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Physical Factors In The Initiation, Growth And Rupture Of Human Intracranial Saccular Aneurysms

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**PHYSICAL FACTORS IN THE INITIATION,
GROWTH, AND RUPTURE OF HUMAN
INTRACRANIAL SACCCULAR ANEURYSMS**

by

Gary Gilbert Ferguson, B.A., M.D.

Department of Biophysics

**Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy**

**Faculty of Graduate Studies
The University of Western Ontario**

London, Canada

June, 1970

"Life is short, and the Art long;
the occasion fleeting; experience
fallacious, and judgement difficult."

- Hippocrates. Aphorisms (I, 1)

"..... the history of science teems
with instances in which keys, after
being long sought amongst the grander
phenomena, have been found at last
not hidden with care, but scattered
about, almost openly, in the most
commonplace incidents of every-day
life which have excited no curiosity."

- Osborne Reynolds

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Mrs. Barbara Anderson typed the first draft of the manuscript and assisted in proof reading the final draft. Mrs. Patricia Daniels typed the final draft.

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Finally, to my wife, Mary, who creates in our home an environment of warmth, encouragement, and love, and to my children, Stephen, Heather, and Sarah, I dedicate this thesis.

Gary G. Ferguson

Department of Biophysics,
The University of Western Ontario,
June 14, 1970.

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ABSTRACT

A review of the literature indicates that human intracranial saccular aneurysms are acquired secondary to a focal degeneration of the internal elastic membrane at the apex of major intracranial bifurcations. However, there is no agreement on the factors responsible for this degeneration, or the mechanism of the initial aneurysmal outpouching, the subsequent enlargement of the aneurysm, and its rupture.

An investigation using glass model bifurcations demonstrated that the apex of bifurcations are subjected to haemodynamic forces (shear stress, pulsatile impulse, and pulsatile pressure head) which are experienced to a lesser extent, or not at all, by other areas of the vessel wall. These forces are thought to initiate the aneurysmal process. The critical Reynolds number (Re) for turbulence was measured in each model. In comparison to long straight tubes, bifurcations lower the critical Re . This decrease is greatest for wide-angled bifurcations and pulsatile flow. The Re values corresponding to flow rates in the human cerebrovascular system are less than the critical Re . Therefore, it was predicted that turbulence does not occur at human intracranial arterial bifurcations. In contrast, marked

turbulence arose within the sacs of glass model aneurysms at low flow rates ($Re = 400$), indicating that turbulence is likely within human intracranial saccular aneurysms.

Bruits, indicative of turbulent blood flow, were recorded with a phonocatheter from the sacs of 12 out of 19 cases of human intracranial aneurysms studied at the time of craniotomy. The bruits were characterized by a diamond-shaped profile, systolic accentuation, a relatively high-pitched tone (440 Hz), and a musical quality. It was argued that in the seven cases in which no bruit was recorded, flow in the aneurysm was less than the critical Re , because of drug-induced hypotension at the time of surgery. Turbulence produces and accelerates degenerative changes in vascular tissue similar to the changes seen in the walls of aneurysms. These changes weaken the wall and allow the aneurysm to enlarge. In four control cases, no bruits were recorded from major intracranial arterial bifurcations.

Direct measurement of intra-aneurysmal pressure was made in four human cases at surgery. In each case the pressure was pulsatile, and the calculated mean pressure was the same as the mean systemic arterial pressure.

The elasticity of seven human intracranial saccular aneurysms was studied using a volume distensibility apparatus, and compared to that of 16 major intracranial arteries. The aneurysms were very non-distensible in comparison to the arteries, because of an alteration in the

elastance of the elastin fibres in the wall of an aneurysm, which is likely the end-result of turbulence. Calculations based on the data of the elasticity studies show that the wall stress to which the average saccular aneurysm is subjected is 10 times that of an intracranial artery.

The factors which determine whether or not an aneurysm will rupture are related by the law of Laplace. It is shown that an increase in intra-aneurysmal pressure, an increase in the size of an aneurysm, a decrease in the minimum wall thickness, or a decrease in the strength of the structural components of the wall, will increase the probability of rupture. By equating the forces acting on the wall of an aneurysm, it is calculated that the critical diameter for rupture of a human intracranial saccular aneurysm is 8 mm.

I. INTRODUCTION

"Humanity is not liable to a more awful visitation than the sudden and invisible stroke which, annihilating sense and motion, prostrates every faculty of the soul in the dust!"

- Anonymous. Medico-Chirurgical Review 1: 1, 1820.

An intracranial saccular aneurysm* is an abnormal pouchlike evagination in the wall of a major intracranial artery (Figure 1a). In contrast to the fusiform aneurysmal dilatations characteristic of extracranial arteries, which involve the circumference of a longitudinal segment of vessel, intracranial aneurysms are approximately spherical in shape and usually arise at the apex of a bifurcation, or branch point, in a cerebral artery (16, 82) (Figure 1b).

These lesions have been described in the clinical and pathological literature under a variety of names. They are commonly known as "congenital intracranial aneurysms," a term first used by Eppinger in 1887 (55). In 1931, Collier (36) introduced the descriptive term

* Aneurysm is defined by the Oxford International Dictionary as a "morbid dilatation of an artery, due to disease, or to a tumour caused by rupture, of the arterial coats" and is derived from the Greek word, aneurusma, meaning to "widen out."

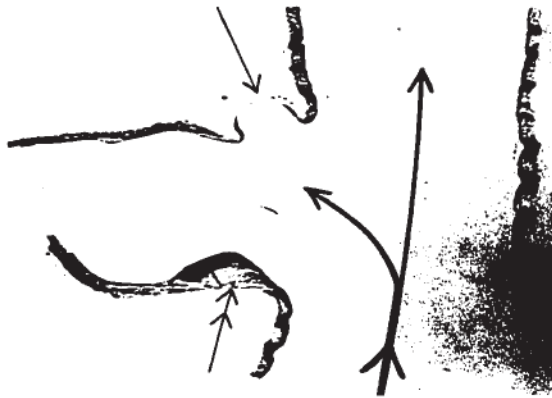
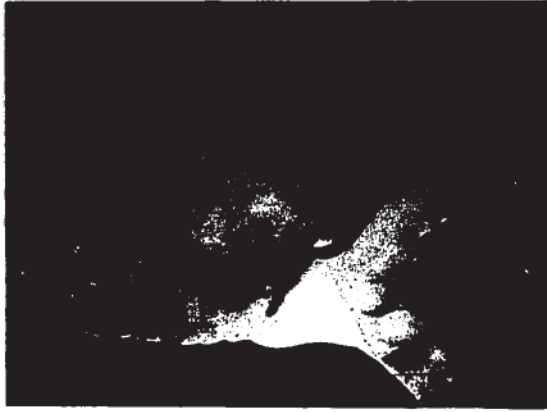
FIGURE 1a

A colour photograph of the gross appearance of a typical human intracranial saccular aneurysm.

From Crawford (38).

FIGURE 1b

A low power photomicrograph of a longitudinal section through the bifurcation of a human cerebral artery with a "minute" intracranial saccular aneurysm at the apex of the bifurcation (→). The intraluminal arrows indicate the direction of blood flow. An intimal cushion (→→) is situated at one lateral angle. From Hassler (82).



"berry aneurysm." Most reports simply refer to these lesions as "intracranial aneurysms" (49, 58, 77) although "saccular" has been added occasionally (16, 131). The expression "intracranial saccular aneurysm" has been chosen because it identifies the subject of this thesis as unique sac-like outpouchings of major intracranial arteries, without implying an aetiological mechanism. It also separates this group from other, less common types of intracranial aneurysms, namely: atherosclerotic (fusiform), septic (mycotic), dissecting, and traumatic aneurysms (16, 151), and the microaneurysms of Charcot-Bouchard (33, 35).

Intracranial saccular aneurysms most often come to clinical attention because of their rupture. Characteristically, this produces bleeding into the subarachnoid space, the fluid-filled space between the arachnoid and pia mater, in which the major intracranial vessels lie. Thus, aneurysms are one cause of subarachnoid haemorrhage, which, in turn, is an important cause of "stroke"*

Early Literature. In contrast to aneurysms elsewhere in the body, knowledge of intracranial saccular aneurysms is recent. Early descriptions of the disease have been reviewed by Bull (21). Although

* "Stroke" means literally, a "sudden disabling attack" and is commonly used with reference to the clinical picture produced by a cerebrovascular accident from any cause.

Morgagni* is given credit by some authors (82, 114) for first describing an intracranial aneurysm, it is doubtful that he personally observed a case (21, 158). Bull (21) gives credit for the first pathological description to Francisci Biumi, a Milanese physician who described, in 1765, a case in which a ruptured intracranial aneurysm had been discovered at autopsy. The first clinical description was by Blackall (15), in 1813, who reported the case of a 20 year old woman. He wrote:

"..... she was attacked suddenly, and without any apparent cause, by a most violent vomiting and diarrhoea, with headache of the most excruciating kind, a sensation as if the scalp were lifted by an internal force, some indistinctness of vision, intolerance of light, etc. She continued many days in the most excessive agony, twenty-four hours before death she fell into an apoplectic stupor."

Autopsy revealed a large basilar bifurcation aneurysm which had ruptured, producing a fatal haemorrhage at the base of the brain.

By the second half of the 19th century detailed clinical descriptions and accurate pre-mortem diagnosis of this entity were becoming common. "Between 1800 and 1880 no fewer than 86 papers were published in which cases of cerebral aneurysm were reported" (158). In 1859, Sir William Gull (73) brought attention, for the first time, to the idea that intracranial saccular aneurysms might be more

* Giovanni Battista Morgagni (1682-1771), Professor of Anatomy at Padua, has been described as the "father of pathology" and is best known for his 3 volume treatise on the cause of disease, "De Sedibus et Causis Morborum."

than medical curiosities. He wrote:

"Aneurism of the cerebral vessels has been regarded as a disease of extreme rarity, and judging by the scanty records of it, we should conclude that the opinion was true. This apparent rarity, however, like all negative conclusions, is doubtful, and I think there is the more reason to suspect it as only apparent and due to careless inquiry since the discovery of these cases has been much more frequent during the last ten years Whenever young persons die with symptoms of ingravescent apoplexy, and after death large effusion of blood is found, especially if the effusion be over the surface of the brain in the meshes of the pia mater, the presence of an aneurism is probable."

In 1872, Bartholow (8) published a remarkably comprehensive review, based on a total of 172 cases collected from the literature, in which he discussed in detail the clinical features of intracranial aneurysms, in an attempt to differentiate them from intracranial neoplasms. In the early part of this century comprehensive clinico-pathological reports appeared; those of Beadles (10) in 1907 and Fearnside (57) in 1916 being most notable. But it was not until 1923, when Sir Charles Symonds (148) published his famous paper, that subarachnoid haemorrhage from ruptured intracranial saccular aneurysm became established as a distinct and important clinical entity. The purpose of his report, which consisted of five cases in which he had made the diagnosis at the bedside, and in three of which confirmation had been obtained at autopsy, was "to draw attention to the possibility of an accurate diagnosis of the condition during life." In spite of this,

Cushing* (42) considered intracranial aneurysms to be of little interest to the neurosurgeon, describing them, with an uncharacteristic lack of foresight as, "... a lesion having such remote surgical bearings ..." important only because of the need to differentiate them clinically from tumours.

Present Clinical Significance. With the introduction of cerebral angiography by Moniz (103) in 1927, a pre-mortem means of confirming a clinical suspicion of ruptured aneurysm became possible for the first time and the modern era of surgical treatment began shortly thereafter. The first planned intracranial operation for a ruptured intracranial saccular aneurysm was undertaken by Professor Norman Dott of Edinburgh in 1931 (48). By 1944, the neurosurgical importance of the disease was such that Dandy (44) published a major treatise on the subject. Since that time, three more major works have appeared: Hamby in 1952 (77); Walton in 1956 (158); and Pool and Potts in 1965 (114). Recently, the results of the Cooperative Study on Intracranial Aneurysms and Subarachnoid Haemorrhage (132), which summarizes the experience over a 7 year period of 19 university centres with 6,368 cases, have been published.

* Harvey Cushing (1869-1939), neurosurgeon, Moseley Professor of Surgery at Harvard University Medical School (1912-1932) was responsible, more than any other individual, for the development of neurosurgery.

Cerebrovascular disease, manifesting itself as "stroke," is the third most common cause of death. The principal causes of "stroke" are cerebral thrombosis (50%), intracerebral haemorrhage (20%), cerebral embolism (15-20%), and subarachnoid haemorrhage (5-10%) (130). The most important cause of subarachnoid haemorrhage is rupture of an intracranial saccular aneurysm, and this entity is now recognized as one of the most frequent causes of death in otherwise healthy young people. Merritt (102) states:

"The seriousness of intracranial aneurysms is indicated by the fact that they are the cause of death in over 50 percent of all fatal cerebral vascular lesions in patients below the age of forty-five years."

Incidence. The exact incidence of intracranial saccular aneurysms is unknown. The figures that are available are based on the results of large autopsy series. The following are representative: Turnbull, 1918 (153) 0.92%; Richardson and Hyland, 1941 (117) 0.87%; Stehbens, 1954 (137) 3.7%; Housepian and Pool, 1958 (88) 2.1%; Chason and Hindman, 1958 (34) 4.9%; Hassler, 1961 (82) 17%; and McCormick, 1970 (97) 8%. Hassler's work is of particular interest. He fixed the vessels for his study at physiological intraluminal pressures and then, using stereomicroscopy, meticulously searched the specimens for "minute" saccular aneurysms (Figure 1b). He defined these as aneurysmal outpouchings less than 2 mm in diameter, and believes that the larger saccular aneurysms, which come to clinical attention, arise from them.

Location. Intracranial saccular aneurysms occur almost exclusively at bifurcations on the circle of Willis,* or the major arteries arising from it (Figure 2). Approximately 85% arise at bifurcations on the anterior circulation; 15% on the posterior circulation. The most common sites on the anterior circulation are at the origins of the anterior or posterior communicating arteries and at the bifurcation of the middle cerebral artery. Each accounts for between 20% and 30% of all intracranial aneurysms (14, 21, 114, 117, 130, 137). The basilar bifurcation is the most common site on the posterior circulation (50).

Natural History. The natural history of intracranial saccular aneurysms is uncertain. Generally, it has been taught that eventual rupture is the rule. However, McCormick (97), in an unselected series of aneurysms from 2,000 consecutive autopsies, found that 72 of 122 cases had unruptured aneurysms. Although the risk of a given aneurysm rupturing is not known, it appears to correlate with the size. For example, McCormick (97) found the average maximum dimension of ruptured aneurysms to be 14.5 mm; while that for unruptured ones was 4.5 mm. In the Cooperative Study, "the greatest number of symptomatic aneurysms were 7 to 10 mm in largest diameter and the greatest number of incidental aneurysms were 3 to 6 mm" (96).

* Thomas Willis (1621-1675), physician-anatomist, Professor of Natural Philosophy at Oxford and founding member of the Royal Society of London, is one of the greatest figures in English Medicine. In "Cerebri Anatome" (1664) he described the anastomotic circle of arteries at the base of the brain, which now bears his name.

FIGURE 2

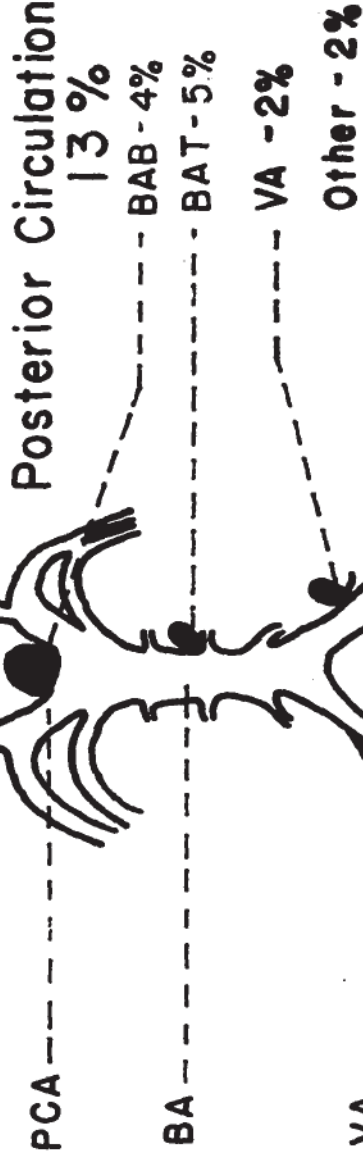
A line drawing of the human circle of Willis adapted from Everett (56). The components of the circle and its major branches are indicated on the left. The most common sites of intracranial saccular aneurysms are shown on the right. The incidence figures are taken from an autopsy series of 206 aneurysms published by Stehbens (137). The interrupted line divides the circle into the anterior and posterior circulation of the brain.

ACA	= anterior cerebral artery
ACoA	= anterior communicating artery
BA	= basilar artery
BAB	= basilar artery bifurcation
BAT	= basilar artery trunk
ICA	= internal carotid artery
ICAB	= internal carotid artery bifurcation
MCA	= middle cerebral artery
PCA	= posterior cerebral artery
PC1A	= pericallosal artery
PCoA	= posterior communicating artery
VA	= vertebral artery

Anterior Circulation Aneurysms



Posterior Circulation Aneurysms



There is little doubt that once an aneurysm has bled the likelihood of a fatal outcome is great. Ask-Upmark and Ingvar (2) estimated that without operation 20% of cases made a good recovery, 20% were crippled for life, and 60% sooner or later died from subarachnoid haemorrhage. Pakarinen (111) has studied the prognosis in 589 cases of saccular aneurysm with subarachnoid haemorrhage, treated non-surgically. The early mortality was 43% and by the end of one year an additional 35% were dead from recurrent haemorrhage.

Surgical Treatment. Since the initial haemorrhage is not invariably fatal, the possibility of successful surgical intervention exists. It is now common practice to prevent further, and possibly fatal haemorrhage, by applying a clip or ligature to the neck of a ruptured aneurysm, or by encasing the sac in muscle, gauze, or plastic. The Cooperative Study (134) showed "an overall mortality rate of 31 per cent for the patients subjected to intracranial operation" and "a useful functional survival of 46 per cent."

Object of This Thesis. In spite of the obvious clinical importance of human intracranial saccular aneurysms, the pathogenesis* of these lesions has remained controversial. Many authors have suggested that physical mechanisms play an important role in three areas: (1) in

* Pathogenesis is defined by Stedman's Medical Dictionary as "the mode of origin or development of any disease or morbid process."

initiating the aneurysmal process; (2) in contributing to its subsequent enlargement; and (3) eventual rupture. However, the nature of the physical factors has remained undefined. The purpose of this thesis is to examine biophysical aspects in each of these areas.

II. THE PATHOGENESIS OF INTRACRANIAL SACULAR ANEURYSMS

HISTORICAL REVIEW

"The Causes of Aneurisma's are divers ... The internal cause is, the impetuosity of the Blood, which ... doth force its way through the side of the vessel ... to produce an Aneurisma in any conspicuous Vessel ... in the Brain, (there causing an Apoplexy;)..."

- Richard Wiseman. Eight chirurgical treatises.
3rd ed. London: 1696.

1) INTRODUCTION

Currently popular theories regarding the pathogenesis of intracranial saccular aneurysms are based, almost exclusively, on pathological descriptions of the lesion. These have been used as evidence in support of various aetiological processes held to be responsible for a localized area of weakness in the vessel wall, from which the aneurysm arises.

In the early literature, luetic arteritis was regarded as the most common cause of this weakness (8, 82). It is now known that aneurysms secondary to infection with micro-organisms are rare (44, 77, 82, 125). A non-specific arteritis (78) has been proposed as the aetiological factor, but this has not been substantiated in large autopsy studies (82, 147).

Presently there is a division of opinion between those who support a congenital or developmental explanation for the weakness (1, 9, 20, 60, 62, 82, 114, 119); an acquired degenerative process (71, 147, 154); or a combination of these (30, 31, 38, 97, 117, 131, 155).

Regardless of the explanation for the weakness, there has been little elucidation of the mechanism by which the vessel outpouches, and the sac subsequently grows and ruptures. In a recent review, Alpers (1) stated:

"... cerebral aneurysm begins with a weakness at some point in the vessel from which, in the course of time and under unknown forms of stress, an aneurysm is developed."

To appreciate the theories to be discussed it is helpful to outline the major histological features of intracranial arteries, bifurcations, and aneurysms.

2) HISTOLOGICAL FEATURES

Intracranial arteries. These conform to the basic arterial plan of three structural layers: the tunica intima, tunica media, and tunica adventitia. However, they differ significantly in detail from muscular arteries of similar size, situated extracranially (43, 82, 131). Their walls are extremely thin in comparison. Virtually all of the elastic tissue is confined to the internal elastic membrane of the tunica intima. There is no external elastic membrane. The tunica media consists almost exclusively of vascular smooth muscle with very little collagen or elastin,

although the collagen content increases with age. The tunica adventitia is a thin layer of finely woven connective tissue.

Intracranial bifurcations. Modifications in the basic structure of intracranial arteries are common at bifurcations and branch points (Figure 3). There may be gaps in the tunica media at the apex and lateral angles. These are known as medial or muscularis defects (Figure 4a) and were first described by Forbus (60) in 1930. Intimal cushions (Figure 1b and 4b), which are localized areas of thickened tunica intima at the lateral angles, are a common finding (82, 83, 84, 128, 141). These consist of a mixture of smooth muscle and elastin, and are situated in the proximal portions of the branches.

Intracranial aneurysms. Although the sac of an aneurysm is approximately spherical in shape, as it increases in size, secondary blebs or loculi develop commonly (38, 39, 41), giving it an irregular, bilocular, or multilocular appearance. An aneurysm is attached to the apex of a bifurcation by its neck, which is usually short and broad (137). The fundus or dome of the aneurysm is the commonest site of rupture (38, 39).

On examination with light microscopy (Figure 5a), the wall of an aneurysm appears to consist of connective tissue only. There is no tunica media and the internal elastic membrane is either absent or extremely fragmented in appearance (38, 60, 109, 131, 137). These features are also seen in "minute" aneurysms (82) (Figure 5b). Commonly,

FIGURE 3

Line drawing illustrating the conventions used in the text to name the structural components of human intracranial arterial bifurcations and aneurysms. The aneurysm is shown in its usual location at the apex of the bifurcation. The arrows indicate the direction of arterial blood flow.

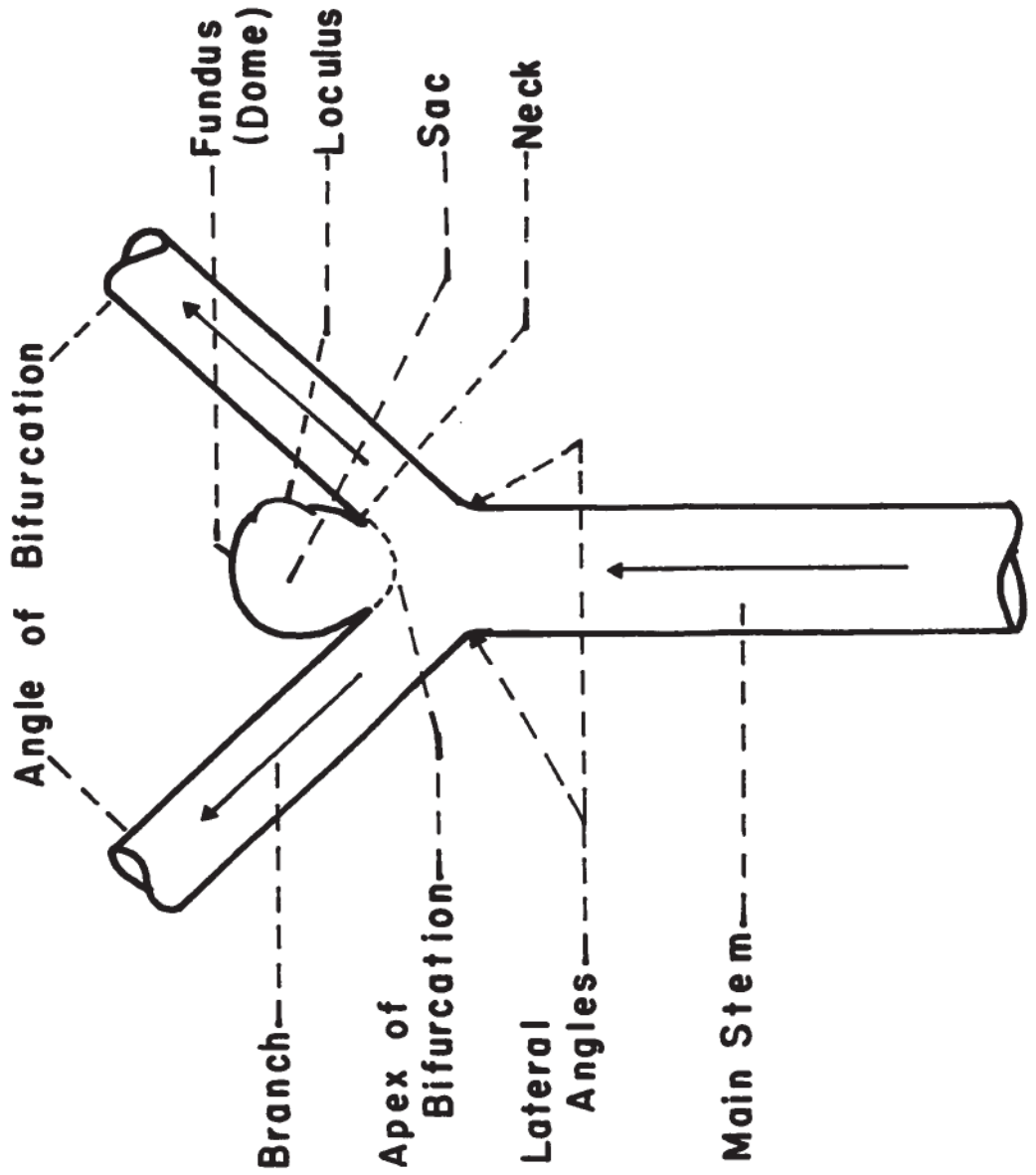


FIGURE 4a

Photomicrograph of a human intracranial bifurcation (Masson's trichrome stain). A prominent medial defect is present at the apex of the bifurcation.

From Sahs (131).

FIGURE 4b

Photomicrograph of a typical intimal cushion (C) at the lateral angle of a human intracranial bifurcation (Masson's trichrome stain). A medial defect, extending from M to M', is beneath the cushion. The lumen of the vessel is to the left.

From Sahs (131).

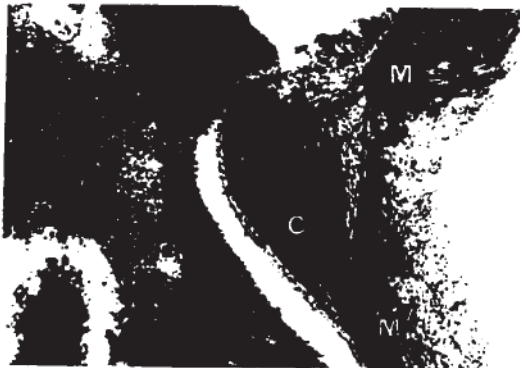


FIGURE 5a

Photomicrograph of a section through a human intracranial saccular aneurysm. The internal elastic membrane and tunica media do not extend into the aneurysm, the wall of which appears to consist only of connective tissue. Note the thinness of the wall of the aneurysm in contrast to the parent artery.

From Forster and Alpers (62).

FIGURE 5b

Photomicrograph of a section through a "minute" aneurysm. As in larger saccular aneurysms, the wall consists only of connective tissue. The elastic membrane becomes fragmented and disappears completely in the neck of the aneurysm. The tunica media is absent in the wall of the aneurysm. The arrow indicates the sac of the aneurysm. From Hassler (82).



there are other degenerative changes in the wall, such as intimal hyperplasia (60, 147, 155), cellular infiltration (39), deposition of lipid-laden macrophages (109, 147) and fibrinoid necrosis (39, 82). With electron microscopy, Nyström (109, 110) has shown that granular, electron-dense remnants of the elastica, and fragments of vascular smooth muscle cells may be seen in the wall.

3) INITIATION OF THE ANEURYSMAL PROCESS

a) CONGENITAL FACTORS

Medial defects. When Forbus (60) described medial defects at the apex of intracranial bifurcations, he stated: "the muscularis defect constitutes unquestionably a locus minoris resistentiae in the wall of the vessel." Furthermore, on the basis of embryological studies, he considered them to be congenital in origin, secondary to a failure of fusion of the tunica media of the parent vessel to that of its branches. With this evidence, many prominent textbooks state that saccular aneurysms are "congenital" lesions (16, 19, 102).

There are a number of difficulties with the idea that the medial defect, in itself, is an adequate explanation for the development of an aneurysm. (1) Defects occur frequently at the lateral angles, a site where aneurysms never occur (19, 41, 82, 131, 139). (2) The anatomical distribution of the defects does not correspond to that of aneurysms (139). (3) Defects commonly occur at bifurcations in extracranial muscular arteries, such as the coronary, renal, splenic, mesenteric, and spinal

arteries (60, 81, 86), where saccular aneurysms are very rare. (4) Defects occur in many animal species, in which intracranial aneurysms are extremely uncommon (19, 40, 52, 82, 138, 146). (5) Defects are found with much greater frequency than aneurysms, suggesting that some additional factor or factors are important in the development of an aneurysm (71).

There is some doubt that the medial defects, alone, represent an area of weakness. Glynn (71) subjected cerebral vessels to 600 mmHg pressure without observing any blow-out or bulging at the apex of bifurcations and concluded that this would not occur, as long as the internal elastic membrane was intact. Stehbens (147) supported this view, stating: "The defects appeared to be involved in, rather than to have caused, the ... evagination."

There is also doubt that the medial defects are congenital in origin (71, 82), as their frequency and size increase dramatically with age. For example, Hassler (82) found only five defects in three individuals among 82 subjects less than 30 years of age; but he found 172 defects in 45 individuals among 75 subjects greater than 30 years of age.

Anomalies of the circle of Willis. Riggs and Rupp (119) postulated that:

"The presence of a high degree of association of aneurysms with anomalies of the circle of Willis, suggests that these structural malformations, by producing local alterations in intravascular dynamics, may provide a mechanical basis for the development of aneurysms in congenitally weak portions of the vascular wall in fields where anomalies provide a potential source of hydraulic imbalance."

Evidence from the literature supports this hypothesis in the case of anterior communicating artery aneurysms, which are clearly associated with a high incidence of congenital hypoplasia or agenesis of the opposite anterior cerebral artery (54, 105, 119, 145, 159). Wilson et al (159) found this in 85% of their cases with anterior communicating artery aneurysms. Stehbens (145) found a similar association in 30 out of 37 patients.

Vestigial remnants. A few authors (9, 20) have suggested that aneurysms arise from the vestigial remnants of primitive cerebral vessels which have undergone incomplete involution during embryological development. This idea has received no support in the literature (82, 145, 147).

Association with known congenital anomalies. Some authors (114, 130) have stated that intracranial saccular aneurysms are associated with a high incidence of congenital abnormalities. Stehbens (143), in a careful statistical study, could find no support for this claim. The incidence of congenital abnormalities in his series of 215 aneurysms was not significantly greater than in a control series of 849 cases. His results did support the belief that there is an unusually high incidence of intracranial aneurysm in association with polycystic disease of the kidneys and coarctation of the aorta. This has been regarded by many as an important observation in support of the congenital hypothesis (2, 13, 44, 77, 158). However, Stehbens (143) emphasizes that both these

congenital diseases produce severe systemic hypertension at an early age. Therefore, the correlation is probably a reflection of arterial degeneration secondary to hypertension, "rather than to hypothetical congenital factors."

Familial incidence. The familial occurrence of intracranial aneurysms is extremely rare. Beaumont (11) reviewed the English language literature on this subject, and found only 12 case reports. He concluded that, "there is little direct evidence that a familial factor is of importance in the pathogenesis of intracranial aneurysms."

Relation to age. Intracranial aneurysms are very rare in children (98, 101, 119). This finding does not favour the congenital theory. Riggs and Rupp (119) did not find one aneurysm in the 102 infants and children under 10 years of age, in their large autopsy series. In a study of 1,125 cases, McDonald and Korb (98) found only two aneurysms in individuals under five years of age. From a large paediatric service, Matson (101) collected 13 cases, three of which were associated with coarctation of the aorta, and one of which was mycotic in origin. The average age of patients with ruptured aneurysms is further evidence against the congenital theory. In a typical series this was 50.2 years (145).

b) ACQUIRED FACTORS

Degeneration of the elastica. Among pathologists, there is now more or less, general agreement that an acquired degeneration of the

internal elastic membrane is a necessary antecedent to aneurysm formation (31, 60, 71, 82, 131, 147, 154, 155). This begins with fraying and fragmentation of the elastica at the apex of a bifurcation (82, 131, 147) and ends with an almost total destruction of the elastica in the wall of an aneurysm (Figure 5a and 5b). However, there is little agreement as to the process responsible for this degeneration.

Popular opinion contends that degeneration of the elastica is secondary to atherosclerosis* (31, 38, 71, 154, 155). On the basis of a pathological study, Carmichael (31) concluded that, "the gap in the elastic membrane is due to degenerative changes alone and chiefly to implication of the membrane in an ordinary atheromatous process." More recently, Crawford (38) has drawn a similar conclusion: "The internal elastic lamina . . . often degenerates at the base of an atheromatous plaque." As well, it has been demonstrated experimentally (131), that one of the earliest lesions in the atherosclerotic degeneration of any artery, is discrete fragmentation of the internal elastic membrane.

* Atherosclerosis is the most common degenerative disease of arteries. It is defined by the World Health Organization as "a variable combination of changes in the intima of arteries (as distinct from arterioles) consisting of focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and associated with medial changes." Atherosclerosis is one of the three pathological entities comprising arteriosclerosis ("Hardening of the arteries"); the others being medial (Mönckeberg's) sclerosis, and arteriolar sclerosis.

Crawford (38) reported a statistical association between aneurysms and coronary atherosclerosis. He compared the findings in men (45 - 70 years of age) in a large control group, to those with ruptured aneurysms. The incidence of severe coronary atherosclerosis was two to three times as great in the aneurysm group.

Others (60, 72, 82, 131) have intimated that the degeneration is a consequence of mechanical factors. For example, Forbus (60) who appreciated, "that no anatomical aneurysm can develop without disintegration" of the elastica, regarded "the traumatic factor of over-distension due to blood pressure" as the essential cause of this disintegration. Hassler (82) thought that the elastic membrane degenerated because of localized structural fatigue, resulting from "over-stretching." Stehbens (147) noted that the apical regions of intracranial bifurcations were common sites of "elastic tissue degeneration from early life," but was undecided between an atherosclerotic or haemodynamic cause.

Localized intimal proliferation (intimal cushions). Hassler (82, 83, 84) believed that intimal cushions were acquired, as the result of a passive remodelling of the vessel wall in response to the forces of blood flow and that they were "in some way connected with the development of aneurysms." In his study, they were rare in newborns and children, although he did find well-developed cushions in a three week old child with polycystic disease of the kidneys. By the age of 20 years, prominent cushions could be found in most individuals. They were always

situated at the lateral angles, "at sites judged to be sheltered from the main blood stream." He considered them "non-atheromatous" and "physiological" in nature, and suggested that they might produce a stenotic narrowing of the lumen and, as a result, turbulence, which would weaken the wall and allow aneurysmal dilatation at the apex.

Stehbens (141) studied intimal proliferation at the bifurcations of cerebral arteries, in infants, ranging in age from a fetus of 28 weeks to a child of eight months. He described lateral "pads," similar in position and structure to the "cushions" of Hassler. These were always associated with some degeneration of the elastica. As well, he described apical "pads," characterized by much less proliferation and greater destruction of the elastica. The size of the "pads" correlated directly with the age of the infant. In contrast to Hassler, he believed these structures to be the earliest sign of atherosclerosis and suggested that:

"... turbulence may occur at the bifurcations and branchings of the cerebral arteries and it may therefore be significant that the lateral and apical pads occur at stagnation points where the eddy currents are likely to occur."

Hassler (82) confirmed the presence of intimal cushions in the intracranial arteries of a variety of species other than man. As well, he confirmed their occurrence in extracranial arteries (81).

Clinical evidence supporting an acquired process. The literature suggests a relationship between systemic hypertension and intracranial saccular aneurysms (38, 39, 144, 155, 158). Crompton (39) stated that 60% of patients with ruptured aneurysms were hypertensive. Stehbens

(144) found that 53.5% of his cases had pre-existing hypertension, as determined by the presence of left ventricular hypertrophy, on pathological examination. This was higher than in a control group. An attempt was made in the Cooperative Study (96) to determine the relation between hypertension and the rate of aneurysm maturation. Increasing size correlated to an increasing incidence of hypertension, but it could not be shown that aneurysms reached a given size earlier in hypertensive patients than in those with normal blood pressure.

Other clinical evidence suggests that acquired disturbances in blood flow within the circle of Willis are associated with aneurysm formation. The development of a "new" aneurysm on the opposite side has been reported following the treatment of intracranial aneurysm by surgical ligation of one common or internal carotid artery in the neck (52, 70, 135). German and Black (70) found two such cases in 35 patients followed for 10 years. Somach and Shenkin (135) reported two cases out of 20. One of these died from the rupture of a large aneurysm at the junction of the right anterior cerebral and anterior communicating arteries. This aneurysm had developed after the ligation of the opposite common carotid artery for a posterior communicating artery aneurysm, seven years previously. The other case developed a large, "new," right posterior communicating aneurysm, detected eight years following ligation for a left-sided aneurysm. They said that they had:

"little doubt that the hemodynamic alterations caused by the unilateral interruption of carotid flow with the consequent increase in contralateral cerebral flow contributed to the etiology of the newly-formed aneurysms."

DuBoulay (52) reported a case in which a pericallosal artery aneurysm developed within one month of clipping the opposite pericallosal artery at surgery.

Experimental evidence supporting an acquired process. Hassler (85) showed that ligation of one, or both, internal carotid arteries in the neck of young rabbits would produce, within five months, large intimal cushions, medial defects, and localized destruction of the internal elastic membrane. These changes occurred only at those intracranial bifurcations that one would expect to be carrying increased flow, because of the ligation. He believed that these findings supported the concept that "hydraulic imbalance" secondary to anomalies in the circle of Willis, or to carotid ligation in the neck, could result in aneurysm formation.

4) GROWTH AND RUPTURE

There is much less information in the literature concerning the mechanism of growth and rupture of intracranial aneurysms. It is widely assumed that once a small aneurysmal outpouching is present, the stress of the normal blood pressure alone, accounts for enlargement and eventual rupture (77, 114, 158).

Mechanical factors. Other mechanical factors have been suggested as possible sources of stress on the wall; in particular, turbulent

blood flow within the sac (60, 67, 68, 72, 92). Forbus (60) said that the intimal proliferation and plaque formation in the wall, might be "a reaction to injury produced by irregular currents within the dilatation." Govaert and Walker (72) suggested that growth might proceed, "under the influence of the abnormal turbulence." Evidence for turbulent blood flow within experimental simulations of saccular aneurysms has been found in animal studies (67, 68, 92).

Jain (89) used latex models of saccular aneurysms to study the effect of pulsatile flow. He noted that the walls of the models pulsed, that flow within them was turbulent, and that when two aneurysms were placed in series, the proximal one invariably ruptured first. He speculated that, "pulsatile flow may cause the rupture of an aneurysm by inducing a resonance frequency in the aneurysmal sac," which could produce structural fatigue of its wall.

Loss of strength in the wall. Pathologists have attempted to identify specific changes which would account for a loss of strength in the wall of an aneurysm, or indicate that rupture was imminent. Stehbens (147) noted that in the region of rupture, the wall was invariably very thin, and contained a patchy infiltration of fibrin, which he thought, signified imminent rupture. Crompton (39) described cellular infiltration of the wall, in the region of the fundus, with polymorphonuclear leucocytes, plasma cells, round cells, fibrin, and red blood cells, in both ruptured and unruptured aneurysms. He believed that these changes

would produce weakness in the wall and suggested that, "this damage may be . . . mechanical due to pulsatile pressure changes in a relatively inelastic sac or turbulent blood flow in an aneurysm." He also stressed the importance of the size of the aneurysm. In 88% of cases with multiple aneurysms, the largest ruptured first. As well, in 70% the more proximal aneurysm was the first to rupture.

Wood (162) studied 105 cases of multiple aneurysms and confirmed the findings of Crompton. In 88% of his cases, "the larger of two aneurysms, or the largest of more than two aneurysms, was the lesion that ruptured." Only 10% of aneurysms under 4 mm in diameter had ruptured. The smallest ruptured aneurysm was 2 mm in diameter.

Crawford (38) emphasized the importance of the development of extremely thin-walled bubbles, or secondary loculi, on the sac of an aneurysm as it grew, since these were often the site of rupture.

Wood (162) described a remarkable case which highlights the importance of loculi. The patient originally bled from an aneurysm 6 x 10 mm in diameter. After an interval of 10 days, the patient experienced a second haemorrhage, which was fatal. Prior to death, angiography revealed that a loculus, at least one-third the size of the original aneurysm, had developed at the fundus during the 10 day interval.

Relation to activity. The relation between the activity of the patient and the rupture of an aneurysm has stimulated some interest in the literature. Pool and Potts (114) state that 10% or more of aneurysms

rupture during activity in which one would expect sudden elevations of blood pressure; such as, elimination, coitus, and physical or emotional stress. Data in the Cooperative Study (95) seemed to support this, but it was noted that one-third of the aneurysms ruptured during sleep, suggesting little relation to activity.

5) SUMMARY

It is impossible to accept the theory that congenital factors alone are responsible for the development of human intracranial saccular aneurysms, for the following reasons: (1) There is doubt that medial defects are either congenital in origin, or a source of weakness in the vessel wall responsible for the initiation of the aneurysmal process. (2) Congenital variations in the structure of the circle of Willis are probably associated with aneurysms only because of the alterations in intracranial haemodynamics which they produce. (3) Aneurysms are known to occur following procedures which likely result in abnormally high flow rates across some intracranial bifurcations. (4) The few congenital diseases which are associated with aneurysms, produce severe hypertension. It is most likely that the hypertension is the explanation for the development of the aneurysms, not some hypothetical congenital factor. (5) Large autopsy studies show that systemic hypertension, from any cause, is associated with an increase in the incidence of ruptured aneurysms. (6) The familial occurrence of aneurysms is rare. (7) Most congenital diseases manifest themselves in early life. Aneurysms

do not. (8) There is no evidence that aneurysms arise from vestigial remnants of primitive cerebral blood vessels. (9) An aneurysm will not develop unless there is localized destruction of the internal elastic membrane at the apex of intracranial bifurcations. Such degeneration is an acquired process.

Therefore, there is little justification in referring to human intracranial saccular aneurysms as "congenital" lesions. It seems more likely that they are acquired secondary to localized degeneration in the arterial wall at the apex of bifurcations. Furthermore, the congenital theory does not explain why an aneurysm enlarges and eventually ruptures, once it has begun.

If one looks upon aneurysms as an acquired disease, the following biophysical questions, concerning their initiation, growth, and rupture, arise: (1) What role do haemodynamic forces such as turbulence, shear stress, and stagnation pressure, play in the initiation of the aneurysmal process? (2) Is turbulent blood flow likely at intracranial bifurcations? (3) What forces produce the original aneurysmal outpouching? (4) Once a small aneurysm has developed, what forces account for its continuing growth? (5) Does turbulence occur within the sac of an aneurysm and contribute to the degeneration of the wall? (6) Is the wall of an aneurysm subjected to greater stress than that of an adjacent cerebral artery? (7) Is the wall of an aneurysm subjected to the same pulsatile pressure fluctuations as an intracranial artery? (8) What are the elastic properties

of the wall of an aneurysm? Is it distensible or non-distensible?

(9) What are the most important factors determining the rupture of an aneurysm? (10) Why are larger aneurysms with thin walls more likely to rupture than smaller aneurysms with thick walls? (11) What is the breaking strength of the wall of an aneurysm? (12) Is it possible to predict a critical size at which an aneurysm will rupture? In the following chapters an attempt is made to answer these questions.

III. MODEL EXPERIMENTS

"The theory that peculiar hemodynamic factors affect bifurcations in such a way as to exert unusual stress on certain apical regions while providing for the proliferation of intimal pads in a proximal location, is a plausible one, and should be investigated further."

- A. L. Sahs (131)

1) INTRODUCTION

To investigate the possible haemodynamic forces contributing to the initiation and growth of human intracranial saccular aneurysms, model experiments were conducted, using glass bifurcations and aneurysms. The patterns of flow within each model were observed, and critical flow values for turbulence measured in each. The findings are discussed in relation to the suggestions from the literature that:

(1) Turbulence or other haemodynamic factors arising at intracranial bifurcations play an important role in the initiation of the aneurysmal process, by contributing to the destruction of the internal elastic membrane at the apex of the bifurcation (60, 72, 82, 131, 141).

(2) Intimal cushions are the result of forces generated at bifurcations by blood flow and play some role in the initiation of an aneurysm (82, 141). (3) Turbulent blood flow may occur within the sac of human aneurysms (60, 67, 68, 72, 92).

No previous study of this nature is available although there have been scattered reports describing disturbed patterns of flow at vascular bifurcations (3, 7, 74, 75, 99, 140), together with the suggestion that they are related to the localization of atherosclerotic plaques about bifurcations (32, 63, 106, 113).

2) FUNDAMENTAL CONSIDERATIONS

A flowing fluid experiences a combination of inertial forces and frictional (viscous) forces (115, 136). The inertial forces per unit volume are proportional to $\bar{V}^2 \rho / D$ where \bar{V} is the average velocity of the fluid, D is the hydraulic depth or tube diameter, and ρ is the fluid density. The frictional forces per unit volume, on the other hand, are proportional to $\bar{V} \eta / D^2$ where η is the fluid viscosity. It can be seen that the inertial forces increase as \bar{V}^2 , whereas the frictional forces increase only as \bar{V} . Therefore, as the fluid velocity increases, a critical velocity is reached where the viscous forces are no longer able to damp out random inertial forces.

Below the critical velocity, viscous forces predominate, and flow is streamlined or laminar (Figure 6a). This flow is characterized by an orderly progression of fluid particles along straight, clean-cut trajectories. With steady flow, the velocity profile is parabolic in shape and the axial or central stream travels at twice the mean fluid velocity. With pulsatile flow, the velocity profile becomes flattened in its central portion (76). When the critical velocity is exceeded, inertial forces predominate,

and flow is turbulent (Figure 6b). Turbulent flow is characterized by chaotic, random, and disordered fluctuations in the pressure and velocity of the fluid particles within the fluid stream.

The factors which determine whether flow is streamlined or turbulent are related by an experimentally determined, dimensionless expression, * known in honour of Reynolds (116), who first discovered the relation, as the Reynolds number (Re),

$$Re = \frac{\rho}{\eta} \cdot \bar{V} \cdot D$$

For the case of a long straight tube, using a Newtonian fluid** (water), Reynolds found that the critical Re number, corresponding to the critical flow velocity at which turbulence occurs, was 1900. A similar value was determined experimentally for blood, by Coulter and Pappenheimer (37). It should be noted, however, that they calculated and published Re values with respect to tube radius, rather than tube diameter. Therefore, their critical Re value of 970 for blood is equivalent to Reynolds' original value of 1900 for water.

The Reynolds number is a useful relation, for it allows one to model hydrodynamically equivalent situations, using differently sized,

* See Appendix I.

** A Newtonian fluid is a fluid whose viscosity does not vary with the rate of shear, or in other words, the viscosity remains constant, at varying rates of flow. Although blood is not a homogeneous fluid (as it contains a suspension of cells), it behaves as a Newtonian fluid, if the internal diameter of the tube, in which it is flowing, is greater than 0.5 mm (99).

FIGURE 6a

Streamlined flow in a long straight tube. The Reynolds number (Re) represents the flow rate at which the photograph was taken. The direction of flow is indicated by the arrow above the model. Evans blue dye has been injected to reveal the flow pattern.

FIGURE 6b

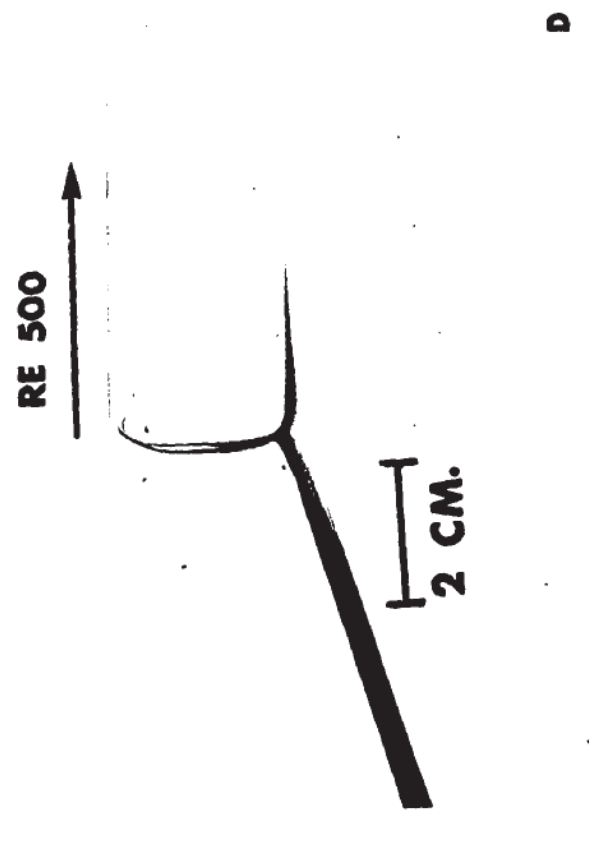
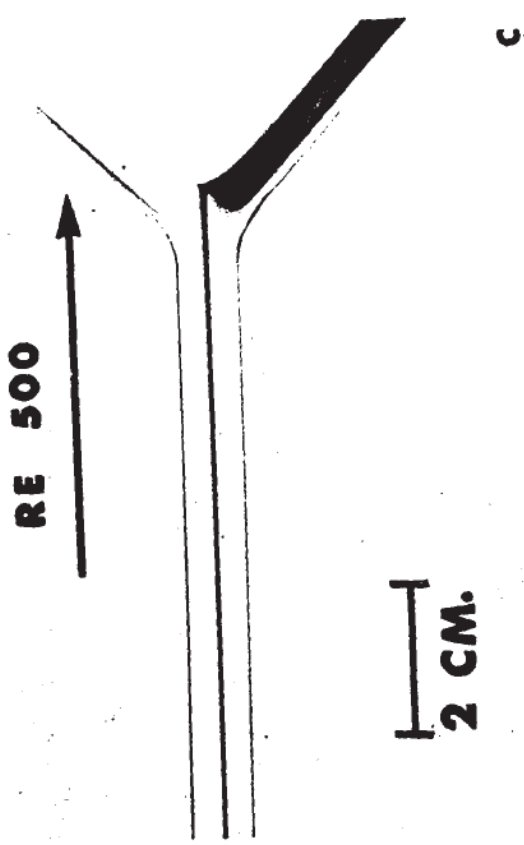
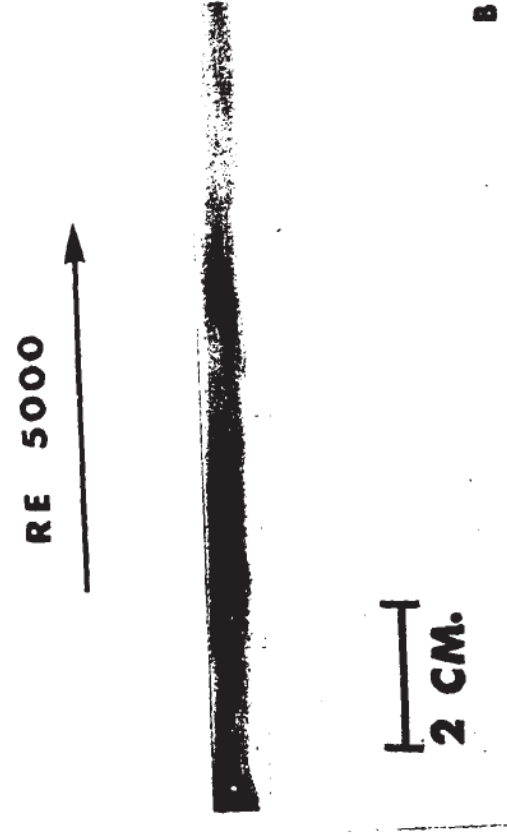
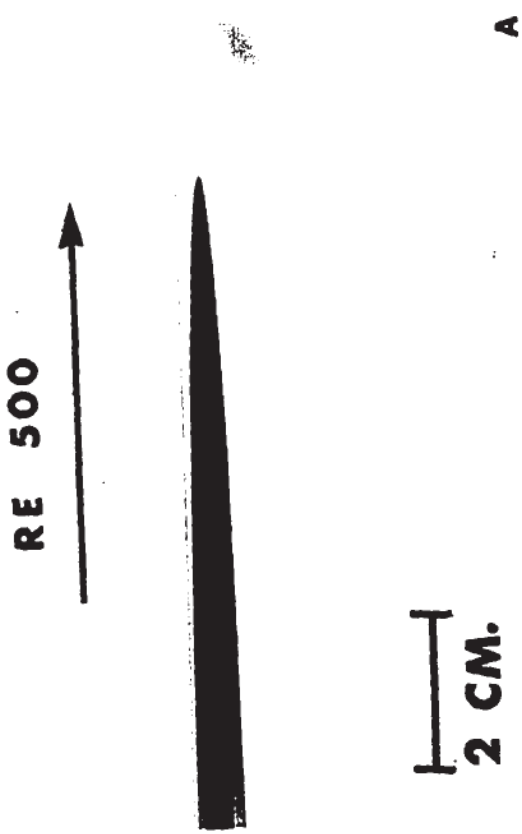
Turbulent flow in a long straight tube. The dye is diffusely scattered across the width of the tube and no streamlines are visible.

FIGURE 6c

Axial stream impinging upon and rebounding from the apex of the symmetrical 90° bifurcation during steady forward flow.

FIGURE 6d

Axial stream impinging upon the apex at the junction of the distal branch and cross-piece in the model of the anterior communicating artery complex. The area of impingement is where anterior communicating artery aneurysms occur. Flow in the upper stem has been clamped off.



but geometrically similar tubes, and dissimilar fluids. This principle of dynamical similarity (115) allows engineers to study, for example, flow conditions in large river basins, using scale models, and the forces which aircraft experience during flight, using wind tunnels. This principle is equally applicable to the study of flow conditions in the human cardiovascular system by the use of models (100).

3) MATERIALS AND METHODS

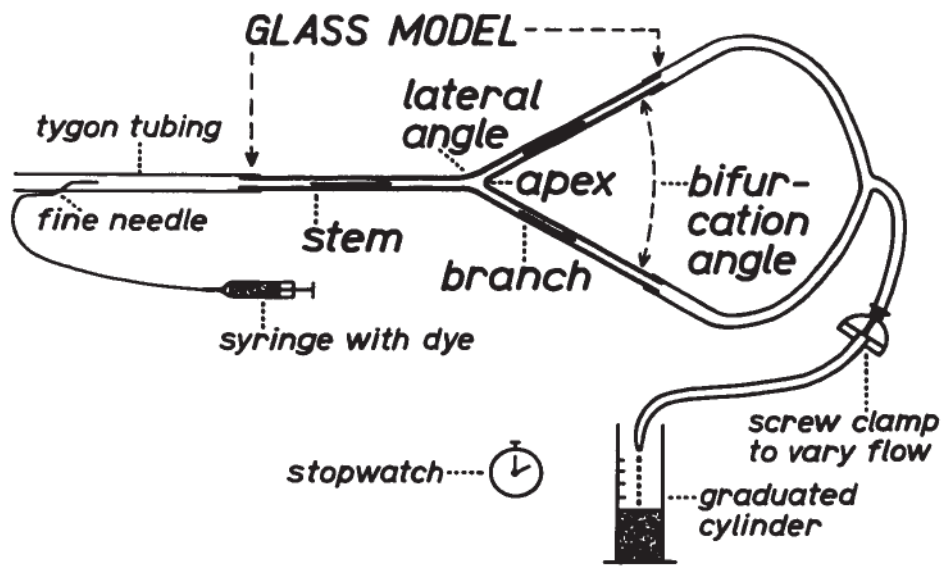
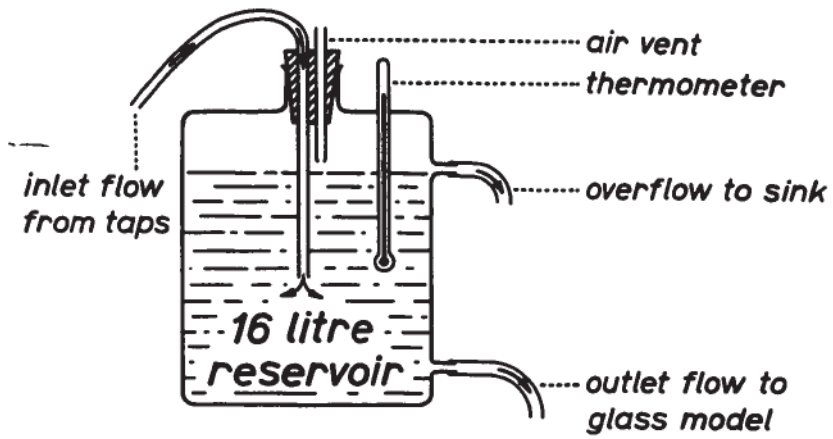
The following glass models, made from Pyrex tubing by an expert glassblower, were used in the experiments: (1) Five straight tubes with an internal diameter (i. d.) of 7 mm and lengths of 12.5, 25, 50, 75 and 100 cm. (2) Four symmetrical bifurcations with stems 20 cm long and 7 mm i. d., branches 15 cm long and 5 mm i. d., and bifurcation angles of 45° , 90° , 135° and 180° . (3) An asymmetrical 90° bifurcation of the same dimensions, except that one branch had an i. d. of 6 mm, and the other, 3 mm. (4) A branch point (simulating the origin of the posterior communicating artery from the trunk of the internal carotid artery) 10 cm long with i. d. 5 mm, arising at an angle of 105° from the main stem, which was 7 mm i. d. proximal to the branch, 5 mm i. d. distal to it. (5) A model simulating the anterior communicating artery complex, with stems 15 cm long and 5 mm i. d., a cross-piece 2 cm long and 3 mm i. d., and branches 15 cm long and 4 mm i. d. Each stem was offset 45° to the axis of the branches. (6) Three bifurcation aneurysms, each with a bifurcation angle of 90° , dimensions the same as the

symmetrical bifurcations, and the sac arising at the apex. These were a small spherical aneurysm, simulating a "minute" aneurysm (neck diameter 7 mm, sac diameter 5 mm), a large spherical aneurysm (neck diameter 10 mm, sac diameter 20 mm), and a large bilocular aneurysm (neck diameter 10 mm, sac diameter 23 mm). The total cross-sectional area of the branches of the symmetrical bifurcations, branch point, and aneurysm models was equal to that of their stems; that of the asymmetrical bifurcation was 8% less. In all the models, the branches arose on the same plane as the stem.

The apparatus (Figure 7) was designed to provide an easily regulated flow of water through the models. A 16 litre reservoir was filled continuously from the taps. A thermometer recorded the temperature of the water, which could be regulated by varying the mixture of hot and cold water coming from the taps. The reservoir was vented to allow air bubbles in the tap water to escape. An overflow lead from the reservoir to the sink and all the experiments were performed using a constant pressure head (100 cm H₂O). Water flowed from the reservoir to the glass models through long, straight connections of appropriately sized Tygon tubing. The flow rate was regulated by a screw clamp distal to the model, and measured by collecting the outflow in a graduated cylinder over a period of one minute, which was timed with a stop-watch. Patterns of flow were observed by injecting Evans blue dye through a fine (26 gauge) bore needle, connected to a 20 cc syringe by a length of fine

FIGURE 7

Diagram of the apparatus used to observe flow patterns and measure the critical Reynolds numbers in glass models. See text for description. The conventions used throughout the text for naming the components of a bifurcation; namely, the stem, lateral angles, branches, apex, and bifurcation angle, are shown in the lower half of the diagram. The run off was directed either to the sink, or to the graduated cylinder to measure the flow rate, by a three-way stop-cock beyond the screw clamp. The stopcock is not shown in the diagram.



polyethylene tubing. Pulsatile flow, superimposed as a sinusoidal pressure wave upon the steady flow, was produced by a Sigmamotor Pump (model T8). The pump rate was 70 per minute. Black and white 35 mm photographs (Kodak Plus-X Panchromatic film with exposure at $f/8$ for $1/125$ sec) and 16 mm movies were made of the flow patterns in the models.

With this apparatus, the Reynolds number is calculated from the measurement of two variables; the flow rate, Q (cm^3/sec), and the temperature of the perfusing water, which determines its viscosity. Substituting $\bar{V} = Q/\pi r^2$ and $D = 2r$ in the original Reynolds expression, gives a new dimensionless expression,

$$\text{Re} = \frac{\rho}{\eta} \cdot \frac{2}{\pi r} \cdot Q$$

The radius, r (cm), of the stem* in each model is known. The density of water, ρ , is 1 (gm/cm^3) and does not change significantly with temperature. The viscosity of water, η (poise), however, varies dramatically with changes in its temperature. As there was some variation in water temperature during the experiments, it was recorded at the beginning and end of each experiment and an average value was used, if necessary. The water temperature in the reservoir was the same as that collected in the graduated cylinder. The viscosity of water at each temperature was taken from the Handbook of Chemistry and Physics. In this way the

* All Re numbers were calculated using the stem radius, rather than the branch radius.

Reynolds number corresponding to any flow rate could be calculated for each model.

4) RESULTS

a) PROPERTIES OF THE APPARATUS

The apparatus provided reproducible flow with repeated runs at low, moderate, and high rates, for both steady and pulsatile flow. The accuracy of measurement was $\pm 2\%$. The relative viscosity of representative samples of the Evans blue dye and water mixture, collected in the graduated cylinder, was measured with an Ostwald viscometer and compared to that of water alone. The variation was less than 1%.

b) CRITICAL REYNOLDS NUMBERS IN THE STRAIGHT TUBES

The average critical Re with steady flow was 2500 ± 230 S.D.* ± 30 S.E.M.** The corresponding value with pulsatile flow was 2090 ± 160 S.D. ± 10 S.E.M. There was no statistically significant difference in the values for the short or long tubes. Thus, it was concluded that the Tygon-glass connections were not creating a significant disturbance in the flow patterns. There was also no difference in the values indicating the earliest signs of turbulence, and those in which the turbulence persisted the full length of the tube.

* S.D. = 1 standard deviation.

** S.E.M. = 1 standard error of the mean.

c) PATTERNS OF FLOW AT THE BIFURCATIONS

Flow patterns over a wide range of flow rates were observed in each of the models, using forward and reverse flow. With forward flow, water entered through the stem and was distributed to each branch. With reverse flow, water entered the model equally through the branches and left by the stem. As the flow rate was increased, the following sequence of patterns, which were basically similar in all the bifurcations with both steady and pulsatile flow, occurred.

i) Axial Stream Impingement

With forward flow, even at the lowest flow rates ($Re = 200$), the axial and peri-axial streams impinged directly upon the apex of the bifurcations (Figure 6c), the site where intracranial saccular aneurysms invariably occur. The incident streams were then reflected into the branches.

With equal flow through both stems of the model of the anterior communicating artery complex, there was no flow through the cross-piece. However, if flow was decreased or stopped in one stem (a situation analagous to hypoplasia or agenesis of one anterior cerebral artery) flow became distributed to the opposite side through the cross-piece. With this situation, the axial stream in the open stem impinged directly upon the apex of the junction between the distal branch and cross-piece (Figure 6d), which is the site where anterior communicating artery aneurysms occur.

ii) Boundary Layer Separation

At low rates of forward flow (Re 200-500) the boundary layer streamline separated from the wall at the lateral angles and then re-attached itself to the wall of the branch (Figure 8a). The profile of the separated streamline is very similar to the contour of intimal cushions at the lateral angles of cerebral arteries (Figure 4b). Eddy formation and turbulence occurred within the area of separation. This was particularly evident in the smaller branch of the asymmetrical bifurcation (Figure 8b). This finding is of interest, since Stehbens (141) found that if there is a considerable difference in the size of two cerebral arterial branches, there is usually only one cushion and this is at the lateral angle on the side of the smaller branch.

With reverse flow, separation with eddy formation occurred at the apex of the models where the two branch streams united to travel into the stem. This also corresponds to a site of cushion formation in the cerebral circulation where the two vertebral arteries unite to form the single basilar artery (84) (Figure 2). In general, the area of separation enlarged with increasing bifurcation angle, and was most prominent with pulsatile flow.

iii) Helical Flow Pattern

As the flow rate was increased, a helical pattern arose within the proximal portion of the branches. This secondary flow pattern was especially obvious in the wide-angled bifurcations (Figure 8c). The dye

FIGURE 8a

Boundary layer separation at the lateral angle of the symmetrical 90° bifurcation during steady, forward flow at a low rate.

FIGURE 8b

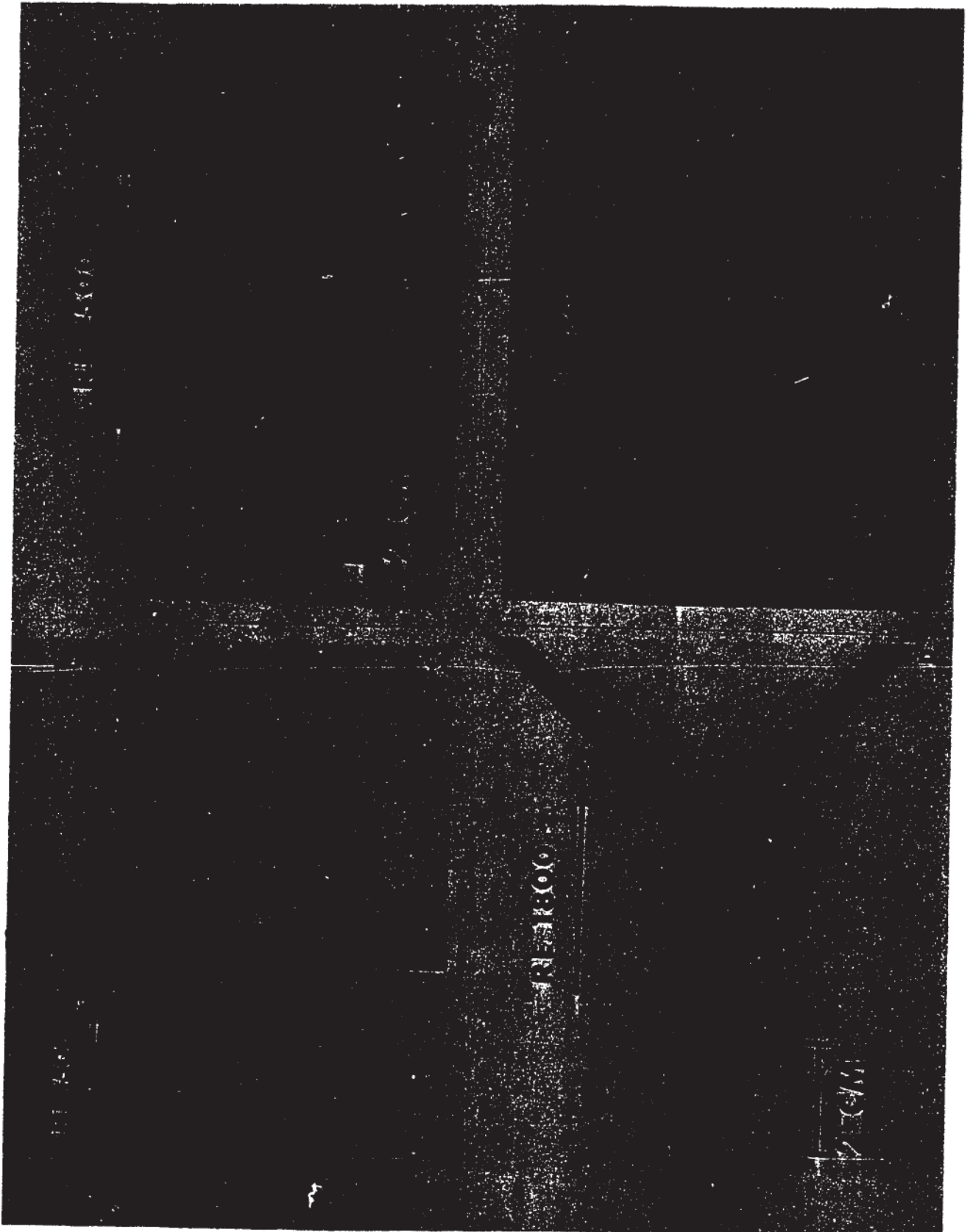
Turbulence in the area of boundary layer separation at the lateral angle adjacent to the smaller branch of the asymmetrical 90° bifurcation during steady, forward flow.

FIGURE 8c

Helical flow patterns in both branches of the symmetrical 180° bifurcation during steady, forward flow.

FIGURE 8d

Turbulence in the branches of the symmetrical 90° bifurcation during pulsatile, forward flow. Turbulence can also be seen within the area of the boundary layer separation at the lateral angles. Dye has cleared from about the apex because of the high flow velocity in that region. Flow in the stem, is streamlined and the next pulse of dye is seen approaching the bifurcation.



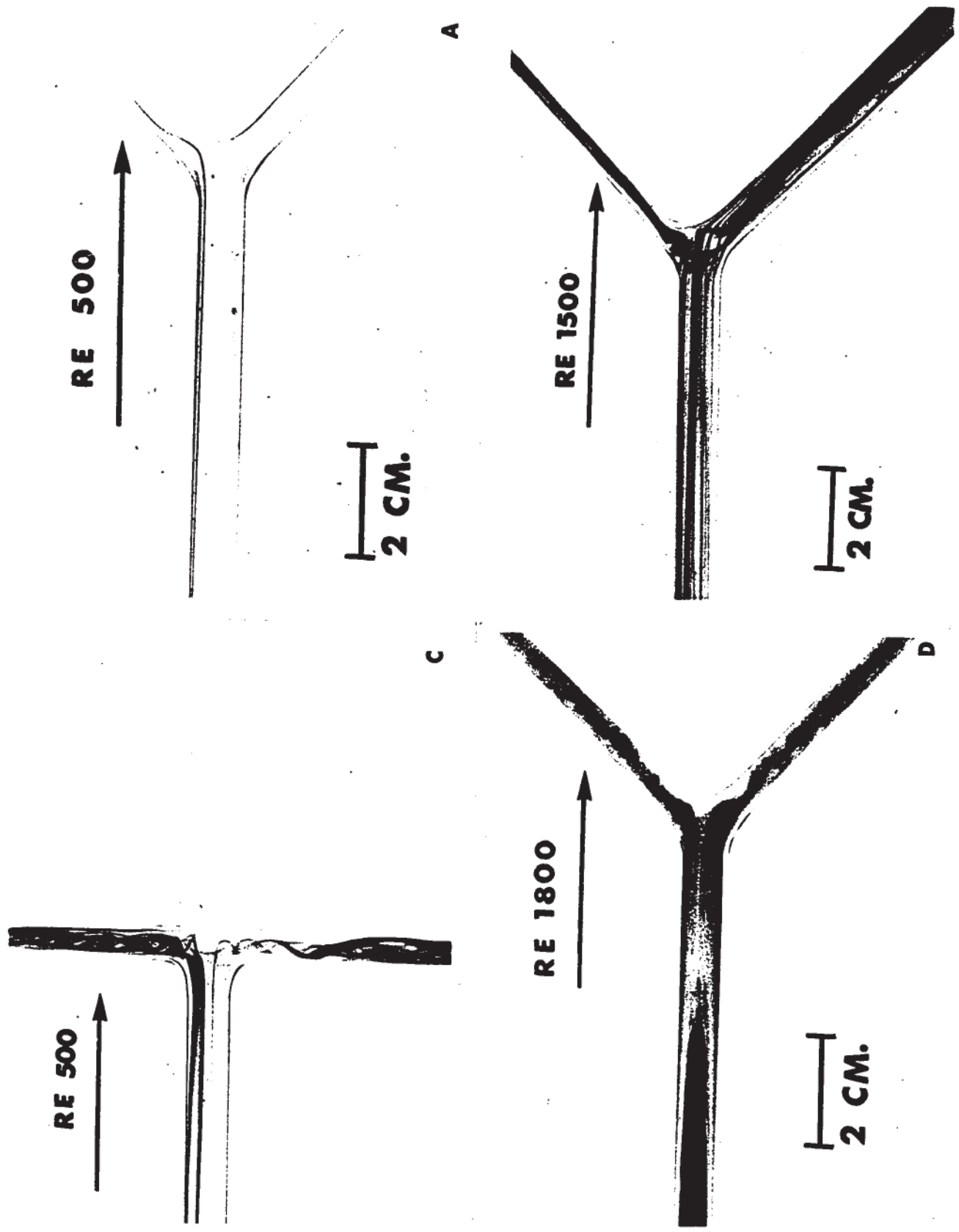
remained in orderly trajectories within the helix, which was transformed to a streamlined parabolic pattern within the first few centimetres of the branch. The helical flow no doubt arose as a result of the reflection of the incident streams from the curved surface at the apex. This flow pattern was neither obviously turbulent, nor strictly laminar, but rather characterized the transition between the two.

iv) Branch Turbulence

A further increase in flow resulted in turbulence, which was localized to the proximal portion of the branches, and damped to streamlined flow in the distal portion. A still further increase in flow produced propagation of this turbulence, in that it appeared to extend the full length of the branch, while flow in the stem and in the region of the apex remained streamlined (Figures 8d and 9a). With reverse flow, even at low flow rates, marked turbulence, with mixing of the two branch streams, occurred in the stem. This was most prominent in the wide-angled bifurcations (Figure 9b). A remarkable feature of this turbulence, with steady flow, was that it arose at the junction of the two branch streams with a regular "whiplash-like" periodicity (approximately 1/sec), which produced the appearance of pulsatile flow in the proximal portion of the stem.

d) PATTERNS OF FLOW IN THE ANEURYSMS

In all three aneurysm models, the flow pattern in the sac was turbulent at very low flow rates (Figures 9c and 9d). At these rates, flow remained streamlined in the stem and branches, although there was



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FIGURE 9a

Branch turbulence, as in Figure 8d, but at a later phase of the pulse cycle. The axial stream is about to impinge at the apex.

FIGURE 9b

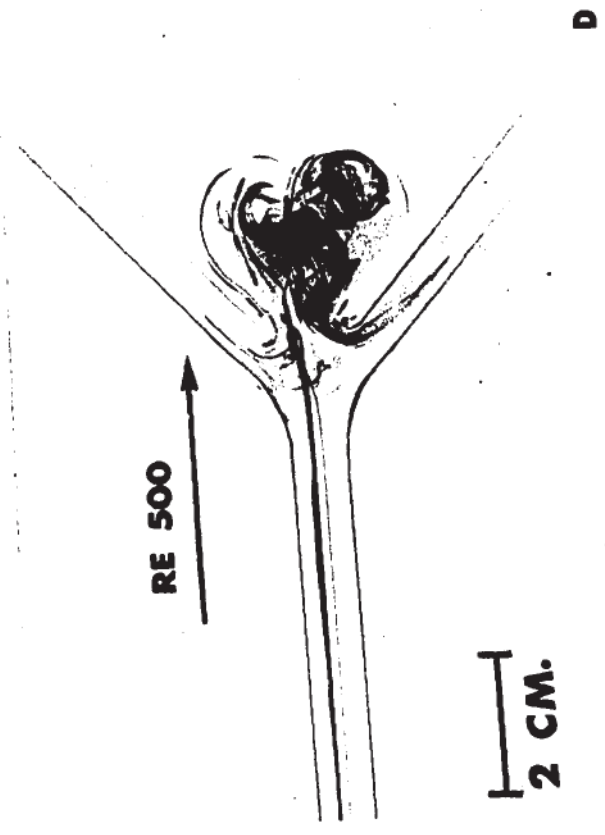
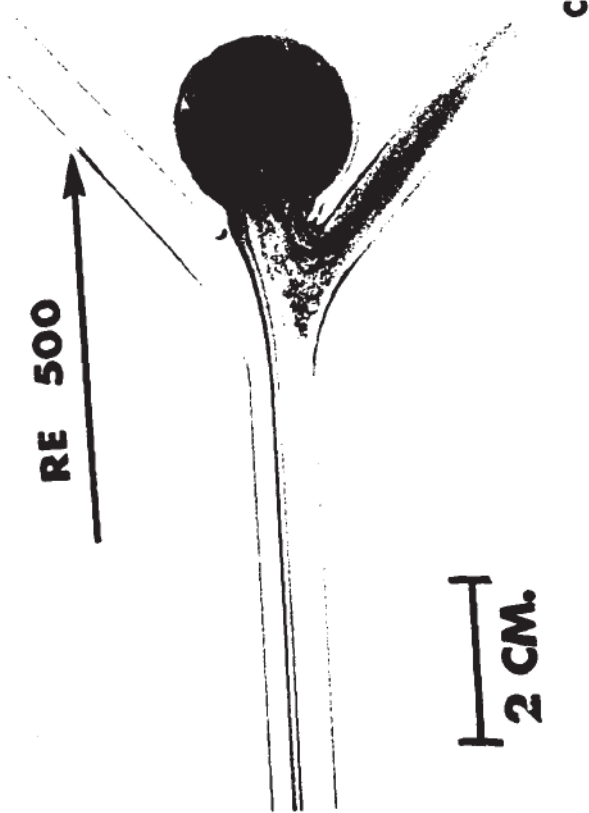
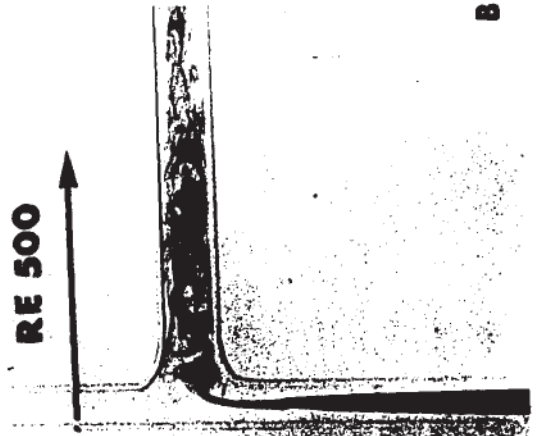
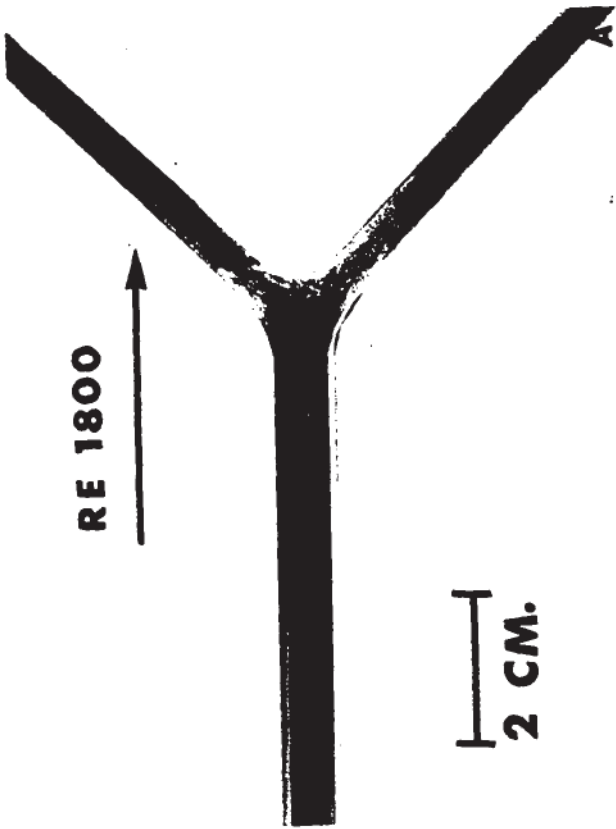
Turbulence in the stem of the 180° bifurcation during steady, reverse flow. Flow is equal in both branches but dye has been injected only in one. Proximal to the junction flow is laminar, but distally it is turbulent. The turbulence arises with a "whiplash-like" periodicity.

FIGURE 9c

Turbulence in the sac of the large spherical glass model aneurysm.

FIGURE 9d

Turbulence in both loculi of the large bilocular aneurysm. Flow in the stem and both branches is streamlined.



instability of flow in the region of the neck. Characteristically, the dye stream entered the sac on one side of the neck and left from the opposite. The turbulence was superimposed upon a circular, whirl-pool like, flow pattern, which resulted in a rapid circulation within the sac, and rapid dilution of the dye.

e) CRITICAL REYNOLDS NUMBERS IN THE MODELS

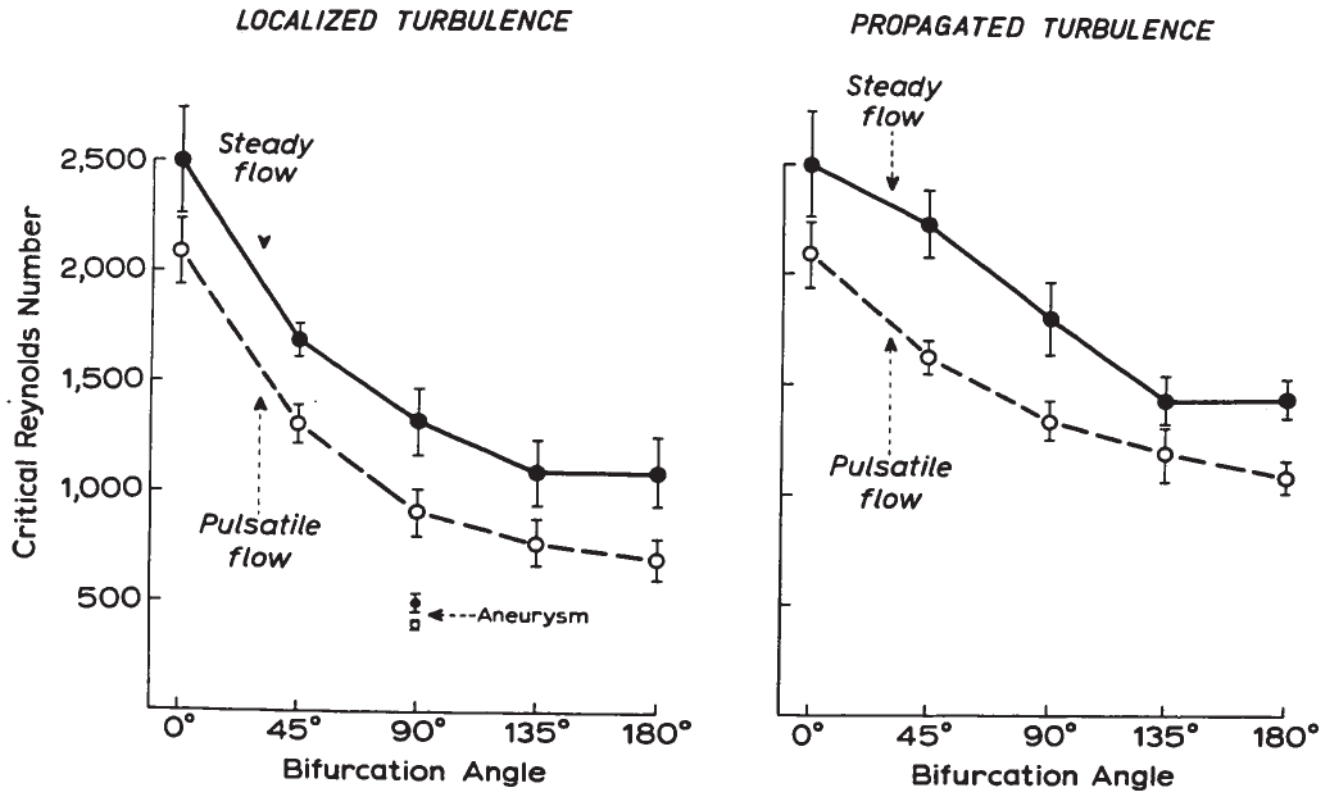
The critical Reynolds numbers were determined for the series of symmetrical bifurcations using steady and pulsatile flow in both the forward and reverse directions, and for the aneurysms in only the forward direction (Figures 10 and 11). There was a difference in the critical values for turbulence localized to the proximal portion of the branches and that propagated the full length of the branches. The critical Re for each situation in each model is an average of a minimum of 20 individual measurements. Such an averaging technique was necessary because the critical flow rate corresponding to the onset of turbulence had to be judged visually with repeated injections of dye, together with a continuous adjustment of the flow rate to the critical value. Therefore, average values should be read from the graphs to the nearest 100 ± 1 S.D., as represented by the bar.

In every instance the critical Re for the bifurcations was less than for the straight tubes. For example, with forward flow and turbulence localized to the proximal portion of the branches (Figure 10), the critical Re for a 90° bifurcation was approximately 50% of that for a straight tube,

FIGURE 10

Graphs comparing the critical Reynolds numbers of symmetrical glass model bifurcations and aneurysms during steady and pulsatile, forward flow. The bars represent ± 1 S. D. about the mean value. See text for description.

FORWARD FLOW



be it steady or pulsatile flow. The critical Re decreased with increasing bifurcation angle (Figures 10 and 11), except in the case of the 180° bifurcation with propagated turbulence during steady, reverse flow (Figure 11). There is no statistically significant difference between the values for the 135° and 180° bifurcations in any of the graphs, except for the case mentioned above. Therefore, it appears that the maximum disturbing effect of a bifurcation on flow is with a branching angle of approximately 135°. Pulsatile flow also decreased the critical Re. For example, in the case of the 90° bifurcation the critical Re for pulsatile forward flow was 30% less than for steady flow (Figure 10). Localized turbulence usually arose at a critical Re approximately 25% less than for propagated turbulence.

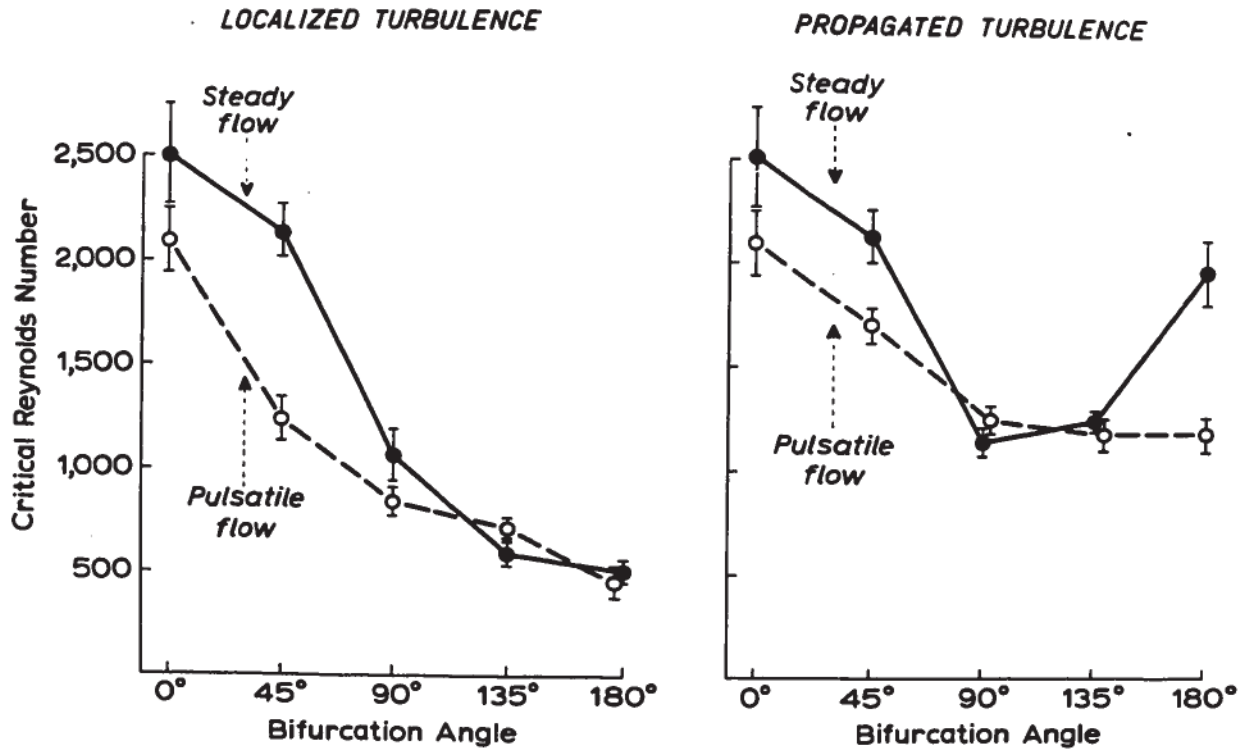
The pattern of results for reverse flow (Figure 11) is not as simple as with forward flow. In general, the critical Re decreased with increasing angle, with the exception already noted. However, the difference between steady and pulsatile flow was much less marked than with forward flow, and was not statistically different except for the 45° bifurcation. Reverse flow usually produced turbulence at lower Re values than forward flow. This was particularly marked for localized turbulence in the 135° and 180° bifurcations (Figure 11).

Turbulence occurred within the sacs of the glass model aneurysms at extremely low flow rates. The average critical Re for all the models with steady flow was 490 ± 50 S.D. and with pulsatile flow, 400 ± 20 S.D.

FIGURE 11

Graphs comparing the critical Reynolds number of symmetrical glass model bifurcations during steady and pulsatile, reverse flow. The bars represent ± 1 S.D. about the mean value. See text for description.

REVERSE FLOW



In contrast, the corresponding values in the 90° bifurcation, without an aneurysm, were 1330 ± 150 S.D. and 920 ± 90 S.D., respectively. Thus one would predict the occurrence of turbulence within the sac of an aneurysm at a flow rate less than one-half that for a normal bifurcation.

5) DISCUSSION

a) SIGNIFICANCE OF THE CRITICAL REYNOLDS NUMBER

Any factor which disturbs flow in a system will decrease the critical Reynolds number. Although Reynolds' original value of 1900 is quoted widely, it does not have general application to all flow situations. The value, 1900, is the critical Re only for a long straight tube, using steady flow, and Reynolds' original apparatus. With other apparatus, the exact value will vary with the magnitude of the disturbing effects produced by it. With elaborate precautions in design, to minimize such disturbances, values as high as 40,000 have been obtained (115). The critical value of 2500, for steady flow in a straight tube, obtained in this study, is in keeping with the results of others (115); and illustrates that the apparatus used produced less disturbance than that used by Reynolds.

Reynolds' original value of 1900 has been widely quoted, as well, for the cardiovascular system, and used in support of the concept that turbulence does not occur in the circulation under normal flow conditions (23). The results of this study illustrate that bifurcations and branch points in the circulation can be expected to lower the critical Re for turbulence considerably. Bifurcations represent a geometrical disturbance

to flow, which increases with increasing bifurcation angle. As well, pulsatile flow and reverse flow (analogous to flow in the venous system, or flow at the junction of the vertebral arteries to form the basilar artery, in the cerebral circulation) lower the value even further.

Some differences in the critical Re values at various bifurcations in the human cardiovascular system in comparison to those found for the models is to be expected, because: (1) vessels are distensible and visco-elastic rather than rigid structures; (2) their lining layer is not as smooth and uniform as that of the glass models; (3) the configurations of bifurcations and branch points are not as simple in the circulation; and (4) the contour of the pressure fluctuations produced by the Sigmamotor pump is not identical to that in the circulation. Since each of these is probably an additional disturbing factor in the circulation, one would predict that the critical Re values in the circulation are even less than in the models. As a first approximation, however, the trend, both in the critical Re values, and the sequence of flow patterns demonstrated in the models, will apply to the circulation.

Stehbens (140), in a less extensive and systematic investigation, also has demonstrated the disturbing effect of bifurcations. He suggested that, even under normal conditions, turbulent flow was likely in the major cerebral arteries (142). Schroter and Sudlow (133) have recently shown that complex non-parabolic flow patterns arise at the bifurcations in models of the human bronchial tree.

b) REYNOLDS NUMBERS IN THE HUMAN CEREBROVASCULAR SYSTEM

What is the likelihood that flow rates in the major cerebral arteries exceed the critical Reynolds numbers as found in the model experiments? For human blood flow at 37°C, the Reynolds formula, based on an estimate for blood density and viscosity (140), becomes,

$$Re = \frac{\bar{V} \cdot D}{0.027}$$

where \bar{V} is the mean flow velocity in the vessel under consideration, and D is the diameter of the vessel. If only the mean flow (Q cm³/sec) is known, then \bar{V} can be found from $\bar{V} = Q/\pi r^2$. If the calculated Re values for the circulation are greater than the critical Re number obtained in the corresponding models, then turbulence is likely in the in vivo situation.

Hardesty et al (79) found an average mean flow of 370 ml/min in the human internal carotid artery. If one assumes an internal diameter of 4 mm, the calculated mean blood flow velocity within the vessel is 50 cm/sec. This corresponds to a calculated Re number of 750. Similar calculations from the data of Tindall et al (149) produce an average Re value of 600. These values exceed considerably the critical Reynolds numbers found for axial stream impingement and boundary layer separation at the lateral angles in the model bifurcations, and for turbulence within the model aneurysms. However, they are less than the values for either propagated or localized turbulence in the model bifurcations.

c) INITIATION OF THE ANEURYSMAL PROCESS

One would predict therefore, on the basis of the model experiments, that normal flow rates in the human internal carotid system are sufficient to produce axial stream impingement and boundary layer separation, but not obvious turbulence, at major intracranial bifurcations. What role might these haemodynamic events play in the initiation of the aneurysmal process?

i) Localized Destruction of the Internal Elastic Membrane

Both Hassler (82) and Stehbens (141) suggested that turbulence at intracranial bifurcations was likely, and might account for local weakness and aneurysmal dilatation at the apex. The results of the model study do not support this hypothesis. Turbulence does not occur in the models until a higher flow rate (Re approximately 1000) is reached than is known to exist in the cerebral circulation. When turbulence does occur, it arises in the proximal portion of the branches and not in the region of the apex, where aneurysms occur.

It seems reasonable to postulate, however, that the impingement of the central (axial and peri-axial) streams at the apex of intracranial bifurcations is an important factor contributing to the localized destruction of the internal elastic membrane at that site. What haemodynamic forces associated with this impingement could be responsible for the damage?

High shear stress. The impingement of the high velocity central streams in the region of the apex results in a much greater velocity

gradient and shear stress at the wall than would be experienced in the main stem or branches (32, 65, 133) (Figure 12). Using the aorta of the dog, Fry (64, 66) has shown that an acute increase in shear stress at the blood-vascular interface will damage the endothelial lining, eventually completely destroying the cells and exposing the underlying basement membrane. This occurs when the shear stress exceeds a critical value. Ling et al (94) have shown that under normal conditions the peak shear stress in the aorta of the dog is one-third the critical value, which is a relatively low margin of safety.

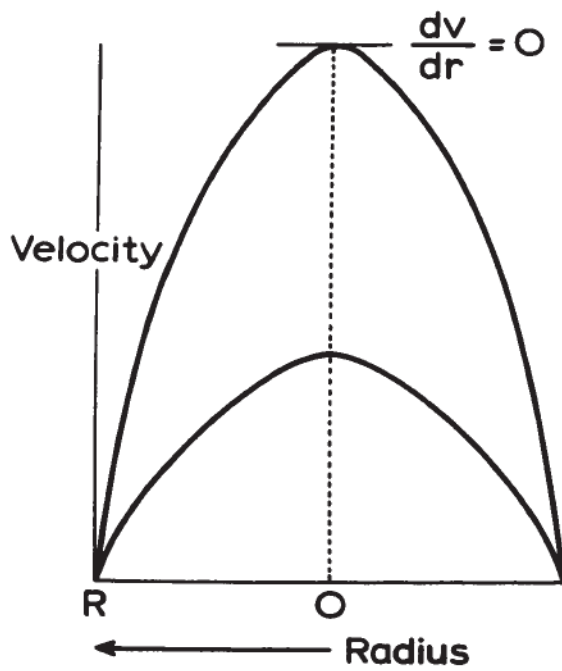
If the basement membrane is exposed, platelets, fibrin, and other blood products accumulate on it (64, 152). Pathologists who favour the "encrustation" theory of atherosclerosis, originally expounded by Rokitansky (127), believe that plaques are the end result of such platelet-leucocyte-fibrin thrombi (53, 104, 106, 107, 113). Such a haemodynamically-induced process would account for the apical "pads" and associated underlying internal elastic membrane destruction, observed by Stehbens (141), since destruction of the elastica is an integral part of the atherosclerotic process. As well, it has been demonstrated that the platelets in a thrombus release an elastase (126) and it has been proposed that this accounts for the destruction of the elastic tissue in an atherosclerotic plaque.

More recently, Fry (66) has found an "increased flux of Evans blue dye across the blood-vascular interface" at levels below the

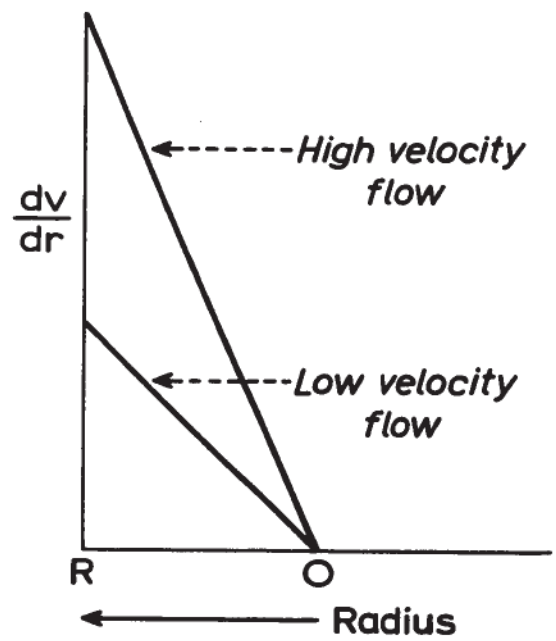
FIGURE 12

The diagram on the left illustrates the parabolic profile of streamlined flow at low and high velocity. On the right, the corresponding shear rates, or velocity gradients, (dv/dr) are shown. The velocity gradient is highest at the wall, and least in the central streams. However, when the high velocity central streams strike the apex of a bifurcation, the velocity gradient, and hence the shear stress on the wall, will suddenly rise to a high value.

Flow velocity Profile



Shear rate



critical shear stress value for acute damage. Therefore, the type of damage to the wall which could initiate destruction of the elastica may occur at less than critical values of shear stress.

Caro et al (32) have taken a totally opposite view with respect to the effect of shear stress. Their conclusions are based on model studies and a study of the distribution of early atheromatous lesions about bifurcations. They believe the development of such lesions is inhibited in areas where local wall shear is high, such as the apex of a bifurcation.

Pulsatile impulse. The momentum* per unit volume of flow will be greatest in the central streams, because of their relatively high flow velocity (99). With pulsatile flow, the impact, and sudden deflection of the central streams at the apex, will result in the periodic transmission of an impulse** to that region of the bifurcation, which will not occur elsewhere in the vessel. The peak force of the impulse will be great, because of the brief impact time. It is conceivable that with time this

* Momentum = mv , where m is the mass and v the velocity. Since momentum is a vector quantity, a sudden change in the direction of motion of an object at the time of impact results in a great change in momentum.

** Impulse equals the change in momentum, and may be expressed as

$$\int_{t_1}^{t_2} F dt$$

where F is the net force producing the change in momentum, and dt is the time of impact. Therefore, for a given change in momentum, a short impact time will give a high force, while a long impact time, will give a lower force.

process will result in structural fatigue of the tissue components of the wall at the apex of the bifurcation.

Pulsatile pressure head. The total pressure, or "pressure head," will also be greater at the apex than elsewhere in the vessel, as a result of the sudden deceleration of the fluid upon impact at the apex, and conversion of its kinetic energy to pressure. The centre of this dammed-up region of flow in front of the apex is a stagnation point, and the excess pressure at this point is the stagnation pressure (115). Stagnation pressure, also known as kinetic or dynamic pressure, equals $\frac{1}{2}\rho v^2$ where ρ is the fluid density and v , the fluid velocity. The total pressure at the apex equals the sum of the transmural pressure* and the stagnation pressure. The magnitude of the stagnation pressure is relatively small in comparison to that of the transmural pressure.** Thus, marked rises in flow velocity will result in relatively minor increases in total pressure at the apex, in comparison to the effect of relatively small changes in transmural pressure. Still the stagnation pressure is an "extra" pressure at the apex, to which other areas of the vessel will not be subjected.

* The transmural pressure is the lateral or distending pressure within a vessel.

** To illustrate this, consider the case of flow in a vessel with a peak systolic pressure of 120 mmHg and peak systolic flow velocity of 150 cm/sec (79, 99). The stagnation pressure is,

$$\frac{1}{2}\rho v^2 = \frac{1}{2} \times 1 \times (1.5 \times 10^2)^2 = 1.0 \times 10^4 \text{ dynes/cm}^2.$$

Since 1 mmHg = 1330 dynes/cm², the stagnation pressure is equivalent to only 8 mmHg pressure, whereas the mean transmural pressure is approximately 100 mmHg.

Summary. Any, or all, of these forces (shear stress, pulsatile impulse, pulsatile pressure head) acting at the apex of an intracranial bifurcation could produce localized degeneration of the internal elastic membrane. Outpouching then occurs because of the pulsatile impulse imparted to the apex by the continuing impact of the central streams.

To propose that haemodynamically, or mechanically induced degeneration of the internal elastic membrane is the initiating cause of intracranial saccular aneurysms, explains some features of aneurysms which cannot be accounted for by any other theory. Thus, aneurysms occur only at the apex of bifurcations (19, 39, 82, 131, 139) because this area is subjected to haemodynamic forces not experienced by other areas of the vessel. It explains why aneurysms are associated with anomalies of the circle of Willis (119, 145, 159) and the ligation of vessels in the neck (52, 70, 135). These conditions produce abnormally high flow rates in some intracranial arteries, in order to maintain a constant total cerebral blood flow (93). The high flow rates will increase the magnitude of the haemodynamic forces acting at the apex of a bifurcation, which will increase the likelihood of aneurysm formation.

Why are intracranial arteries so much more susceptible to the development of saccular aneurysms than extracranial arteries? There are three factors which may account for the difference. (1) Intracranial arteries are very thin-walled in contrast to extracranial arteries of similar size (82, 131). (2) There is very little elastic tissue in

intracranial arteries. (3) The intracranial arteries lie in the subarachnoid space, and are not supported by surrounding tissue. Each of these factors decreases the ability of an intracranial artery to resist the forces which tend to make it outpouch at the apex of a bifurcation.

ii) Localization of Intimal Cushions

There is a remarkable similarity between the location and contour of the boundary layer separation, as seen in the models, and the location and shape of intimal cushions in cerebral arteries. Eddy formation and turbulence occur within an area of separation (115). This was seen in the models. Fry (64) demonstrated that turbulence is as capable of damaging the endothelial lining of a vessel as shear stress. Therefore, intimal cushions may be the remnants of platelet thrombi which have occurred at the lateral angles secondary to damage at this site induced by separation. Caro et al (32) again take a different view. They believe that early atheromatous lesions (in which they include intimal cushions) arise only in areas of low shear and relatively thick boundary layers, such as occurs at lateral angles. They believe that true separation at such sites is unlikely. However, Gutstein and Schneck (74, 75), who have also observed separation in models, believe that it does occur in the circulation. They believe also that it produces localized trauma to the wall, resulting in plaque formation.

The model studies suggest no role for cushions in initiating the aneurysmal process, but they do support the concept that the cushions are

acquired secondary to haemodynamic stress on the wall (82, 141).

d) TURBULENCE IN ANEURYSMS

The critical Re values in the model aneurysms were considerably less than the Re values calculated for the human cerebrovascular system. Therefore, one would predict that once a small aneurysmal outpouching has developed, turbulent blood flow will occur within it, and persist as the aneurysm enlarges. Further investigation of the question of turbulence in aneurysms, and a discussion of its role in the growth of these lesions, is the subject of the next chapter.

6) SUMMARY

On the basis of this investigation of the patterns of flow and the critical Reynolds numbers in a series of glass model bifurcations and aneurysms, it is concluded that: (1) Turbulence is unlikely at major intracranial arterial bifurcations, and plays no role in the initiation of the aneurysmal process. (2) Haemodynamic forces (shear stress, pulsatile impulse, pulsatile pressure head) related to the impingement of the central streams in the region of the apex of a bifurcation are responsible for localized destruction of the internal elastic membrane and the initiation of the aneurysmal process. (3) Separation of the boundary layer at the lateral angles of bifurcations plays a role in the development of intimal cushions, but intimal cushions are not related to the initiation of the aneurysmal process. (4) Once a small aneurysmal outpouching has occurred, flow within it is turbulent, and will remain so, as the sac enlarges.

IV. TURBULENCE IN HUMAN INTRACRANIAL SACCULAR ANEURYSMS

"Streamlined flow is silent.
Remember that my boys,
But when the flow is turbulent
There's sure to be a noise."

- A. C. Burton (26)

1) INTRODUCTION

Turbulent blood flow within a vessel will cause its wall to vibrate. This vibration can be detected clinically, either as an audible bruit* or a palpable thrill** (27, 122, 123, 124), as is commonly found, for example, distal to a vascular stenosis. The recording of bruits from human intracranial saccular aneurysms, and the failure to record sound from normal intracranial bifurcations, would support the conclusions, made on the basis of the model experiments, that turbulence occurs in aneurysms, but not at major intracranial bifurcations.

* A bruit is an abnormal auscultatory sound. "Murmur" is a synonym. "Bruit" is commonly used in reference to sound heard on auscultation over arteries or veins (vascular bruit), whereas "murmur" is used in reference to sound heard on auscultation over the heart (cardiac or heart murmur).

** A thrill is the vibration, accompanying a vascular bruit or a cardiac murmur, which can be felt on palpation.

2) METHOD

A method of detecting sound in human intracranial aneurysms and bifurcations was developed which could be used in the operating room. An intracardiac phonocatheter (AEL Model 191)* with a tip diameter of only 2 mm was used (Figure 13). The phonocatheter was held either in an especially designed catheter-holding forceps or by hand, and was applied directly to the external surface of the aneurysms, and bifurcations under investigation, which were exposed during surgery.

The instrumentation used with the phonocatheter, to record and playback any detected signal, is shown in Figure 14. The signal was amplified by, and visually displayed on, an oscilloscope (Tektronix Type 561). It was then recorded, as a permanent record, on one channel of a two-channel tape recorder (Roberts 400X). The second channel was used for a voice monitor. The pulsatile systemic arterial pressure was measured with an electronic pressure transducer (Statham Model P23DEc) connected to the radial artery and recorded on a paper chart-recorder (Beckman Type R Dynograph). The reference level for pressure was adjusted to correspond to the level of the circle of Willis. Mean arterial pressure was read either directly from a highly-damped anaeroid manometer connected to the cannulated artery (165), or calculated from the pulsatile pressure.**

* American Electronic Laboratories, Inc.

** Mean arterial blood pressure = systolic pressure + 2 diastolic pressure / 3 (27).

FIGURE 13

Photograph of the intracardiac phonocatheter used for recording bruits from human intracranial saccular aneurysms exposed at surgery.

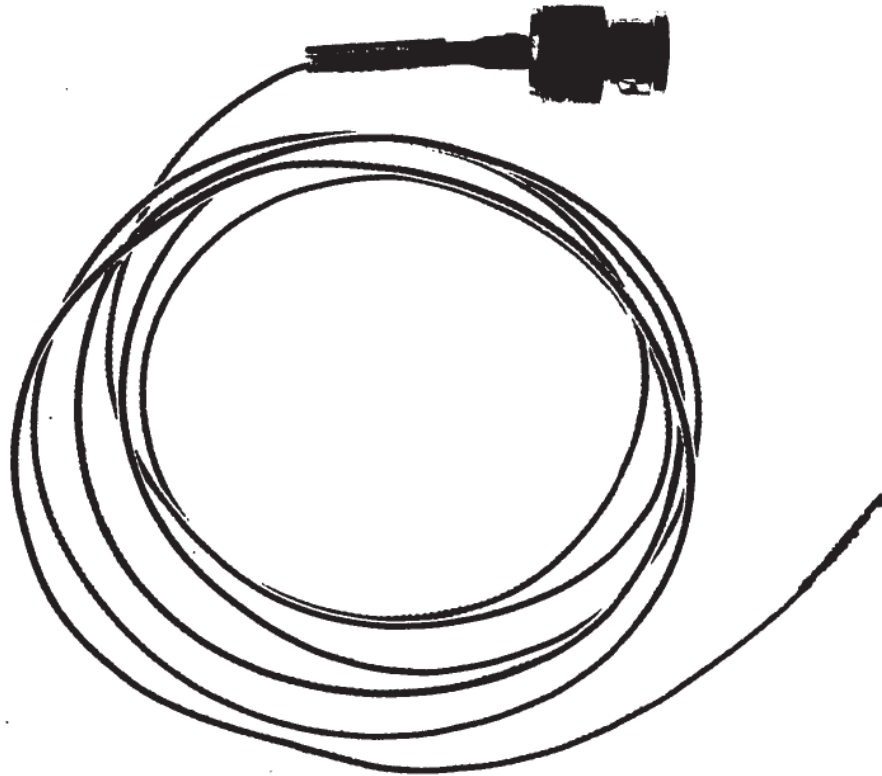
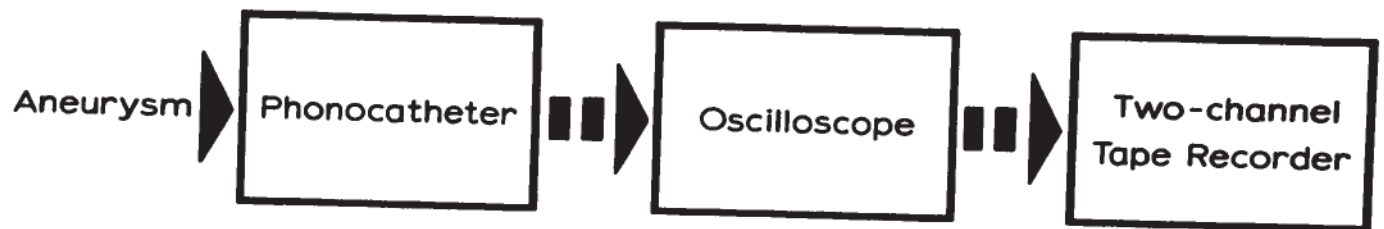


FIGURE 14

Block diagram of the instrumentation used for the recording and analysis of bruits. See text for description.

BLOCK DIAGRAM OF CATHETER INSTRUMENTATION

Recording Mode



Playback Mode



For analysis, the tape record was played back through a band-pass filter (Krohn-Hite Model 310-AB) between 200 - 5000 Hz. The low-pass filtering was necessary to remove the fundamental and harmonic frequencies of 60 Hz interference. The bruits were monitored both audibly and oscillographically, while a permanent paper record of them was made with a light-beam oscillograph (Honeywell 2106 Visicorder).

Recorded bruits were analyzed for their predominant frequency components and their relative amplitudes. The predominant frequencies were determined by counting the number of cycles or spikes in a given unit of time on a high speed oscillograph record (40 - 100 cm/sec) of a bruit and expressing this in cycles per second (Hz). This was repeated for consecutive bruits in the same record and the results were then averaged. The relative amplitude of a bruit was estimated by measuring its peak-to-peak amplitude on a low speed oscillograph record. Again the values were averaged by measuring the amplitude of a consecutive series of bruits. The results were expressed in microvolts (μv) relative to a standard calibrating signal of 500 μv (peak-to-peak amplitude) recorded on the magnetic tape at the beginning of each clinical study.

Frequency response of apparatus. According to the specifications reported by the manufacturers, all of the electronic apparatus used in this study have flat frequency responses in the frequency range of interest (200 - 800 Hz). Each component was tested to confirm this.

Mr. Tom Olien of the Department of Biophysics tested the Visicorder. The frequency response was flat $\pm 1\%$ from 100 - 1000 Hz. The tape recorder had a flat response ± 1 db from 100 - 20,000 Hz. With a 5000 Hz bandwidth, the oscilloscope had a flat response from 0 - 1000 Hz.

The AEL phonocatheters, which contain a barium titanate crystal, are reported to have a flat response from 180 - 20,000 Hz as tested in a U.S. Navy sonar tank (156). An attempt was made to confirm a flat response in the phonocatheter used in this study. Sine-wave signals of varying frequencies from a Wavetek (Model 116) generator were amplified to drive a loudspeaker (Fanon Model HOA-5A-8) coupled to a water-filled plexiglass cylinder* in which the phonocatheter was suspended. The amplitude of the signal from the phonocatheter was monitored on a Heathkit (Model AV-3) AC Voltmeter. The reference signal was 500 Hz at 0 db. The response of the phonocatheter was tested from 100 - 10,000 Hz and was flat ± 1 db from 200 - 800 Hz (Figure 15). The amplitude peaks at 1000, 2800, 5000, and 6900 Hz probably represent resonant frequencies in the test system rather than the phonocatheter, since the response of a second phonocatheter was similar.

3) RESULTS

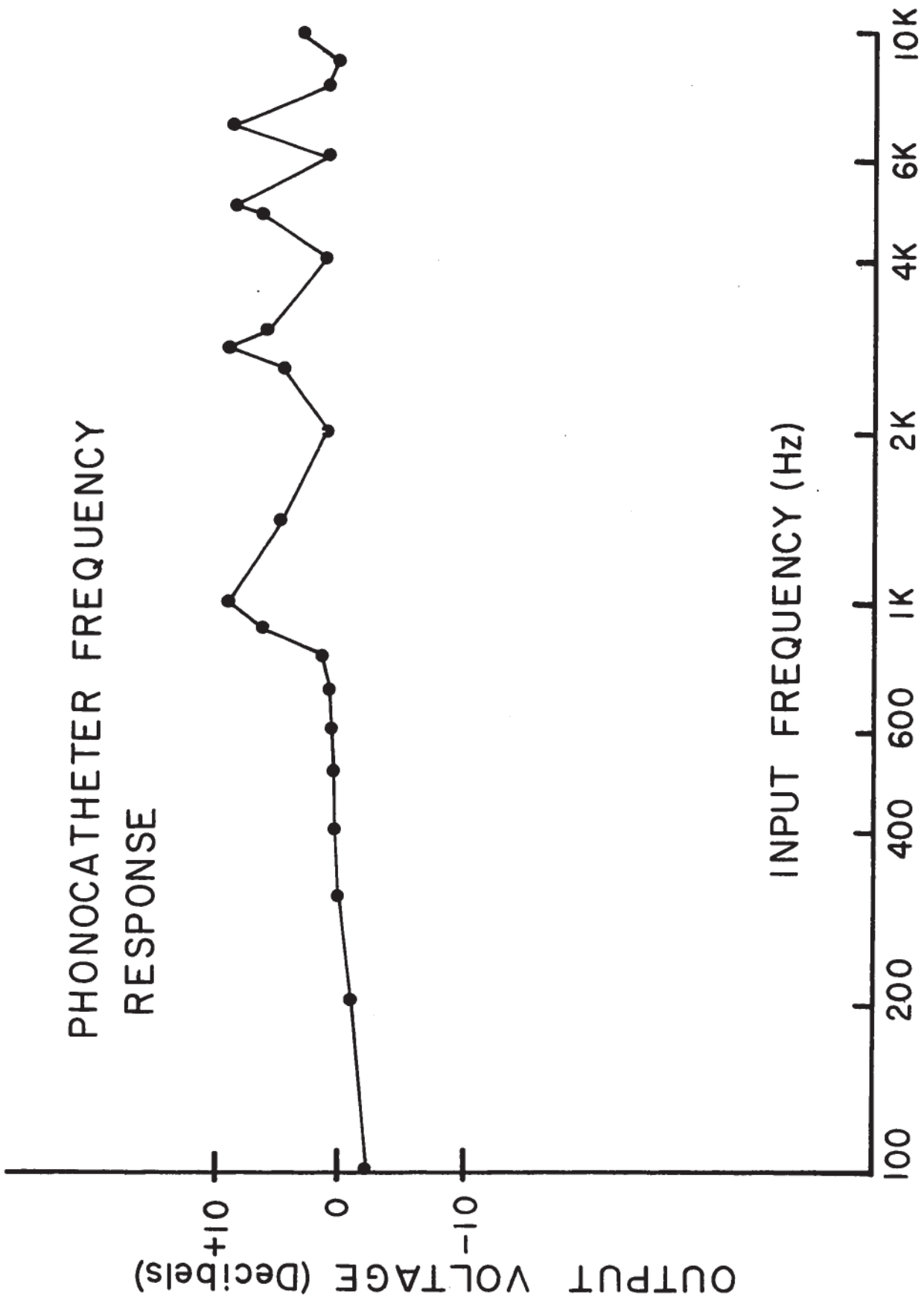
a) CONTROL CASES

Recordings were made from major intracranial arteries and

* This apparatus was designed by Dr. Derek Boughner of the Department of Biophysics.

FIGURE 15

Frequency response curve of the intracardiac phonocatheter used in the study of turbulence in human intracranial saccular aneurysms. The output voltage of the phonocatheter (decibels), relative to a reference signal of 500 Hz at 0 db, has been plotted as a function of the input frequency (Hz). See text for further description. K = kilo.



bifurcations, at normal systemic arterial pressure, in four patients undergoing craniotomy for reasons other than an intracranial aneurysm; two for extirpation of tumour, one for frontal lobectomy for post-traumatic epilepsy, and one for the repair of post-traumatic CSF rhinorrhea. In no instance was a bruit recorded.

b) ANEURYSM CASES

A summary of the results from 19 unselected, representative cases of intracranial aneurysm is given in Table 1. It should be noted that it is the practice of the Neurosurgical Unit at the University of Western Ontario to use deep hypotension, produced by the intravenous administration of trimethaphan camphorsulfonate,* in all cases during the dissection of the aneurysm (50). At the time of recording, the mean systemic arterial pressure was often considerably less than the pre-operative values, although on occasion it was possible to increase the mean pressure prior to recording. In spite of the disadvantage of hypotension, from the point of view of this investigation, a bruit was recorded from the aneurysm in 12 of the 19 cases.

There was considerable variation in the mean arterial pressure at which the bruits became audible. With the exceptions of case 10 and case 14, where the bruits were of low intensity, no sound was recorded

* Trimethaphan camphorsulfonate (Arfonad) is an autonomic ganglionic blocking agent and, as well, has a direct vasodilating effect on peripheral vessels. Its extremely short action allows "minute-to-minute" control of the blood pressure during surgery.

TABLE 1

SUMMARY OF RESULTS OF PHONOCATHETER STUDIES IN 19 CASES

Site & Case	Sex	Age	Pre-operative Blood Pressure (mmHg)*****	Aneurysm		Mean BP (mmHg) [†]	Characteristics of Bruit			Relative Amplitude (μV ± S.D.)
				Size (mm)	Shape		Bruit Present	Predominant Frequency (Hz ± S.D.)		
Middle Cerebral Bifurcation										
1.	F	58	200/100	10x10	S**	80	Yes	660 ± 10		630 ± 10
2.*	M	58	135/90	12x12	S	90	Yes	290 ± 10		380 ± 10
3.	F	52	180/90	10x10	B***	50	No	---		---
4.*	F	38	140/80	10x10	B	80	Yes	560 ± 30		630 ± 70
5.*	M	44	150/90	5x5	S	80	Yes	520 ± 50		190 ± 30
6.	M	44	160/110	10x7	S	50	Yes	180 ± 10****		250 ± 60
Anterior Communicating Artery										
7.	M	40	160/100	10x15	B	50	No	---		---
8.	F	56	150/85	3x6	B	70	Yes	270 ± 5		100 ± 5
9.	M	57	200/110	12x12	S	70	No	---		---
10.	M	43	190/110	5x5	B	40	Yes	580 ± 30		70 ± 15
11.	F	67	190/110	5x10	B	90	Yes	Too faint to measure		
12.	F	45	140/90	4x4	S	50	Yes	470 ± 40		660 ± 90
13.	F	30	140/90	7x12	B	50	Yes	460 ± 30		230 ± 40

Posterior Communicating Artery

14. F	63	160/110	6x8 B	45	Yes	310 ± 5	150 ± 30
15. F	23	130/80	10x5 B	55	Yes	560 ± 40	130 ± 30

Basilar Bifurcation

16. F	43	220/120	10x5 B	60	No	---	---
17. F	44	170/100	15x7 B	60	No	---	---

Anterior Choroidal Artery

18. F	39	130/90	8x8 B	45	No	---	---
-------	----	--------	-------	----	----	-----	-----

Pericallosal Artery

19. M	38	185/130	12x10 B	90	No	---	---
-------	----	---------	---------	----	----	-----	-----

† - mean arterial systemic pressure at which bruit recorded or highest mean pressure at which recording attempted in those cases where no bruit found.

* - case report given in text.

** - S = spherical aneurysm.

*** - B = bilocular or multilocular aneurysm.

**** - the lower band-pass filtering was not used in this case because of the low-pitched nature of the bruit.

***** - these values were taken from the patients' charts. Since subarachnoid haemorrhage is often associated with an increase in blood pressure, these values may be greater than the normal values for blood pressure in each case.

unless the mean pressure was 50 mmHg or above. In each case the amplitude of the bruit would vary with the mean pressure; being least at low pressures and greatest at high pressures. Often bruits could be recorded from the vessels either immediately proximal or distal to the aneurysm, but they were always of less intensity than the bruit from the sac of the aneurysm.

All of the aneurysmal bruits had similar features. They were musical in quality and quite high-pitched in tone; the average predominant frequency being $440 \text{ Hz} \pm 150 \text{ S.D.}$ They had a diamond-shaped oscillographic profile, similar to that found with cardiac systolic ejection murmurs. At higher pressures, the bruits were often continuous in both systole and diastole, with marked accentuation in systole.

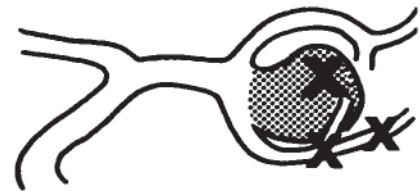
Case 2. This 58-year-old man had a large spherical middle cerebral bifurcation aneurysm (Figure 16a). He was normotensive and had no clinically evident cardiac murmurs, or neck and cranial bruits. At surgery, the aneurysm was exposed at a mean pressure of 60 mmHg. At this pressure no sound was recorded either from the sac or the bifurcation. The pressure was then raised slowly. A faint bruit became audible at 80 mmHg. Recordings (Figure 16b) from the sac of the aneurysm, a small bifurcation lying on the sac, and a branch vessel 3 mm distal to the bifurcation, were made at a mean systemic pressure of 90 mmHg. The amplitude of the bruit was maximal from the sac, being $380 \pm 110 \mu\text{V}$. In contrast, at the same pressure, the amplitude of the

FIGURE 16a

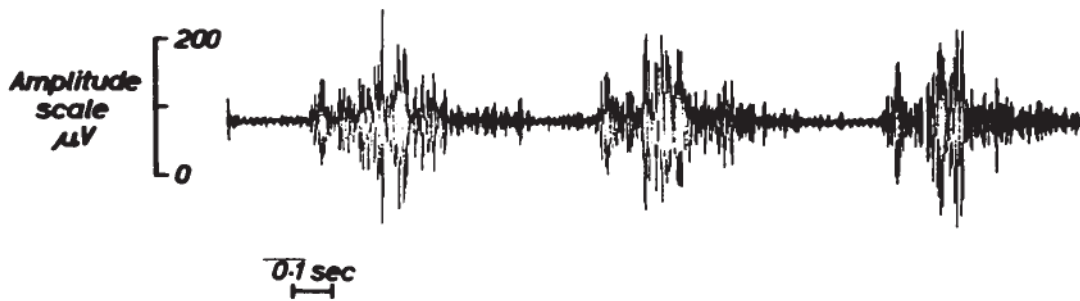
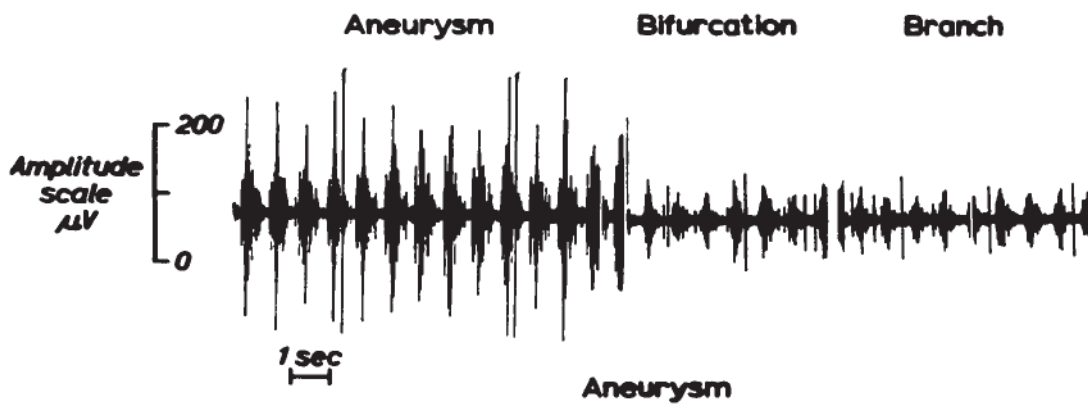
Case 2. Angiogram. Left middle cerebral bifurcation aneurysm, anteroposterior view. The line drawing on the right shows the three phonocatheter recording sites used in this case; the fundus of the aneurysm, a small middle cerebral bifurcation, and a branch of that bifurcation.

FIGURE 16b

Case 2. Light-beam oscillograph record of bruits at mean systemic arterial pressure of 90 mmHg. The amplitude scales on the left are relating to a standard calibrating signal of 500 μ V. The upper records are at a chart speed of 1 cm/sec. The amplitude is maximal from the aneurysm. The lower record is at a chart speed of 10 cm/sec and illustrates the characteristic diamond-shaped profile of the bruits and their systolic accentuation.



A



B

bruit recorded at the bifurcation was $80 \pm 25 \mu V$, and from the branch, $100 \pm 10 \mu V$. No sound was recorded from cortical vessels in the area. The frequency of the bruit recorded from the aneurysm was 290 ± 10 Hz at a mean pressure of both 90 mmHg and 110 mmHg. The frequency of the bruit from the branch was 320 ± 10 Hz, and at the bifurcation, 260 ± 10 Hz, both of which are significantly different than from the aneurysm ($p < 0.001$).

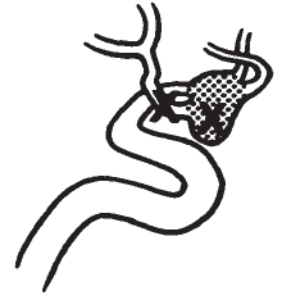
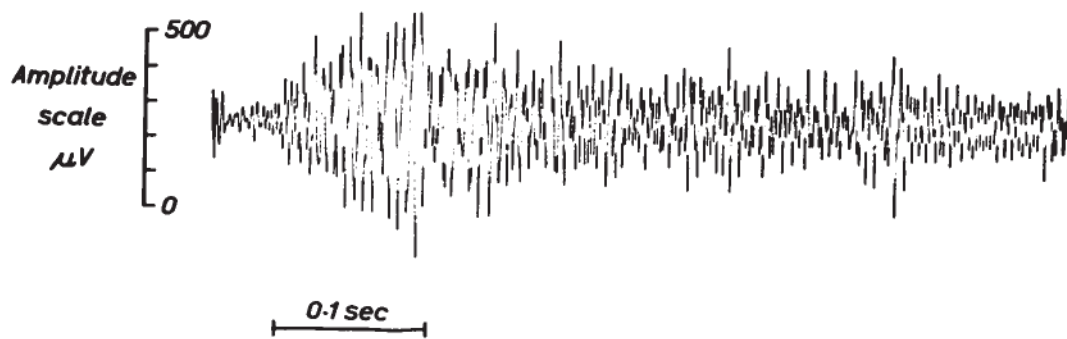
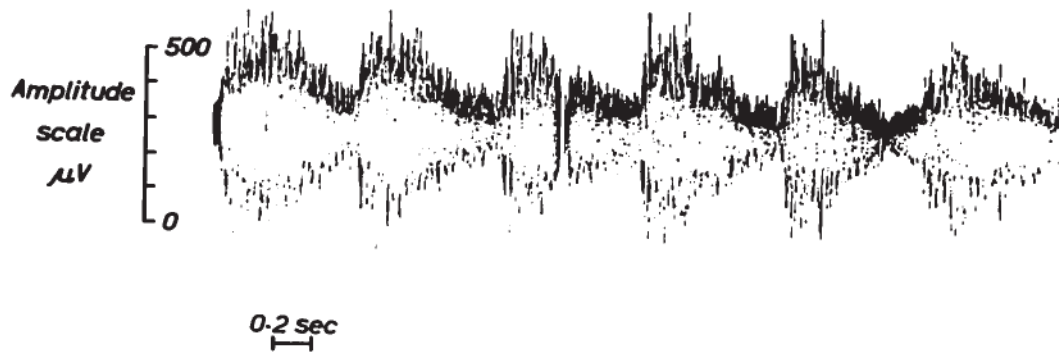
Case 4. This 38-year-old woman bled from a large bilocular middle cerebral bifurcation aneurysm (Figure 17a). She had a five year history of mild hypertension (150/100). There were no clinically evident murmurs or bruits. At operation, initial recordings were made at a mean pressure of 80 mmHg. A loud bruit was recorded from the sac (Figure 17b). This bruit was continuous in both systole and diastole, with sudden accentuation in systole. The maximum amplitude was $630 \pm 70 \mu V$, while the frequency of the systolic component was 560 ± 30 Hz and the diastolic component, 430 ± 5 Hz. This frequency difference is statistically significant ($p < 0.001$). No sound was recorded from adjacent cerebral tissue, but a very faint bruit (amplitude $35 \pm 4 \mu V$) was recorded from a branch of the middle cerebral bifurcation, 5 mm distal to the aneurysm. The mean pressure was lowered to 45 mmHg prior to ligation. At this pressure, a faint systolic bruit ($60 \pm 15 \mu V$) could still be heard, but only from the aneurysm.

FIGURE 17a

Case 4. Angiogram. Right middle cerebral bifurcation aneurysm, lateral view. Phonocatheter recordings were made from the sac and neck of the aneurysm and a main branch of the bifurcation.

FIGURE 17b

Case 4. Light-beam oscillograph record of bruits from the sac of the aneurysm at a mean systemic arterial pressure of 80 mmHg. The upper record is at a chart speed of 5 cm/sec, the lower at 40 cm/sec. In this case the bruit is continuous through systole and diastole, with sudden accentuation in systole. The predominant frequency of the murmur (560 ± 30 Hz) can be calculated from the fast record by counting the number of spikes (cycles or vibrations) over a given time period.

**A****B**

Case 5. This 44-year-old man bled from a moderate-sized spherical middle cerebral bifurcation aneurysm. The aneurysm was exposed at a mean pressure of 60 mmHg. At this pressure no sound was recorded from the sac of the aneurysm, its neck, or the intracranial portion of the internal carotid artery. The patient was given 0.25 mg of metaraminal bitartrate.* At a mean pressure of 80 mmHg, no sound was recorded at the neck but a faint bruit was audible from the sac. With a further increase in the mean pressure to 85 mmHg, the intensity of this bruit rose dramatically. Its duration was very brief, however, occurring over only 10% of the heart cycle, and synchronously with the peak of systole (Figure 18). The frequency was 520 ± 50 Hz; the amplitude 190 ± 30 μ V. At this pressure, a bruit was also audible from the neck of the aneurysm. Its amplitude was 130 ± 20 μ V. No sound was recorded from the internal carotid artery. Following the application of the clip, the bruits were no longer present.

Case 12. This 45-year-old woman bled from a small anterior communicating artery aneurysm while straining to remove a stuck oil-filter cap from her car (Figure 19a). There was a history of mild hypertension but she was normotensive on admission. She had a grade 1/6 cardiac systolic ejection murmur along the left sternal border, but no

* Metaraminal bitartrate (Aramine) is a vasopressor agent used commonly to raise the blood pressure during surgical anaesthesia.

FIGURE 18

Case 5. Dynograph chart record of the bruit recorded from the aneurysm, and the simultaneous radial artery pressure, following the administration of 0.25 mg of Aramine intravenously. The signal from the phonocatheter has been passed through an integrating circuit with a time constant of approximately 0.1 sec. At a mean pressure of 65 mmHg no bruit is recorded. At 80 mmHg a faint bruit is evident and at 85 mmHg the amplitude of the bruit has increased considerably.

DYNOGRAPH CHART RECORD
Case 5

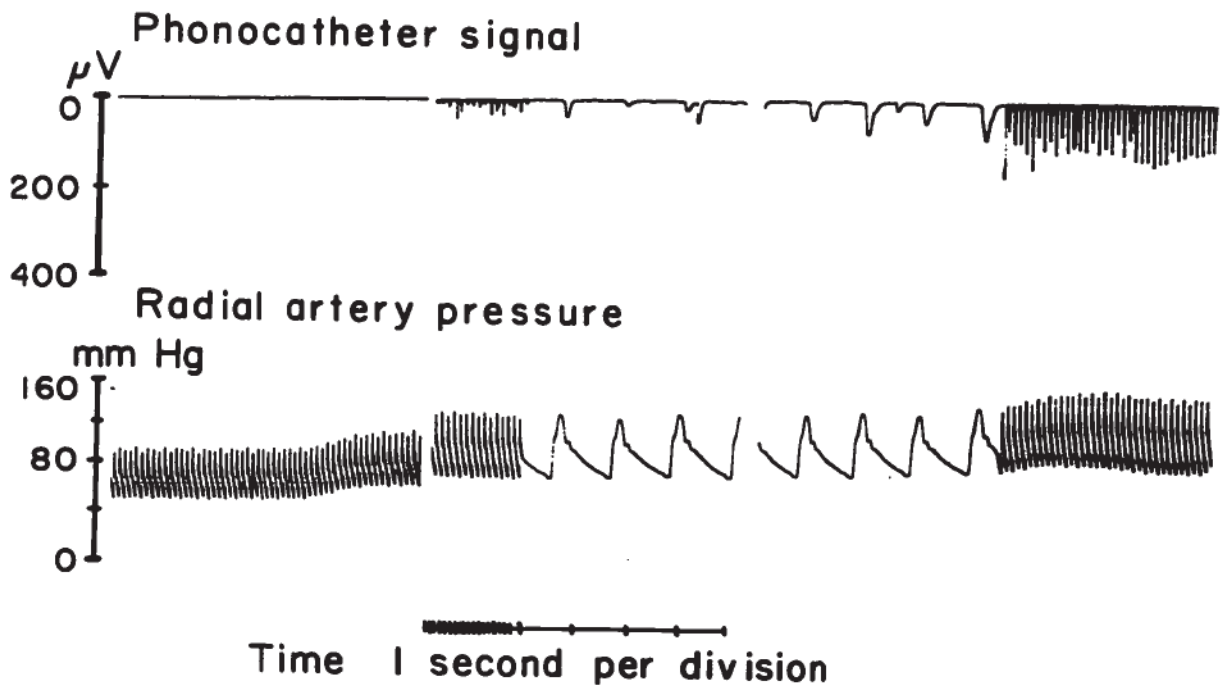


FIGURE 19a

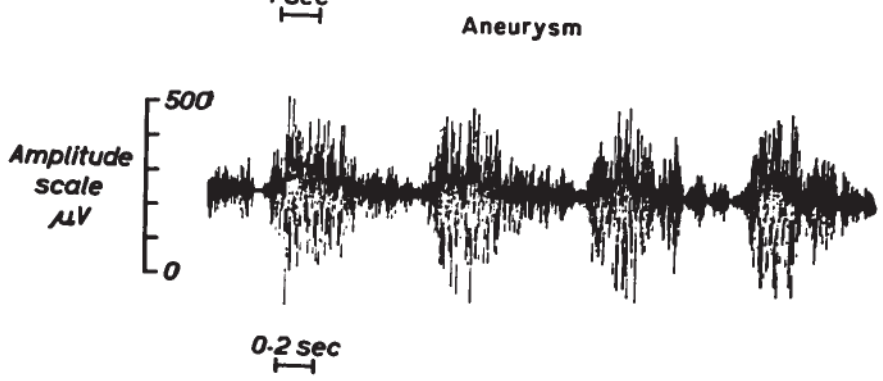
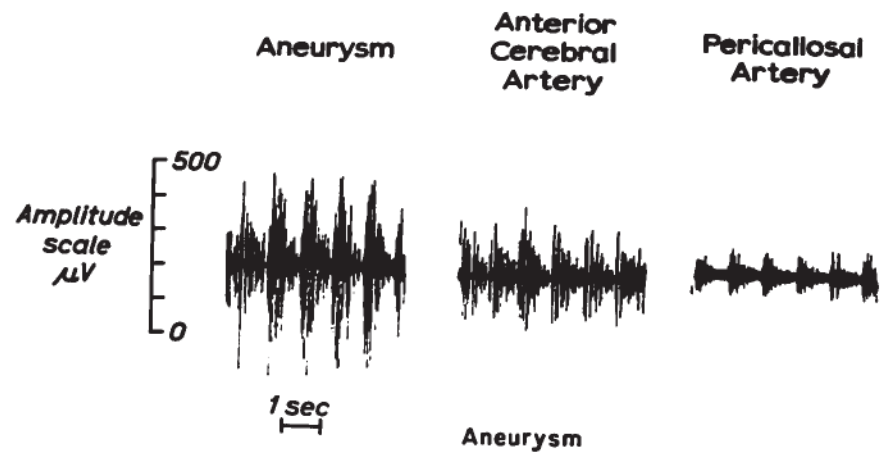
Case 12. Angiogram. Right anterior communicating artery aneurysm, oblique view. Phonocatheter recordings were made from the sac, the right anterior cerebral artery, and the right pericallosal artery.

FIGURE 19b

Case 12. Light-beam oscillograph record of bruits at a mean systemic arterial pressure of 50 mmHg. The upper records are at a chart speed of 1 cm/sec, the lower at 5 cm/sec.



A



B

bruit could be heard in her neck. There was no cranial bruit. The aneurysm was exposed at a mean pressure of 50 mmHg. Even at this low pressure, a remarkably loud and almost continuous bruit was recorded from the aneurysm (Figure 19b). The amplitude was $660 \pm 90 \mu V$; the frequency 470 ± 10 Hz. Less intense bruits were recorded from the right anterior cerebral artery, 5 mm proximal to the neck of the aneurysm ($400 \pm 110 \mu V$), and the ipsilateral pericallosal artery, 2 mm distal ($140 \pm 35 \mu V$). A very faint bruit could be heard over the internal carotid artery, approximately 2 cm proximal to the aneurysm.

4) DISCUSSION

a) HISTORICAL REVIEW

Prior to this investigation, there has been no direct evidence for turbulent blood flow in human intracranial saccular aneurysms. However, it has been widely assumed that turbulence is likely. Sir Geoffrey Jefferson* is reported (118) to have exclaimed on first being shown the whirlpool rapids at Niagara Falls, "I say what a magnificent example of the circulation in an aneurysm."

Clinical evidence. In the clinical literature there have been a few reports describing cranial bruit** in association with saccular aneurysms.

* Sir Geoffrey Jefferson, F.R.S., Professor of Neurosurgery at the University of Manchester, was a famous, pioneering British neurosurgeon.

** A cranial bruit is an auscultatory sound heard over the skull. The commonest causes are arteriovenous malformations of the brain and carotid-cavernous fistulae. In each case abnormally high blood flow produces turbulence.

Walton (158) found references to 13 cases. Eight of these were in a series reported by Richardson and Kofman (118), who considered the bruits to have been produced by the aneurysms. Cranial bruits were not heard in any of the cases in this study. Presumably they are not a more common finding because of the low intensity of the bruit in an aneurysm and the attenuation which occurs during the transmission of the sound from its site of origin, deep in the head, to the surface of the scalp.

Experimental evidence. Experimental simulations of saccular aneurysms in animals have suggested that blood flow is likely to be turbulent in the human case. German and Black (67, 68, 69) used dogs, in which they sutured a vein-pouch graft to the wall of the common carotid artery. Turbulence in these "side-aneurysms" was confirmed by the presence of a palpable thrill and audible bruit from the sac. Kikut (92) used the same model, and with the aid of magnification, visualized turbulence by illuminating the sac with an intense light. These animal models are not comparable to the clinical situation, however, for intracranial saccular aneurysms arise at the apex of a bifurcation rather than from the side wall of a vessel.

b) THE PRESENT STUDY

Site of origin of the turbulence. There seems little doubt that the bruits recorded in this study were the result of turbulent blood flow within the aneurysms. In every case the amplitude of the bruit was

maximal on recording from the sac or neck. Bruits recorded from nearby vessels were invariably of lower amplitude, the result of attenuation of the sound as it was transmitted from its site of origin in the aneurysm, along the vessel, to the recording site. With an increase in arterial pressure, the bruits became audible first from the aneurysm, and with a decrease, disappeared last from the aneurysm, again indicating that the aneurysm was the site of origin. With sufficient decrease in systemic pressure, a previously recorded bruit would disappear entirely. For example, in case 8, a continuous bruit had been recorded from the aneurysm at 70 mmHg, whereas at 45 mmHg the bruit had disappeared completely.

Effect of hypotension. There was considerable variation, from one aneurysm to another, in the mean pressure at which the bruits became audible. This no doubt reflects the variation in the precise haemodynamics within each sac, because of differences in aneurysm size and geometrical configuration. As well, it reflects the variation in flow at any given pressure, from patient to patient. No doubt, this variation in flow explains why a bruit was not recorded in every case.

In normotensive individuals, total cerebral blood flow is maintained near normal levels, in the face of a falling systemic blood pressure, until a mean pressure of approximately 50 mmHg is reached (93). This is the result of autoregulation of the cerebral blood flow. Below this pressure, autoregulation fails, and there is a precipitous decline

in flow. In the presence of hypertension, this abrupt decrease in flow may occur at a much higher mean pressure (59). Finnerty et al (59) found that signs and symptoms of cerebral ischemia appeared with an average fall in cerebral blood flow to 60% of normal values. In normotensive individuals this occurred at a mean arterial pressure of 30 mmHg, in those with essential hypertension at 50 mmHg, and in those with malignant hypertension at 90 mmHg.

In each of the cases in this study in which no bruit was recorded there was a history of hypertension, with the exception of case 18. Although there was no means of measuring flow, it is likely that, in these hypertensive cases, the drug-induced hypotension was sufficient to have produced a decrease in flow to the point where the critical Reynolds number for turbulence in the sac of the aneurysm was not reached. In the cases with bruits, the average decrease in mean systemic blood pressure at the time of recording was $41 \pm 17\%$; in those with no bruit, $53 \pm 6\%$. The difference is statistically significant, but not to a high degree ($p < 0.10$). At the time of recording, if the mean pressure in those patients with hypertension had been closer to their normal pre-operative pressures, a bruit may have been recorded in every case. However, the relation between pressure and flow is not simple. For in cases 6, 10, and 14, all of whom were hypertensive, faint bruits were recorded at very low pressures.

Case 19 was the only one in which a bruit was not recorded when the mean pressure was above 70 mmHg. In this case a recording was attempted at a mean pressure of 90 mmHg, 40% below the normal mean systemic pressure of 150 mmHg. In view of the findings of Finnerty et al (59), one would expect that in such a hypertensive patient there had been a considerable reduction in flow at this pressure. Also, this aneurysm had an exceptionally broad neck, such that the largest Mayfield clip backed off the neck repeatedly, and eventually had to be ligated in place. It is possible that in cases with a broad neck, in relation to sac diameter, higher than normal flows are necessary to reach the critical Reynolds number.

Geometry and size. Perhaps other factors, such as the geometry and size of the aneurysm, contribute to the absence of a bruit. No bruit was heard in six of the 15 bilocular or multilocular aneurysms, and in one of the four spherical aneurysms. This difference is not significant. The average maximum diameter of the aneurysms with a bruit was 9 ± 3 mm, and 12 ± 3 mm in those cases without a bruit. This difference is statistically significant ($p < 0.02$), and may indicate that flow is relatively sluggish, and below the critical Reynolds number, in larger aneurysms.

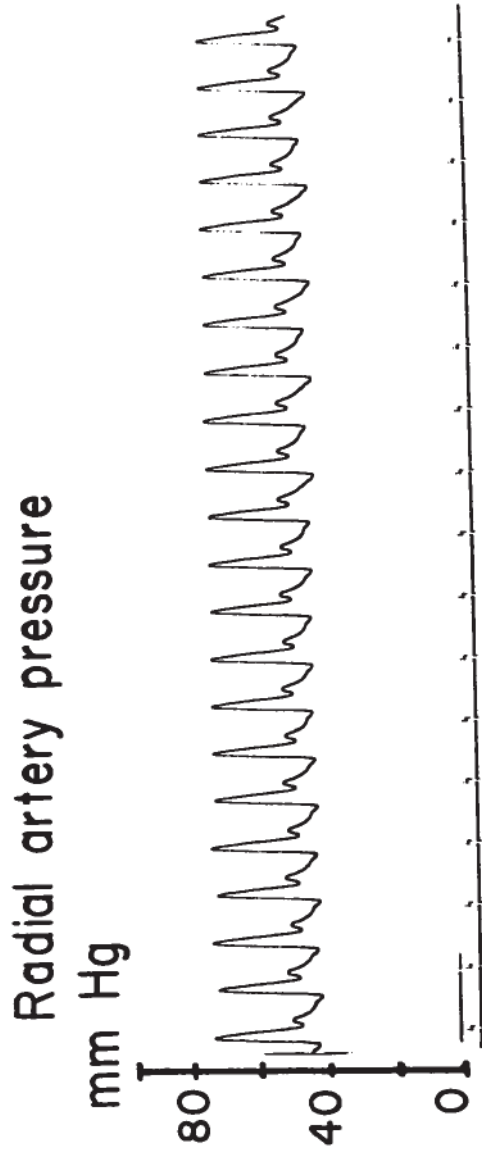
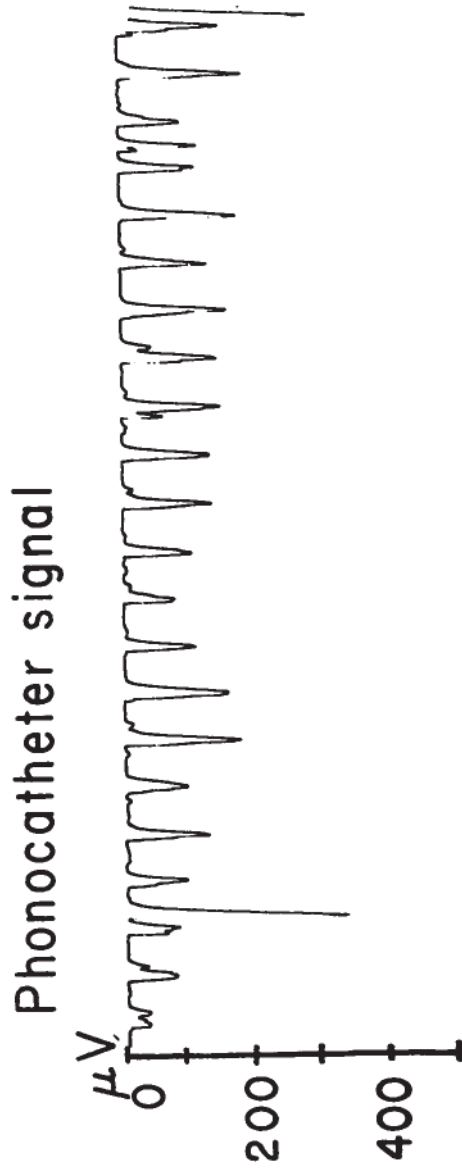
Timing of the bruit. In those cases in which the bruit was not continuous during both systole and diastole, the bruit was coincident with systole. This is seen in the chart record from case 6 (Figure 20). As systole corresponds closely to the time of peak flow velocity within the

FIGURE 20

Case 6. Dynograph chart record to illustrate the time correlation between systemic arterial pressure (radial artery) and the bruit recorded from the aneurysm. The maximum amplitude of the bruit occurs during systole.

DYNOGRAPH CHART RECORD

Case 6



Time 1 second per division

circulation (27, 99), it will also correspond to the time of highest flow within the aneurysm, when the critical Reynolds number will be exceeded and turbulence produced. In those cases with a continuous bruit (Figure 17b), the maximum amplitude of the bruit occurred during systole, again correlating with the highest flow velocities.

Presence of cardiac murmurs. In cases 5, 12, and 14, a grade 1/6 cardiac systolic ejection-type murmur was heard along the left sternal border. It is unlikely that these faint murmurs were transmitted to the intracranial vessels and confused with the bruits from the aneurysms. In each case, no bruit was heard on auscultation over the carotid arteries in the neck. As well, in case 5, no bruit was recorded intracranially. In case 12, the amplitude of the intracranial bruits was maximal from the sac of the aneurysm. In case 14, at 45 mmHg pressure, a distinct bruit was recorded from the neck of the aneurysm, but no sound was heard on the internal carotid artery, 1 cm proximal to the neck.

The distinctive high-pitched nature of the bruits recorded from the aneurysm (with the exception of case 6) is in contrast to cardiac murmurs, where the predominant frequencies are less than 200 Hz (157). This may reflect differences in the total mass of tissue being vibrated in each case.

Findings after occlusion of the neck. Although it was not possible to re-record from the aneurysm in every case following ligature or clip

application, in those cases where it was possible, the bruits were no longer present. However, when the pressure had risen to normal or near normal levels, low intensity bruits were sometimes heard in the region of the clip or ligature. There are a number of explanations for this finding. For example, in case 14, a moderately loud bruit was recorded at 80 mmHg from the internal carotid artery, 1 mm distal to the clip. On the post-operative angiogram, a small portion of the neck was still filling. No doubt this was producing the turbulence. It is also possible that in some cases the clip slightly stenosed or kinked the parent vessel. This was true in case 15. A faint bruit was recorded at 95 mmHg from the proximal anterior cerebral artery 1 mm from the neck after the application of the clip. Kinking of the vessel by the clip could be seen and it had to be reapplied.

Method of frequency analysis. The method of determining the predominant frequency in an aneurysmal bruit, by averaging the number of spikes or vibrations per second on a high speed oscillograph record was chosen because of its relative simplicity. To be satisfied that the mean frequency values obtained were reasonably representative, a more detailed analysis was carried out in case 4. A very high speed record (400 cm/sec) was made of the bruit recorded from the aneurysmal sac. On this record, each millimetre was equivalent to 0.25 msec in time. The period or interval between each spike was measured with a pair of calipers; the accuracy of measurement being ± 0.5 mm. The

results were converted to frequency by dividing the period (in milliseconds) into 1000, and plotted as a frequency histogram for both the systolic and diastolic components of the bruit (Figure 21). With this method, the calculated, average frequency of the bruit in systole was 580 ± 80 Hz, and in diastole, 485 ± 80 Hz. The corresponding values by the averaging method were 560 ± 30 Hz and 430 ± 5 Hz. There is no statistically significant difference in the results using either method.

Frequency differences in systole and diastole. A continuous bruit was present in five cases, in which the predominant frequencies could be calculated for both the systolic and diastolic portions of the bruit (Table 2). The frequency difference observed in case 4 was present in each of the other cases; the frequency being consistently higher in systole than diastole. These frequency differences may be the result of variations in the tension in the wall of the aneurysm during the heart cycle. As the pressure rises during systole, the wall tension rises (27), as does the frequency at which the wall vibrates in response to the turbulent flow within the aneurysm. The effect is analagous to increasing the pitch of a stringed instrument, by increasing the tension in the string (90).

c) TURBULENCE AND GROWTH OF ANEURYSMS

The demonstration of turbulence within human intracranial saccular aneurysms raises the consideration of whether or not it plays any role in the formation, subsequent enlargement, or subsequent rupture

FIGURE 21

Case 4. Frequency histogram of bruit recorded from the aneurysm to illustrate the frequency components of the bruit, and the differences between systole and diastole. See text for description of method. Although the average frequencies calculated using this method are the same as those found by averaging the number of spikes over a given time period, this method demonstrates a wide distribution of frequency components about the predominant frequency.

FREQUENCY HISTOGRAM

Case 4

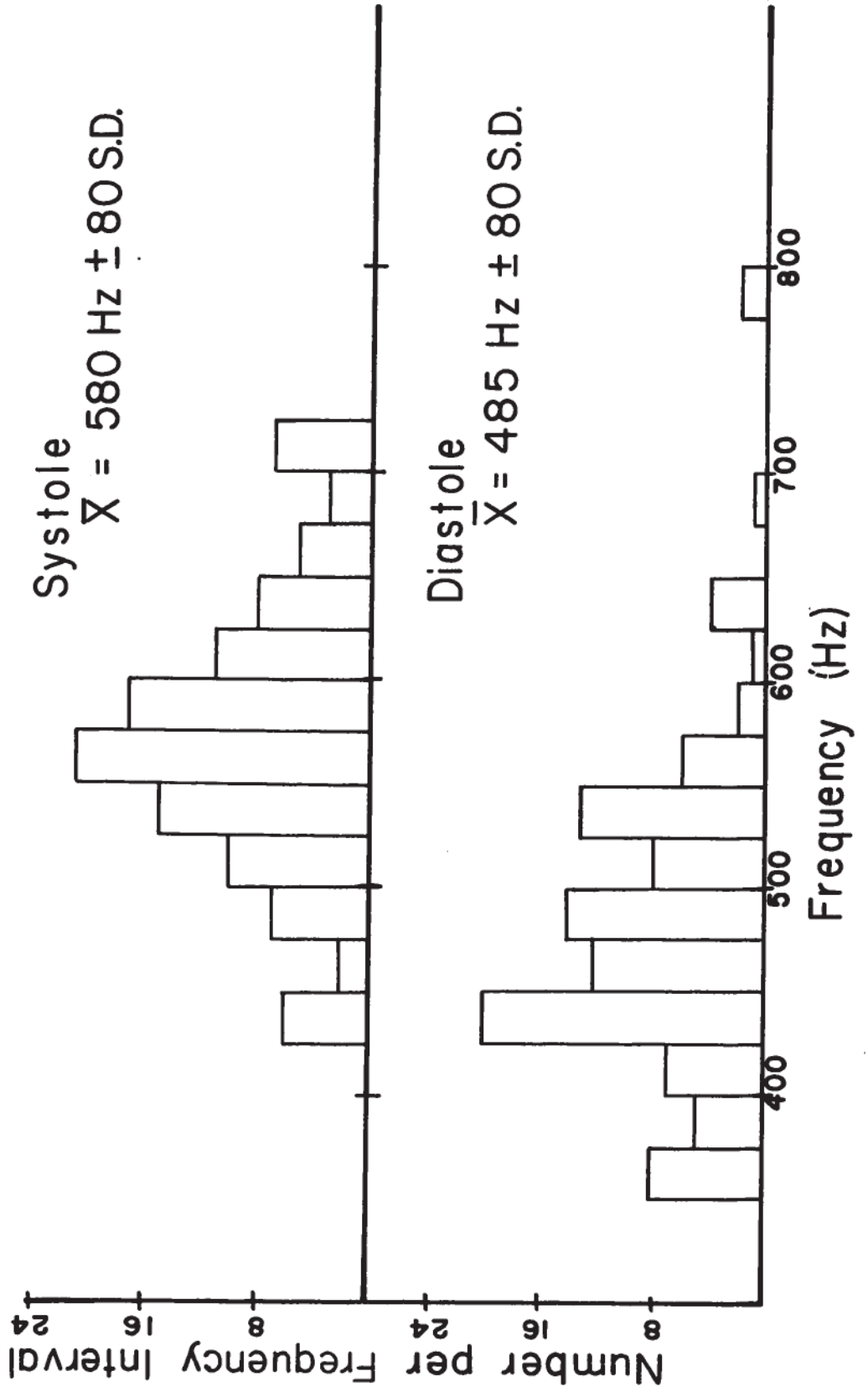


TABLE 2
FREQUENCY DIFFERENCES IN SYSTOLE AND DIASTOLE

Case	Systole (Hz \pm S. D.)	Diastole (Hz \pm S. D.)	p Value
4	a) averaging method 560 \pm 30	430 \pm 5	<0.001
	b) direct measurement 580 \pm 80	485 \pm 80	<0.001
8	270 \pm 5	230 \pm 15	<0.001
12	470 \pm 40	370 \pm 20	<0.001
13	460 \pm 30	300 \pm 20	<0.001
14	310 \pm 5	215 \pm 5	<0.001

of these aneurysms. On the basis of the values for critical Reynolds numbers found in the model experiments, it was predicted that turbulence would not normally occur at intracranial arterial bifurcations. This was confirmed in the control cases, from which no bruits were recorded. This further substantiates the conclusion based on the model experiments, that turbulence plays no role in initiating the outpouching which is destined to become a saccular aneurysm. But once a small outpouching has occurred, it seems reasonable to postulate that the violently fluctuating pressures of turbulence within the sac, contributes to its enlargement and eventual rupture. Just as the turbulent flow conditions of Niagara Falls erode rock with the passage of time, so the turbulence within an aneurysm may contribute to the degenerative changes seen on microscopic examination of their walls. In particular, these are degeneration of the internal elastic membrane and atherosclerotic-like changes, such as intimal hyperplasia, deposition of lipid-laden macrophages, and fibrinoid degeneration (see Chapter II). Some writers (38, 155) believe all these changes result from degeneration of the wall in a primary atherosclerotic process. But others (39, 82, 147) consider them secondary to injury to the wall.

Effect of turbulence on vascular tissue. There is considerable evidence that turbulence is capable of damaging vascular tissue. Roach (122, 123, 124) has shown that the vibrations of a vessel wall by turbulence distal to a stenosis in extracranial arteries, "weaken the elastin

fibres, and possibly break down links between the collagen fibres, so that the wall becomes more distensible." Foreman and Hutchison (61), using extracranial dog and human arteries in vitro, have investigated the frequency spectrum of the wall vibration produced by the turbulence beyond a stenosis. They concluded that turbulence "excites the artery to vibrate over a wide range of frequencies within which are discrete frequencies which coincide with the resonant frequencies of the artery." They noted further that if vessels do vibrate at a resonant frequency, relatively low forces can result in relatively high strains, making structural damage to the wall likely. Fry (64) has demonstrated that turbulence beyond a stenosis in the aorta of dogs will destroy the endothelial cells and expose the basement membrane, upon which a platelet thrombus forms. This may initiate atherosclerotic degeneration of the wall as outlined in Chapter III. Finally, Tominaga (150) produced aneurysms on the common carotid artery of dogs by injecting the adventitia with nitrogen mustard and scratching the intima at the same site with a fine bore needle. Outpouching and rupture inevitably resulted from this procedure. Proximally placed stenoses, which produced turbulence in the area of vessel damage, accelerated the time to rupture, suggesting that the turbulence contributed to the degenerative process in the vessel wall.

Conclusions. In view of this evidence for the damaging effects of turbulence on vascular tissue, it seems reasonable to conclude that the

turbulence in human intracranial saccular aneurysms is an important factor contributing to their enlargement and rupture. Once there is a small aneurysmal outpouching at the apex of an intracranial bifurcation, turbulence occurs within it. The resulting incessant vibration of the wall of the aneurysm probably produces the advanced state of degeneration seen on microscopy, by a process similar to the vibrational fatigue of other structural materials (61). The elastic tissue of the internal elastic membrane is particularly vulnerable to this process (122, 123, 124). The atheroma-like changes in the wall are also a consequence of the same process. The end result is a loss of strength in the wall of the aneurysm and an alteration in its elastic properties, such that it is less able to withstand the pulsatile stress to which it is subjected in the circulation.

5) SUMMARY

(1) Bruits, indicative of turbulent flow, were recorded with an intracardiac phonocatheter from 12 out of 19 cases of human intracranial saccular aneurysms studied at the time of craniotomy.

(2) The bruits were characterized by a diamond-shaped profile, systolic accentuation, a relatively high-pitched tone ($440 \text{ Hz} \pm 150 \text{ S. D.}$), and a musical quality.

(3) In those cases in which no bruit was recorded, flow in the aneurysm was less than the critical value for turbulence. All but one of

these patients had systemic hypertension. The drug-induced hypotension at the time of recording was significantly greater in the group without bruits than in the group with bruits. A bruit would quite likely have been recorded in every case, if the systemic pressure at the time of recording had been closer to the normal pre-operative pressure.

(4) There is no doubt that turbulence produces and accelerates degenerative changes in vascular tissue. It seems likely that the turbulence within aneurysms plays an important role in the degeneration of the elastica and in the production of the secondary atheroma-like changes seen in their walls. This weakens the wall and renders the aneurysm less able to withstand the stress to which it is subjected, resulting in enlargement of the sac, and in some cases, rupture of the aneurysm.

(5) Turbulence does not occur normally at human intracranial bifurcations. This confirms the conclusion, made on the basis of the model studies, that turbulence does not initiate an aneurysm.

V. THE DIRECT MEASUREMENT OF PULSATILE
INTRA-ANEURYSMAL PRESSURE

"It is considered probable that the mean pressure within aneurysms is the mean blood pressure, ..."

- E. H. Wood (162)

1) INTRODUCTION

There have been a number of reports on the direct measurement of blood pressure in human intracranial arteries (6, 17, 163). These indicate that there is no pressure drop between the arteries in the neck, which supply the brain, and the major intracranial arteries. Because of the possible dangers involved in obtaining the measurements, there is very little comparable information regarding intra-aneurysmal pressure (164); although it has been assumed that the pressure within intracranial aneurysms is similar to that in the intracranial arteries (162).

To obtain more information on this subject, a study was carried out in conjunction with the study on turbulence in aneurysms to determine, whether or not, the mean intra-aneurysmal pressure is equal to the systemic arterial pressure, and whether or not, the

intra-aneurysmal pressure is pulsatile. The answer to each of these questions has a direct bearing on the nature and extent of the stress acting on the wall of an aneurysm (Chapter VII).

2) METHOD

To record the blood pressure from aneurysms during their surgical exposure, a 22-gauge needle with a metal shaft was used. This was connected by a 100 cm length of fine polyethylene tubing to an electronic pressure transducer (Statham Model P23 DEc), the output of which was recorded on a paper chart-recorder (Beckman Type R Dynograph). This length of connecting tubing was necessary in order to position the transducer well away from the sterile operative field. Either a 1.5 inch or a 4 inch needle; and either polyethylene tubing i. d. .030 inches (PE 60 Clay Adams Intramedic), or i. d. .047 inches (PE 190 Clay Adams Intramedic), were used, depending on the requirements of the experiment. The PE 60 tubing is known to give a faithful reproduction of the pulse pressure contour (87). A 10 ml syringe, filled with heparinized saline, was connected to the other outlet of the transducer by a two-way stopcock, and used to flush through and fill the transducer, tubing, and needle. Care was taken to eliminate any bubbles from the system which would damp pressure oscillations. The syringe was excluded from the system at the time of recording by closing the stopcock. Systemic arterial pressure was recorded simultaneously from the radial artery at the wrist, using a

large bore polyethylene needle (15 gauge), as outlined in Chapter IV. The pressure transducers were calibrated at the beginning and end of each experiment with a mercury manometer. The reference level during recordings, for both transducers, was usually the mid-axillary line.*

Because of the uncertainty about the effect of inserting a relatively large bore needle into a thin-walled aneurysm, cases were chosen with great care. The ultimate decision in each case was made by the operating surgeon. Recordings were made only in those cases in which the aneurysm and its neck had been uneventfully and completely dissected; and in which it was known that a clip could be applied safely and easily, if rupture of the aneurysm and uncontrollable bleeding resulted from insertion of the needle. The needle was inserted into the sac of the aneurysm, well away from the neck. When the needle was removed, the aneurysm was clipped immediately. Recordings were made at hypotensive levels of blood pressure, except in case 19.

3) RESULTS

Intra-aneurysmal pressure measurements were made in four cases. There were no unusual difficulties with bleeding, and no complications from the procedure, in any of the cases.

* The mid-axillary line is at the level of the left ventricle of the heart when a patient is lying in the supine position.

Case 3. This 52-year-old woman had a haemorrhage from a large bilocular middle cerebral bifurcation aneurysm, while bending over to pick up her shoes. The 1.5 inch needle and PE 60 tubing were used. Excellent pulsatile intra-aneurysmal pressure recording were obtained, which followed faithfully the systemic arterial pressure (Figure 22). At the time of insertion of the needle into the aneurysm, the pulsatile radial artery pressure was 58/40 and the calculated mean pressure, 46 mmHg. The intra-aneurysmal pressure recorded simultaneously was 60/42 (mean pressure = 48 mmHg). After a 30 second interval, during which the systemic pressure rose, the radial artery pressure was 72/52 (mean pressure = 59 mmHg) and the intra-aneurysmal pressure was 74/54 (mean pressure = 61 mmHg).

Case 13. This 30-year-old woman bled from a large bilocular anterior communicating artery aneurysm. Because of the depth of the aneurysm within the skull, the 4 inch needle connected to the PE 60 tubing was used. The systemic pressure was 54/36 (mean = 42 mmHg) and the intra-aneurysmal pressure was 48/40 (mean = 43 mmHg). Although the pulse pressure* in the aneurysm (8 mmHg) appeared to be considerably less than that in the systemic circulation (18 mmHg), this difference was probably the result of damping of the aneurysmal pulse pressure by the recording apparatus. This will be discussed further at the end of this section.

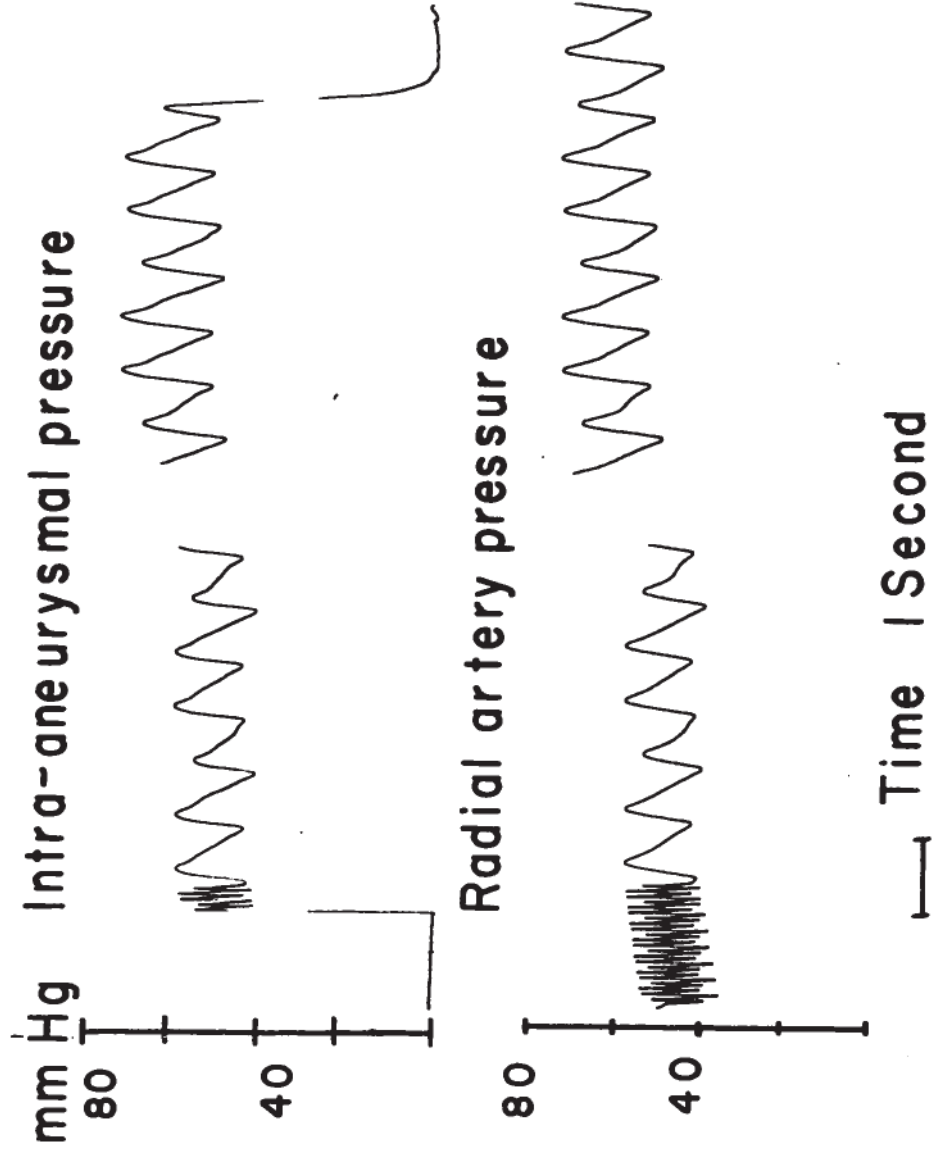
* The pulse pressure is the difference between the systolic and diastolic pressures.

FIGURE 22

Case 3. Dynograph chart record of the simultaneous recording of pulsatile intra-aneurysmal pressure and systemic arterial pressure (radial artery). See text for description.

INTRA-ANEURYSMAL PRESSURE

Middle Cerebral Aneurysm - Case 3



Case 16. This 43-year-old woman bled from a moderately large basilar bifurcation aneurysm. The 4 inch needle, connected to the PE 190 tubing, was used. This system damped the pressure oscillations almost completely, such that mean intra-aneurysmal pressure was recorded for comparison to mean systemic pressure (Figure 23). The mean intra-aneurysmal pressure was 60 mmHg; the mean systemic pressure, 59 mmHg.

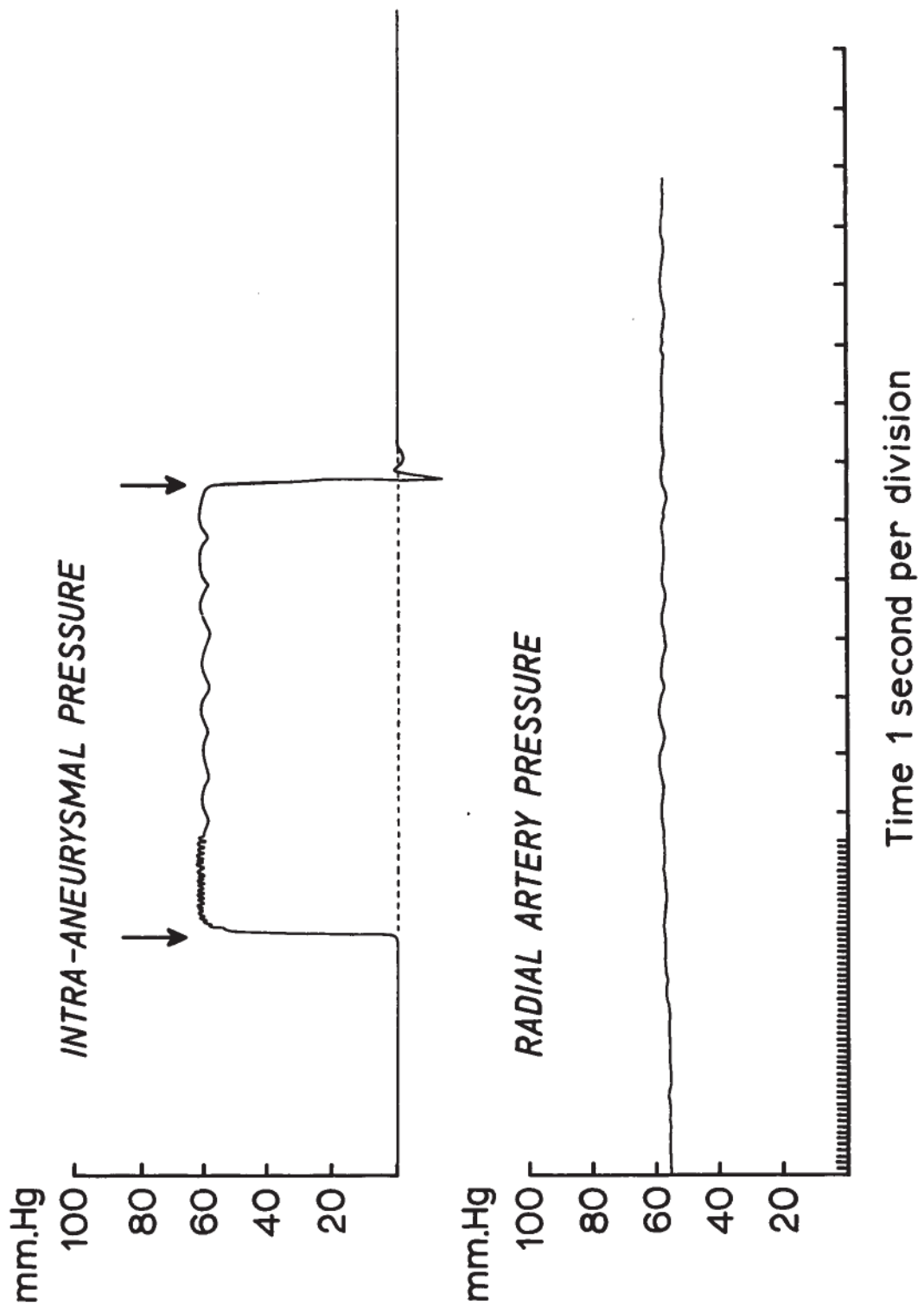
Case 19. This 38-year-old man had a haemorrhage from a pericallosal artery aneurysm. A continuous recording of radial artery pressure was not available in this case. Therefore, brachial cuff pressures were used. The 1.5 inch needle and PE 60 tubing were used. Intra-aneurysmal pressure was 100/80 (mean = 87 mmHg). Brachial cuff pressure was 135/80 (mean = 98 mmHg). The head was elevated in this case, such that the level of the aneurysm was 15 cm above that of the brachial artery. The pressure transducers were at the level of the radial artery and aneurysm, respectively. If allowance is made for this difference in height, by adding 11 mmHg pressure* to the mean intra-aneurysmal pressure, a mean value of 98 mmHg is obtained, which is identical to the calculated mean systemic pressure. The marked difference in pulse pressure (55 mmHg versus 20 mmHg)

* Since 1 mm of mercury produces a pressure equivalent to 1.36 cm of water, 15 cm of water is equivalent to 11 mmHg pressure.

FIGURE 23

Case 16. Dynograph chart record of the simultaneous recording of mean intra-aneurysmal pressure and systemic arterial pressure. The arrows indicate the moment of insertion of the needle into the sac of the aneurysm and its withdrawal. The total recording time was 25 seconds.

INTRA-ANEURYSMAL PRESSURE
BASILAR BIFURCATION ANEURYSM - HC 16



probably reflects the difference in the methods of recording pressure. The limits of systole and diastole are found more accurately with the cuff measurement of pressure.

The effect of the apparatus in damping pulsatile pressure measurements was investigated in one of the control cases, by comparing the pressure values obtained from one radial artery using the various needles and tubing simultaneously. The 4 inch needle and PE 190 tubing damped the pulse pressure almost completely, as in case 16. There was much less damping with the PE 60 tubing. The 1.5 inch needle and PE 60 tubing produced the least damping, as in case 3.

4) DISCUSSION

Historical Review. The only previous report on intra-aneurysmal pressure is that of Wright (164), who studied three cases of middle cerebral bifurcation aneurysms. In two of his cases, the mean intra-aneurysmal pressure was only one-third of the systemic pressure, and in the third case it was slightly less. The pressures were pulsatile, but intra-aneurysmal pulse pressures were much less than systemic arterial pulse pressures. He did not discuss these low values, which are an unexpected finding. For, if they are correct, there would be a pressure gradient for flow into, but not out of, an aneurysm. This would result in no intra-aneurysmal flow, which is obviously not the case.

The Present Study. On the basis of this study, the following conclusions are made regarding intra-aneurysmal blood pressure:

- (1) The mean intra-aneurysmal pressure, as measured in aneurysms at four different sites on the circle of Willis, is equal to the mean systemic arterial pressure, within the error of measurement (± 2 mmHg). Any differences in the mean pressures are accounted for by differences in the height of the aneurysm and the recording site for systemic pressure.
- (2) The pressure within an aneurysm is pulsatile. This agrees with the observation made commonly by surgeons, that intracranial saccular aneurysms appear to pulsate (51).
- (3) The intra-aneurysmal pulse pressure is the same as the systemic pulse pressure. The damping of pulse pressures in some of the cases was the result of the recording apparatus used.

Significance. The results show that human intracranial saccular aneurysms experience the full force of systemic arterial pulsatile pressure. The relation of this finding to the stress in the wall of an aneurysm, and how it effects the chance of rupture is the subject of Chapter VII.

VI. THE ELASTICITY OF HUMAN INTRACRANIAL SACCULAR ANEURYSMS

"This damage (to the wall of an aneurysm) may be mechanical, due to pulsatile pressure-changes in a relatively inelastic sac"

- M. R. Crompton (39)

1) INTRODUCTION

In contrast to the major intracranial arteries from which they arise, the principal structural component of human intracranial saccular aneurysms is collagen. Recent electron microscopic studies (109, 110) have shown, however, that remnants of the internal elastic membrane may be present in the wall of an aneurysm (Figure 24). The degeneration of the elastic tissue elements, which may be the end-result of turbulence (Chapter IV), suggests that the elastic properties of aneurysms will differ from those of intracranial arteries; and that any elastin remaining in the wall will be functionally inactive. If this is so, it could be a further factor contributing to the enlargement and eventual rupture of aneurysms.

Although the static elastic properties of extracranial arteries

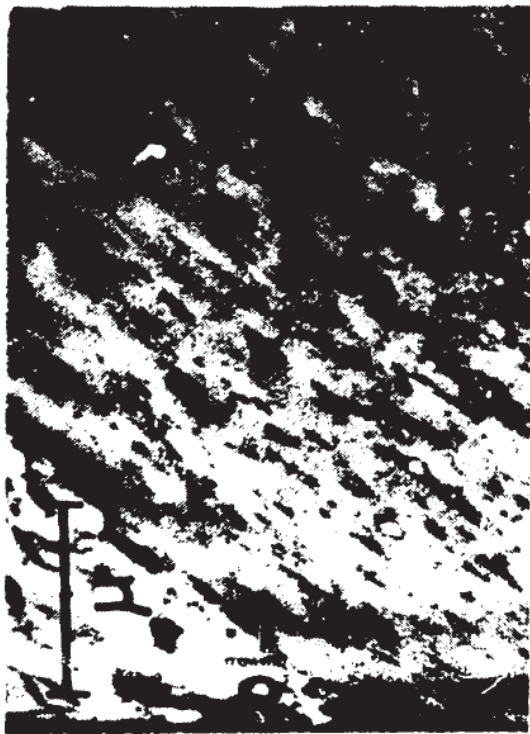
FIGURE 24

Electron microscopic section of the internal elastic membrane of a normal human cerebral artery, contrasted to that of its remnant, in the wall of a human intracranial saccular aneurysm. The elastica of the artery has a uniform, fibrillary appearance, whereas in the aneurysm the elastica is fragmented, with a granular and electron-dense appearance. el = elastica, col = collagen.

From Nyström (109).

INTERNAL ELASTIC MEMBRANE

Cerebral Artery



Saccular Aneurysm



have been extensively studied (4, 5, 12, 24, 25, 112, 121, 129) there is only one report on the elasticity of intracranial arteries (29). There have been no studies of the elasticity of intracranial aneurysms.

2) GENERAL PRINCIPLES OF ARTERIAL ELASTICITY

The elastic properties of arteries have been the subject of many reviews; those by Burton (24, 25, 27) are particularly noteworthy. A brief résumé will be given here. Elasticity is "the property of materials which enables them to resist deformation by the development of a resisting force" (24); it is the relation between stress, the applied force or "load" and strain, the resulting deformation of the structure. For simple homogeneous substances, the strain is directly proportional to the stress (Hooke's Law*). This linear relation holds until the "elastic limit" or "yield point" of the material is reached. Beyond this point, permanent deformation occurs. Eventually, with a continuing increase in stress, the "breaking stress," or "breaking strength," is reached and rupture of the structure results.

The constant of proportionality, relating stress to strain, is the elastic modulus. In the case of tensile stress, where equal and opposite forces are acting on a material, so as to lengthen it (or in the case of vessels, so as to cause distension), the appropriate modulus is Young's

* Robert Hooke, 1635-1703, British physicist and naturalist, Charter Member of the Royal Society.

Modulus, Y. That is,

$$Y = \frac{\text{stress}}{\text{strain}}$$

$$\text{or } Y = \frac{F/\Delta L}{A/L_0} *$$

where, F, is the applied force (dynes), A, is the cross-sectional area over which it acts (cm²), L₀, is the unstretched or resting length of the material (cm), and, ΔL, is the change in length (cm).

In the case of vessels, the stress equals the total wall tension, T (dynes/cm), divided by the thickness of the wall, t (cm). The strain is the corresponding distension of the vessel, or the increase in radius, ΔR, over the unstretched or resting radius, R₀. That is,

$$Y_{\text{arterial}} = \frac{T/\Delta R}{t/R_0}$$

Roy (129) was the first to note that the typical stress-strain diagram** of an artery is non-linear. An artery becomes less distensible with increasing distension; that is, its Young's Modulus increases with increasing stretch. Burton (24) proposed that this is a reflection of the heterogeneous nature of the arterial wall. This hypothesis was confirmed experimentally by Roach and Burton (120). Arteries have two structural components contributing to their elastic diagram, elastin and collagen, which have very different elasticities.

* The units of Young's Modulus are dynes/cm².

** Synonymous terms are "elastic diagram" or "distensibility curve."

The initial slope of the curve represents elastin, which is highly distensible; the final slope, collagen, which is relatively non-distensible (Figure 25).

Elastic diagrams are obtained by the simultaneous measurement of pressure and volume in isolated vessels, and the application of the law of Laplace.* This law was introduced to the biophysical and physiological literature by Burton, to explain the physical equilibrium of blood vessels.** The general form of the law is,

$$P = T \left(\frac{1}{R_1} + \frac{1}{R_2} \right)$$

where P is the intraluminal pressure (dynes/cm²), which is the force tending to distend and stretch the vessel wall; T is the tangential tension*** in the wall (dynes/cm), which is resisting this distension; and R₁ and R₂ are the principle radii of curvature (cm) of the structure.

In the case of a cylindrical arterial segment, one radius of curvature is infinite; so the relation between the distending pressure and the wall tension becomes,

$$P = \frac{T}{R} \text{ or } T = PR$$

* Laplace, 1749-1827, French mathematician and astronomer. This law is contained in his work, "Mécannique Celeste."

** Detailed development of the theory of the application of the law of Laplace to blood vessels may be found in the review by Burton, published in the Handbood of Physiology (25).

*** If a tangential slit were made in the wall of a vessel, the tangential tension is the force with which the edges would pull apart (27).

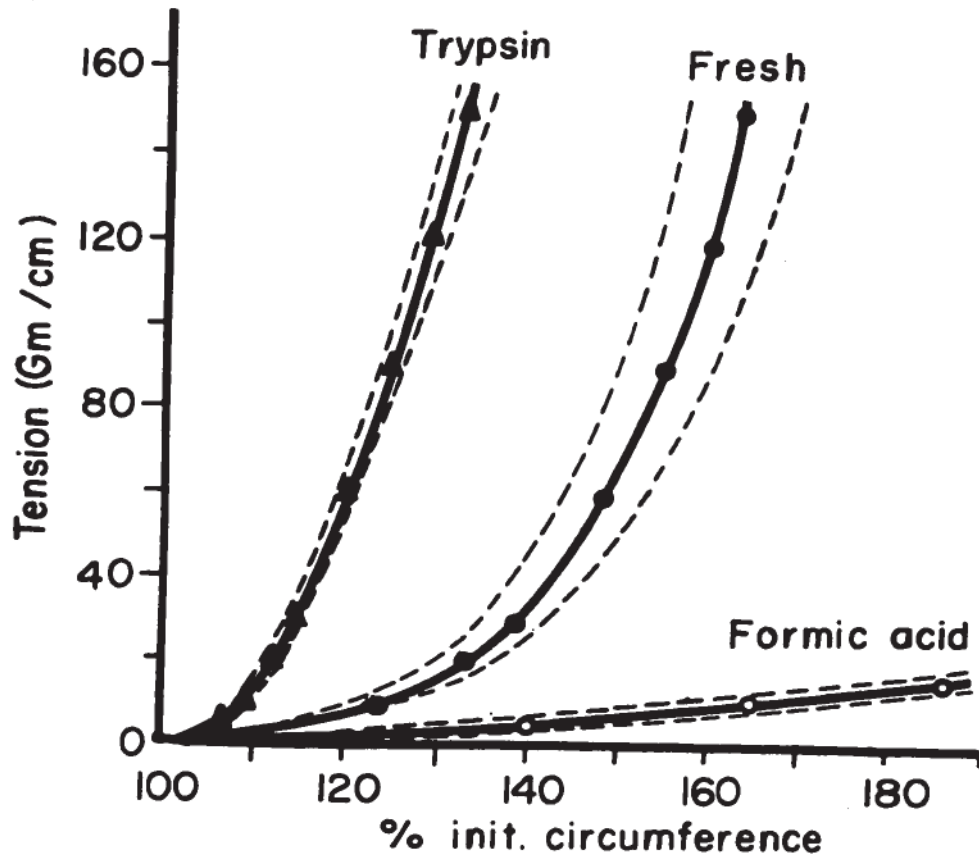
FIGURE 25

The reason for the shape of the distensibility curves (elastic diagrams) of arteries. A typical curve is shown for a fresh artery. Wall tension is plotted as a function of percent increase in circumference. The relation of this curve to the structural components of an artery has been studied by selective digestion. Trypsin, which contains an elastase, removes elastin but leaves the collagen fibres, which are relatively non-distensible, intact. Formic acid removes collagen. The remaining elastin is very distensible.

Therefore, the initial part of the arterial distensibility curve is due to elastin fibres and the final part to collagen fibres.

The intermediate or transitional portion represents the progressive recruitment of originally unstretched collagen fibres, which are now being stretched.

From Roach and Burton (120).



In the case of a spherical object, such as a saccular aneurysm, the principle radii of curvature are equal, and the relation becomes,

$$P = \frac{2T}{R} \quad \text{or} \quad T = \frac{PR}{2}$$

3) METHOD

The elastic properties of isolated human intracranial saccular aneurysms and segments of major intracranial arteries were studied using the method of measuring the volume distensibility of vessels previously described by Nichol (108), Roach and Burton (120), and Busby (29). The apparatus (Figure 26) consisted of a finely machined brass cylinder and piston driven by a micrometer screw. A steel spring kept the piston in contact with the micrometer head. The cylinder was connected by three-way stopcocks to a dye reservoir (containing Evan's blue dye to detect leaks in the apparatus and specimens), a mercury manometer, and the specimen under study. All connections were made with BD Luer locks, and leakage was prevented by the use of Dow Corning high vacuum grease. Using this apparatus, a specimen may be distended by increasing the volume in small increments, and recording the corresponding pressures.

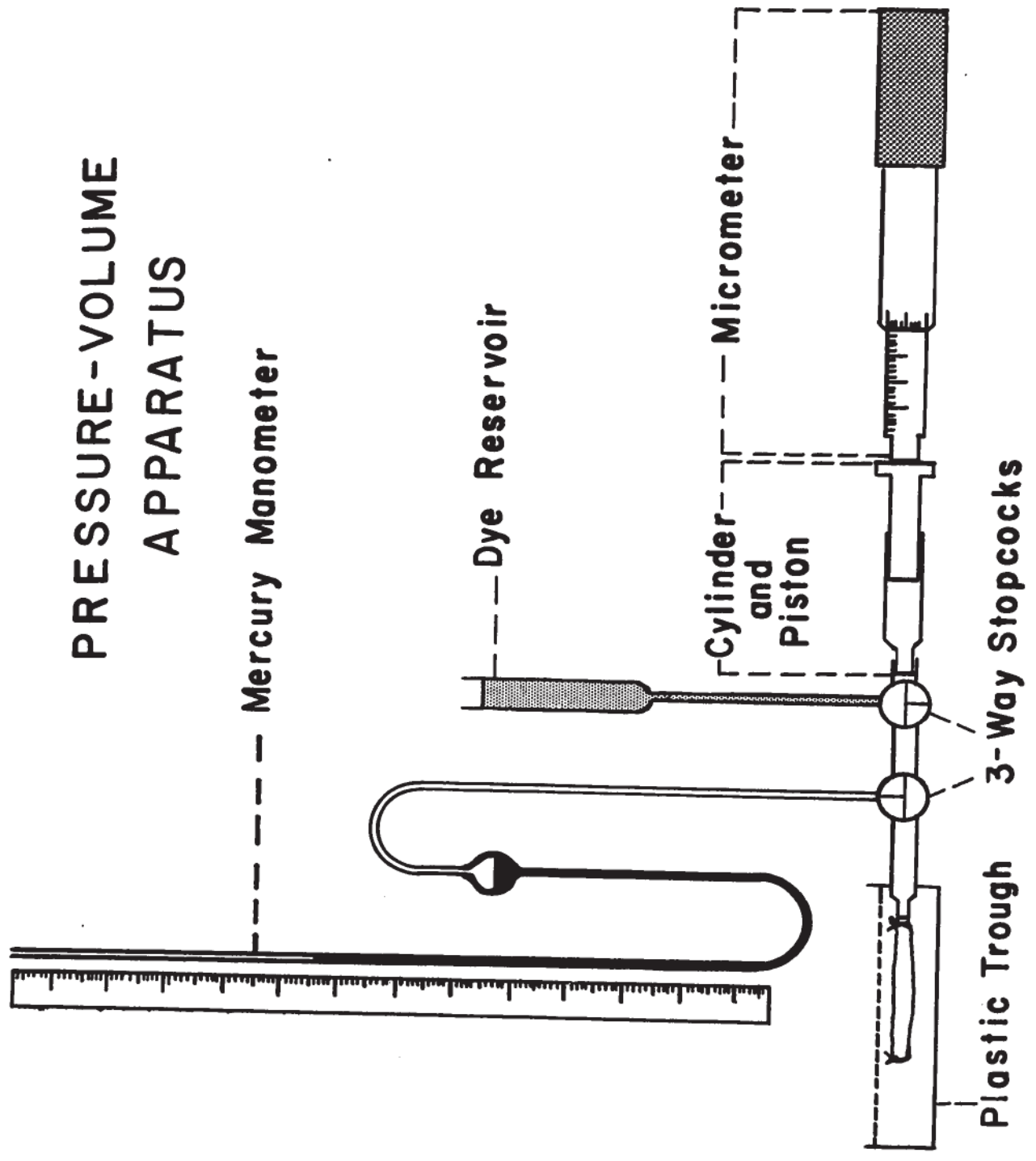
The apparatus was filled with water. Care was taken to eliminate all air bubbles. The volume of the cylinder and piston was calibrated using previously calibrated, capillary tubing. One division of the vernier scale on the micrometer screw equalled 1.0×10^{-3} ml,

FIGURE 26

Schematic diagram of the pressure-volume apparatus used for the study of the elastic properties of human intracranial saccular aneurysms and major intracranial arteries.

See text for description.

PRESSURE-VOLUME APPARATUS



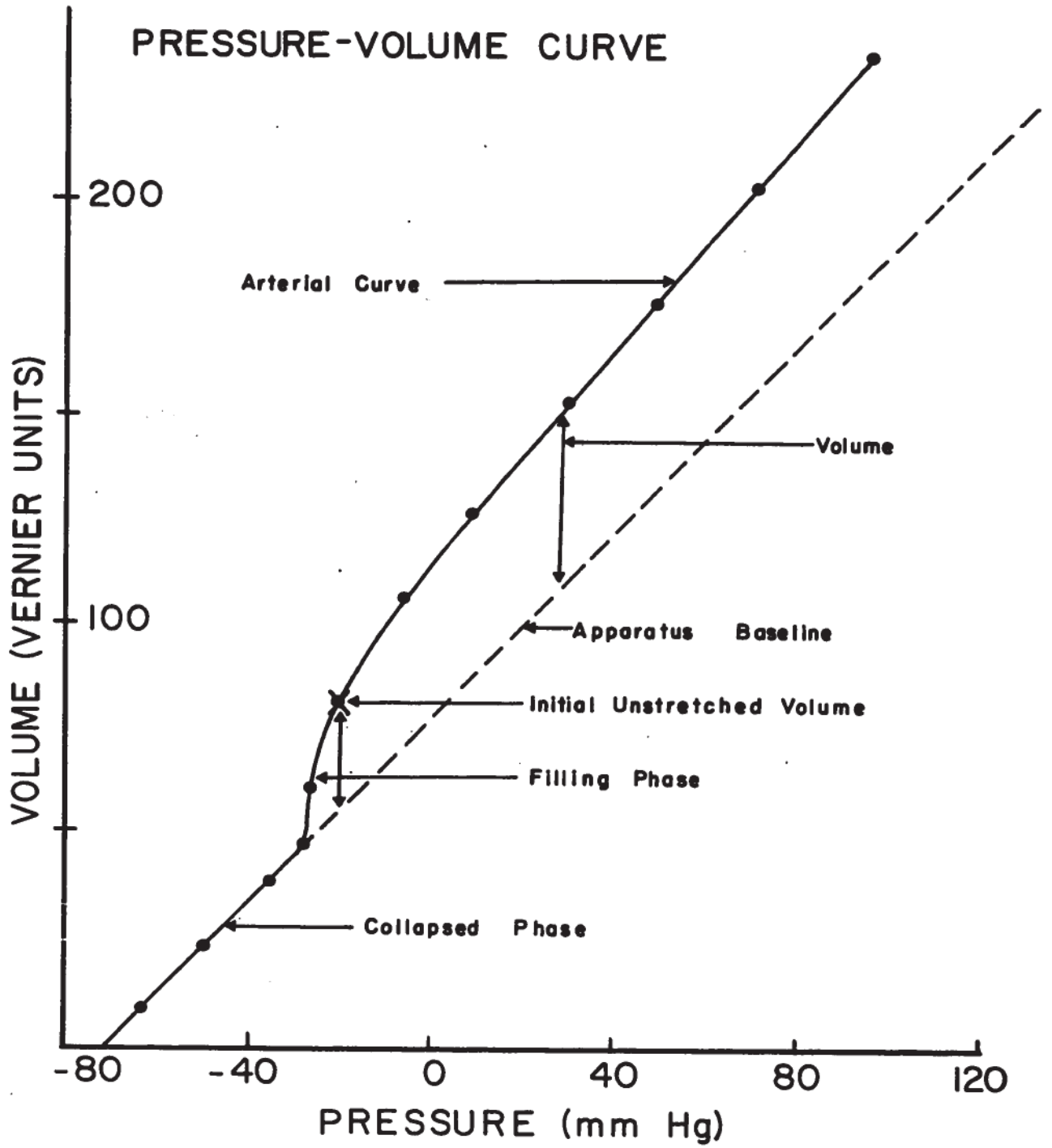
which was the smallest volume change measurable.

The entire circle of Willis, in the cases with intracranial aneurysms and in control cases, was dissected carefully from brains at autopsy and stored in their fresh, non-fixed state in 1/10,000 merthiolate in Ringer's lactate solution at 4°C, prior to use. This method of storage does not alter the elastic properties of arteries (120). The aneurysms, some of which had ruptured and others of which were intact, were prepared for study by the insertion of a grooved metal cannula, directed from the parent artery through the neck of the aneurysm. The aneurysm was then secured by tying a fine silk ligature about its neck. Any hole in the sac of the aneurysm was repaired with fine silk ligature. Segments of major intracranial arteries, between 1.0 and 2.0 cm in length, were prepared from the circle of Willis in each case. The many tiny branches which arise from the major arterial segments were tied off flush with the vessel wall. One end of the isolated arterial segment was then tied over a metal cannula and the opposite end ligated. All specimens were tested carefully for leaks.

To make pressure-volume measurements, the specimens were mounted on the apparatus, where they were suspended in a water-filled plastic trough. The apparatus baseline was determined by excluding both the dye reservoir and specimen, and measuring the change in volume of fluid in the system, as a function of pressure. The pressure-volume curve for the specimen (Figure 27) was then found by excluding

FIGURE 27

A typical pressure-volume curve for a major intracranial artery. During the filling of the artery to its initial unstretched volume, there is little pressure change. The transmural pressure at the initial unstretched volume is zero mmHg. To make calculations of elasticity the pressure scale is adjusted accordingly. The volume at each pressure is found by subtracting the "apparatus baseline" from the arterial pressure-volume curve. See text for further description.



only the dye reservoir. To begin a run, the micrometer screw was adjusted so as to produce a negative pressure within the specimen until it was completely collapsed, and its pressure-volume curve was parallel to that of the apparatus baseline. The volume within the specimen was then increased by small increments, and a plot of micrometer readings versus pressure was made.

The most critical measurement was the estimation of the initial unstretched volume of the specimen, upon which all calculations of elasticity were based. In the case of the cylindrical arterial segments, the unstretched volume corresponded to the point at which the sides of the vessel were parallel; in the case of the aneurysms, to the point at which all wrinkles disappeared from the wall. The transmural pressure (opening pressure) at the initial unstretched volume is zero mmHg.

The pressure-volume curves were converted into elastic diagrams (tension versus radius) using the law of Laplace. The volume at any pressure was measured directly from the original pressure-volume curve in "vernier units" and recalculated in millilitres. The tension, T (dynes/cm), at any pressure was then found using the following relationships, based on the law of Laplace:

(1) For the cylindrical arterial segments,

$$T = 1330 P (V/\pi l)^{\frac{1}{2}}$$

Multiplication by 1330 converts the pressure, P , in mmHg to dynes/cm² and $(V/\pi l)^{\frac{1}{2}}$ is the radius of the segment (cm), from the formula

for the volume of a cylinder, $V = \pi r^2 \ell$. The length, ℓ (cm), was measured at the opening pressure. Since it is known that the intracranial arteries of individuals 30-years-old and older, do not elongate with distension (29), no corrections were made in the calculations for changes in length with increasing pressure.

(2) For the spherical aneurysms,

$$T = \frac{1330P(3V/4\pi)^{\frac{1}{3}}}{2}$$

where $(3V/4\pi)^{\frac{1}{3}}$ is the radius of the aneurysm (cm), from the formula for the volume of a sphere, $V = 4/3\pi r^3$.

To compare elastic diagrams, from case to case, radius at each pressure was calculated as a percentage of the initial unstretched radius at opening pressure.

4) RESULTS

The elasticity of seven human intracranial saccular aneurysms and 16 major intracranial arteries, from a total of nine autopsy cases, were studied. Four of the aneurysms had ruptured and caused death; three were intact, having been found incidentally at autopsy. The aneurysms were from a variety of sites; basilar bifurcation (two), middle cerebral artery bifurcation (two), internal-carotid - ophthalmic artery bifurcation (two), and internal carotid artery bifurcation (one). The intracranial arterial segments were also from a variety of locations on the circle of Willis; pericallosal artery (eight), middle

cerebral artery (three), posterior cerebral artery (two), posterior communicating artery (two), and basilar artery (one). The age of the patients was distributed evenly from the fourth to the seventh decade of life.

a) TYPICAL TENSION-RADIUS CURVES

Case 1. This 58-year-old man died from a ruptured basilar bifurcation aneurysm approximately 8 mm in diameter (Figures 28a and 28b). As well, there was an unruptured, "minute" aneurysm, approximately 1.5 mm in diameter, at the bifurcation of one middle cerebral artery. The sac of the basilar bifurcation aneurysm consisted of a patch-work of thickened areas of atherosclerosis and extremely thin, transparent, non-sclerotic areas. Rupture had occurred at one of the thin areas.

The elasticity of both the aneurysms and a 1.7 cm segment of one pericallosal artery were studied in this case (Figure 29). Both aneurysms were very non-distensible in comparison to the pericallosal artery. The shape of the pericallosal curve is similar to that of typical extracranial arteries; reflecting the elasticity of the elastin and collagen fibres in its wall. In contrast, the curves of the aneurysms are similar to the "collagen curve" obtained in extracranial arteries following removal of the elastin fibres (120).

During the first distensibility run, the basilar aneurysm leaked (at 35 mmHg pressure) from its fundus, away from the site of the

FIGURE 28a

Case 1. Photograph of the basilar bifurcation aneurysm immediately following its removal at autopsy. The large hole in the sac, at the fundus, is the site of rupture.

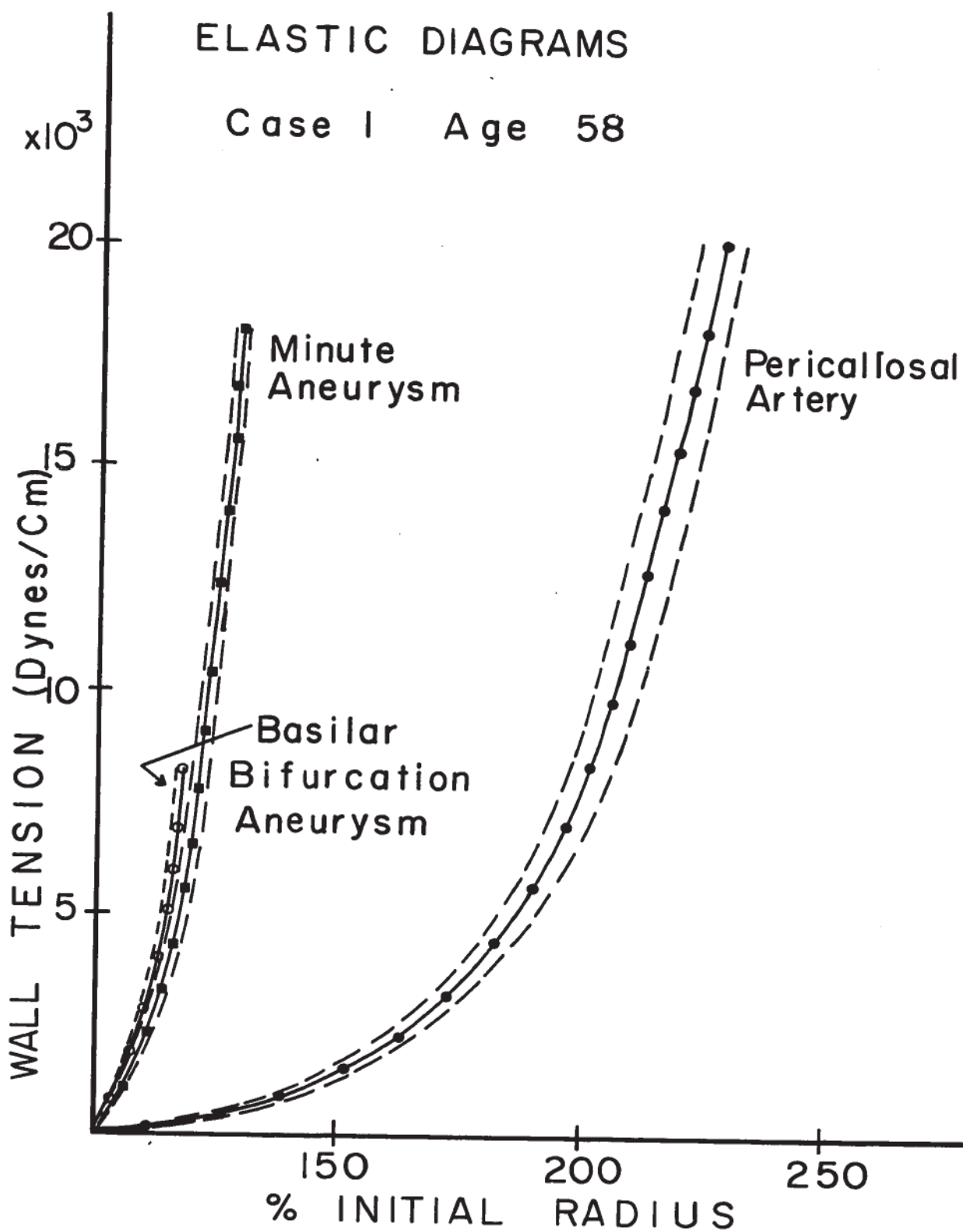
FIGURE 28b

Case 1. Photograph of the same aneurysm prepared for pressure-volume measurements. A metal cannula has been inserted through the neck of the aneurysm, and ligated in place. The hole in the sac has been repaired with a metal clip and silk ligature.



FIGURE 29

Case 1. Elastic diagrams of the basilar and middle cerebral bifurcation aneurysms, and a segment of one pericallosal artery. Total wall tension (dynes/cm) is plotted as a function of the percentage increase in initial radius. In this and subsequent diagrams, the dashed lines represent one standard error of the mean. See text for description.



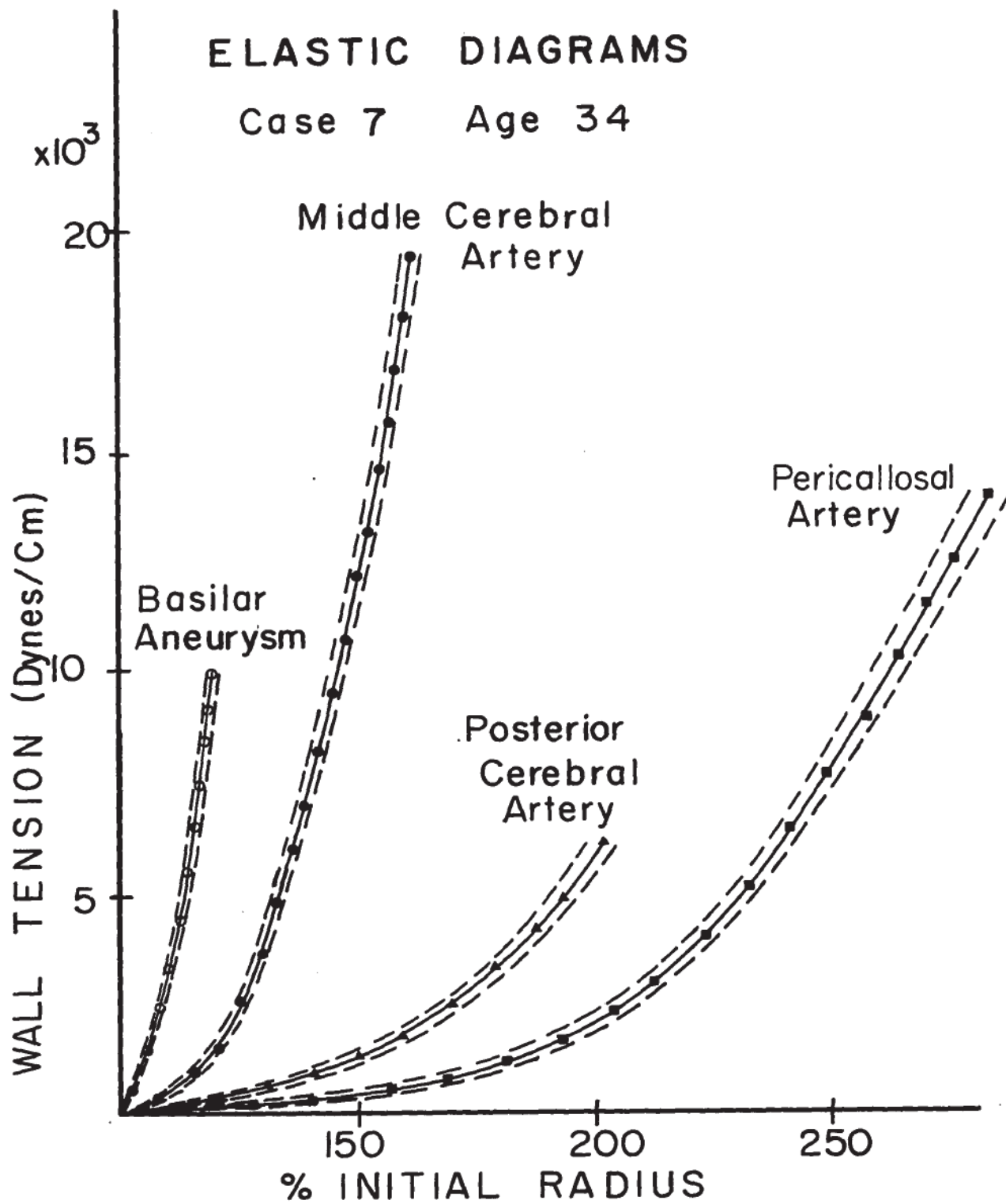
original rupture. During the final run, the aneurysm withstood pressure to 145 mmHg, when a large leak occurred at the base of the aneurysm near its neck. The "minute" aneurysm withstood a pressure to 360 mmHg and a calculated tension of 47×10^3 dynes/cm, before a slow leak developed at the fundus. Complete disruption of the aneurysm did not occur even with a rapid increase in pressure to 500 mmHg, the maximum pressure the apparatus would withstand.

Case 7. This 34-year-old woman died from a ruptured basilar bifurcation aneurysm, 4 mm in diameter. On close examination, rupture had occurred at the fundus, directly opposite the neck. The aneurysm was almost perfectly spherical in shape, and appeared to be uniformly thin-walled and transparent. There was no gross evidence of atherosclerosis. A segment of one posterior cerebral, one middle cerebral, and one pericallosal artery were also available for study. All of the arteries were significantly more distensible than the aneurysm (Figure 30). The variation in arterial distensibility seen here is typical of the results in other cases. However, an insufficient number of different arteries were studied to draw any conclusions regarding a pattern of elasticity differences among major intracranial arteries.

Four runs were made with the aneurysm in this case. On the first run, it withstood a pressure to 68 mmHg, when a small leak developed close to the original site of rupture. This was repaired

FIGURE 30

Case 7. Elastic diagrams of the basilar bifurcation aneurysm and arteries studied in this case. See text for description.



successfully. Thereafter, it withstood pressures to 90 mmHg, 58 mmHg, and 128 mmHg, when a leak occurred near the neck, preventing further measurements.

b) SUMMARY OF CASES

A comparison of the mean elasticities of all the aneurysms and intracranial arteries studied confirms the marked differences noted in case 1 and case 7 (Figure 31). As a group, the aneurysms are very non-distensible in contrast to the major intracranial arteries, which have distensibility curves similar to those of arteries elsewhere in the body. Part of the variation in the elasticity of the arteries, is, no doubt, a reflection of decreasing distensibility with increasing age (29, 121). There were too few cases to examine this question in detail in this study.

Roach and Burton (120) introduced the concept of "elastance"* or "resistance to stretch" of an artery. The slope of the initial part of the arterial distensibility curve is an approximation of the elastance of the elastin fibres in the wall; while the slope of the final part, corresponds to that of the collagen fibres.**

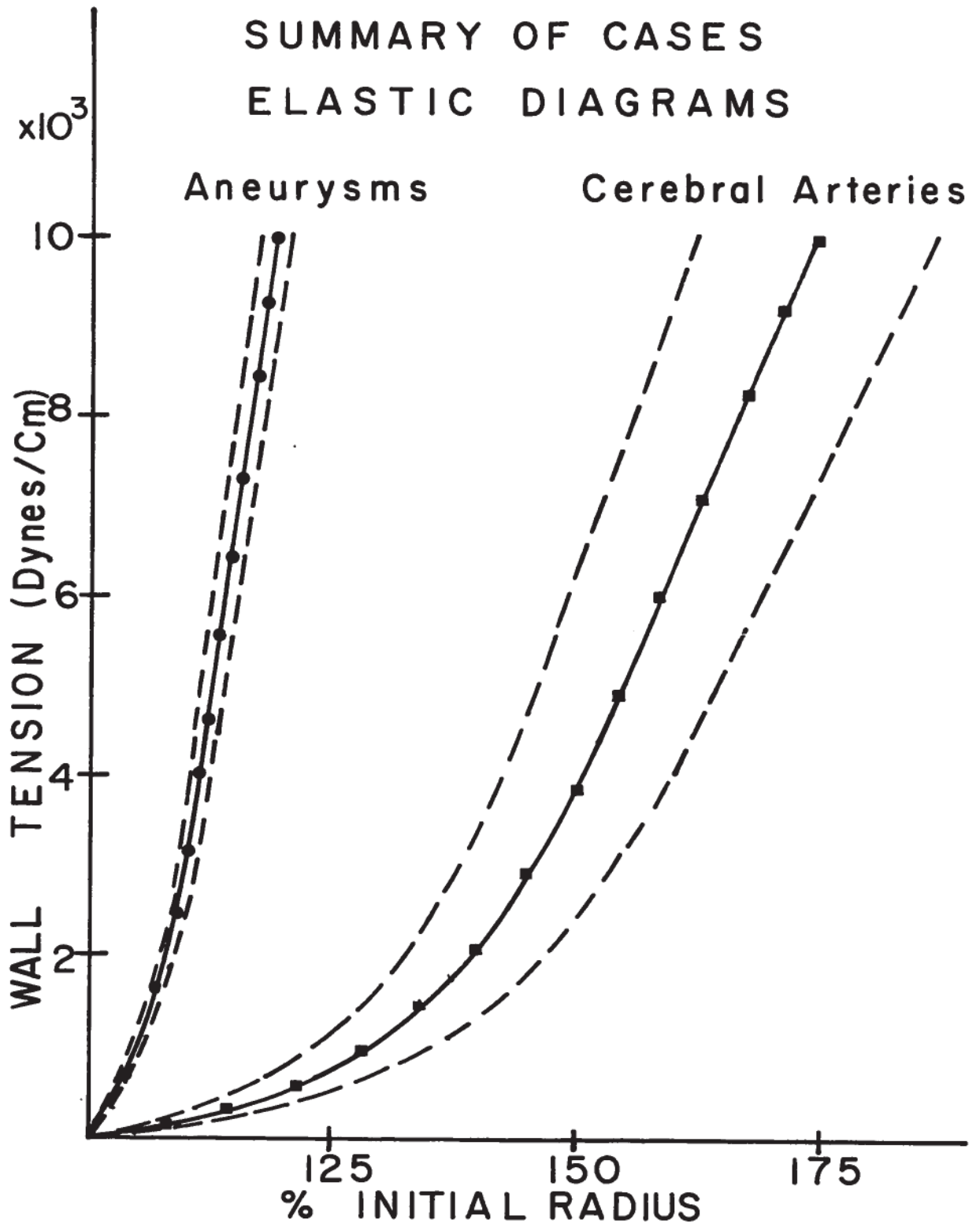
The mean value for the initial slope (elastance of elastin) of the distensibility curves of the aneurysms was 13.5 ± 5 (S. D.) $\times 10^3$ dynes/cm; while that of the arteries was $6 \pm 5 \times 10^3$. This difference

* Elastance was defined as Young's Modulus times the cross-sectional area of the wall. Its dimensions are force/unit length.

** See Appendix III.

FIGURE 31

Elastic diagrams summarizing the results from all the cases.
The mean elasticity of seven aneurysms is compared to that of
16 major intracranial arteries. See text for description.



is very significant ($p < 0.005$). There was no significant difference in the mean values of the final slope (elastance of collagen). That of aneurysms was $67 \pm 25 \times 10^3$; of arteries, $57 \pm 35 \times 10^3$. These data indicate that the difference in the distensibility of an aneurysm and an intracranial artery is due to an alteration in the elastin fibres in the aneurysm.

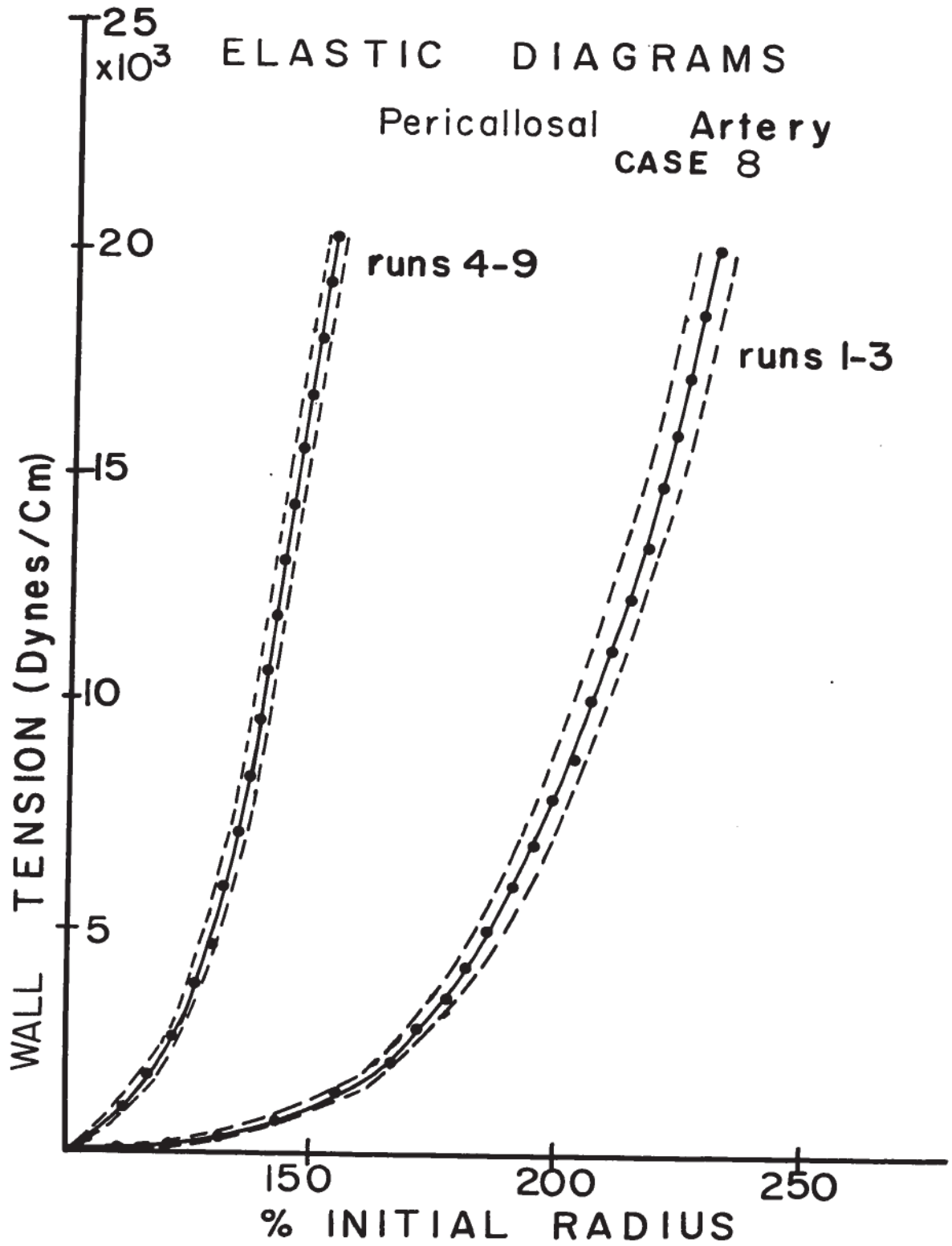
Data on the maximum pressures withstood by the other aneurysms in the study are of interest. Case 2 was a ruptured middle cerebral bifurcation aneurysm which developed a large blowout at both the fundus and base at 170 mmHg. Case 3 was an intact internal carotid-ophthalmic artery bifurcation aneurysm, and case 4 was an intact internal carotid artery bifurcation aneurysm. Case 3 withstood pressure to 350 mmHg, when a large blowout occurred in three areas; while case 4 leaked near the neck, but not at the fundus, at 325 mmHg. Case 6 was a ruptured internal carotid-ophthalmic artery bifurcation aneurysm which only withstood a maximum pressure of 80 mmHg. None of the intracranial arteries studied leaked with distending pressures as high as 500 mmHg.

c) CHANGES IN ARTERIAL ELASTICITY WITH HIGH PRESSURE DISTENSION

In case 8, one of the control cases, a sudden change in distensibility was noted in one pericallosal artery following three runs to 200 mmHg pressure. Six additional runs were made to the same level but no further change occurred (Figure 32). The change in

FIGURE 32

Case 8. Elastic diagrams illustrating the results of repeated distensibility measurements with one pericallosal artery over a period of two weeks. Each run was made to a maximum pressure of 200 mmHg. Between runs 3 and 4, which were made within one hour of each other, on the second day following removal of the specimen at autopsy, a sudden change in distensibility occurred. See text for discussion.



elasticity was accompanied by an increase in the initial unstretched radius of the vessel from 0.33 mm to 0.58 mm. Deterioration of the specimen with time does not explain this change, since runs 1 and 2 were made within 24 hours of the death of the patient and run 3, which was identical to runs 1 and 2, was made the following day. Run 4 was made only one hour following run 3. No further change in elasticity was noted, even though runs 8 and 9 were made two weeks later.

The mean value of the initial slope for runs 1 - 3, was 2 ± 1 (S.D.) $\times 10^3$ dynes/cm; for runs 4 - 9, $8 \pm 1 \times 10^3$, a very significant difference ($p < 0.001$). There was also a difference in the mean value of the final slopes ($42 \pm 6 \times 10^3$ versus $82 \pm 28 \times 10^3$), but the level of significance was less ($p < 0.01$). Therefore, the change in distensibility was produced by a large change in the elastance of elastin, and a smaller change in the elastance of collagen.

In view of the above findings, the results in three other arteries, in which there had been repeated runs to 200 mmHg pressure, were re-examined. In each case, a similar dramatic shift in elasticity between either the second and third, or third and fourth, runs was found.

In a final control case, case 9, the effect of six runs to 200 mmHg pressure in one pericallosal artery was compared to the effect of six runs to 100 mmHg pressure in the other. All runs were made the day following the removal of the specimens at autopsy. With the higher

pressure, a sudden change in elasticity, similar to that found in the previous cases, occurred between runs 3 and 4. There was no change, after six runs, in the artery experiencing the lower pressure.

Because of these changes in elasticity with repeated distension at high pressures, only the results of the first two or three runs with each artery is used for comparison to the mean elasticity of the aneurysms (Figure 31). Similar changes in distensibility were never found with the aneurysms.

5) DISCUSSION

Elasticity of aneurysms. The results of this investigation show that, in contrast to the major intracranial arteries from which they arise, intracranial saccular aneurysms are relatively non-distensible. Analysis of the values for the initial and final slopes of the mean distensibility curves of each, demonstrates that this is the result of a change in the elasticity of the elastin fibres in the wall of an aneurysm.

The distensibility curve of an aneurysm has virtually no elastin component and is very similar to that of arterial collagen alone (120). This corresponds with the typical collagenous appearance of an aneurysm on light microscopic examination. This correlation is additional support for the hypothesis that the initial part of an arterial distensibility curve represents elastin, and the final part, collagen (24, 120). The findings also support the conclusion that the remnants

of elastica which Nyström (109, 110) found in the walls of aneurysms with electron microscopy are not functionally active.

What is the possible significance of the functional loss of elastin in the wall of an aneurysm. Burton (24) stated that:

"..... the elastic fibres,, have the function of producing maintenance tension against the normal blood pressure and the normal pressure fluctuation. The collagenous fibers, because of the architecture of the wall, are stretched only at higher than normal blood pressures and have a protective supporting role."

Obviously in the wall of an aneurysm, the collagen fibres are providing the maintenance tension alone.

Nyström (109, 110) noted changes in the periodicity of the inner-banding structure of collagen fibrils in the walls of aneurysms. Intermingled with normal fibrils, which have a periodicity of 640 \AA , were smaller fibrils with a periodicity of 800 \AA . The smaller fibrils were not present in intracranial arteries. These structural differences are not reflected in a difference in the elasticity of the collagen fibres in arteries and aneurysms. It is possible that the structurally altered collagen found in an aneurysm is the result of degeneration induced by the turbulence within the sac; by a process of vibrational fatigue, similar to that postulated to be responsible for the degeneration of the elastin fibres (Chapter IV). If these smaller fibrils are weaker and less able to withstand the pulsatile stress to which they are subjected, and which they must withstand alone, then the likelihood of

enlargement and rupture of the aneurysm is increased.

Effect of pressure on intracranial arteries. The observation, that a dramatic shift in the distensibility of major intracranial arteries occurred after two to three runs to 200 mmHg pressure, was unexpected. Most of this shift was the result of an alteration in the elastin component of the wall, which in the case of intracranial arteries is contained exclusively in the internal elastic membrane. It is conceivable that the pressure exceeded the breaking strength of the elastin fibres in the membrane, the rupture of which produced the increase in the unstretched radius of the artery. If this hypothesis is true, then extreme pressures are not required to alter the elastica in intracranial arteries. This supports the idea that the pulsatile pressure head acting at the apex of an intracranial bifurcation contributes to the degeneration of the internal elastic membrane, and the initiation of the aneurysmal process (Chapter III).

No histological confirmation of rupture of the elastica is available in this study. However, complete tears of the elastica (Reuterwall's tears) are known to occur in intracranial arteries, and Hassler (82) found that they are unusually common in patients with aneurysms.

The effect of high pressure distension may explain the difference in the mean distensibility of intracranial arteries found in this study, compared to the study of Busby (29). In this investigation intracranial

arteries were as distensible as extracranial arteries, whereas Busby found them to be less distensible. However, he noted that to obtain reproducible results it was necessary to distend the arteries several times to high pressures (28). This distension no doubt altered the elastic fibres, resulting in inelastic distensibility curves, similar to those found in this study after two or three runs.

6) SUMMARY

(1) The elasticity of seven human intracranial saccular aneurysms was compared to that of 16 major intracranial arteries. The aneurysms were relatively non-distensible in comparison to the arteries.

(2) Analysis of the elastance of elastin and collagen showed that the difference in distensibility is the result of alteration in the elastin fibres in the walls of aneurysms. This functional difference correlates with morphological evidence of destruction of the elastica in the wall of an aneurysm.

(3) It is proposed that this change is the result of turbulent blood flow within the aneurysm, and that it weakens the wall of an aneurysm.

(4) Examination of the ruptured aneurysms prior to the elasticity studies showed that rupture had occurred, in each case, where the wall was thin.

(5) Previously ruptured aneurysms withstood only relatively low pressures (the maximum pressure was 170 mmHg in case 2). Previously intact aneurysms withstood higher pressure before rupturing (maximum value was 350 mmHg in case 3). The minute aneurysm (case 1) developed a leak at 360 mmHg. Intracranial arteries withstood pressures to 500 mmHg.

(6) A sudden decrease in the distensibility of five intracranial arteries was noted after two or three runs to 200 mmHg pressure. It is proposed that this was due to rupture of the fibres in the internal elastic membrane.

VII. THE PHYSICS OF ANEURYSMAL RUPTURE

"..... tension in a dilated wall, according to Laplace's formula, tends to increase in proportion to the radius of curvature of the sacculation. Thus rather marked increases in tension may occur in the walls of aneurysms"

- B. Woodhall et al (163)

1) INTRODUCTION

The rupture of an aneurysm is clearly a physical phenomenon which occurs only when the stress acting on the wall exceeds the strength of its structural components. There has been very little discussion in the literature of the physical factors pertaining to rupture (160, 162, 163). The paper by Woodhall et al (163) is the only one which mentions the importance of the law of Laplace in understanding the rupture of intracranial saccular aneurysms. The size of the aneurysm, the intraneurysmal pressure, the thickness of the wall, and the strength of its structural components, are the factors which have a direct influence on the likelihood of rupture.

2) STRESS IN THE WALL OF AN ANEURYSM

The stress in the wall of an aneurysm may be calculated from the data obtained in the elasticity studies (Chapter VI) and compared to the

stress in the wall of intracranial arteries, if the wall thickness in each case is known.*

Estimates of wall thickness. There is very little information upon which to base these estimates. Busby (29) found that the mean wall thickness of the intracranial portion of the vertebral arteries, measured in the collapsed state, was $250 \pm 20 \mu$. This is undoubtedly an overestimate of the value at physiological pressures, since Wolinsky and Glagov (161) measured wall thickness in the rabbit aorta, as a function of distending pressure, and found that wall thickness had decreased by 60% at 80 mmHg, beyond which it remained constant. Bader (4, 5) has made similar observations in human arteries.

Published information on aneurysmal wall thickness is almost non-existent. Hassler (82) noted that the thickness of the wall in most "minute" aneurysms, at the thinnest place, was 30-60 μ . In larger aneurysms, a number of authors (38, 39, 147, 162) have emphasized that the site of rupture is most commonly an extremely thin-walled secondary loculus. Photomicrographs (Figure 5a) show that the wall of an aneurysm may be much thinner than its parent vessel, although patches of the wall may be thickened with atherosclerosis. It seems reasonable to assume that in most cases the thickness of the wall at the site of rupture is considerably less than that of an intracranial artery.

* Wall stress (dynes/cm²) = wall tension (dynes/cm) divided by wall thickness (cm).

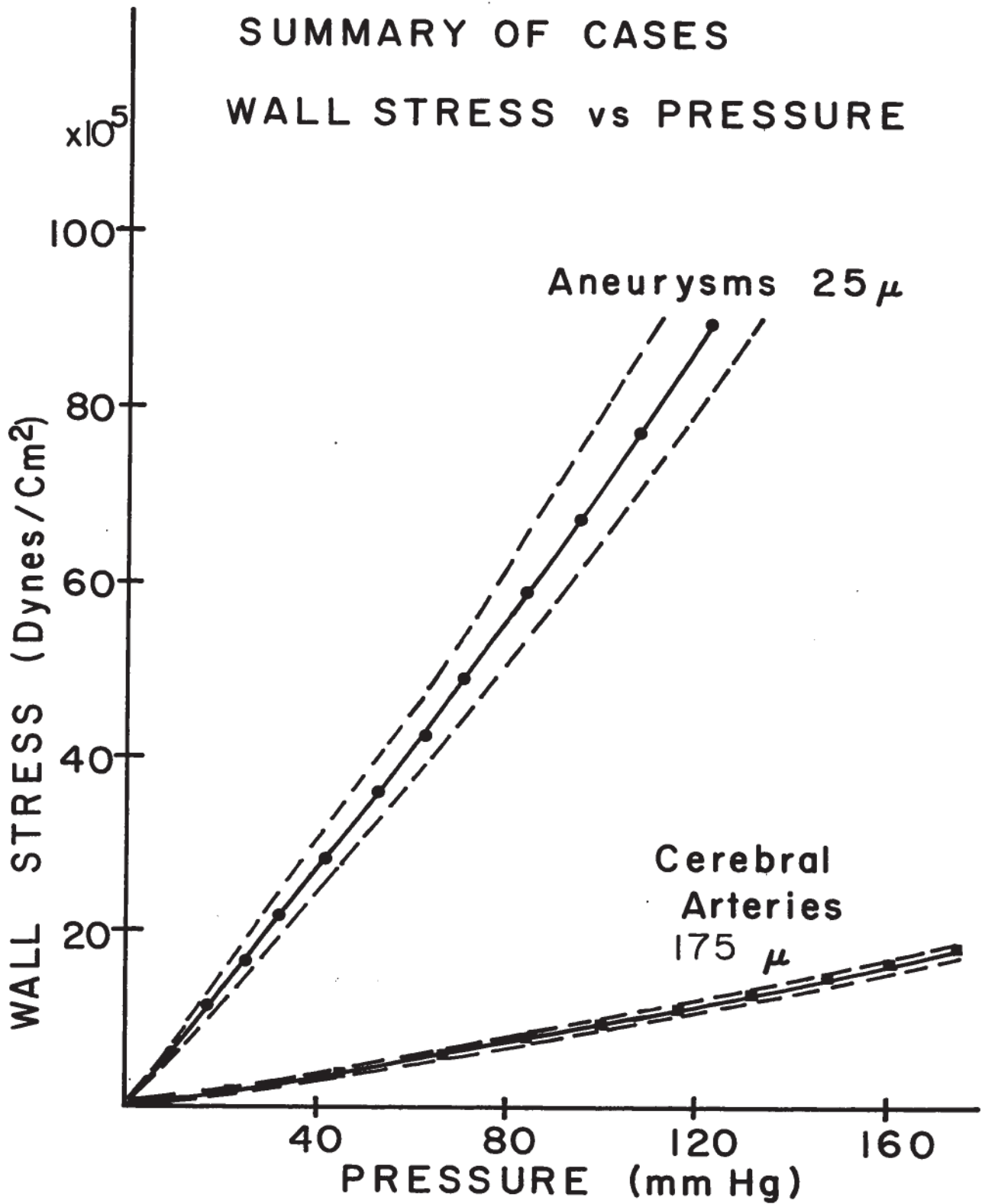
In conjunction with the elasticity studies, measurements of wall thickness were made on five intracranial arteries and one aneurysm (case 4). The specimens were fixed with 10% buffered formalin at a distending pressure of 80 mmHg and processed for histological examination using the methods outlined by Hassler (82). Measurements were made from each quadrant of serial sections with a microscope fitted with a micrometer eye-piece, which had been calibrated with a stage micrometer. The mean value of arterial wall thickness was $140 \pm 35 \mu$. Allowing for a 20% shrinkage during fixation (29) a reasonable estimate of mean intracranial arterial wall thickness, at physiological pressures, is 175μ .

The aneurysm in case 4 ruptured during the elasticity study near its neck, at the site of a secondary loculus. On microscopic examination, the wall contained large areas of atherosclerotic thickening, but at the site of rupture it was thin, measuring only 20μ . Although it is admittedly an estimate based on a very limited sample, for the sake of illustration, a minimum wall thickness of 25μ was chosen for the calculation of wall stress in aneurysms.

Wall stress as a function of pressure. Wall stress was calculated as a function of intraluminal pressure for all the aneurysms and arteries on which pressure-volume measurements were made. Figure 33 summarizes the results. It is apparent that, at any pressure, the aneurysms experience greater wall stress than the arteries. Thus, one would predict that the pulsatile pressure changes, in vivo, will produce much greater fluctuations in wall stress in saccular aneurysms than

FIGURE 33

Graph summarizing the results of the calculation of wall stress (dynes/cm²) as a function of intraluminal pressure (mmHg) in all the aneurysms and intracranial arteries on which data was available from the elasticity studies. The calculations were made with the assumption that the minimum wall thickness of the aneurysms was 25 μ , and that of the arteries was 175 μ . No allowance has been made for increased wall thickness at pressures less than 80 mmHg. If taken into account, the increased wall thickness at these lower pressures would result in a lower calculated wall stress than indicated on the graph, and a more curvilinear appearance to the initial part of the curves than is shown. The dashed lines represent one standard deviation. See text for discussion.



intracranial arteries. This is another factor contributing to the structural fatigue and degeneration of the wall of an aneurysm.

3) RUPTURE AND THE LAW OF LAPLACE

The law of Laplace, as it applies to an intracranial saccular aneurysm, may be written in the form

$$\sigma = \frac{PR}{2t}$$

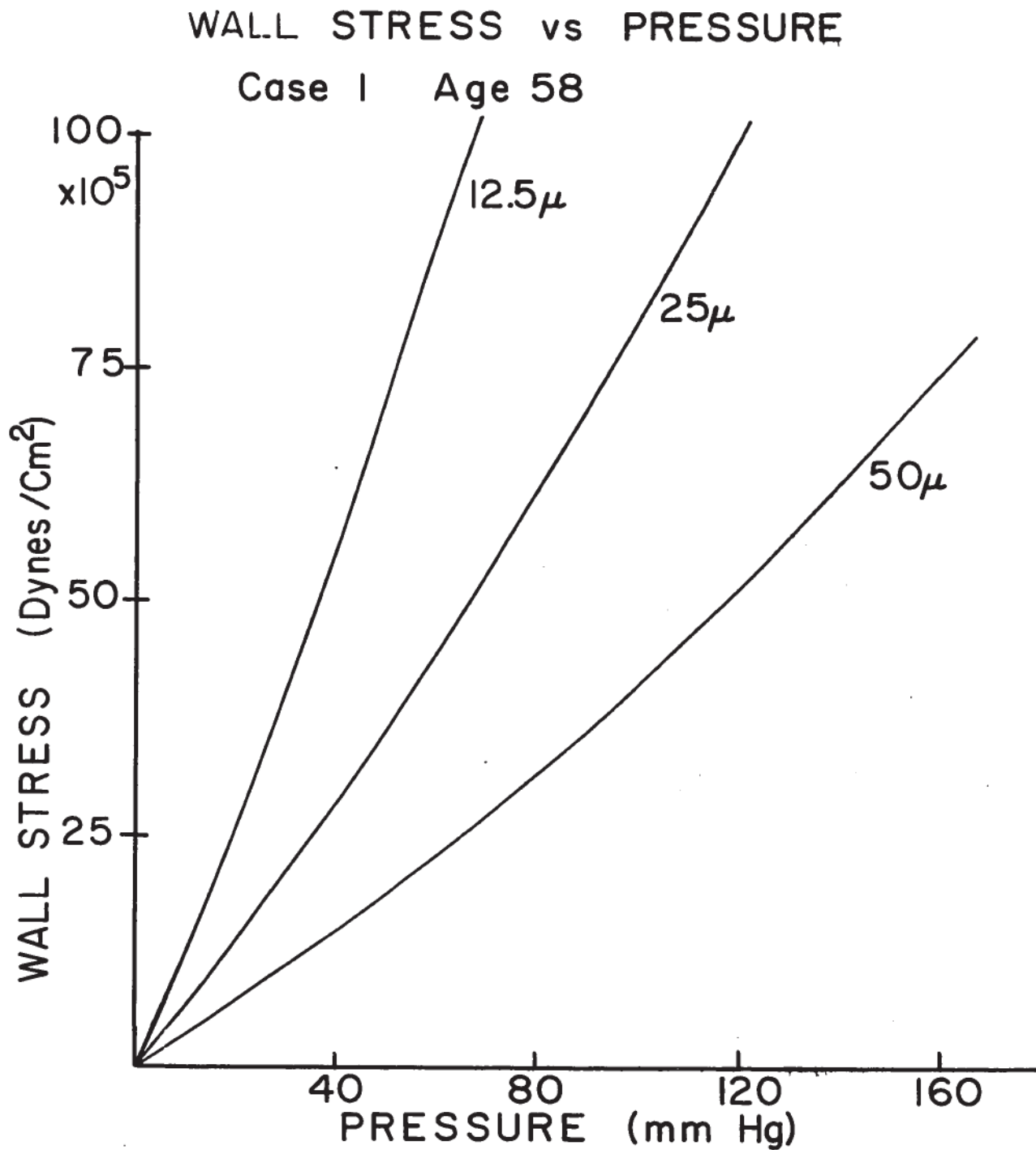
where σ is the wall stress (dynes/cm²), P is the intra-aneurysmal pressure (dynes/cm²), R is the radius of the aneurysm (cm) and t is the minimum wall thickness (cm). It can be seen from this expression that any event which increases the intra-aneurysmal pressure or the size of an aneurysm, or decreases the minimum thickness of its wall, will increase the wall stress and the likelihood of rupture.

Importance of wall thickness. Figure 34 illustrates the effect of changing the estimate of minimum wall thickness in an aneurysm. With a thinner wall the same total wall tension is distributed across a smaller cross-sectional area, and as a result, the stress (force per unit area) must increase. This explains why a secondary locus, which invariably has a thin wall, is a common site for rupture (38, 39, 147, 162).

Intra-aneurysmal pressure. Any increase in systemic or intracranial arterial pressure will be reflected in an increase in intra-aneurysmal pressure (Chapter V). Therefore any sudden rise in systemic pressure, such as may occur during elimination, coitus, and emotional

FIGURE 34

Graphs illustrating wall stress (dynes/cm²) as a function of pressure (mmHg) for the basilar bifurcation aneurysm from case 1, with varying estimates of minimum wall thickness. See text for discussion.



or physical stress, will produce a rise in the wall stress in an aneurysm. It is not surprising, then, that the moment of rupture is often associated with these activities (95, 114). Also, one would predict that aneurysms should be associated with systemic hypertension. Reports in the literature indicate that this is so (38, 39, 144, 155, 158). Finally, realization that the stress in the wall of an aneurysm is directly proportional to the intra-aneurysmal pressure is a strong argument in favour of lowering the systemic blood pressure during surgery on aneurysms, as is now being practised in some neurosurgical units (50). The resulting decrease in wall stress should decrease the risk of rupture during the dissection of the sac.

Aneurysmal size. Considering the law of Laplace, one would predict that the chance of rupture must increase, as the size of an aneurysm increases. This prediction is clearly substantiated in the literature. Crompton (39) found in his series that the average diameter of ruptured aneurysms was 5 mm and unruptured aneurysms, 2 mm. McCormick's (97) corresponding figures were 14.5 mm and 4.5 mm, respectively. Data from the Cooperative Study (96) indicated that the critical size for rupture was 7-10 mm.

Physical characteristics of the wall. The magnitude of the stress that the wall of an aneurysm can withstand will depend on the breaking strength of its structural components. The theoretical upper limit is $0.5 - 1.0 \times 10^9$ dynes/cm², which is the measured breaking strength of pure collagen extracted from mammalian tendon (80). However, the

value for the wall of an aneurysm will almost certainly be less. The wall does not consist solely of collagen. Other tissue, such as remnants of muscle and elastin, and areas of atherosclerotic infiltration and fibrinoid necrosis, will reduce the breaking strength in proportion to the area of the wall which they occupy. As well, some of the collagen in the wall is structurally abnormal and possibly weak (109, 110).

An estimate of the breaking strength of the wall in a previously unruptured aneurysm is available from the data in case 4 of the elasticity studies. The aneurysm in this case ruptured at a pressure of 325 mmHg and a radius of 0.25 cm. The wall thickness at the site of rupture was 20 μ . If these values are substituted into the expression for wall stress in an aneurysm, $\sigma = PR/2t$, a value of 0.2×10^8 dynes/cm² is found. This equals the breaking strength of the wall at the moment of rupture.

4) PREDICTION OF THE CRITICAL SIZE FOR RUPTURE*

It is possible to predict the critical size at which an aneurysm will rupture by equating the forces acting on its wall. To make the calculations the following assumptions regarding aneurysms and their rupture were made. (1) An aneurysm may be considered a simple sphere, the wall thickness of which is very small relative to its radius. (2) The

* Dr. Peter Canham of the Department of Biophysics assisted greatly in organizing the author's thoughts for this section.

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volume of tissue comprising the wall of the aneurysm equals the volume of a patch of tissue originally at the apex of the bifurcation, from which it arose. The area of this patch is 3 x 3 mm and its thickness 175 μ , the average thickness of an intracranial artery. (3) The breaking strength of the wall of an aneurysm is 0.5×10^8 dynes/cm². (4) The intra-aneurysmal pressure at the moment of rupture is 150 mmHg.*

The force generated by the intra-aneurysmal pressure, P , acts over the cross-sectional area of the aneurysm, πr^2 , and equals $P\pi r^2$ (Figure 35). This force tends to distend the aneurysm and produce rupture. The opposing force, produced within the wall of the aneurysm, is the wall stress σ , acting over the cross-sectional area of the wall, $2\pi r t_a$, and equals $2\sigma\pi r t_a$, where t_a is the wall thickness of the aneurysm. Prior to rupture these forces are equal in magnitude and opposite in direction. Equating them, gives the expression

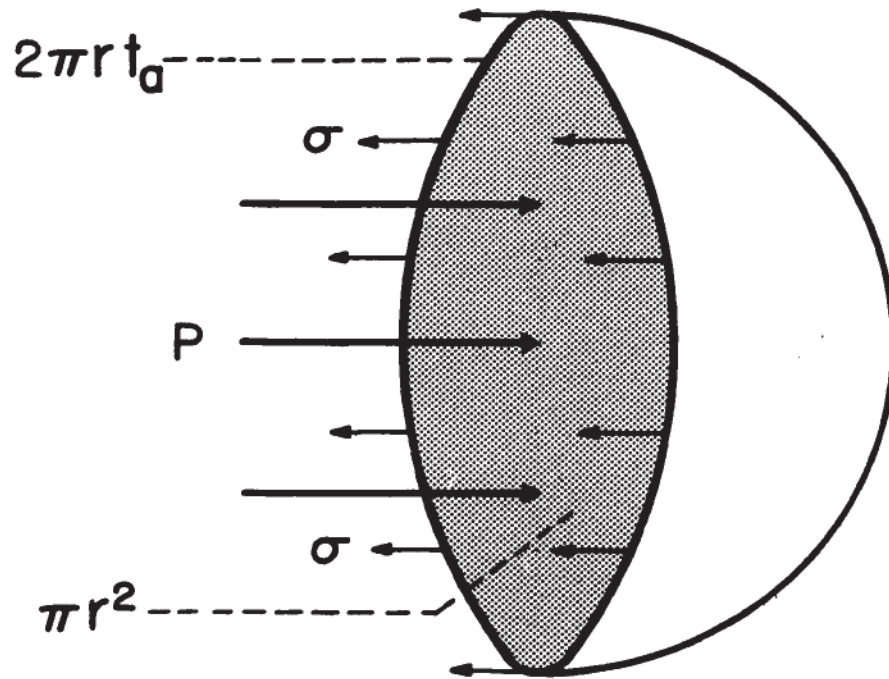
$$P\pi r^2 = 2\sigma\pi r t_a \quad \dots\dots\dots (1)$$

The aneurysmal wall thickness, t_a , may be found as a function of the radius of the aneurysm, r , from the expression for the volume of the wall of a sphere, $4\pi r^2 t_a$, on the assumption that the volume of tissue in the aneurysm, V , remains constant, and equals the volume of the original patch from which it arises, $A t_b$, where A is the area and t_b the thickness of the apex of the bifurcation. Thus

* Aneurysms likely rupture during systole and 150 mmHg is a realistic value for peak systolic pressures in patients of the age group in which aneurysms occur.

FIGURE 35

Diagram illustrating the equilibrium of forces acting on the wall of an aneurysm. The cross-section revealed by slicing an aneurysm in half, as if it were an orange, is depicted. Imagine that the other half is back in place. The intra-aneurysmal pressure, P , is acting over the cross-sectional area of the sphere enclosed by the wall, πr^2 (stippling), so as to force the two halves apart. The stress in the wall, σ , acts in the opposite direction over the cross-sectional area of the wall, $2\pi r t_a$. Prior to rupture these forces are in equilibrium. At the moment of rupture, the force generated by the intra-aneurysmal pressure exceeds the breaking strength of the wall. Since the radius of an aneurysm is large relative to its wall thickness, it has been assumed that there is no difference in the radius of the enclosed surface and the radius of the wall.



$$P\pi r^2 = 2\sigma\pi r t_d$$

$$V = At_b = 4\pi r^2 t_a = \text{constant} \quad \dots\dots\dots (2)$$

$$\therefore t_a = \frac{A \cdot t_b}{4\pi r^2}$$

Substituting equation 2 in equation 1, and solving for the critical radius for rupture, r_c , gives the expression

$$r_c = (0.5\sigma A t_b / \pi P)^{\frac{1}{3}} \quad \dots\dots\dots (3)$$

Substituting the originally assumed values for each variable in equation 3 gives the result,

$$\begin{aligned} r_c &= \left(\frac{0.5 \times 0.5 \times 10^8 \times 0.9 \times 10^{-1} \times 1.75 \times 10^{-2}}{3.14 \times 1.5 \times 10^2 \times 1.33 \times 10^3} \right)^{\frac{1}{3}} \text{ cm} \\ &= (0.0628)^{\frac{1}{3}} \text{ cm} = 4 \text{ mm.} \end{aligned}$$

Thus one would predict that on the average an aneurysm will rupture at a critical diameter of 8 mm. This value agrees remarkably well with those from large autopsy series, found in the literature (39, 97), and suggests that the assumptions made originally are realistic.

5) SUMMARY

In this chapter it was shown that each of the variables in the law of Laplace (intra-aneurysmal pressure, the size of an aneurysm, its wall thickness, and the breaking strength of its structural components) influence the likelihood of rupture. Furthermore, all of these factors operate together, to the disadvantage of the aneurysm. For example, increasing size, will thin the wall and increase the stress, which increases the chance of a further increase in size and stress - a type of

positive feedback. An increase in intra-aneurysmal pressure has a similar unstabilizing effect. Therefore, as an aneurysm enlarges, the probability rises steadily, that the breaking strength of the wall will be exceeded, and that rupture will result.

VIII. SUMMARY AND CONCLUSIONS

The purpose of this thesis has been to investigate biophysical aspects of the initiation, growth, and rupture of human intracranial saccular aneurysms. Although these lesions are commonly labelled "congenital," the review of the literature indicated that there is little evidence in support of that concept. Rather, the literature suggests that intracranial aneurysms are acquired, secondary to a focal degeneration of the internal elastic membrane at the apex of intracranial arterial bifurcations. This results in a weakness in the wall at that site, which allows aneurysmal outpouching of the vessel. Even if one accepted a congenital factor as the explanation for this weakness, it would not explain the mechanism of the initial aneurysmal outpouching, or the subsequent enlargement and rupture of the aneurysm.

The investigations were carried out in an attempt to answer questions which were based on the assumption that physical processes operating on intracranial bifurcations and aneurysms would explain the pathogenesis of these lesions. The results of the study are as follows:

- (1) The apex of an intracranial bifurcation is subjected to haemodynamic forces (shear stress, pulsatile impulse, and pulsatile

pressure head) which are experienced either to a lesser extent, or not at all, by other areas of the vessel wall. These forces are the result of the impingement of high velocity central streams. I propose that these forces produce the localized destruction of the internal elastic membrane at the apex of intracranial bifurcations.

(2) Separation of the boundary layer at the lateral angles of intracranial bifurcations plays a role in the development of intimal cushions, but intimal cushions are not related to the development of aneurysms.

(3) In comparison to long straight tubes, bifurcations lower the critical Reynolds number for turbulence, because they are a geometrical disturbance to flow. This disturbance is greatest in wide-angled bifurcations, and with pulsatile flow. However, the critical Reynolds numbers at bifurcations, as determined experimentally, are greater than those calculated for known flow rates in the cerebrovascular system. Therefore, it was predicted that turbulence would not occur at normal human intracranial bifurcations. This prediction was confirmed in the control cases in the phonocatheter study. In the model experiments it was found that when turbulence does occur at a bifurcation, it arises in the proximal portion of the branches, not in the region of the apex of the bifurcations. For these reasons it was concluded that turbulence does not occur at intracranial bifurcations, and is not responsible for the initiation of the aneurysmal process.

(4) I suggest that aneurysmal outpouching occurs because of the incessant pulsatile impulse and pressure head that is transmitted to the weakened apex by the impingement of the central streams.

(5) It has been demonstrated that turbulent blood flow occurs in human intracranial saccular aneurysms, once a small aneurysmal outpouching occurs. This finding was suggested by the model experiments and confirmed in the human case, at surgery. Bruits, indicative of turbulence, were recorded in 12 out of 19 cases. It was argued that turbulence would have been recorded in every case, if drug-induced hypotension had not been used, and the systemic arterial pressure of the patient had been closer to normal at the time of recording. Turbulence is known to produce and accelerate degenerative changes in vascular tissue; in particular, the elastin component. It was argued that the turbulence in aneurysms produces the degenerative changes in the elastin and collagen tissue of the walls of aneurysms by a process of vibrational fatigue. This process weakens the wall and allows the aneurysm to enlarge.

(6) Direct measurement of intra-aneurysmal pressure was made in four human cases at the time of surgery. The mean intra-aneurysmal pressure is the same as the mean systemic pressure, and pulsatile pressure fluctuations occur within aneurysms. The magnitude of the intra-aneurysmal pressure fluctuations is the same as the systemic fluctuations. It was shown that any differences in the pulse pressures

recorded were the result of damping produced by the recording apparatus. Therefore, the wall of an aneurysm is subjected to the same pressure fluctuations as intracranial arteries.

(7) The elastic properties of seven human intracranial saccular aneurysms were studied, and compared to that of 16 major intracranial arteries. The aneurysms were very non-distensible in comparison to the arteries. This is the result of a functional alteration in the elastin fibres of the wall of an aneurysm, and correlates with light and electron microscopic evidence for damage to the elastin tissue in an aneurysm. I propose that this structural alteration is the end-result of the turbulence, and that it weakens the wall of an aneurysm.

(8) Taking into account the difference in the average minimum wall thickness of aneurysms and intracranial arteries, it was shown that the wall stress to which the average aneurysm is subjected at any pressure is 10 times that of an intracranial artery. Therefore, with each heart beat, the wall of an aneurysm is subjected to much greater fluctuations in wall stress than an intracranial artery. This is an additional factor which can weaken the wall.

(9) The factors which determine whether or not an aneurysm ruptures are the size of the aneurysm, the intra-aneurysmal pressure, the thickness of the aneurysmal wall, and the strength of the structural components of the wall. These factors are related by the law of

Laplace, which shows that an increase in intra-aneurysmal pressure, an increase in the size of an aneurysm, a decrease in the minimum thickness of the wall, or a decrease in the strength of the structural components, increases the probability of rupture. Rupture occurs when the stress on the wall of an aneurysm exceeds the strength of the wall.

(10) It was possible to predict the critical radius at which an aneurysm will rupture by equating the forces acting on the wall. The critical diameter was found to be 8 mm, which agrees remarkably well with data from the literature on the average size of aneurysms at rupture.

In summary, human intracranial saccular aneurysms are acquired secondary to a localized degeneration of the internal elastic membrane at the apex of major intracranial arterial bifurcations. This degeneration is the result of haemodynamically-generated forces which act at the apex and weaken the wall. The pulsatile impulse and pressure head transmitted to the apex with each heart beat produces the initial aneurysmal outpouching. Growth, or enlargement, occurs because the structural components of the wall are progressively weakened by a process of structural fatigue resulting from the vibration of the wall, produced by the turbulent blood flow in the sac of the aneurysm. Enlargement causes thinning of the wall, which in itself increases the stress to which the wall is subjected by the pulsatile intra-aneurysmal pressure. This results in further enlargement. Rupture occurs when the combination of intra-aneurysmal pressure, aneurysmal size, and minimum aneurysmal wall thickness exceeds the breaking strength of the degenerating structural components of the wall.

IX. SUGGESTIONS FOR FUTURE RESEARCH

A number of additional questions arise from this study. These questions suggest possible avenues for future investigations.

(1) Which force acting at the apex of intracranial bifurcations (shear stress, the pulsatile impulse or the pulsatile pressure head) is the most critical one for the initiation of the aneurysmal process?

(2) Can these forces be measured quantitatively?

(3) To what extent does an increase in the flow rate across a bifurcation, or an increase in systemic arterial pressure, effect the magnitude of these forces?

(4) Is a detailed analytical development of the hydrodynamics of flow at bifurcations possible?

(5) Does the apex of a bifurcation undergo greater displacement during systole than adjacent areas of the arterial wall?

(6) Is it possible to demonstrate damage to the endothelial cells of a bifurcation by producing acute hypertension with drugs?

(7) How much does the geometrical configuration of a bifurcation influence the forces acting upon it?

(8) What is the relation between the haemodynamic stress on the wall of an artery at bifurcations and the localization of atherosclerotic

plaques about bifurcations?

(9) How does turbulent blood flow damage the structural components of the wall of an aneurysm?

(10) Can vibration of an arterial wall produce changes in the electron microscopic appearance of the structural components of an artery?

(11) What is the relation between the diameter of the neck of an aneurysm and turbulence within the sac?

(12) Does the wall of an aneurysm vibrate at a resonant frequency in response to the turbulent blood flow within it?

(13) Will elastase digestion of major intracranial arteries produce a shift in their distensibility similar to the shift that occurs with high pressure distension?

(14) Is it possible to confirm damage in the internal elastic membrane of intracranial arteries following high pressure distension, histologically?

(15) What is the average wall thickness of major intracranial arteries at physiological pressures?

(16) What is the average wall thickness of aneurysms at the site of rupture?

(17) What is the bursting strength of major intracranial arteries and intact aneurysms?

(18) What is the time course for development of an aneurysm?

(19) Why are saccular aneurysms so uncommon in extracranial arteries?

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APPENDIX I

Analysis shows that the Reynolds number is dimensionless. The fundamental units of viscosity (which Newton described as the internal friction or "lack of slipperiness" between adjacent layers of a fluid experiencing shear stress) are found from the expression,

$$\frac{F}{A} = \eta \cdot \frac{dv}{dr}$$

where F is the tangential "drag" force between adjacent laminae of the fluid, A is the area of contact between the laminae, and dv/dr is the velocity gradient or shear rate. Rearranging this expression gives η , the fluid viscosity.

$$\begin{aligned} \eta &= \frac{F}{A \cdot dv/dr} = \frac{\text{dynes}}{(\text{cm}^2) (\text{cm/sec-cm})} = \frac{\text{gm-cm}}{\text{sec}^2} \cdot \frac{\text{sec-cm}}{\text{cm}^3} \\ &= \frac{\text{gm}}{\text{sec-cm}} = 1 \text{ poise} \end{aligned}$$

By substituting the fundamental units of viscosity, together with the fundamental units for the other variables in the Reynolds number, it is seen, following cancellation, that Re has no dimensions.

$$\begin{aligned} Re &= \frac{\rho}{\eta} \cdot \bar{V} \cdot D \\ &= \frac{\text{gm}}{\text{cm}^3} \cdot \frac{\text{cm}}{\text{sec}} \cdot \text{cm} \cdot \frac{\text{sec-cm}}{\text{gm}} \\ &= \text{dimensionless} \end{aligned}$$

The Reynolds number is, in fact, a ratio of inertial forces to viscous forces within a fluid (115). The ratio is,

$$\frac{\bar{V}^2 \rho / D}{\bar{V} \eta / D^2} = \frac{V^2 \rho}{D} \cdot \frac{D^2}{\bar{V} \eta} = \frac{\rho \bar{V} D}{\eta} = \text{Re}$$

APPENDIX II
AN EXPERIMENTAL ATTEMPT TO PRODUCE
INTRACRANIAL SACCULAR ANEURYSMS IN DOGS

The investigations reported in this thesis were conducted on human operative cases and human autopsy material, out of necessity. Intracranial saccular aneurysms are virtually unknown in other species (40, 52, 82, 138, 146). Hassler (82) found reports of an intracranial aneurysm in a colt and a llama, and described what was probably a "minute" aneurysm in a cow. Stehbens (146) reported a case of a chimpanzee that died from a subarachnoid haemorrhage. Autopsy revealed eight aneurysms on its circle of Willis.

A satisfactory method of producing experimental intracranial aneurysms in animals has not been described. Such a model would be a great asset in the investigation of the pathogenesis of these lesions. Hassler (85) has shown that carotid ligation in the neck of rabbits will result in bulging of the arterial wall at the apex of certain intracranial bifurcations in 25% of the animals at the end of five months. The appearance is similar to that of early "minute" aneurysms in humans. The study implied that anything which increases the flow rate across a particular intracranial bifurcation will increase the haemodynamic

forces acting on it. In turn, this will increase the likelihood of the formation of an aneurysm.

On the basis of this reasoning, preliminary experiments were made on eight mongrel dogs in an attempt to produce intracranial saccular aneurysms by the selective ligation of intracranial and extracranial arteries. The dog was chosen as the experimental animal for the following reasons: (1) The configuration of the major components of the circle of Willis is similar to that of man (18, 45, 46, 47, 91). (2) Structural modifications, similar to those in man, occur at major intracranial bifurcations in dogs (82, 138, 146). (3) In vivo intracranial angiography is possible in the dog, and the canine intracranial circulation has been thoroughly studied by this method (18, 46, 47). (4) The dog tolerates major surgery well, and, therefore, chronic studies are possible.

Two series of experiments were done. In four animals, the right posterior communicating artery was exposed through a temporal craniectomy (91) and ligated with a metallic clip. When the dog had recovered from this procedure, both vertebral arteries and the opposite internal carotid artery were ligated in the neck. One dog died during the intracranial procedure. Three survived without any neurological deficit. The purpose of these ligations was to increase the flow across the right internal carotid artery bifurcation, immediately distal to the ligated posterior communicating artery, in the hope of producing an

aneurysm at that site. The animals were studied with repeated intracranial angiography, but no aneurysms were seen. At the end of nine months they were sacrificed, and the brains were removed, so that the vessels of the circle of Willis could be studied histologically. No aneurysms were seen on gross inspection. Satisfactory histological specimens were not obtained.

There are a number of factors which may account for the failure to produce aneurysms in this series. (1) There are extensive collaterals between the extracranial and intracranial circulations in the dog, which do not exist in man (18, 45, 46, 47).* It is probably impossible to completely isolate the intracranial circulation from the extracranial circulation in the dog. (2) On the basis of the study by Jewell and Verney (91), it was thought that flow in the posterior communicating artery (which is much larger in the dog than in the human) was directed from the anterior to the posterior circulation of the brain. Therefore, it was reasoned that ligation of this vessel would direct and increase flow across the internal carotid artery bifurcation immediately distal to it. However, it was subsequently discovered that flow in the posterior communicating artery likely occurs in the opposite direction (47).

* A major source of intracranial blood flow in the dog is derived from the ramus anastomoticus (18). This vessel arises from the external ophthalmic branch of the internal maxillary artery, which is the terminal branch of the external carotid artery, and joins the internal carotid artery in the cavernous sinus of the skull. Because of its location, it cannot be exposed and ligated.

(3) Extensive scarring and fibrous tissue formation occurred about the operative site intracranially, which may have prevented the formation of an aneurysm.

The second series of experiments was designed to avoid these difficulties. In four dogs, both internal carotid arteries were ligated intracranially, immediately proximal to the origin of the posterior communicating artery. This prevents blood flow to the brain from the anastomotic artery, as well as the internal carotid artery. In order for the blood supply to the brain to remain constant (93), a large percentage of the total supply must now be carried by both vertebral arteries and the basilar artery. This should increase the likelihood of aneurysm formation at bifurcations on the posterior circulation, in particular, at the basilar bifurcation. One animal died on the fifth post-operative day from a subdural haematoma. A second dog died four months following surgery. Although it had been perfectly well, it was found by the attendants one morning lying in its cage, apparently paralyzed, but alive. The animal was sacrificed without the author's knowledge, and no autopsy was obtained. It is conceivable that this animal died of a subarachnoid haemorrhage. The remaining two animals survived uneventfully for 12 months, at which time they were sacrificed. No aneurysms were seen on gross examination of the circle of Willis in each case.

Although the results of this investigation are discouraging, I

remain convinced that if one could design a chronic experiment in which flow is increased across a given intracranial bifurcation, there is a strong probability that a saccular aneurysm would develop.

APPENDIX III

The structural properties of the walls of the aneurysms were compared to those of the intracranial arteries, by calculating the "elastance" of the elastin and collagen in each from the initial and final slopes of their elastic diagrams. A difficulty with this comparison is the anisotropic nature of vascular tissue, which cannot be accounted for in the calculations. It is also recognized that it is not customary to calculate strain for a spherical structure. To make the calculations more general, strain was considered as a change in surface area, $\Delta A/A$, rather than simply a change in radius, $\Delta R/R$.

In the case of a cylindrical artery, it is assumed that strain occurs only in one direction, circumferentially. Since the surface area of a cylinder, $A=2\pi R\ell$ and $\Delta A=2\pi\Delta R\ell$, then

$$\frac{\Delta A}{A} \text{ (cylinder)} = \frac{2\pi\Delta R\ell}{2\pi R\ell} = \frac{\Delta R}{R}$$

However, in the case of a spherical aneurysm, the strain occurs simultaneously in two directions. Since the surface area of a sphere, $A=4\pi R^2$ and $\Delta A=8\pi R\Delta R$, then

$$\frac{\Delta A}{A} \text{ (sphere)} = \frac{8\pi R\Delta R}{4\pi R^2} = 2\left(\frac{\Delta R}{R}\right)$$

Since "elastance" is fundamentally a calculation of stress/strain, in determining the elastance of aneurysms, the value obtained from the slopes of the elastic diagrams were divided by two.