 32% were the same size or smaller. When repeated angiography was performed as a checkup, only 65% of the aneurysms were larger and 35% were the same size or smaller. Of four incidental aneurysms that ultimately bled, three were larger at the time of hemorrhage. Four of 12 incidental aneurysms ultimately ruptured (their sizes were not specified in this study), as did four of 33 lesions that were associated with a ruptured aneurysm that had previously bled. The authors were impressed by the striking biological variability in aneurysm growth rates. Long-term follow-up angiography was performed between 1 and 20 years in five patients in whom ruptured aneurysms had been completely clipped; in six patients harboring multiple aneurysms, of which the ruptured one had been completely obliterated but a small unruptured one had remained undiagnosed; and eight patients with unruptured aneurysms that were either asymptomatic or symptomatic. Four of six fast-growing aneurysms (> 8% increase/year) subsequently ruptured, whereas none of 14 slow-growing lesions (with lower annual growth rates) subsequently bled during follow up (p < 0.01). The annual growth rate did not correlate with hypertension, patient age, or aneurysm location. One hundred seventeen patients with unruptured aneurysms were followed up for periods between 1 month and 14 months (mean 15.4 months), and two of these patients suffered from SAH. In 42 of 45 patients who underwent repeated MR angiography, the sizes of the unruptured aneurysms had not changed within a few years.

Factors Influencing Formation and Growth

It is likely that formation and growth of aneurysms are influenced by multiple genetic, structural, hemodynamic, and metabolic factors. A single intracranial aneurysm excised from a 3-year-old girl was analyzed using a global gene expression analysis approach. The aneurysm tissue displayed a highly dynamic cellular environment in which wound healing and tissue—ECM remodeling was taking place. There was a significant overexpression of genes encoding ECM components and those involved in ECM
growth. In 16 cases angiography was used to follow the growth of intracranial aneurysms. Clinical deterioration paralleled to a variable degree the enlargement of the lesions. In all these patients with growing aneurysms, the lesions were irregular in shape and/or bi- or multiloculated.

De Novo Aneurysms. Among 31 patients studied using follow-up angiography, no de novo aneurysms occurred in 19%. The approximate rate of formation of such lesions was 2.2%/year. The rate for patients harboring multiple aneurysms was slightly lower at 1.6%. De novo aneurysms were not associated with hypertension, patient age, or the growth rate of the largest lesion. The number of de novo aneurysms increased directly with the interval between angiographic assessments. According to Juvela and colleagues, the risk of experiencing an SAH from a de novo aneurysm was so low that routine angiographic monitoring could not be recommended.

Patient Age. Wiebers, et al. found no significant correlation between patient age and aneurysm size in their study of unruptured lesions. In patients older than 59 years the rupture rate was 48% after diagnosis of an unruptured aneurysm, which was twice the rate found in younger patients (24%). These figures were applicable for patients harboring aneurysms 10 mm or larger. Fifty-five of 130 patients died during follow up: 25% due to intracerebral hematoma, 22% due to coronary artery disease, 18% due to cancer, and the remainder died due to a variety of causes. A series of 14 patients older than 70 years of age who harbored incidental unruptured aneurysms was analyzed. Five patients received surgical treatment. None of them sustained any surgical morbidity or mortality. Of 10 patients who did not undergo surgery, during a follow-up period ranging from 3 months to 7 years, two patients (20%) experienced aneurysm rupture.

Hemodynamic Factors. Model aneurysms were constructed of elastic tissue and collagen and subjected to pressure pulse waves of water or blood. Pressure was monitored within the system. Increasing systolic pressures produced a nonlinear N-shaped pressure–volume curve. Initially, the volume of the aneurysm was increased in a linear fashion, until there was an abrupt point of nonlinear compliance at which the pressure increased. The volume then abruptly jumped to a new stable equilibrium volume. Further increases in pressure measuring approximately 24 mm Hg caused rupture at thinner, more compliant sites of the aneurysm wall. Higher pulse rates caused the jump in aneurysm volume to occur at a smaller volume.

Cigarette Smoking. Current cigarette smoking affects both aneurysm formation and growth. Although a study by Juvela, et al. was composed mainly of multiple aneurysms associated with SAH occurring in younger patients, it would be surprising, in my opinion, if the results in this series did not also apply to patients with incidental lesions. Eighty-seven patients with 111 unruptured aneurysms and seven patients with de novo aneurysms were followed for 18.9 years. In more than one-third (36%) of patients with unruptured aneurysms, impressive lesion growth (≥ 3 mm) was observed. Of several potential risk factors, only cigarette smoking (OR 3.48, 95% CI 1.14–10.64, p < 0.05) was associated with this magnitude of growth. Risk factors for aneurysm formation (adjusted for age and hypertension) were female sex (OR 4.73, 95% CI 1.16–19.38) and cigarette smoking (OR 4.07, 95% CI 1.09–15.15). This study also established that the majority of aneurysms did not grow significantly during the long-term follow-up review.

Factors Influencing Rupture

To determine the risk of aneurysm rupture, Rinkel and colleagues evaluated nine studies in which there was a total of 3907 patient years. The overall risk of rupture per year was 1.9% (95% CI 1.5–2.4). The risk of rupture was higher in women (RR 2.1) and for aneurysms that were symptomatic (RR 8.3), larger than 10 mm (RR 5.5), or located in the posterior circulation (RR 4.1). In this group of unruptured aneurysms, 93% were 10 mm or smaller and only 7% were larger than 10 mm. In an investigation of asymptomatic aneurysms covering 1145 patient years, nine aneurysms ruptured, providing a risk of rupture per 100 patient years of 0.8 (95% CI 0.4–1.5). In an investigation of multiple aneurysms for 1997 patient years, there were 27 ruptured aneurysms, for a risk of rupture of 1.4 (95% CI 0.9–2.9). In an investigation of symptomatic aneurysms for 463 patient years, there were 30 ruptured aneurysms, providing an incidence of 6.5 (95% CI 4.4–9.1). The RR of rupture of a symptomatic aneurysm was 8.2 times that of an asymptomatic one, whereas the RR of rupture of a multiple lesion compared with an asymptomatic one was 1.7.

In the remarkable series conducted in Finland by Juvela, et al. 142 patients with 181 unruptured aneurysms were followed until death or SAH occurred, or for at least 10 years after diagnosis of the unruptured lesion. Ninety-two percent of these lesions were part of a multiple aneurysm constellation in which the initial ruptured lesion had been definitively treated. Only 4% of the patients had incidentally discovered aneurysms and only 4% had symptomatic unruptured ones. The median length of follow up was 13.9 years (range 0.8–30 years), and the mean annual incidence of rupture was 1.4%. Fifty-two percent of the ruptures were fatal. For the main subgroup of unruptured aneurysms the only variable that tended to predict rupture was the age of the patient, with risk being inversely associated with age. In an extension of their previous studies, Juvela and colleagues studied 142 patients with 181 unruptured aneurysms from the 1950s until 1998. The median follow-up time was 19.7 years (range 0.8–38.9 years). During 2575 patient-years of follow up, there were 33 first-time episodes of bleeding from previously unruptured aneurysms, providing a mean annual incidence of 1.3%. The mortality rate was 52%. The accumulated rate of bleeding was 10.5% at 10 years, 23% at 20 years, and 30.3% at 30 years after diagnosis.

Aneurysm Size. In a study of 177 aneurysms in 125 patients treated at the University of Iowa, it was noted that the percentage of cases in which aneurysms ruptured increased from 0% for aneurysms 2 to 3 mm to 100% for aneurysms 16 to 20 mm. Forty-one percent of aneurysms measuring 6 to 10 mm ruptured. Data from 10 patients with 12 incidental aneurysms were reported in an early...
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series.\textsuperscript{215} Five of these lesions were smaller than 3 mm, three were 3 to 6 mm, and one was 10 mm in diameter. One of the patients died of a pulmonary embolus 2 months after treatment. Three of the nine survivors underwent follow-up angiography 12 to 16 months later, and no change in the appearance of the aneurysm was observed. The nine patients were observed for a mean of 37 months (maximum 90 months) during which no SAH occurred.\textsuperscript{215}

In their initial report on unruptured aneurysms, Wiebers and colleagues\textsuperscript{205} presented 65 cases in which there were 81 unruptured aneurysms. The size of the aneurysm was the only variable known to influence its tendency to bleed subsequently. All aneurysms that produced symptoms were larger than 8 mm. Of the eight patients who ultimately died, 38\% harbored multiple aneurysms, 25\% had multilobed aneurysms, and 75\% experienced symptoms before rupture. Multivariate analysis failed to show that symptomatic aneurysms (other than those producing SAH) were more likely to bleed than others. In a subsequent long-term follow-up study of 132 patients with 161 unruptured aneurysms,\textsuperscript{206} the mean diameter of lesions that subsequently ruptured was 21.3 mm, compared with 7.5 mm for those measured after rupture at the same institution. Initial angiographic studies that led to the diagnosis of unruptured aneurysm were performed in 22\% of the patients because the lesions were producing mass effects, in 32\% because there were ischemic cerebral vascular symptoms, in 8\% because the patients were experiencing seizures, and in 15\% because the patients suffered from headaches. A variety of symptoms were present in the other patients. Patients were followed up for at least 5 years or until death, intracerebral hematoma, or aneurysm surgery occurred. The mean follow-up interval was 8.3 years, with a total follow-up time of 1079 patient years. Sixty-three percent of the 161 aneurysms were smaller than 10 mm wide and none of these ruptured during the follow-up period. Ultimately, 9.3\% of the aneurysms ruptured. Fifty-three percent of the 15 patients who subsequently experienced aneurysm ruptures had a history of hypertension. Forty-two percent of the BA aneurysms ultimately ruptured, whereas the rates for ICA, ACoA, and ACA aneurysms were all less than 7\%. Forty percent of the ruptures occurred within the first 6 months after the aneurysm had been discovered. The authors from the Mayo Clinic sought to explain the fact that the mean diameter of unruptured aneurysms that ultimately bled was much larger than the mean diameter of ruptured aneurysms. Three possible explanations for this discrepancy were offered. 1) Small aneurysms could outnumber large ones to such an extent that the very low percentage of small aneurysms that rupture could still represent a significant fraction of all ruptured aneurysms. The authors rejected this notion as being unlikely on the basis of known size distributions. 2) An aneurysm that bled might decrease in size after rupture; this decrease in size might occur because of partial collapse of the aneurysm at the time of rupture due to thrombus formation in the sac. 3) Intracranial saccular aneurysms might develop over a relatively short time and rupture at the limits of elasticity of their walls. If rupture does not occur, however, reinforcement of the wall by collagen might reduce the likelihood of bleeding until the aneurysm is much larger. Aneurysms that do not rupture shortly after formation may reach a stable size and never rupture. This may explain why the average size of both ruptured and unruptured aneurysms does not increase with age, whereas the frequency of formation of aneurysms does. The authors emphasized that they excluded patients with any suggestion of SAH from their series of unruptured aneurysms subjected to follow-up review.

Wiebers and colleagues\textsuperscript{206} later suggested that unruptured lesions that are part of multiple aneurysm constellations may have a greater propensity for future rupture than intact aneurysms in patients who have not experienced a previous rupture. These authors opined that if the majority of aneurysms that ruptured do so at the time of, or soon after, their initial formation, screening procedures would have limited value.

In the long-term follow-up of unruptured aneurysms conducted in Helsinki,\textsuperscript{24} the RR for rupture according to the diameter of the aneurysm was 1.11 per millimeter in diameter (95\% CI 1–1.23, p = 0.05). Patient age at diagnosis was inversely related to the RR (0.97/year, 95\% CI 0.93–1, p = 0.05). Aneurysm size and patient age remained significant independent predictors for subsequent rupture after adjustment for patient sex, hypertension, and aneurysm group. The estimated RR of aneurysm rupture among lesions measuring 7 mm or larger was 2.19 compared with smaller ones. The average annual risk of aneurysm rupture among lesions 7 mm or larger was 2.5\% (nine first ruptures during 364 patient years) and 1.1\% (18 ruptures during 1580 patient years) among aneurysms smaller than 7 mm in diameter.\textsuperscript{24}

A retrospective review of 139 consecutively managed, incidental unruptured aneurysms was conducted by Mizoi and associates.\textsuperscript{122} Conservative management was chosen for 49 patients (35\%). During the follow-up period (mean 4.3 years) 16\% of these patients experienced aneurysm rupture and 88\% of the patients died of hemorrhage. The mean size of aneurysms with late hemorrhage was significantly larger than that of lesions without subsequent rupture. None of 26 tiny aneurysms (< 4 mm) bled. Of the 65\% of patients with 119 incidental aneurysms (all of which were < 25 mm in diameter) who were surgically treated, there was no surgery-related morbidity or mortality. The male/female ratio in these patients was 1:1.4 and their mean age was 58 years. In this series 35\% of patients clearly harbored incidental aneurysms, 42\% harbored lesions discovered during investigation for other significant neurological diseases, and 24\% harbored lesions found at the time of examination of a coexisting ruptured one (that is, multiple aneurysms). Sixty-five percent of the patients were selected for surgery on the basis of an estimated low surgical risk, age younger than 70 years, favorable general medical condition, and no associated established neurological deficits. Unruptured aneurysms located in the anterior circulation were surgically treated more often (71\%) than those located in the posterior circulation (16\%). Of 49 patients with unruptured aneurysms who did not undergo surgery and who were followed up for an average of 4.3 years, 16\% subsequently experienced intracranial bleeding from this source. These bleeding episodes occurred, on average, 3.7 years after diagnosis (range 3 months–7 years). The patient age at diagnosis averaged 67
years. The sizes of aneurysms with subsequent ruptures were 5, 10, 15, 17, 18, 24, 25, and 26 mm. It is noteworthy that there was one 5-mm aneurysm that subsequently bled. The mean diameter of aneurysms that subsequently ruptured was 18 mm, compared with a mean diameter of 7 mm in those lesions that remained clinically asymptomatic.\(^{122}\)

Based on 27 ruptures in 3742 patients with aneurysms 10 mm or smaller and 27 ruptures in 675 patients with larger aneurysms, the RR of rupture of larger aneurysms was 5.5 (95% CI 3.3–9.5), with an incidence of 4 (95% CI 2.7–5.8) compared with 0.7 (95% CI 0.5–1) in a literature review by Rinkel and colleagues.\(^{150}\)

Aneurysm Growth. Nineteen patients with aneurysms underwent repeated CA angiography sessions performed at intervals of 2 weeks to 10 years without intervening surgical procedures. All these patients had initially experienced aneurysmal SAH and their mean age was 40 years. In 10 patients in whom aneurysm growth was definitely established at intervals between 2 weeks and 10 years, six patients suffered a recurrent SAH. In eight patients in whom the size of the aneurysm was unchanged at intervals between 4 and 88 months after the first angiogram was obtained, none experienced a second SAH.\(^{6}\)

Growth of aneurysms between successive angiographic examinations was shown in 25 patients. In 11 the interval was less than 1 month and in 14 it was longer, ranging up to more than 15 years. In patients who underwent short-term follow up, all initial angiograms were obtained because a rupture had occurred. Four of the 11 patients had experienced repeated hemorrhages and in all of them aneurysm enlargement or development of an aneurysmal loculus was demonstrated on angiograms. Rebleeding did not appear to be affected by the growth rate or by the initial size of the aneurysm.\(^{67}\)

Fifty-four patients with 72 unruptured aneurysms were followed up for an average of 44 months.\(^{7}\) The 5-year survival rate was 56%. Twenty percent of patients harbored aneurysms that ruptured during the follow-up period, and 91% of these patients died. The annual bleeding rate was 1.92%. The average size of the 11 aneurysms that subsequently ruptured was 13 mm; however, bleeding occurred in two unruptured aneurysms, one of which measured 4 mm and the other 5 mm. The shape and location of the aneurysm and the presence of hypertension were considered to predict subsequent rupture. Multilobular VBA and MCA aneurysms measuring 10 to 19 mm were considered to carry high risks. Twenty of 28 patients with unruptured aneurysms were followed up with repeated angiography.

In the large series of unruptured aneurysms conducted by Juvela, et al.,\(^{85}\) which covered a median follow-up period of 14 years, the mean diameter of aneurysms that either ruptured or remained intact during the follow-up period was 4 mm. The aneurysms that subsequently ruptured (17 patients) displayed a significant increase in size. Among the 14 patients in whom angiographic follow up was available and in whom there was no sign of rupture, there was no significant increase in aneurysm size. The median diameter of the four incidental aneurysms was 8 mm and that of the symptomatic unruptured ones was 15.5 mm; these diameters were significantly larger than the mean 4-mm diameter of the lesions in the multiple unruptured aneurysm constellation. The risk of bleeding from an unruptured aneurysm was nearly constant over the three decades following diagnosis in this series.

Aneurysm Site. During a 10-year period (1979–1989), 22 patients harboring 24 petrous and cavernous ICA aneurysms were observed. All of these lesions were unruptured aneurysms. The mean diameter of aneurysms that subsequently ruptured was 18 mm, compared with a mean diameter of 5 mm (range 2–17 mm) were followed for 11 months to 10.5 years (mean 4.7 years). None of these 16 aneurysms ruptured and 94% remained asymptomatic.\(^{65}\)

Of 769 aneurysms in the series conducted by Inagawa and coworkers,\(^{46}\) 67% were ruptured and 33% were unruptured. Eighty-nine percent of ACoA aneurysms were ruptured compared with 62% of MCA, 58% of ICA, and 53% of VBA aneurysms. Of those lesions with widths 9 mm or smaller, ACoA aneurysms were more than twice as likely to be ruptured as MCA ones, and more than 1.5 times as likely as ICA ones. Aneurysms located at the vertebrobasilar junction were slightly less likely to be ruptured than ICA lesions and slightly more likely to be ruptured than MCA ones. Only 10% of ACoA aneurysms were 10 mm or larger, whereas 30% of ICA and 21% of MCA aneurysms were that size. Of all ruptured aneurysms 9 mm or smaller, 46% were located along the ACoA and only 20% along the ICA. Eighty-nine percent of the unruptured aneurysms were smaller than 9 mm, as were 77% of the ruptured lesions. The ACoA and PerA aneurysms comprised 21% of the unruptured and 43% of the ruptured lesions. The frequencies were reversed for MCA aneurysms, which constituted 33% of the unruptured and only 26% of the ruptured ones. Aneurysms located on the ICA comprised 38% of the unruptured and 26% of the ruptured ones. Intact aneurysms located on the ACoA were found less frequently with advancing age, whereas the reverse occurred with those located on the ICA. There is no clear trend with aneurysms located at an MCA or a VBA site. Rupture rates expressed as percentages were calculated by dividing the number of ruptured aneurysms by the total number of ruptured and intact lesions for a given patient age and aneurysm site. The rupture rate for ACoA aneurysms increased from 85% in patients younger than 60 years of age to 97% in patients older than 70 years. For VBA aneurysms the rupture rates also increased slightly but progressively with age. The reverse was true in cases of ICA or MCA aneurysms. The overall rupture rates by site in decreasing order were as follows: ACoA, 89%; MCA, 62%; ICA, 58%; distal ACA, 52%; and, VBA, 40%. Of the 55 unruptured aneurysms for which follow-up data are available, only four were larger than 10 mm. Only two were located along the ACoA. The high rupture rate of ACoA aneurysms depended on the site as such.

For all sites, unruptured aneurysms were much more likely to be 4 mm or smaller than 10 mm or larger, by a factor of approximately fourfold for the major sites. For intact aneurysms, those located at the ACoA and PerA were approximately six times more likely to occur in patients 59 years or younger than in patients 70 years or older, in contrast with those located at MCA sites, which
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would occur three times more often in patients 70 years of age or older than in patients 59 years or younger. The ICA site was also more common in the oldest group of patients with unruptured aneurysms, that is, 50% of the 70 years and older age group compared with 2% for ACoA aneurysms. Only one patient in that group harbored an unruptured aneurysm at the ACoA site; this was one of 209 ACoA lesions. For ICA aneurysms it was 13% (29 of 230 aneurysms) and for those at the MCA it was 8% (17 of 216 aneurysms) of aneurysms, which occurred in this oldest age group. Twenty-five percent of 509 unruptured aneurysms were 4 mm or smaller. It was opined that the critical size for rupture of unruptured lesions should be settled at 5 mm or larger. Based on their 47 patients with unruptured aneurysms who did not undergo surgery, only one giant symptomatic BA lesion bled, which constitutes a rupture rate and fatality rate per year of 4% and a rate for asymptomatic unruptured aneurysms of 0%. Among the 55 unruptured aneurysms in this series, however, 30 were located on the ICA and only two were located on the ACoA.

Hypertension. Cerebral aneurysm formation and rupture were studied in 20,767 elderly patients whose records were stored in a US Medicare database. Hospitalized Medicare patients with unruptured aneurysms were compared with a random sample of hospitalized Medicare patients. Hypertension was present in 43.2% of patients with unruptured aneurysms and in 34.4% of the random sample. The 2.5 years of follow-up data were examined. For patients harboring unruptured aneurysms as the primary diagnosis, hypertension was a significant prognostic factor for future SAH (risk ratio 1.46, 95% CI 1.01–2.11), whereas surgical treatment reduced the chance of a future SAH (risk ratio 0.29, 95% CI 0.09–0.97). Unruptured aneurysm was the primary diagnosis in 39% and the secondary diagnosis in 61% of the 18,119 patients. The mean age of the patients was 73 years for cases in which unruptured aneurysm was the primary diagnosis and 75 years for those in which it was the secondary diagnosis. Hypertension was present in 42% and 46%, respectively. Interestingly, 27% of patients with a primary diagnosis of unruptured aneurysm in this age group underwent surgery, as did 3% of those with the secondary diagnosis. Patients who received surgical treatment were, on average, younger and had fewer comorbid conditions. Subarachnoid hemorrhage was diagnosed within 2.5 years of initial hospitalization in 119 patients (1.7%) with unruptured aneurysm as a primary diagnosis and in 98 patients (0.9%) in whom it was a secondary diagnosis. Twenty-nine percent of the patients died during the 2.5 years of follow-up review from causes other than SAH. Hypertension was a significant risk factor for future development of SAH (RR 1.46, 95% CI 1.01–2.11). Advanced age of the patient produced a small but statistically significant protective effect against developing SAH. Surgical treatment reduced the RR to 0.29 (95% CI 0.09–0.97). The authors of this study considered that their estimate of the incidence of SAH was low because it did not include patients who died outside the hospital. A literature survey of 24 studies composed of 26,125 aneurysm cases, 97% of which were clinical and 3% of which were autopsy cases, established a rate of hypertension and aneurysm of 44%. In a normal population larger than 1 million, only 25% had a similar diastolic blood pressure of greater than 90 mm Hg.

Associated Disease. Three hundred sixty patients with unruptured aneurysms were treated conservatively between 1969 and 1992 in Akita, Japan. In 65% of these patients follow-up data were available. The mean follow-up time was 75 months (range 3–270 months). At the last follow-up review 25% of the patients had died of other diseases, 3.8% had undergone surgery, and 34 patients (14.5%) had bled from a previously unruptured aneurysm. These initial hemorrhages were fatal in 53% of instances. The average annual rupture rate for all patients was 2.3%. The average annual rupture rates created by categorization according to initial presentation were as follows: SAH from a different aneurysm, 3.2%; cerebral infarction, 2.2%; intracerebral hematoma, 3.2%; and other diseases 3.6%. The rupture rates were not significantly different among patients according to their underlying disease or aneurysm site. Cumulative rate of bleeding for all patients was 20% at 10 years and 35% at 15 years following diagnosis. The cumulative probability of rupture was significantly higher for multiple than for single aneurysms (p < 0.001). The annual rupture rate for multiple aneurysms was 6.8% compared with only 1.9% for single ones. The size distribution of those intact aneurysms that subsequently bled was not given. During the period from 1984 to 1992, 2489 cases of aneurysmal SAH were registered with this study. The mortality rate for ruptured aneurysms was 31% and the morbidity rate was 15.3%.

Comparison of Ruptured and Unruptured Aneurysms

Autopsy Series

In the classic Crompton autopsy study there were 199 ruptured aneurysms with diameters 10 mm or smaller (75% of all ruptured aneurysms) and 113 unruptured aneurysms with diameters 10 mm or smaller (96% of all unruptured lesions). At the University of Iowa, McCormick and Acosta-Rua performed an important autopsy study on 136 consecutive patients in whom there were 54 ruptured aneurysms and 137 unruptured ones. Aneurysms were arbitrarily determined to exist at a size of 2 mm or larger. Forty-four percent of the ruptured aneurysms were 10 mm or smaller. The decade of life in which the most aneurysms were found was 60 to 69 years. The ratio of aneurysms to the total number of autopsies was highest within the decade 40 to 49 years (12.6%). Of those patients harboring aneurysms, the percentage with ruptured lesions decreased progressively as patients became older, from the period of 20 to 29 years to the period of 80 to 89 years. In patients who are found to harbor aneurysms at autopsy, the younger the patient the more likely that the aneurysm will have ruptured and caused death. In this series there was no increase in aneurysm size associated with an increase in age. Six aneurysms were isolated and inflated with saline solution at 70 mm Hg pressure. Prematurely values ranged from 4 mm (range 2–7.2 mm) and increased to 5.6 mm (range 3.2–11 mm); this was a 40% increase in diameter. It is possible that in
In the absence of prompt effective aneurysm obliteration, approximately half of the patients who experience lesion rupture will die within 1 month posthemorrhage. For patients with untreated aneurysms who survive 6 months, there is a 2% rerupture rate over the first 10 years, which falls to just under 1% per year during the following decade. Rebleeding is associated with a mortality rate approaching 80%. Currently, the mortality rate for patients of patients who survive until operation is approximately 10%, with approaching 80%. Currently, the mortality rate for patients with SAH, or an unrelated disease. Only 0.7% were dependent on others. Only 10% of the patients were known to harbor familial aneurysms. Anterior circulation aneurysms comprised 70% and posterior circulation ones 30%. Aneurysm sizes in this study were as follows: smaller than 10 mm in 94%, ICA in 40%, ACoA and ACA in 32%, MCA in 21%, VBA in 5%, and other in 3%.

Four hundred seven patients experienced at least one clinical episode of SAH. The prevalence of multiple aneurysms was 18%. The maximum diameters of lesions producing one, two, or three episodes of clinical bleeding did not differ significantly. The number of episodes of bleeding did not appear to be influenced by lesion location or size. Sixty-eight percent of patients harboring aneurysms 9 mm or smaller experienced at least one episode of SAH.

Comparisons of unruptured and ruptured aneurysms are given in Table 10. Symptomatic unruptured aneurysms were much more likely to be located on the proximal ICA than incidental unruptured aneurysms. The group of incidental unruptured aneurysms included more MCA aneurysms and fewer ACoA and PerA lesions than the group of single ruptured aneurysms. In the initial Cooperative Aneurysm Study, 40% of patients with incidental aneurysms were older than 60 years of age compared with only 27% of patients with ruptured aneurysms. In the first Cooperative Aneurysm Study symptomatic unruptured aneurysms included 80% ICA lesions, compared with the ruptured aneurysm group, which only included 36% ICA lesions.

Angiography performed in 1612 patients between 1980 and 1989 revealed 2.7% asymptomatic aneurysms. Unruptured aneurysms were more common in women older than 60 years of age. These lesions were less likely to occur along the ACoA (12.8%) and the MCA (6.4%), compared with 638 ruptured aneurysms treated at that institute during the same period. In the unruptured aneurysm group, 10.6% of the aneurysms were located in the cavernous ICA, 19% in ICA–OphA, 19% in ICA–PCoA, and 12.8% in ICA–anterior choroidal artery sites. The mean diameter of unruptured aneurysms was 4.8 mm and 80% were smaller than 6 mm. In the ruptured aneurysm group 32% were located on the ACoA and 27% on the MCA.

In a relatively recent review from the Mayo Clinic, it was suggested that the frequency of intracranial aneurysms is 1 to 8% of the general population and that 90% of these patients experience SAH. Following SAH, 8 to 60% of patients die before they can reach a hospital. After hospitalization, the mortality rate is 37% according to the authors of the report. I believe that most of these figures are excessively high. Of 1947 patients treated between 1969 and 1990 at this clinic, 9% had a poor outcome and 5% died. This reflects not only an excellent standard of care, but also the fact that many patients who underwent surgery did so while not in the acute phase of SAH.

Two years after aneurysm rupture, outcomes were worse in patients who harbored the largest lesions. Patients with larger aneurysms were more likely to experience prolonged unconsciousness and intracerebral hematoma associated with their SAH. The mortality rate was 47% in patients with aneurysms smaller than 5 mm, 39% in those with lesions measuring 5 to 10 mm, and 51% in those harboring larger ones. Aneurysms located along the ACoA made up 36% of all fatal lesions reported in the study by Inagawa, et al. Together, ACoA and ACA aneurysms made up 43%, MCA lesions made up 26%, and ICA lesions made up 26% of the total. A metaanalysis of series on unruptured saccular intracranial aneurysms treated using direct surgery was performed by Raaymakers and colleagues. The median year of publication in these series was 1981 (range 1959–1992). The mean age of the 2460 patients was 50.2 years. There were 61 studies in all. Only 9% of the patients were asymptomatic and without signs. Ninety percent were independent, but displayed symptoms or signs from a symptomatic unruptured aneurysm, a previous SAH, or an unrelated disease. Only 0.7% were dependent on others.

Between 1998 and 2000, 146 consecutive patients presented with 216 aneurysms to the University of Iowa. Fifty-five percent of the patients had ruptured aneurysms, and 13% of these patients harbored multiple lesions. The mean age in this group was 58 years. In patients harboring ruptured aneurysms 43% of the lesions were located along the ACoA, 20% along the ICA (PCoA), and only 16% along the MCA. Aneurysms smaller than 4 mm comprised 10%; those 4 to 9 mm, 68%; those 10 to 24 mm, 23%; and those larger than 24 mm, 0%. In a 4-year period all cases of patients with SAH who were admitted to a Philadelphia hospital were reviewed. Eighty-six percent of all ruptured aneurysms were less than 10 mm in diameter. Aneurysms of the ACoA ruptured at sizes smaller than 10 mm in 94% of cases. Similarly, 88% of PCoA aneurysms were smaller than 10 mm. There were 362 cases in this review.

In recent large studies of ruptured aneurysms and the drug tirilazad, the mortality rate in patients treated with vehicle alone varied with age: younger than 45 years, 11%; 45 to 64 years, 18%; and 65 years and older, 24%. In a group of 2007 patients (including those receiving the drug), the locations of the ruptured aneurysms were as follows: ACoA and ACA, 36%; ICA, 28%; MCA, 17%; and
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within the posterior circulation 14%. The aneurysm size distribution was as follows: 12 mm and smaller, 74%; 13 to 24 mm, 23%; and 25 mm and larger; 4%. Approximately 90% of all patients were admitted 24 hours or sooner post-SAH and underwent early surgeries. The 3-month outcomes for patients who received vehicle only were good recovery in 57%, disabled or vegetative state in 27%, and death in 18% (UpJohn Co., personal communication, 1999).

Rate of Rupture of Unruptured Aneurysms

Multiple Aneurysms

A constellation of multiple aneurysms was found in 31% of 289 consecutive autopsies performed by Crompton. According to Mount and Brisman, before 1973 they found only 40 cases of unruptured aneurysms in which craniotomy had been performed; good results were recorded in 98% and poor results in the rest. There were no deaths. These authors reviewed 158 cases of unruptured multiple aneurysms that were followed for less than 11 years; there was a 10% bleeding rate and a 4% mortality rate. In 130 cases of multiple intracranial aneurysms that remained untreated, 70 patients survived more than 6 months. Late SAH occurred in 30% of these patients. Among 46 patients who underwent craniotomy for the ruptured aneurysm alone, three patients subsequently experienced SAH from one of the other lesions during an average 7-year follow-up period. One hundred eighty-two patients with multiple aneurysms who had suffered a rupture were followed for a mean of 7.7 years. Twenty-one (30%) of 70 patients who initially were treated with bed rest alone suffered a late hemorrhage. All the late hemor-

rhages were considered to be caused by a repeated rupture of the original aneurysm. In 50 patients who underwent craniotomy and treatment of the initial ruptured aneurysm, 38 were alive at 6 months postoperatively. Ten patients suffered a second SAH, three from a previously unruptured aneurysm, in the 2nd and 4th year of follow up. The minimum risk of rupture in this group for an intact aneurysm was estimated to be 1% per year.

In 84 patients with multiple aneurysms, the ruptured lesion was definitely identified at operation. Ten of these patients experienced a recurrent hemorrhage during follow-up periods ranging from 4 months to 11 years. In eight of the 10 patients there was recurrent hemorrhage from a previously unruptured aneurysm. Forty percent of patients died as a result of the second SAH. The surgical mortality rate was 9% for the 84 patients with multiple unruptured aneurysms. Of the 76 patients who lived on under the risk of a second hemorrhage, 13% actually experienced a second one. The mortality rate among the original 76 survivors with multiple unruptured aneurysms was therefore 4%. It was not possible to ascribe an annual fatal rupture rate on the basis of data provided in the paper. Sixty-one patients with multiple aneurysms who had experienced an SAH underwent surgery to have the ruptured lesion clipped. During a 10-year follow-up period, seven patients bled from a previously unruptured aneurysm and four of these hemorrhages were fatal. Three additional patients suffered fatal bleeding more than 10 years after the initial one occurred. In 1979 the surgical mortality rate for operation on an unruptured aneurysm was 4.2%. The mortality rate from rebleeding during an average 16 years of follow up was 11.5% and, thus, surgery for multiple unruptured aneurysms was considered slightly preferable to conservative treatment management. Forty-three patients with multiple intact aneurysms whose initial ruptured lesion had been treated underwent surgery a second time. One patient died of myocardial infarction 3 weeks after surgery, resulting in a surgical mortality rate for the group of 2.3%. One patient also sustained a permanent neurological deficit consisting of hemiparesis and dysphasia. The surgical risks were considered to be smaller than the natural ones. In the study conducted in Helsinki the median greatest diameter of multiple unruptured aneurysms was 4 mm. The median greatest diameter of a ruptured aneurysm in patients harboring multiple unruptured lesions was 10 mm (mean 10.3 mm, range 4–28 mm). During the 14 years of follow up, the percentage of unruptured aneurysms that ruptured was as follows: five cases with incidental unruptured aneurysms, 20%; six with symptomatic unruptured ones, 33%, and 131 with multiple intact aneurysms, 18%. In the latest report published in 2000, the percentage of patients without SAH ranged between 65% and 80% at 20 of years follow up, and the percentages did not seem to differ significantly when multiple, symptomatic, and incidental aneurysms were compared.

In patients with multiple aneurysms, one of which had ruptured, the largest lesion averaged 10 mm, the second largest 5.6 mm, the third 4.2 mm, and the fourth 3 mm. The most common sites were the ACoA in 32%, PCoA in 21%, and MCA in 18%. The maximum diameters were inversely related to the frequency of occurrence; 7.4 mm for aneurysms of the ACoA, 8.2 mm for those of the PCoA, and 9.1 mm for those of the MCA. The maximum sizes of aneurysms that produced a single hemorrhage were not significantly different from the average size of those that produced multiple hemorrhages. There was no statistically significant difference in the size of aneurysms in relationship to the number of days post-SAH that angiography was performed.

In Japan in a series of 109 ruptured aneurysms, 17% had diameters 4 mm or smaller and 46% had diameters 5 to 9 mm. In 21 patients with multiple aneurysms, unruptured ones were smaller than the ruptured ones in 63%, equal in size in 33%, and larger than the ruptured aneurysms in 4% (one case). Of 24 patients with multiple aneurysms and including one ruptured lesion, the sites of the unruptured ones included the ICA in 50%, MCA in 33%, and ACoA in 25%; thus, the ICA site is twice as likely to contain an unruptured aneurysm as the ACoA site. In 481 patients with ruptured aneurysms, multiplicity of lesions occurred in 30% of those patients younger than 59 years and in 27% of older patients. The difference was not statistically significant. The age distribution for patients with multiple aneurysms was similar to that for patients with single lesions. The highest rupture rates were observed in ACoA aneurysms in both groups, with a more prominent tendency in patients 59 years or younger (79%) than in older patients (59%). In older patients rupture rates were 50% for PerA aneurysms, 40% for ICA aneurysms, and 28% for MCA aneurysms. Surgical outcomes for mul-

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multiple lesions in elderly patients were considered to be satisfactory, but it was stressed that rupture rates should be considered when deciding on surgery for unruptured aneurysms. The treatment mortality rate in all grades of ruptured aneurysms attributable to all causes in one study was 24% in patients with multiple ICA lesions compared with 20% in those with single lesions. The incidence of multiplicity was 23% of 1314 patients. In a 1997 study conducted by Yasui and associates, in 30% of cases, surgery was performed in 92% of cases and aneurysm neck clipping in 71%. There was a 6% rate of moderate-to-severe disability. The surgery-related mortality rate in cases of giant aneurysms was 20% (unpublished data).

Incidental Aneurysms

In the 1969 Cooperative Aneurysm Study, 52 patients were found to harbor incidental aneurysms. Two (4%) of these 52 patients died within 5 years after the diagnosis was made. This was a better prognosis than that given to patients with symptomatic unruptured aneurysms. This would produce a rupture rate for asymptomatic unruptured aneurysms of approximately 0.8%/year. In this study there were 320 unruptured aneurysms (9.6% of total), excluding lesions within the cavernous sinus. There were 165 patients with symptomatic unruptured aneurysms who were at risk for SAH. Seventy-nine percent of these unruptured aneurysms were treated surgically, and thus 34 cases were left untreated and the natural course of the disease was studied. Thirty-five percent of untreated unruptured aneurysms were followed for 20 months to 12 years, during which time 26% of the patients harboring these lesions died of SAH.

In a relatively small recent clinical series, 20% of the unruptured aneurysms were symptomatic, 32% were asymptomatic and components of multiple aneurysm constellations, and 48% were true incidental lesions. The clinical features of 14 patients older than 70 years of age with incidentally discovered unruptured aneurysms were analyzed by Yasui and associates. Four patients who ranged between 70 and 72 years underwent surgery. Ten patients who did not undergo surgery were followed up for periods ranging between 3 months and 7 years. In two of these patients it is presumed that aneurysm rupture developed.

Between 1976 and 1997 at a single hospital in Japan, 62 patients were observed for more than 6 months to follow their saccular, nonthrombotic, noncalcified unruptured aneurysms located at sites unrelated to the cavernous sinus. These aneurysms were demonstrated on cerebral
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angiograms obtained for causes other than SAH. The observation periods ranged from 6 months to 7 years, with a mean of 4.3 years. In seven patients (11.3%) CT-confirmed SAH developed at a mean interval of 4.89 years. Six of the seven patients died and the remaining one suffered a major deficit. The cumulative risks of CT-confirmed SAH calculated using the Kaplan–Meier method at 5 and 10 years for all aneurysms were 7.5% and 22.1%, respectively. For aneurysms greater than 10 mm, the 5- and 10-year rates were 33.5% and 55.9%, respectively. For aneurysms smaller than 10 mm, the corresponding rates were 4.5% and 13.9%.

Between 1999 and 2000, 427 patients with unruptured aneurysms were registered in the prospective Japanese Ministry of Health study of unruptured aneurysms. Sizes of the 145 incidental unruptured aneurysms (34% of cases) were the following: 2 to 5 mm in 31%, 6 to 9 mm in 36%, 10 to 24 mm in 26%, and larger than 25 mm in 4% of cases. Therefore, two thirds of incidental unruptured aneurysms were smaller than 10 mm. In one of 97 cases the size of the lesion increased within 48 months and the aneurysm was therefore clipped. Thirty-seven percent of patients with incidental unruptured aneurysms received surgical treatment. In four of the 48 untreated cases, the aneurysms ruptured; three of these four lesions were larger than 10 mm. Of the four patients in whom the lesions ruptured, two died, one fell into a vegetative state, and one underwent surgery and is mildly disabled. A total of 110 unruptured aneurysms were untreated, and seven (6%) of these bled during the 1- to 2-year follow-up period. Of these ruptures four were from incidental aneurysms, two were from symptomatic lesions, and one was associated with cerebral ischemic disease (T. Tsukahara, personal communication, 2001).

The 10-mm Barrier

On the basis of his study of 289 ruptured and 115 unruptured aneurysms measuring larger than 2 mm, Crompton suggested that the critical size at which an aneurysm appears to become more likely to rupture is between 2 and 5 mm, at which point approximately equal numbers of ruptured and unruptured aneurysms were found. In 1987 Rogers reported on a fatal case of ruptured aneurysm in which the patient had been advised 6 months earlier that the aneurysm was “too small to cause trouble.” Schievink, et al., in a report from the Mayo Clinic and Savanna, Georgia, reported on three patients with previously documented asymptomatic intact intracranial aneurysms smaller than 5 mm in diameter that subsequently ruptured. A 70-year-old man bled from a 4-mm MCA aneurysm that had been discovered incidentally 2.5 years previously during evaluation for ischemic symptoms. A 10-mm ICA aneurysm and a contralateral 4-mm MCA aneurysm had not ruptured. A 66-year-old woman bled from a 4-mm PerA aneurysm that had been identified 9.5 years previously when she suffered an SAH from a 9-mm PCoA aneurysm. The PerA aneurysm had not enlarged, but a daughter loculus had developed. The third patient was a 35-year-old woman who bled from a 5-mm PICA aneurysm that had measured 2 mm on an angiogram obtained 4 years previously. At the time that angiogram was obtained, the patient had suffered an SAH from a 12-mm PCoA aneurysm. All patients were part of a multiple aneurysm group and two of them had previously experienced SAH.

In the 1993 series conducted by Juvela, et al., 18 (67%) of 27 aneurysms that subsequently ruptured were 6 mm or smaller. The authors therefore concluded that the size of the lesion does not predict bleeding. Nevertheless, the proportion of aneurysm ruptures increased almost constantly according to size category. In patients with multiple unruptured aneurysms, the largest lesion was the one that ruptured in 88% of cases. In two patients the two unruptured aneurysms were both the same size, and there was only one patient in whom the smaller unruptured aneurysm was the one lesion in a multiple aneurysm constellation that subsequently bled. The population studied by Juvela, et al., differed from that of Wiberg, et al., in that the aneurysms were initially smaller (median diameter 4 mm compared with 6 mm), the patients were approximately 15 years younger, and the great majority of patients seen by Juvela, et al., harbored multiple unruptured aneurysms rather than symptomatic or incidental ones. In addition, the length of follow-up review in the series by Juvela, et al., was significantly longer.

For the purposes of the ISUIA, interobserver variability in angiographic evaluation was systematically analyzed. A single set of high-quality angiograms of 55 aneurysms were evaluated using blinded interpretations and several statistical approaches. Correction for geometric distortion was the most critical factor influencing size measurement. Diameters of internal lumina of aneurysms and vessels were measured to the nearest millimeter. Two highly experienced radiologists at the Mayo Clinic and the University of Western Ontario performed the assessments. The mean differences in aneurysm size in three dimensions ranged from 0.2 to 0.469 mm. Of the 32 aneurysms judged by one expert neuroradiologist to measure 9.9 mm or less, two were judged by the other to be larger than 10 mm. Thus, two potential patients could have been judged eligible for treatment at one center and not at the other. Calibration techniques are considered to reduce uncertainty about size arising from geometric distortion to 10% or less. Loculations or daughter sacs were identified in nine instances by one observer and in 11 by the other. Extra lobes were identified by one observer on seven angiograms and by the other on two angiograms.

The ISUIA, which was published in late 1998, created a sensation. One thousand four hundred forty-nine patients with 1937 unruptured aneurysms were divided into two groups in the retrospectively studied arm: patients with a history of SAH and those with no history of bleeding. The mean duration of follow-up was 8.3 years, with a total of 12,023 patient years. The group without a history of SAH (Group 1) numbered 727 cases. Patients in Group 1 had a mean age of 56 years and 25% harbored multiple aneurysms. The mean diameter of the aneurysms was 10.9 mm, and 58% were smaller than 10 mm. Only 10% were located along the ACeA or ACA, and 16.9% were located in the cavernous sinus. Among the 722 patients who had histories of SAH from previously treated aneurysms (Group 2), the mean age was 49.4 years and 25.2% still harbored multiple lesions. Among the 727 patients in Group 1, only one aneurysm with a diameter of 9 mm or
less in 424 patients had a confirmed SAH. Of 641 patients in whom a multiple aneurysm constellation was present, there were 17 patients who had confirmed ruptures of lesions smaller than 10 mm in size. The rupture rates were calculated to be approximately 0.05% per year for cases with no history of SAH and in which the aneurysm was smaller than 10 mm, and approximately 0.5% per year for multiple aneurysm cases in which the lesion was smaller than 10 mm. Of the 32 patients in whom subsequent hemorrhage was confirmed, the fatality rate was 66%. Of the 205 patients who died during 7.5 years of follow-up review, 182 died of intracerebral hematoma, 36 of cancer, and 50 of cardiac disease.

Patients were admitted into the retrospective group studied in the ISUIA for the years 1970 to 1991 only if hard-copy arteriograms and medical records were available. Retrospective patient follow up was accomplished through standardized patient questionnaires, which were mailed to and returned by patients at least 5 years after the diagnosis of an unruptured intracranial aneurysm and annually thereafter.76

The same paper contained information on a prospective cohort of 1172 patients, 961 of whom had no history of SAH and 211 of whom had a history of bleeding from a SAH and 211 of whom had a history of SAH. The corresponding figure for patients with a history of SAH was 15.7% for patients with unruptured aneurysms and no history of SAH. The patient presenting with a progressive neurological deficit and increasing symptomatology represents an entirely different clinical problem from patients who have truly asymptomatic unruptured aneurysms. The patient presenting with a progressive neurological deficit and increasing symptomatology represents an entirely different clinical problem from patients who have truly asymptomatic unruptured aneurysms. The patient presenting with a progressive neurological deficit and increasing symptomatology represents an entirely different clinical problem from patients who have truly asymptomatic unruptured aneurysms. The patient presenting with a progressive neurological deficit and increasing symptomatology represents an entire different clinical problem from patients who are found to have aneurysms in the course of an examination for other symptoms or conditions.

In the retrospective group of patients with no history of SAH who were covered by the retrospective arm of the study and the high morbidity and mortality rates for those covered by the prospective arm. One can question this on general scientific grounds. The compared groups differed in the following respects: one was studied prospectively, the other retrospectively; the cohorts were different and not obtained by randomization; postoperative morbidity and mortality rates of patients in the prospective arm were compared with the exceedingly low rupture rates of those in the retrospective arm; and the postoperative morbidity and mortality rates for patients with all sizes of aneurysms were contrasted with the exceedingly low rupture rates in the retrospective group of patients with no history of SAH. Further, the study included fewer small aneurysms than most series of ruptured aneurysms (33% of 2–5 mm wide and 26% of those 6–9 mm wide). A relatively high percentage of lesions were in locations less associated with rupture (cavernous ICA, 17%; ICA, 25%) and a relatively low percentage were in locations more associated with rupture at a smaller aneurysm size (ACoA or ACA 10%). There were also fewer current smokers (53% compared with 70%) among patients who had not previously experienced SAH. Follow up was terminated at surgery for the aneurysm or at loss of contact with the patient, and, thus,
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future SAHs could have been missed. During follow up, 42 patients died of intracerebral hematoma and, in the absence of complete autopsy and excellent radiographical studies, it is certainly possible that one or two of these deaths could have been due to aneurysm rupture. In the prospective arm of the study, surgically treated and non-surgically treated groups were not randomized and were unlikely to have been balanced for prognostic factors.

Bias is a process tending to produce results that depart systematically from true values. A selection bias results from comparisons between groups of patients who differ in outcome determinants other than the one under study. In addition, even if the sample is unbiased, observations in a sample of patients may not be representative of the population as a whole due to mere chance. Both bias and chance may occur simultaneously. A study such as the ISUIA can have high internal validity with excellent design, data collection, and analysis, but investigators can still reach conclusions that are only valid for the population sampled and not generalizable to the entire universe of unruptured aneurysms.

The article by ISUIA investigators published in the New England Journal of Medicine in 1998 was, for the most part, skeptically viewed by neurosurgeons. The criticisms focused on the select nature of the retrospective cohort and the comparison between the prospectively gained morbidity data and the very low rupture rate for patients in the historical cohort, who had been selected for nonoperative intervention. It was believed that the researchers ignored the fact that the overwhelming majority of ruptured aneurysms that are presented to neurosurgeons are smaller than 10 mm. It was suggested that the retrospective group had excluded patients with the highest risk of rupture and introduced data collection bias, artificially lowering the estimated annual hemorrhage rate for previously ruptured aneurysms. It was noted that the cognitive status of patients undergoing surgery was not compared with a possible deterioration in cognitive status appearing in patients with unruptured aneurysms who did not undergo surgery. Furthermore, surgical complications generally occur within the year following surgery, whereas the risk of an untreated aneurysm is a continuing one. The retrospective group of patients with unruptured aneurysms were also believed to have a disproportionately high presence of cavernous and proximal CA lesions in relationship to ACoA aneurysms, a circumstance that is different from that in most surgical series. In the ISUIA, the authors did not make a clear distinction between the risks of symptomatic and truly incidental unruptured aneurysms and did not determine the influence of genetic factors, smoking history, or concurrent diseases such as ADPKD. It was suggested that the patients enrolled in the retrospective cohort between 1970 and 1991 might represent only a small portion of the total group of patients harboring unruptured aneurysms seen at the 53 participating centers. Patients may have been selectively included who were considered to harbor calcified, partly extracranial aneurysms, who were elderly and had other medical problems, or who harbored tiny laterally located aneurysms deemed at low risk of rupture.

It has also been hypothesized that the relatively few small aneurysms in the retrospectively studied unruptured aneurysm group with no history of SAH might have artificially raised the apparent size threshold for rupture (unpublished data).

Caplan writes, how do physicians make such difficult therapeutic decisions? Evidence-based medicine emphasizes the importance of relying on data from randomized therapeutic trials. But many conditions are not suitable for randomized trials, which requires that the condition be common, with clear end points that occur within a relatively short period. There have been no such trials of patients with unruptured aneurysms. Even when information from trials is available, it may not be useful in individual cases. To acquire samples large enough to yield statistically significant results, investigators often combine various subgroups of patients. The results are generally valid but not necessarily easily applied to particular patients.

Class 1 evidence comes from prospective randomized controlled trials. Class 2 evidence is prospectively collected data or retrospective analysis based on reliable information such as observational, cohort, or case control studies. Class 3 evidence is based in retrospective clinical series reports, case reports, or expert opinion. In a literature study of unruptured aneurysms, 45 articles were reviewed, none of which were considered to meet the criteria for Class 1 evidence. Seven articles on the natural history of unruptured aneurysms and seven on the risks of surgery met the criteria for Class 2 evidence. The reviewers concluded that there was sufficient evidence to recommend a standard of management. Despite this, they proceeded to suggest as a therapeutic guideline that unruptured aneurysms smaller than 10 mm and asymptomatic nongiant aneurysms in older people should not be surgically treated. I disagree with their recommendation.

Members of the Stroke Council concluded that incidental aneurysms smaller than 10 mm in patients without a previous SAH should be observed rather than treated. Exceptions to the rule could include aneurysms approaching the 10-mm diameter size and those with daughter sac formations and other unique hemodynamic features. Patients with a family history of aneurysmal SAH also deserve special consideration for treatment. Surgery is favored in patients with youth, a previous aneurysm rupture, a family history of lesion rupture, larger sized lesions, symptoms, observed aneurysm growth, and a record of low treatment risk. Factors favoring conservative management include increased age, decreased life expectancy, comorbid medical conditions, and asymptomatic small aneurysms.

Between 1976 and 1997, 62 patients underwent observation for more than 6 months for saccular, nonthrombotic, noncalcified unruptured aneurysms at locations distal to the cavernous sinus. The mean observation period was 4.3 years (6 months–17 years). Subsequent SAH was diagnosed in 11.3% of cases at a mean interval of 4.8 years by using CT scanning. The mortality rate associated with aneurysm rupture was 86%, and the only surviving patient experienced a major deficit. One patient died of the mass effect exerted by the unruptured aneurysm and another died after a suspicious headache of sudden onset. The 5- and 10-year cumulative risks of CT-confirmed SAH were 7.5% and 22.1%, respectively, for all cases. The 5- and 10-year risks were 33.5% and 55.9%, respectively, for aneurysms larger than 10 mm and 4.5% and 13.9% for those smaller than 10 mm. This was a single-
institution series, but the data were interpreted to support preventive surgical treatment of incidental aneurysms. If incidental unruptured aneurysms smaller than 10 mm really do pose a significant threat of rupture, why have there been so few accounts in the literature? Most neurosurgeons have only recently been interested in this phenomenon because CT and MR imaging have become widely used. I have personal knowledge of two such cases. In the ISUIA there was one case, in the report by Juvela, et al., there was one case, and Tsukahara (personal communication, 2001) also reports one case. Tsutsumi, et al., reported subsequent SAH in patients with asymptomatic aneurysms that were smaller than 10 mm: one was a 4-mm ACoA aneurysm that ruptured after 3 years in a patient who also harbored a larger MCA lesion and the other two included an 8-mm PCoA aneurysm that ruptured at 7 years and a 4-mm MCA lesion that ruptured at 3 years. The patients were older than 67 years. In other accounts, it is unclear whether the unruptured aneurysm was incidental or multiple. Asari and Ohmoto reported two cases and Mizoi, et al., one case. It is hoped that the Japanese registry and the ongoing ISUIA will provide more data. The review by Rinkel and colleagues, published in 1998, suggests an annual SAH rate of 0.7% in patients with aneurysms with 10 mm or less diameter, but does not differentiate asymptomatic from multiple-aneurysm cases (Table 12). Systematic collection of such data in a prospective fashion should be encouraged by neurosurgical organizations.

Surgery for Unruptured Aneurysms

Indications for Surgery

Severe Progressive Related Symptoms. The presence of severe progressive symptoms from an aneurysm within the subarachnoid space would be considered by most clinicians to be a good indication for treatment, regardless of the size of the unruptured aneurysm. Piepgras has stated that symptomatic lesion should be subjected to urgent treatment, with the exception of intracavernous ICA aneurysms.

Ninety-two patients whose aneurysms were surgically clipped following SAH were questioned regarding pre-SAH symptoms. Prior to aneurysm rupture, 74% of these patients had experienced headache, eye pain, and neck pain. Less frequent symptoms included visual, motor, and sensory disturbances. Of 40 patients who attained complete relief of their pre-SAH headache and pain, 48% had experienced headache for 1 week to 1 month before the onset of SAH and 23% had experienced headache for several years before SAH occurred.

In another series 111 patients with 132 unruptured aneurysms were studied. The mean age of these patients was 51.2 years. The patients were classified according to the manner in which they presented with their aneurysms, as follows: acute presentation in 17%, chronic presentation in 32%, and asymptomatic presentation in 51%. The sizes of unruptured aneurysms in these three groups averaged 2.1, 2.2, and 1.1 cm, respectively. The patients who presented with the acutely symptomatic aneurysms suffered from ischemia in 37%, headache in 37%, seizures in 18%, and cranial neuropathy in 12% of cases. In patients presenting with chronic signs or symptoms, these included headache in 51%, decreased visual acuity in 29%, pyramidal signs in 11%, and facial pain in 9%. Symptomatic unruptured aneurysms tend to be found along the proximal ICA and very rarely at the midline sites (Table 10). Their diameters are never smaller than 3 mm, although the diameters of the majority of symptomatic unruptured

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>No. of UAs</th>
<th>Mean Age in Years (range)</th>
<th>M/F Ratio</th>
<th>No. of SAHs</th>
<th>Follow Up</th>
<th>Annual SAH Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locksley, 1966</td>
<td>34</td>
<td>34</td>
<td>54 (28–75)</td>
<td>10:24</td>
<td>9</td>
<td>47 mos</td>
<td>7</td>
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<tr>
<td>Asari &amp; Ohmoto, 1993</td>
<td>54</td>
<td>72</td>
<td>60.5 (34–74)</td>
<td>20:34</td>
<td>11</td>
<td>43.7 mos</td>
<td>1.9</td>
</tr>
<tr>
<td>Taylor, et al., 1995</td>
<td>primary*</td>
<td>7113</td>
<td>72.7</td>
<td>28.72%</td>
<td>119</td>
<td>2.5 yrs</td>
<td>1.5, 1.7, &amp; 2.0†</td>
</tr>
<tr>
<td></td>
<td>secondary*</td>
<td>11,066</td>
<td>74.7</td>
<td>33.67%</td>
<td>98</td>
<td>2.5 yrs</td>
<td>0.9, 1.0, &amp; 1.3†</td>
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<td>Yasui, et al., 1997</td>
<td>ISUIA, 1998</td>
<td>234</td>
<td>59.6 (24–84)</td>
<td>110:124</td>
<td>34</td>
<td>75.1 mos</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>no prior SAH</td>
<td>727</td>
<td>56 (9–87)</td>
<td>29.71</td>
<td>12</td>
<td>8.3 yrs</td>
<td>0.05†/&lt;1§</td>
</tr>
<tr>
<td></td>
<td>prior SAH</td>
<td>977</td>
<td>49.4 (13–80)</td>
<td>26.74</td>
<td>20</td>
<td>75907</td>
<td>1.9 (1.5–2.4)</td>
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<tr>
<td>Rinkel, et al., 1998</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>75</td>
<td>0.5†/&lt;1§</td>
<td></td>
</tr>
<tr>
<td>Juvela, et al., 2000</td>
<td>142</td>
<td>181</td>
<td>41.9 (14.6–60.7)</td>
<td>66.76</td>
<td>33</td>
<td>0.05†/&lt;1§</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>&lt;1§</td>
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</tr>
</tbody>
</table>

* Primary indicates that unruptured aneurysm was the primary diagnosis; secondary indicates that unruptured aneurysm was the secondary diagnosis. Abbreviation: — = not given.
† Within 1, 2, and 2.5 years after diagnosis, respectively.
‡ For aneurysms 10 mm or smaller.
§ For aneurysms larger than 10 mm.

Summary of studies of the natural history of unruptured aneurysms
Unruptured aneurysms

Aneurysms are 3 to 10 mm. This is especially evident for unruptured PCoA aneurysms.

Increase in Aneurysm Size. A documented increase in aneurysm size would tilt the scales in favor of active treatment, other factors being equal, but some unruptured aneurysms have ruptured without an increase in size.

Of 111 unruptured aneurysms followed for almost 19 years, most were multiple (only four were incidental and four were symptomatic). Subsequent rupture of these aneurysms was associated very significantly (p < 0.001) with lesion growth during the follow-up period. The average annual aneurysm rupture rate was 1.6% for 87 patients. Lesions that ruptured had grown significantly more than the largest aneurysms harbored in patients who had not experienced lesion rupture (mean growth 6.3 mm compared with 0.8 mm; mean growth/year 0.95 mm compared with 0.04 mm/year; and % growth/year 38.3% compared with 0.9%/year). The mean diameter of intact aneurysms at the time of rupture was 11.2 mm compared with 6 mm for the remaining lesions. The mean diameter of fatal ruptured aneurysms was 13.2 mm compared with 10 mm for nonfatal ruptured lesions, a finding that may be significant.

Midline Site. Several lines of evidence suggest that ACoA, PerA, and, possibly, BA aneurysms should be treated while they are smaller than laterally situated lesions. In 88% of 90 cases in which there were multiple aneurysms, the one with the greatest maximum external diameter ruptured. Of 36 cases in which two or more aneurysms were located on the same side or on the same artery or its branch, the proximal lesion ruptured in 70%. The increased tendency of ACoA aneurysms to rupture was found in the fact that, of the 11 cases in which the distal aneurysm ruptured, seven cases were a combination of ruptured ACoA and unruptured ICA lesions.

Anticipated Mortality and Morbidity Rates From Aneurysm Rupture. The mortality rate from rupture of previously unruptured aneurysms seems inordinately high and ranges upward to 80% or greater. Of 49 patients with intact aneurysms, 16% experienced rupture a mean of 4.3 years after diagnosis and 88% of these patients died. In 1998 ISUIA of 1449 patients with intact aneurysms, there were 32 lesions that subsequently ruptured. The mortality rate was 83% in the group of patients who had not experienced previous SAH from different aneurysms, and the rate was 55% in those who had such a history. The mortality rate for patients with the 27 ruptures of previously intact aneurysms in the 1993 series conducted by Juvela, et al., was 52%; this rate was unchanged in the authors’ 2000 follow-up report.

Mortality Rate of Surgery

Unruptured Aneurysms. In a review, Mount and Brisman documented 60 patients with 138 aneurysms that were treated intracranially during 100 operations. Only 2% of the patients experienced poor results and 2% died. In 40 cases in which elective craniotomy was performed for unruptured aneurysms, good results were obtained in 97% and poor results in 3%; no death was reported. Mount and Brisman contrasted these results with those of 158 cases of aneurysms in three different multiple aneurysm series with follow-up periods ranging from 0.1 to 11 years and in which SAH had occurred in 10% and death in 4% of cases. In an early report of surgical results in 49 patients with unruptured aneurysms treated over a 57-month period before 1977, there was no incidence of surgery-related mortality, although there was a 6.3% rate of permanent morbidity and a 14.3% rate of transient morbidity. Ninety-four percent of the aneurysms were 10 mm or smaller. Fifty-five percent of the patients initially underwent angiography for cerebral ischemic episodes and 10% for headaches. The average age of these patients was 57 years.

An analysis of unruptured aneurysms treated at 12 hospitals was published in 1983. This was a retrospective analysis that involved the study of 107 incidental lesions (7%) from the total aneurysm material. These aneurysms were all smaller than 2.5 cm and excluded those associated with intracerebral hematoma, AVM, or tumor. The surgical morbidity rate was 7% and the transient morbidity rate was 8%. Morbidity was related to the size of the aneurysms: smaller than 5 mm, 2%; 6 to 15 mm, 7%; and 16 to 24 mm, 14%. Morbidity rates also varied by site: ACoA, 16%; ICA and OphA; 12%; PCoA, 5%, and MCA, 8%. No relationship was evident between the number of operations performed on aneurysms and the outcomes, but the average number of cases in which surgery was performed on asymptomatic unruptured aneurysms was only one or two cases per year. The morbidity rates were highest in patients with symptoms of ischemia (11%) compared with those patients presenting with headache (6%) or SAH from a different aneurysm (2%). At that point the authors considered that 260 incidental aneurysms had been surgically treated without any mortality. They attributed 43% of serious morbidity to technical errors in MCA aneurysm surgery. In a 6-year review of surgery on 114 unruptured aneurysms in 99 patients, there was no diameter injury noted and only one death, which was due to a massive pulmonary embolism.

A Medline search of publications from 1966 to 1992 revealed 28 articles containing data on 733 patients with unruptured aneurysms. In these patients the mean age was 49 years and the male/female ratio was 1:1.22. The morbidity rate was 4.1% (95% CI 2.8–5.8%) and there were seven deaths, which provides a mortality rate of 1% (95% CI 0.42%). There was insufficient statistical power to detect differences in morbidity or mortality rates by using factors such as year of publication; patient sex or age; or aneurysm size, location, or category (incidental, multiple, or unclassifiable).

In 1994 Solomon and associates reported on 202 consecutive operations undertaken for attempted clipping of unruptured aneurysms. Excellent or good outcomes were achieved in 100% of patients with aneurysms smaller than 10 mm, 95% of those with lesions 11 to 25 mm, and 79% of those with aneurysms larger than 25 mm. Size was the key predictor of surgery-related morbidity. The sites of these unruptured aneurysms included the following: ICA in 50%, MCA in 19%, AICA in 14%, BA in 14%, and vertebral artery and other sites in 4% of cases. Eighteen percent of patients had presented with headache. Twenty-seven percent had experienced SAH from a different aneurysm, and only 17% of the lesions were considered to be incidental. Fifty-six percent were symptomatic or associated with other lesions. Eighty-five percent of the 202
unruptured aneurysms were treated by neck clipping. Minor complications occurred in 5% and major complications in 7%. The postoperative mortality rate was 3.5% for these 202 operations. Of the 34 patients with truly incidental aneurysms, the mortality rate was 2.9%. Of 1314 consecutive patients with aneurysms from a population of 870,000 in Finland, 43% had MCA lesions. Multiple intracranial aneurysms were present in 39% of these patients. Three quarters of the patients with multiple intracranial aneurysms had at least one MCA lesion. Giant aneurysms were significantly more frequently found to be single MCA lesions than any other single aneurysm. The highest frequency of SAH (42%) occurred in patients with MCA aneurysms. There were no deaths in 33 patients with unruptured aneurysms. In those patients with ruptured aneurysms, the death rate increased from 4 to 46% in a graded fashion between Hunt and Hess. Grades I and II.

Eighty-three aneurysms were treated with 65 operations performed in 62 patients. Locations of these unruptured aneurysms included the MCA in 35%, ICA (PCoA) in 22%, OphA in 12%, ICA bifurcation in 11%, ACoA in 11%, and VBA in 5% of cases. Eight percent of these unruptured aneurysms were definitely symptomatic, 58% were definitely asymptomatic, and 34% were indeterminate. Postoperative complications (1.5% of patients were severely disabled and 3% died) were related to surgical technique or atherosclerosis. Patients with symptomatic cerebral aneurysms were treated at four tertiary care surgical services during a 19-month period. Twenty-five percent of these 217 patients were initially given misdiagnoses. Of those patients with ruptured aneurysms who were in good clinical condition, a good or excellent outcome was achieved in 91% of those given correct initial diagnoses, but in only 53% of those who were initially given misdiagnoses, thus leading to rebleeding or preventable deterioration. During 1994, 80 patients underwent aneurysm surgery at one institution in Sendai. Forty percent of these persons underwent surgery for unruptured aneurysms that were larger than 5 mm. Outcomes were good in all 32 cases. In Matsumoto, Japan, during the 5-year period leading up to 1994, 1558 patients with aneurysms were treated by direct operation. Patients harboring unruptured aneurysms comprised 20% of this series. Of those patients with unruptured aneurysms, 95% had a favorable outcome. The only patient who died harbored a giant VA aneurysm, giving the group a mortality rate of 0.3%. Eighty-two percent of the unruptured aneurysms were single and 18% were multiple. Forty-two percent of the patients presented with headache and 13% with mass effect. Strokelike attacks or TIAs were present in 11% of 253 patients harboring single unruptured lesions. Excellent results were obtained in 88% of these patients and there was no death. The size distribution of unruptured aneurysms in 310 patients was the following: smaller than 6 mm in 46%, 6 to 15 mm in 41%, 16 to 25 mm in 8%, and larger than 25 mm in 5% of cases. The only death occurred in a patient with a giant aneurysm. Excellent outcome was less common in patients harboring unruptured aneurysms of the posterior circulation (72%) than in those with lesions of the anterior circulation (88%).

In the most exhaustive metaanalysis, Raaymakers and colleagues reported that the postoperative mortality rate for intracranial operations in 2460 patients with unruptured aneurysms was 2.6% (95% CI 2.2–2.3%). In 62% of studies they reviewed, a zero mortality rate had been reported (range 0–29%). The mortality rate tended to decrease in more recent years of publication and in accordance with a higher proportion of aneurysms located in the anterior circulation. The increased rate associated with giant aneurysms did not change in more recent years.

Between 1990 and 1995, a state-wide database was established in California. Surgical clipping of unruptured aneurysms was performed in 1321 patients at 453 hospitals. The patient population was divided into quartiles. Adverse events included in-hospital death or discharge to a nursing home or rehabilitation hospital. Adverse outcomes occurred more frequently in patients at low-volume hospitals (first quartile compared with fourth quartile, 40% and 23%, respectively; p < 0.0001, chi-square test). In-hospital death was 2.5 times more likely to occur in patients at low-volume hospitals (5.6% compared with 2.3% at higher volume hospitals, p = 0.03). The mean length of stay was also longer at low-volume hospitals. Hospitals in which large numbers of patients with cerebral aneurysms are treated are associated with better outcomes in patients with ruptured aneurysms. One thousand six hundred forty-four patients were treated for unruptured aneurysms. Death in the hospital or discharge to a rehabilitation hospital occurred in 31% of patients treated surgically and in 18% of patients treated with endovascular therapy. The differences persisted after adjustment for age, sex, race, source of admission, and year of treatment. In-hospital deaths occurred in 4% of surgical cases and 2% of endovascular cases (p = 0.06); the difference was not significant after adjustment in multivariate models. Total length of stay and hospital charges were greater in surgically treated cases (both p < 0.0001).

Between 1971 and 1988, Rice and colleagues treated 167 patients with 179 unruptured aneurysms located in the posterior circulation; of these lesions 84% were located at the BA bifurcation. The size distribution of these aneurysms was smaller than 12 mm in 72% and 12 to 25 mm in 28% of cases. Giant aneurysms and some tiny ones were not included in this review. Sixty-eight percent of the aneurysms were part of a multiple constellation. The aneurysms were asymptomatic in 89% of patients. Eleven percent of patients presented with mass effects or embozilization. The combined surgery-related morbidity and mortality rate was 2.4%, compared with an overall management mortality and morbidity rate of 4.2%. Most patients displayed some degree of oculomotor dysfunction, which returned to normal within 3 months. Only one individual in this series of 179 patients died, and major incidences of morbidity occurred in six patients (5.4%).

Ruptured Aneurysms. To place the results of surgery performed on unruptured aneurysms in perspective, they should be compared with those following surgery on ruptured aneurysms.

In a survey of 133 neurosurgical clinics in Japan, which was conducted between 1974 and 1975, 4750 aneurysm cases were collected. The surgical mortality rate was 51% for cases treated with surgery within 24 hours, and
Unruptured aneurysms

this rate fell to 30% for those cases treated within the 2nd week. Definitive aneurysm treatment was performed in 78% of cases.

In a prospective study of 81% of Sweden’s 8.59 million people conducted between 1989 and 1990, 145 patients with Hunt and Hess neurological Grades I through III underwent surgery for supratentorial aneurysms in the 72 hours following SAH. Fifty-eight percent of these patients had a good recovery. The morbidity rate was 12% and the mortality rate was 7%. Unfavorable outcome was most frequently the result of surgical complications, which occurred in 8% of the total. In Sweden between 1989 and 1993, a total of 275 patients with uneruptured SAH were admitted to the hospital. Seventy-one percent were admitted within 24 hours, and these patients had a mean age of 54.3 years. The male/female ratio was 1:1.18. At the 3-month follow-up review, good recovery was observed in 59% of patients, morbidity in 20%, and death in 21%. Of 51 Grade V patients, only two made a good recovery. Poor outcome was related to the patient’s initial poor neurological condition, the amount of extravasated blood, and a posterior circulation location of the aneurysm.

Of 1314 patients with cerebral aneurysms treated in Eastern Finland between 1977 and 1992, 14% harbored PCoA aneurysms. Complete recovery occurred in 89% of patients who underwent surgery within 3 days of symptom onset, 67% of those treated within 4 to 6 days, and 31% of those treated later. When the operation was performed more than 4 weeks after onset of oculomotor palsy, only 17% of the patients recovered completely. Between 1994 and 1995, 95 patients with ruptured aneurysms were admitted to a hospital in Canada. Ninety-three percent were admitted within 24 hours of rupture. Fifteen percent of patients were in such poor condition that they were not considered for surgery. As of the 1-year follow-up review, 29% of the patients had died, 7% had severe disabilities, 51% had made a good recovery, and 64% had returned to their previous work status.

In the tilizad-treated patients who underwent surgery in the 1990s, severe disability occurred in 11%, vegetative state in 2%, and death in 18% (Upjohn Co., personal communication, 1999).

Morbidity Rate of Surgery

Unruptured Aneurysms. Of nine patients with asymptomatic intact lesions not associated with ruptured ones, three had giant aneurysms. Two patients harbored bilateral lesions of the MCA and five had solitary lesions along this artery. All aneurysms were clipped. There was no incidence of mortality or significant morbidity.

In another study 83 patients were examined using a battery of cognitive tests 1 year after aneurysm rupture. Twenty-five percent of patients had failed to return to work, 25% reported impaired social relations, and 56% suffered from subjective or clinical mental impairment. One third were disabled according to criteria established in the Glasgow Outcome Scale. Cognitive deficits and poor outcomes were associated with diffuse brain damage.

Of 72 patients who underwent surgery for unruptured aneurysms, 25% experienced neurological deficits postoperatively. In 17 of these 18 patients, the deficits disappeared within 2 weeks postoperatively. One of 72 patients exhibited a permanent postoperative speech disturbance. Patients with postoperative neurological deficits had a lower mean cerebral blood flow (36.2 ml/100 g/min) compared with that in patients in whom such deficits did not develop (46.2 ml/100 g/min, p < 0.001). Of 82 patients who underwent surgery for aneurysms, 44 were treated for unruptured lesions and the major surgery-related morbidity rate in this group was 2%; in another series unruptured aneurysms were treated surgically, and the morbidity rate was 13.1%. Some of these deficits resolved and the final morbidity rate was 5.9%. Morbidity was associated with the presence of comorbid conditions, increasing aneurysm size, location of the aneurysm in the posterior circulation, and multiplicity of lesions.

Neuropsychological evaluation was performed in 20 patients with unruptured aneurysms and 27 patients with ruptured ones 3 months after surgery. Twelve patients with unruptured aneurysms underwent both pre- and postoperative evaluation. In the patients harboring unruptured lesions, there were significant differences between pre- and postoperative performances on only a few tests of verbal recall and frontal lobe function. Performances of patients harboring ruptured aneurysms were significantly poorer than those of patients with unruptured aneurysms, although significant impairments were seen in only a minority of patients in the ruptured aneurysm group. Some postoperative deficits were considered to reflect premorbid deficits.

Permanent postoperative deficits occurred in 248 (10.9%) of 2270 patients with unruptured aneurysms (95% CI 9.6–12.2%). Approximately half of the patients with postoperative deficits had become dependent on others. In seven studies offering the best data, as judged by the reviewers, postoperative sequelae occurred in 12.7% (95% CI 10.1–15.3%). The mean follow up covered the period leading to discharge in five of these studies and 24 postoperative weeks in the other two studies. Assessment of neuropsychological function or quality of life was not performed in any of these studies. The greater incidences of morbidity and mortality found in the meta-analysis conducted by Raaymakers, et al., compared with those documented in the study performed by King, et al., was attributed to the exclusion by King and colleagues of symptomatic lesions, a higher proportion of smaller aneurysms located in the anterior circulation than that contained in the study by Raaymakers and colleagues, and a less complete study retrieval (one third the number of patients).

In the ISUIA the patient population used to calculate risks of surgery consisted of 1172 patients, of whom only 211 had a history of SAH from a previously treated aneurysm. Intracranial surgery was performed in 83% of patients in the non-SAH group and in 94% of the previous SAH group. Remaining patients were treated by endovascular procedures. Many patients in the prospective cohort might be considered to have symptomatic and not truly incidental unruptured aneurysms. For instance, 34% suffered from headache, 14% from cranial nerve deficits, 11% from coexisting ischemic cerebrovascular disease, 6% from aneurysm-induced mass effects, 5% from epilep-
sy, 0.4% from subdural hemorrhage or intracerebral hematoma, 0.4% from brain tumor, and 0.3% from neurological degenerative disease. One year after surgery, 30 patients in the group with no previous SAH had died of surgery-related complications, compared with only two patients in the group with a history of SAH and successful treatment. Why did patients with no previous SAH fare so much worse? Partial explanations may be obtained from the following factors: they were older (53 years as opposed to 47.2 years), their aneurysms were much larger (> 10 mm in 51% compared with 26.9% of cases), and they had more lesions in difficult midline and posterior circulation locations (26.4% compared with 17.6% of cases). The report of the ISUIA did not contain information on the distribution of comorbid conditions between the two groups in the prospective cohort. The high morbidity rates in the ISUIA are explicable on the basis of rigorous tests of qualitative status, which previously were not generally applied during follow-up assessment of patients post-SAH and posttreatment. In addition, it is unclear whether a cohort with similar comorbid conditions might not also contain some cases in which deterioration in the Rankin Scale score would be observed after a year of follow-up, even without surgery.

In the ISUIA,127 patient age was the only independent indicator of poor surgical outcome in a prospectively studied group of 995 surgically treated patients. The combined rate of morbidity and mortality at 1 year for patients younger than 45 years was 6.5%, for those 45 to 64 years 14.4%, and for those older than 64 years, it was 32% (p < 0.001).

Unruptured aneurysms with atherosclerotic or calcified walls were considered to pose significant risks for ischemic complications. Among six patients with such lesions, there was a 50% rate of ischemic complication following direct aneurysm clipping.133 Ischemic cerebral vascular disease has an adverse effect on the results of surgery for unruptured aneurysms. In one series of eight patients with mild or no clinical symptoms and in whom small, low-density areas appeared on CT scans, postoperative complications occurred in two patients, although there was no incidence of death.2 Both patients had undergone surgery on the side ipsilateral to the ischemic lesion shortly after onset of ischemic symptoms. Great care is required during clip application because the partly thrombosed aneurysms may become the source of emboli, which lead to ischemic lesions.

Outcomes following surgical clipping of 604 unruptured aneurysms in 493 patients were studied prospectively between 1992 and 1999.13 Six months or longer postoperatively, the outcomes were analyzed. The mean patient age was 53 years, and the mean lesion size was 8.8 mm. Sites of aneurysms included the following: ICA in 43%, MCA in 28%, ACoA and ACA in 17%, and VBA in 11%. Factors independently associated with a high risk of poor outcome or death were as follows: aneurysm size (β = 0.122, p = 0.001), patient age (β = 0.0308, p = 0.05), and lesion location along the VBA (β = 1.37, p = 0.008). The risk of treatment for younger individuals with aneurysms 10 mm or smaller was 1 to 2%, whereas individuals older than 70 years of age who harbored lesions larger than 10 mm faced a 5% risk of poor outcome if the aneurysm was in the anterior circulation and a 15% risk if the aneurysm was in the posterior circulation.19

Over a 10-year period, 126 patients with multiple aneurysms were retrospectively reviewed.65 Both ruptured and multiple unruptured lesions were treated in 71% of cases, and only the ruptured ones were clipped in 29% of cases. Thirteen small unruptured aneurysms were discovered during surgery. The surgical outcome of patients with multiple lesions was comparable to that of 128 patients with single ruptured aneurysms who underwent surgery during the same period at the same hospital.

Ruptured Aneurysms. The extent of morbidity resulting from an operation to secure a ruptured aneurysm is very difficult to separate from the extent of morbidity due to the actual rupture itself.

Postoperative Initial Bleeding

An operation performed to clip an unruptured aneurysm may not be technically perfect; a portion of the weakened lesion wall may be unprotected or become injured during surgery and, thus, rupture may occur for the first time following the operation. This is rare and probably will become less likely with widespread use of intraoperative angiography.

One hundred thirty-nine patients surgically treated by clipping of ruptured or unruptured aneurysms of the posterior circulation underwent postoperative angiography.148 Complete aneurysm obliteration was observed in 81% of these patients and minor residual necks (1–2 mm) in 20%. On angiograms, two aneurysms displayed significant filling; one lesion progressed to complete thrombosis and the other to fatal rupture. Another BA aneurysm ruptured 3 years after direct treatment, despite the fact that only minor residual filling of the neck was observed on postoperative angiograms.148

In Iceland in the decade before 1968, there were 86 patients who experienced their first SAH from aneurysms.134 Forty-seven percent of these patients died of the initial rupture within 2 months. In patients who underwent surgery and survived, recurrent SAH occurred in 5% of those who were followed for a minimum of 24 years. In patients who survived in normal or near-normal condition until 6 months after SAH, the survival rate was similar to that of the general population.134

One hundred two patients with 160 surgically treated aneurysms underwent late angiographic follow-up at a mean of 4.4 years postsurgery (range 2.6–2.7 years).30 Of 135 clipped aneurysms that initially had displayed no residual lesion, 1.5% later exhibited recurrence. Of 12 aneurysms with known residua, 25% had enlarged during the follow-up period. Among the 102 patients, one hemorrhage developed, thus revealing a risk of SAH of 1.9% per year. In a subgroup of patients with known broad-based residua, significant regrowth appeared in three of four cases. Eight new lesions were found in six patients, for an annual risk of new aneurysm development of 1.8% per year. The presence of multiple aneurysms predisposed toward new lesion formation.

In the series of 202 operations for unruptured aneurysms conducted by Solomon and associates,79 there was no documented postoperative incidence of SAH during a mean follow-up period of 33 months (range 3–78 months). One hundred fifteen patients with unruptured aneurysms were surgically treated and their cases were fol-
Endovascular Treatment

Unruptured Aneurysms: Morbidity and Mortality Rates Associated With Clipping and Coil Embolization

The mortality rates for endovascular coil embolization have been decreasing over the past decade as technological improvements have occurred. A systematic review of coil embolization for aneurysms revealed 48 studies totaling 1383 patients.13 Permanent complications of embolization occurred in 3.7% (95% CI 2.7–4.9%). Complete aneurysm occlusion occurred in only 54% (95% CI 50–57%). The results in subgroups of ruptured, unruptured, and BA bifurcation aneurysms were essentially the same as the overall results, which would not be the case with clipping.13

A cohort study of patients with unruptured aneurysms treated at 60 university hospitals between 1994 and 1997 was performed.78 Treatment consisted of surgery in 2357 cases and endovascular coil placement in 255 cases. Inhospital deaths and discharges to nursing homes or rehabilitation hospitals (that is, adverse outcomes) occurred in 18.5% of surgically treated cases and in 10.6% of endovascularly treated cases (p = 0.002). The in-hospital mortality rate was higher in surgically treated cases (2.3% compared with 0.4% in endovascularly treated cases, p = 0.039), but the difference was not significant in the multivariable model.78

An aneurysm that demonstrated complete vascular occlusion 6 months postembolization subsequently ruptured 18 months posttreatment.34 One hundred twenty incidental aneurysms in 115 patients were subjected to embolization with Guglielmi detachable coils.158 Complete or near-complete occlusion occurred in 91% of aneurysms and incomplete occlusion in 4%; 5% of patients could not be treated with coil placement at all. Patients remained neurologically intact or unchanged from their initial clinical status in 95% of cases, and deterioration from procedural complications occurred in 4.3%. All these complications occurred in the first 50 patients and none in the subsequent 65. One partially embolized aneurysm ruptured 3 years after coil embolization. The morbidity rate was 0% in the last 65 patients who underwent embolization of their aneurysms.126

Four hundred thirty-five patients were treated for unruptured aneurysms at the University of California at San Francisco.77 Of these, 216 were retrospectively judged, in a blinded fashion, to have been eligible for either surgical or endovascular therapy. One hundred eighteen were treated surgically and 98 by endovascular means. In the surgically treated group, 51% of aneurysms were incidental and 39% produced compressive symptoms. The primary outcome score was a new moderate disability or worse (a decrease of two or more points in the Rankin Scale score occurring between hospital admission and discharge). Twenty-five percent of the surgically treated group displayed this degree of deterioration by the time of hospital discharge, whereas only 8% of the endovascularly treated group did so. Length of stay for surgically treated patients was 7.7 days compared with 5 days for endovascularly treated patients, and hospital charges were greater for the former group. At an average of 3.9 years posttreatment, 34% of surgically treated patients displayed persistent or new symptoms compared with 8% of endovascularly treated patients. The risk of poor outcome from surgical treatment of an aneurysm located in the posterior circulation was 24 times greater than that from coil embolization. In the anterior circulation the risk was still 6.4% in favor of coil embolization.77

Two thousand sixty-nine patients were treated for unruptured aneurysms in California between 1990 and 1998.81 Adverse results occurred in 25% of surgically treated patients and in 10% of endovascularly treated patients. An adverse outcome was defined as an in-hospital death or discharge to a nursing home or rehabilitation hospital at any point throughout the treatment course. The OR for an adverse outcome was 3.1 times greater for surgery than for endovascular treatment. During the time course of the study (1991–1998), adverse outcomes declined for patients who underwent endovascular treatment but not for those who underwent surgery. Deaths occurred in 3.5% of surgically treated and 0.5% of endovascularly treated cases. Institutional treatment volume was associated with outcome. The OR of in-hospital death was 6.3 times greater for patients who underwent surgery than for those who underwent endovascular treatment. The mean sizes of the aneurysms in patients treated using these different methods was not provided in this study report. Sixteen percent of surgically treated patients were admitted to treating hospitals through the emergency department, compared with only 1% of those treated endovascularly. This suggested that the two groups might not be entirely comparable. The only SAH identified following treatment occurred in patients whose lesions had been surgically clipped. The small sample size did not permit a statistical conclusion regarding the lesser durability of treatment by surgery.

The difficulties of evaluating coil embolism technology stem from the fact that the procedure is constantly being refined and additional experience is being gained. Intent-to-treat failures occurred frequently during the early experience of surgeons. Patients selected for coil embolization had an excess of difficult locations for surgical approaches and, in some series, were in poorer clinical condition than those undergoing surgery. It seems possible that coil embolization will be refined and/or replaced by new technologies such as biologically active coils and programmable stents.112 In a recent review, the authors concluded that elective clipping of asymptomatic unruptured aneurysms is associated with a morbidity rate of 10.9% and a mortality rate of 3.8%. Coil embolization treatment, for which there is less long-term follow-up data, has been found to be associated with a 4% morbidity rate and a 1% mortal-
ty rate; however, aneurysm occlusion has only been achieved in 52 to 78% of cases.198

Aneurysm Recurrence After Coil Embolization

A case has been documented in which rupture of an aneurysm occurred 18 months after endovascular occlusion.8 The aneurysm was initially identified when the patient experienced a seizure. Angiograms obtained at 6 months revealed a totally occluded lesion. This case raises serious doubt regarding the durability of coil embolization. In a consecutive series of 100 patients who underwent coil embolization of 104 aneurysms, clinical outcomes were judged at an average of 3.5 years (range 2–6 years).101 Only nine patients were treated during the acute phase of SAH, and seven of them died of the initial hemorrhage. Twenty patients underwent subsequent procedures that did not include the placement of coils. Six patients died of unrelated causes before reaching the 2-year survival point. At midterm, post–coil embolization hemorrhage rates were 0% for small aneurysms, 4% for large ones, and 33% for giant lesions.101

Two hundred patients underwent coil placement for 206 unruptured aneurysms between 1990 and 2000.210 Aneurysms located in the posterior circulation constituted 33% of the treated group. Thirty-eight percent of aneurysms were smaller than 1 cm, 46% were 1 to 25 mm, and 16% were giant. Ninety to 99% occlusion was achieved in 65% of cases and total occlusion in 7%. New neurological deficits developed in 8%. Two patients (1%) subsequently experienced fatal SAH of the treated aneurysm.210 Of 455 aneurysms treated using Guglielmi detachable coils before 1998, 39% were found to have residual necks post-embolization.52 Long-term angiographic follow up was obtained in 71 patients with 73 aneurysms. The mean duration of follow up was 17.3 months. Recanalization occurred in 17% of patients with small aneurysms with small necks, 42% percent of patients with small lesions with wide necks, and 87% of patients with large aneurysms. Of the giant aneurysms only 10% remained unchanged and 90% recanalized. Recanalization was twice as likely to occur as progressive thrombosis.

Complications of Angiography

The risks associated with angiography must be considered because this invasive procedure is still an integral component of treatment risks for unruptured aneurysms. The combined risk of permanent and transient neurological complications for patients with aneurysms or AVMs without SAH was only 0.3%.26

Experience and Outcomes

Surgical Experience

Four hundred forty-nine aneurysms were surgically treated in 366 patients by 10 different surgeons at the Cleveland Clinic.25 Twenty-seven percent were asymptomatic and 78% were treated using microsurgical clipping. The modified Rankin Scale score at 6 weeks was significantly worse than that documented at baseline, but there was no significant difference between the baseline and 6-month scores. At that time 94% of patients exhibited no significant worsening in function as a result of treatment. A strong predictor of a better functional outcome was the number of aneurysms treated by a specific surgeon (r = 0.99, p = 0.05). Increasing patient age (r = 0.16, p = 0.003) and increasing aneurysm size (r = 0.15, p = 0.004) were predictors of a worse functional outcome.

Hospital Experience

An inverse relationship between the volume of craniotomies performed for cerebral aneurysm and in-hospital mortality rates was demonstrated by Solomon, et al.79 A retrospective analysis of 47,408 patients receiving Medicare who were treated over an 8-year period was performed.84 The mortality rate was 14.3% for patients with SAH who were 65 years or older and who were treated surgically in hospitals in which an average of five or more craniotomies were performed per year. In hospitals in which fewer craniotomies were performed, the mortality rate was 18.4%, and in hospitals in which the average was less than one such operation per year the rate was 20.5%. The surgery-related mortality rate for patients in teaching hospitals in which the average number of craniotomies was three to five per year was 16.3%, compared with 23.1% for patients in nonteaching hospitals with the same surgical volume.83

In the 2069 patients with unruptured aneurysms treated in California between 1990 and 1998, institutional treatment volume was associated with outcome, but did not account for the better outcome associated with endovascular therapy.51 Adverse outcomes were more likely to occur in hospitals in which endovascular therapy was used less frequently and in hospitals in which a smaller portion of patients were treated using endovascular means. Adverse outcome had an OR of 1.6 (95% CI 1.1–2.1, p = 0.005) when the lowest quartile of case volume was compared with the highest quartile.81

Preventable Factors for Aneurysm Formation and Rupture

Effect of Cigarette Smoking

In a case-controlled study of SAH in 35- to 64-year-old patients, it was found that, after adjusting for age, cigarette smokers carried a significantly increased risk for SAH with RRs of 3 for men and 4.7 for women.4 The strength of the risk increased with the number of cigarettes smoked. Smokers who also suffered from hypertension had an increased risk of SAH of almost 15-fold, compared with those who neither smoked nor had been treated for hypertension. The estimated population-attributable risk was 43% for cigarette smoking compared with only 28% for hypertension in the studied population. In another case controlled study, the RR of SAH for smokers compared with nonsmokers was 2.7 in men and 3 in women.40 A population-based controlled study of smoking and SAH was performed in the state of Washington.108 Compared with patients who never smoked, the OR for current heavy smokers (> 20 cigarettes/day) was 11.1; for current light smokers it was 3.1, and for former smokers it was 1.8. Alcohol use of more than two drinks per day was also associated with an increased OR of 2.3 after adjusting for
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smoking status. These associations were not altered by confining factors such as hypertension. Patients from five prospective studies of aneurysm rupture comprised nearly 3500 cases. In virtually all age and sex subgroups and in all five trials, the reported current smoking rates were 2.5 times higher than that expected based on European and US national surveys of smoking (p < 0.0001). Cigarette smoking is also associated with younger patient age and onset of SAH by 5 to 10 years (p < 0.0001). According to findings of the long-term study in Finland, active smoking status at the time of diagnosis was a significant risk factor for subsequent aneurysm rupture (RR 1.46, 95% CI 1.04–2.06, p = 0.033). Active smoking status as a time-dependent covariant was the most important risk factor for aneurysm rupture (adjusted RR 3.04, 95% CI 1.21–7.66, p = 0.02). It is clear that patients who harbor unruptured aneurysms and are not given definitive treatment should at least be given advice that smoking cessation would still be worthwhile.

Effect of Hypertension

Hypertension is approximately twice as common in patients with aneurysms than in others and, thus, is likely to be involved in the growth and rupture of aneurysms. In a recent review of 24 clinical and/or autopsy studies, the mean incidence of preexisting hypertension was 43.5% in patients with aneurysms, compared with 24.4% in the healthy population. In the USA Medicare Study, in 20,767 total cases of unruptured lesions with a primary diagnosis of aneurysm, 42% of the patients were hypertensive; in those with a secondary diagnosis of aneurysm, 46% of patients were hypertensive. It therefore seems prudent to treat hypertension in patients with unsecured unruptured aneurysms.

Economic Aspects

The various studies of the economic consequences of treatment and nontreatment of unruptured aneurysms generally are limited by the degree of reality of the numerous assumptions that must be made. Van Crével and colleagues used a decision analysis to recommend management of incidental unruptured aneurysms. They calculated a break-even point for the age break between the selection of conservative management and surgery. For an otherwise healthy 45-year-old woman, surgery was the option with the greatest expected utility. A decision–analysis approach was used by ter Berg and colleagues to study the treatment of intact familial intracranial aneurysms. Discounted quality-adjusted life years were used as the outcome measure. Probability estimates were extracted from the literature when available. These authors called for further study of the probability of lesion rupture, the probability of the development of other lesions, and the results of operations on intact intracranial aneurysms to refine their analysis. Eskesen and colleagues used a theoretical evaluation of lifetime probabilities of different outcomes in patients with unruptured aneurysms by using a life table method. In a patient with an unruptured aneurysm, various possibilities are present during any single follow-up period. The patient may be alive without having suffered an SAH, may have suffered an SAH resulting in either death or survival, or may have died due to unrelated causes. Factors of importance in deciding on treatment for the unruptured aneurysm were considered to be bleeding rates, morbidity and mortality rates from SAH, the size and location of the aneurysm, treatment-associated morbidity and mortality rates, and individual patient attitude and life expectancy. For patients older than 50 years of age, the 20-year life expectancy is reduced as much as 34%, assuming an annual rate of rupture of 2% per year for unruptured aneurysms. Assuming an annual risk of aneurysm rupture of 2%, the probability of survival after diagnosis without bleeding is reduced below the expected probability of survival by 19%, 34%, 46%, 56%, 64%, and 72%, respectively, at 10, 20, 30, 40, 50, and 60 years of age.

Wiebers and colleagues estimated that lifetime cost (including hospitalization, surgery, morbidity, and mortality) for patients hospitalized each year with unruptured aneurysms in the US is $522,500,000, compared with $1,755,600,000 for patients with aneurysmal SAH. Health outcomes of a hypothetical cohort of 50-year-old women were modeled over the projected lifetime of the cohort and costs were assessed. For patients harboring unruptured aneurysms smaller than 10 mm with no history of SAH from a different aneurysm, both clipping and coil embolization resulted in a net loss of quality-of-life years and the CIs were not compatible with benefits from treatment. For patients harboring aneurysms 10 mm or larger, in whom the lesion was symptomatic or in whom there was a history of SAH from a different aneurysm, treatment was cost effective. Five mathematical modeling techniques were used by King and colleagues to assess the cost effectiveness of elective surgery for the treatment of asymptomatic unruptured aneurysms. Using baseline model assumptions for a 50-year-old patient, elective aneurysm surgery was considered to provide an average of 0.88 additional quality-adjusted life years compared with nonsurgical treatment. The incremental cost effectiveness of elective aneurysm surgery was calculated to be $24,200 per quality-adjusted life year. Surgery for asymptomatic unruptured aneurysms was considered to be cost effective provided that the mortality and morbidity rates were at assumed levels, patients had a life expectancy of at least 13 additional years, and patients experienced a decrease in quality of life from knowing that they harbored unruptured lesions.

A decision analysis for asymptomatic aneurysms was developed by Leblanc and Worsley. Assuming a 2% annual rate of rupture, a 73% risk of death or disability associated with rupture, and a 6.5% risk associated with elective surgery, these authors calculated a gain of at least 1 year of survival free from neurological sequelae for patients whose life expectancy was 19.5 years (corresponding to age 63.5 years for male patients and 68 years for female patients). Theoretical survival curves were obtained by solving differential equations based on the survival rate for patients treated either surgically or conservatively. Life expectancies were calculated as areas under the curve. Greater surgical benefit was demonstrated in younger patients. Using certain generally accepted assumptions, it was calculated that the gain in average life expectancy provided by surgery was 3.9 years in a 40-year-old patient, 2.4 years for a 50-year-old patient, 1.3 years for a 60-year-old patient, and 0.6 years for a 70-year-old patient.
A cost-effectiveness analysis for screening, which they believed would be effective, assuming an aneurysm rupture rate of 1 to 2% per year. Combined incremental cost and effectiveness data revealed a cost per quality-adjusted life year of $7760, for an annual rate of 0.02 for SAH resulting from unruptured aneurysms. This cost would be $39,450 for an aneurysm rupture rate of 0.01. There would be no benefit (negative quality-adjusted life-year benefit) if the rupture rate was only 0.005. An actuarial risk analysis of the treatment of unruptured aneurysms, based on data from the ISUIA, was performed. Based on that data it was concluded that life years would be lost at all ages among those harboring aneurysms smaller than 10 mm and having no history of SAH if they were treated surgically. For those harboring lesions smaller than 10 mm and having a history of SAH (multiple aneurysm cases), approximately 4 years of life would be saved if the patient was 20 years of age, and this declined to 0 life years by the time the patient was approximately 50 years of age. For aneurysms 10 mm or larger, 8 life years would be saved in a patient 20 years of age and 0 life years would be saved in a patient approximately 50 years of age. It is obviously important to know if the ISUIA data apply to the universe of patients with unruptured aneurysms, because this kind of analysis appears to contraindicate surgery on all lesions smaller than 10 mm and in all patients older than 50 years of age.

There has been an interest in screening for lesions, but aneurysm prevalence varies; the rupture rate is low and noninvasive imaging tests are not yet accurate enough to preclude small aneurysms. The morbidity and mortality rates associated with surgical treatment for unruptured aneurysms is relatively high and, thus, the indications for and the cost effectiveness of screening remain unclear. In my opinion, further studies are strongly indicated, particularly if high-risk groups are targeted.

**Methodological Considerations**

Although evidence-based medicine depends on data from randomized therapeutic trials, it is not applicable to conditions that are unsuitable for such trials. Inclusion in a randomized therapeutic trial requires that the condition be common and have clear end points that occur within a relatively short time period. The information obtained from such trials, even when available, might not be useful in individual cases because statistically significant results might require unobtainably large sample sizes. In addition, randomized trials frequently exclude patients on the basis of age, frailty, and pregnancy.

In the 449 patients who were retrospectively studied in the ISUIA, 28 experienced aneurysm rupture within the first 7.5 years of follow-up review. Two other patients experienced SAH, but were excluded because they harbored coexisting AVMs and it could not be proved that the aneurysms were the source of the SAH. Only a single patient in Group 1 (no previous SAH) experienced a confirmed aneurysmal SAH in less than 7.5 years of follow-up. An additional patient in this group subsequently suffered an SAH (D Wiebers, personal communication, 2000). The authors of the ISUIA stated that, although they could not identify systemic bias, it may have been introduced due to the nature of the retrospective cohort. If the findings of this study were generalizable, the goal of reducing the 50% case mortality rate from aneurysm rupture by preemptive treatment of small unruptured lesions might be unattainable.

Members of the Stroke Council have stated that for unruptured aneurysms, there only exists evidence generated from nonrandomized historical cohort comparisons between current patients who receive therapy and former patients who received no therapy, and from series without a control group. This level of evidence supports recommendations at only a Grade C level. A Grade C recommendation may suggest an array of potential clinical actions, all of which might be appropriate. This type of recommendation is supported by evidence of level 4 (nonrandomized historical cohort comparisons between current patients who are receiving therapy and former patients who did not) and level 5 (case series without control subjects). This expert group has asserted that patients with an environmental risk factor such as cigarette smoking and alcohol use have an increased risk of SAH, but that this risk has not been associated with an increased frequency of intracranial aneurysms. The Stroke Council members believe that it is premature to judge the effectiveness or efficacy of endovascular treatment for unruptured aneurysms. A case-controlled randomized prospective trial will be required to compare adequately this procedure with clipping. In my opinion, such a trial is extremely unlikely to be undertaken in the foreseeable future. The Stroke Council members recommend that the treatment of unruptured aneurysms should be influenced by lesion structure, extensive calcification, thrombosis, and, more rarely, encountered clinical features such as previous documentation of the aneurysm and the stability of its size. The council members also suggested that the treatment of small intracavernous aneurysms is not generally indicated. They opined that symptomatic intradural aneurysms of all sizes be considered for treatment, bearing in mind that the increasing size of a lesion is associated with higher surgical risks and demands greater surgical and center expertise. According to members of the Stroke Council, aneurysms with a history of SAH and a BA apex location carry a relatively high risk of rupture, and such aneurysms, if they are to be observed, should be periodically reevaluated using CT or MR angiography or even contrast-enhanced angiography in select cases.

The authors of the longest follow-up study of patients with unruptured aneurysms (mainly multiple intact lesions harbored by patients who previously received treatment for ruptured ones) concluded that intact lesions should be treated surgically regardless of aneurysm size or the patient’s smoking status, especially in young and middle-aged adults, provided that it is technically possible and that there are no concurrent disease contraindications.

Nine longitudinal and 11 case-controlled studies were analyzed in 1995 and 1996. Significant risk factors for SAH included the following: 1) smoking, RR 1.9 (95% CI 1.5–2.3) from longitudinal studies, OR 3.5 (95% CI 2.9–4.3) from case-controlled studies; 2) hypertension, RR 2.8 (95% CI 2.1–3.6), OR 2.9 (95% CI 2.4–3.7); and 3) alcohol ingestion greater than 150 g/week, RR 4.7 (95% CI 2.1–10.5), OR 1.5 (95% CI 1.1–1.9). Use of oral
contraceptives or other hormones, hypercholesterolemia, and physical activity were not related to risk of SAH. This suggests that avoidance of the risk factors would be a sound therapeutic strategy.

The care of patients with unruptured aneurysms has been described as the most vexing scientific question confronting neurosurgeons, neurologists, and interventional neuroradiologists. Settlement of this quandary by reference to a randomized multicenter trial is considered unlikely, because of the unattainable sizes of large study groups (comparison of conservative management, clipping, and coil embolization); impractical, long follow-up requirements, and the continual evolution of treatment modalities. Establishing a registry (epidemiological survey) has been suggested as an alternative. 92

Conclusions

Many factors must be considered in making treatment choices. At present, no definite standard can be advocated for the management of unruptured aneurysms. The young patient with a recent onset of oculomotor palsy from an unruptured PCoA aneurysm of any size, under ordinary circumstances, would be a clear-cut candidate for lesion clipping or coil embolization. An octogenarian with a 3-mm cavernous ICA aneurysm without symptoms should be reassured and left alone. Between such extremes is a gray zone in which both components of medicine—art and science—must be brought to bear.

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