THE PHYSICS OF CEREBRAL ANEURYSMS

Though the process of this potentially deadly disease is complex, one can understand many aspects of the formation, growth and rupture of cerebral aneurysms in terms of relatively simple biophysics and fluid mechanics.

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According to the most recent statistics, cerebrovascular disease is the third leading cause of death in the United States, ranking behind heart attack and all forms of cancer.[1] One form of cerebrovascular disease is the cerebral aneurysm, which manifests itself as a dilatation, or pouching, of the arterial wall. The dilatation develops at a diseased site along the wall into a distended sac of stressed arterial tissue. Fully developed cerebral aneurysms are typically from 5 to 10 millimeters in diameter. Aneurysms can and do occur at any point within the cardiac and peripheral vasculature. However, cerebral aneurysms tend to assume a simple spherical form that makes them well suited to a biophysical analysis. They also pose the greatest risks to the patient. Left untreated, an aneurysm continues to expand until it ruptures, causing hemorrhage, severe neurological complications and possibly death. It is for these reasons that this article concentrates on cerebral aneurysms. Many aspects of the treatment given here will be applicable to other types of aneurysms.

Scientific and clinical research into the origin, development and rupture of cerebral aneurysms has yielded inconclusive results, and theoretical explanations of the aforementioned stages of aneurysm development are, at best, speculative.[2] The unpredictable nature of aneurysms primarily limits their study *in vivo* to clinical observations of patients and tissue specimens retrieved at autopsy. However, a variety of *in vitro* methods exist for characterizing and studying the development and rupture of intracranial aneurysms. These methods include:

▷ numerical modeling and simulation of blood flow through a cylindrical artery structured with a geometric representation of an aneurysm[3] (see figure 1)

▷ experiments on blood flow through transparent glass and plastic arteries constructed or fitted with artificial aneurysms of a size, location and geometry typically found in clinical cases[4]

▷ experimental induction or surgical creation of aneurysms in animals[5]

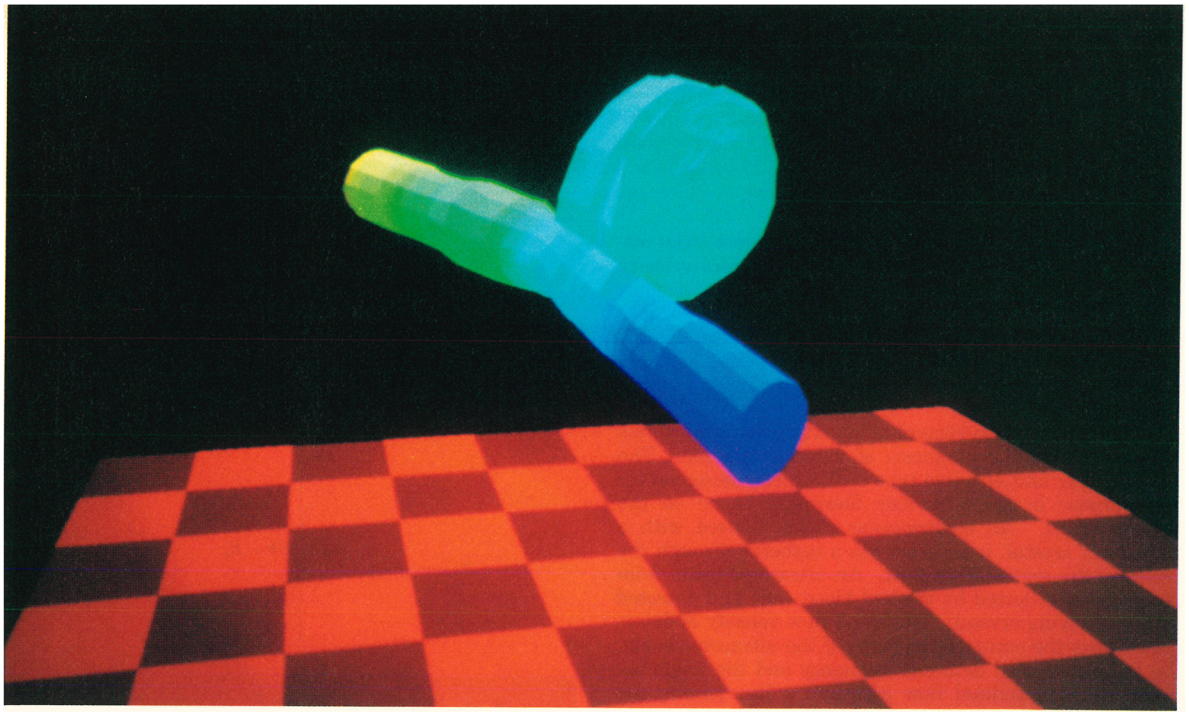
▷ biomathematical modeling of the aneurysm based on biophysical principles and physiological phenomena.[6]

Individually each method allows one to study the behavior of the aneurysm under controlled conditions. Together these methods can be used to correlate and substantiate clinical observations.

While the development of aneurysms is generally quite complex, one can qualitatively understand many aspects of their formation and growth in terms of relatively simple biophysical phenomena and interactions[7] that occur as a direct result of blood flow within tortuous segments, bends, bifurcations and other irregular arterial geometries commonly encountered in the human cerebrovasculature. These interactions involve the static tensile, viscous, pressure and impulse forces exerted by the bloodstream on vulnerable points of the artery geometry and the shear stress and vibrational displacements experienced by the elastic artery wall in response to distending forces. Such biophysical effects tend to induce abnormal blood flow, which in turn degrades the artery wall and causes the aneurysm. Thus to understand cerebral aneurysms, one must examine the physical properties of the artery wall, characteristics of blood flow and the interactions between blood and the artery wall.

Physics of the circulatory system

The heart is an elastic, muscular pump whose rhythmic contractions provide the force that circulates the blood



VIRTUAL REALITY SIMULATION. This three-dimensional image of a cerebral aneurysm was reconstructed from a sequence of digital-subtraction-angiography projection radiographs. Displaying the image in a virtual reality environment affords a medical team the opportunity to experiment with possible therapies before interacting with the patient. In this diagram color conveys information about the relative pressure distribution, with green and yellow indicating high and blue low pressures. The checkerboard background serves as a coordinate system in two dimensions. FIGURE 1

through the vast network of vessels making up the circulatory system. Blood is continually pumped directly from the heart into the arteries under systolic pressures ranging from 70 to 140 mm Hg. Hemodynamics is the study of the forces that drive this flow and how the circulatory system responds to those forces. The arteries are the vessels most susceptible to degradation by hemodynamic forces and are thus the most likely candidates for aneurysm development.

One can visualize the artery as an elastic cylindrical tube. As blood flows within the artery, it exerts hemodynamic forces against the artery wall. These forces, along with oscillations that propagate along the artery, weaken the artery wall, allowing aneurysms to develop. One can describe the behavior of the elastic artery in terms of stress and strain. Two types of stress are pertinent to arterial blood flow: tensile, or longitudinal, stress produced by pressure forces acting in a perpendicular direction to stretch the artery; and the viscous shearing stress of blood flowing against the inner surface of the artery wall.[8] For a cylindrical artery the strain ε is equal to $(R - R_0)/R_0$, where R is the radius of the artery in the deformed state and R_0 is the original radius in the undeformed state.

The components of the arterial wall that are primarily responsible for its mechanical strength are the structural proteins collagen and elastin. Collagen, which serves a protective function, is very extensible and breaks at a stress of about 5×10^9 dynes/cm^2 (500 megapascals). Elastin fibers can stretch to about 250% of their original length and have a modulus of 6×10^6 dynes/cm^2 (0.6 MPa). Collagen's larger modulus means that it is the substance that gives the artery its large resistance to the distensions from hemodynamic forces.

Blood is a complex fluid with a liquid component (plasma) and a solid component consisting of various particulates. Blood typically has a density of 1.056 g/ml and a kinematic viscosity of 3.5 centipoise. In reality, blood is a non-Newtonian fluid, since its viscosity is not constant but changes with velocity, causing a variable shear stress along the artery wall.[9] However, these effects become significant only in the smallest blood vessels, such as the capillaries and the arterioles. In larger blood vessels such as the aorta and major arteries, blood behaves more or less as a Newtonian fluid.

The flow of blood of density ρ, kinematic viscosity ν and velocity v under pressure P is well described by the Navier–Stokes equation,

$$\partial v/\partial t + (v\cdot\nabla)v + 1/\rho(\nabla P) + \nu\nabla^2 v = 0 \qquad (1)$$

which is equivalent to conservation of kinetic energy and momentum for an incompressible fluid, and by the continuity equation,

$$\nabla\cdot v = 0 \qquad (2)$$

which is equivalent to conservation of mass. With the appropriate initial and boundary conditions, one can determine the velocity and pressure from these equations at any time using finite-element techniques.

The artery's inner wall surface is extremely sensitive to adjacent hemodynamic effects. Such effects have been implicated in a variety of pathologic processes. The viscous drag of blood produces shear stresses τ at the wall surface equal to $-\nu(dv/dr)$ where ν is the viscosity.

An oversimplified view of blood flow in an artery of radius R is provided by the velocity profile, which represents the distribution of axial velocities along the cross-sectional radius of the artery. For laminar flow it is easy to see, by equating the pressure head of the blood $(P_1 - P_2)$ to the viscous frictional forces along the length L of the artery, that the velocity profile for blood flow through a cylindrical artery segment follows Poiseuille's law:

$$v = [(P_1 - P_2)R^2/4\nu L][1 - (r/R)^2] \quad (3)$$

This profile is parabolic, with the greatest axial velocity at the center of the artery ($r = 0$) and zero velocity at the walls ($r = R$). However, once the blood flow reaches a critical velocity $v_c = \nu \mathrm{Re}/\rho R$ (Re is the Reynolds number for the system containing the blood), it becomes chaotic, or turbulent. For a normal artery the transition between laminar and turbulent flow occurs at a Reynolds number of approximately 2300.

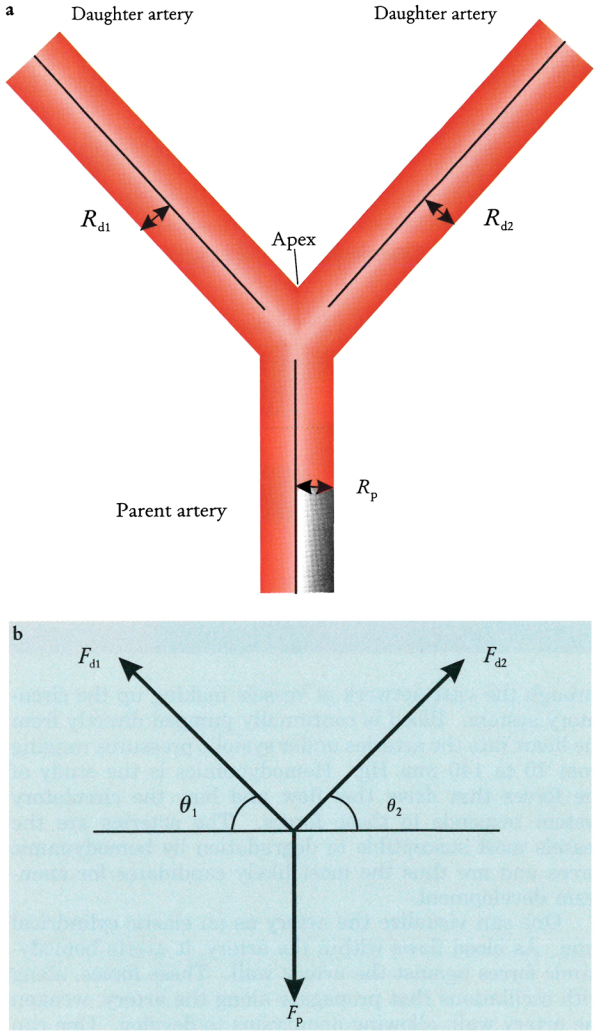
The *in vivo* measurement of blood flow within arteries is important in the diagnosis of vascular disease. The most popular and effective type of flowmeter designed for this purpose is the ultrasonic flowmeter based on the Doppler effect. An endovascular probe, housed with a transducer crystal, is inserted via a catheter through the artery to the region of interest. An ultrasonic beam from the probe is reflected by the red blood cells and detected by the receiving crystal. The blood flow velocity is determined from the emitted frequency of the ultrasonic beam, the Doppler-shifted detected frequency and the angle between the longitudinal flow axis and a line joining the two crystals.

Initiation of cerebral aneurysms

Ninety percent of the cerebral aneurysms encountered are berry or saccular aneurysms, which occur most often at points of bifurcation along the large arteries of the cerebrovasculature. At an arterial bifurcation (see figure 2a), a parent artery with a radius R_p branches into two daughter arteries with radii R_{d1} and R_{d2} positioned at angles θ_1 and θ_2, respectively, with respect to the plane bisecting the bifurcation apex. The tensile forces exerted at the apex of the bifurcation by the parent and daughter arteries weaken the wall, increasing the probability that an aneurysms will form there. (See figure 2b.) The risk of aneurysm at the apex is further increased because it is the site of maximum hemodynamic stress. (See figure 3.) Although individually the cross-sectional areas A_{d1} and A_{d2} of the daughter arteries are smaller than the cross-sectional area A_p of the parent artery, the sum $A_{d1} + A_{d2}$ is greater than A_p, so that the blood-flow velocities in the daughters are less than that in the parent. This means that a considerable amount of bloodstream kinetic energy must be dissipated at the bifurcation apex. This transfer of hemodynamic kinetic energy and momentum acts to degrade the artery wall around the apical region, as demonstrated by the skewed velocity profiles. Because the area of the apex is small, the kinetic energy is dissipated there under a higher pressure gradient, further aggravating deterioration of the artery. The increased total cross-sectional area and decreased radius and blood-flow velocity in the daughter arteries also result in a decrease of the critical Reynolds number, from 2300 to about 400. This reflects the increased probability of turbulence, which can also contribute to the initiation of aneurysms at the bifurcation apex.

Another important factor in the formation of aneurysms is the vibrational energy transferred to the arterial wall by the blood flow.[10] The aneurysm is subjected to both free and forced vibrations that tend to weaken the structural integrity of the aneurysm wall and magnify the existing state of destructive fatigue.

The combined effects of the velocity, kinetic energy, impulse and vibrational energy cause a bulge or small pouch to form at the damaged region of the artery wall. Exactly



ARTERIAL BIFURCATION GEOMETRY. **a:** Aneurysms occur most often at the apex of an arterial bifurcation, where blood from a parent artery of radius R_p is directed into two daughter arteries of radii R_{d1} and R_{d2}. **b:** One reason for the vulnerability of the bifurcation apex is evident in this vector diagram of tensile forces of the parent artery F_p acting down and the daughter arteries F_{d1} and F_{d2} acting at θ_1 and θ_2, respectively. FIGURE 2

what role each of these hemodynamic factors plays in the initiation and development of the aneurysm is unknown. However, from a biomechanical standpoint, the resultant forces from these hemodynamic factors are sufficient to fragment the elastin of the arterial wall and induce a bulge. Once the bulge has been initiated, a pocket of highly disturbed secondary flow, referred to in the literature as turbulence,[11] develops within the dilatation. Growth of the aneurysm is now imminent and is facilitated by secondary physiological and health factors such as high blood pressure (hypertension),[12] the presence of other aneurysms and other vascular diseases—anything that could disturb the balance of intravascular pressures within the local vessels.

Development and rupture

Figure 4a shows a cerebral aneurysm as a spherical

dilatation of the arterial wall that develops at the apex of a bifurcation. The circular arc or semicircle denoted by L represents the original circumferential length of the arterial segment before it was distended. The aneurysm in its developmental stage consists almost entirely of collagen, because the distending forces have fragmented the majority of the elastin. Figure 4b shows the aneurysm as a spherical dome of radius R and uniform wall thickness h. A pressure P exerts an outward force against the aneurysm wall and is countered by a circumferential tension T. For a thin-walled spherical aneurysm ($R \gg h$) in static equilibrium, T is related to the pressure P by Laplace's law: $T = PR/2$. The stress S in the aneurism wall, is similar to T and is given by $S = PR/2h$.

From the differential of Laplace's law,

$$dS = d(PR/2h) =$$

$$\tfrac{1}{2}[(R/h)dP + (P/h)dR - (PR/h^2)dh] \qquad (4)$$

it can be seen that the stress may increase not only because of increasing pressure but also because of an increase in radius or a decrease in wall thickness. S can also be expressed by Hooke's law:

$$dS = d\varepsilon\, E \qquad (5)$$

where $d\varepsilon = dR/R$ is the circumferential strain and E is the elastic modulus of the aneurysm under physiologic conditions. By equating the differential of equation 5 with equation 4, we can find the rate at which the aneurysm expands with increasing pressure:

$$\frac{dR}{dP} = \frac{R/h - (PR/h^2)(dh/dP)}{2E/R - P/h} \qquad (6)$$

Alternatively, the volume distensibility for a spherical aneurysm is

$$\frac{dV}{dP} = \left(\frac{dV}{dR}\right)\left(\frac{dR}{dP}\right) = 4\pi R^2 \times \frac{R/h - (PR/h^2)(dh/dP)}{2E/R - P/h} \qquad (7)$$

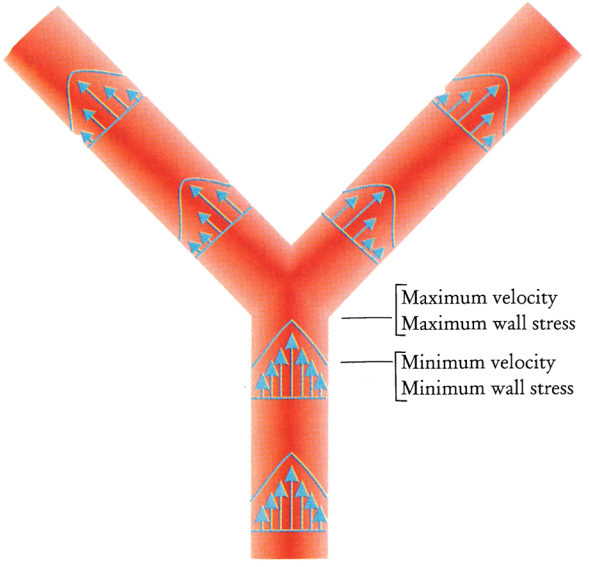
When the stress of the aneurysm wall exceeds the force produced by the structural components, the cerebral aneurysm ruptures. Because the fully distended aneurysm wall consists primarily of collagen, the force required to induce rupture is directly related to the force needed to exceed the "breaking point," or elastic limit, of collagen—that is, the elastic modulus. However, the inner wall is not isotropic. Typically, a localized region, usually at the top of the aneurysm, is in a much more advanced state of degradation than the rest of the wall. As the hemodynamic forces continue to stress this localized region, the aneurysm wall continues to expand uniformly, placing the underlying collagen within the region in an ever higher state of stress.[13] When the spacing between the collagen molecules of this region exceeds the bond length, the bonds break and a slight crack results. The location and dimensions of the crack depend on the intermolecular spacing and the surface energy per unit area, which are properties of the aneurysm tissue, that is, collagen. As one sees in various applications in engineering sciences,[14] a pressurized elastic sphere with a crack exhibits a much higher increase in tension or stress around the immediate area of the crack. This condition is sufficient to precipitate rupture at the locally weakened region. This mechanism of aneurysm rupture is supported by the observation that rupture of the aneurysmal sac usually occurs at the top of the aneurysm, is less frequent at the side and is unlikely at the base of the aneurysm.[15]

One can better understand the process of rupture from equation 7. Assuming a constant value for the elastic modulus E (typically on the order of 10^7 dynes/cm^2), one can see that the volume distensibility diverges when the denominator in equation 7 vanishes, that is, when $2E/R = P/h$. This in turn yields an expression for the critical radius of the aneurysm:

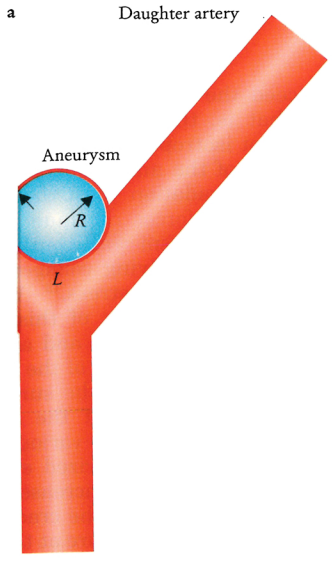
$$R_c = 2Eh/P \qquad (8)$$

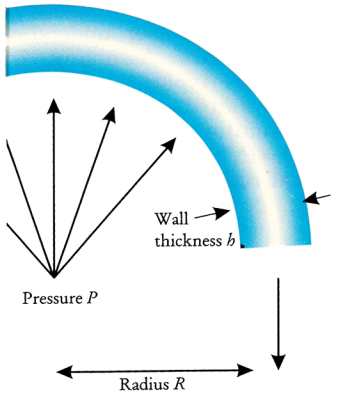
Any change that would upset this equality could induce aneurysmal rupture. The graphs in figure 5 show the influence of pressure P and wall thickness h on the critical radius of the cerebral aneurysm, using clinically common values.

Vibrations in the circulatory system have been implicated in weakening of the artery wall and in the subsequent origin and development of aneurysms. It is interesting to speculate whether pulsatile hemodynamic forces and the vibrational displacement of the aneurysm



HEMODYNAMIC FORCES play a major role in weakening the apex of an arterial bifurcation. As blood passes from the parent artery into the daughter arteries, which have a combined cross-sectional area greater than that of the parent, it flows more slowly. Excess kinetic energy and momentum of blood leaving the parent artery must be dissipated in the apical region, damaging arterial tissues and promoting turbulent flow of the blood. In this velocity profile, the length of the arrows corresponds to the velocity of blood flow. The higher blood velocities near the apex make this region the site of maximum hemodynamic stress. FIGURE 3





A CEREBRAL ANEURYSM develops (**a**) as a spherical bulge of radius R and wall thickness h. As the arterial tissue is stretched from its original circumferential length L, its elastin fibers break, leaving collagen to bear the load. At equilibrium, the tension within the aneurysm wall opposes the pressure forces (**b**). Other cerebrovascular disease or hypertension can upset this equilibrium, causing the aneurysm to grow and ultimately rupture. FIGURE 4

wall;nificant role in aneurysm rupture.oes a resonant frequency exist betwl and the pulsatile blood flow?[17]

ıuencies of normal physiological funcbody are between 20 and 200 hertɔlogical processes, particularly thosthat are susceptible to turbulent flowıcies, usually from 400 to 500 hertːetical resonance frequencies of aneu are around a kilohertz, it is unlilrysm would rupture as a direct cons However, resonant frequencies of asely with their size. This fact mayːal observations that the larger an a likely it is to rupture.

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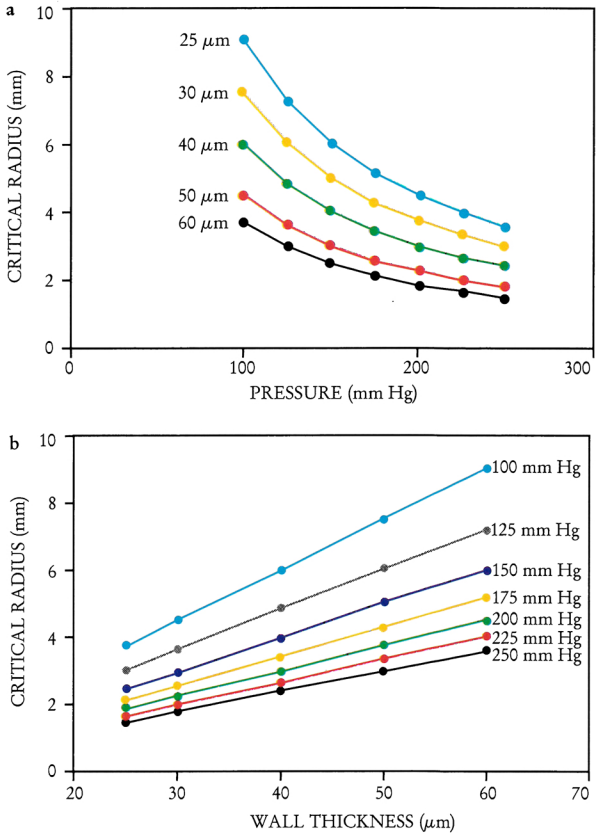
In aof cases patients with cerebral aneuence neurological symptoms and seekly after the aneurysm is fully deven poses a severe risk to the patiwhich an aneurysm is prone to ruptɔnce an aneurysm is suspected or dɔlogist can use several imaging techıted tomography, magnetic resonance imaging, digital subtraction angiography and ultrasound, to further elucidate its size, shape and location. With this information the doctors and patient can begin to discuss therapeutic options.[18]

A novel and major advance in the diagnosis and planning of therapy for cerebral aneurysms is the application of virtual reality.[19] (See figure 1.) Using specially designed software and a head-mounted display, the neurosurgeon–neuroradiologist not only can display the aneurysm in three dimensions but can visually interact with the aneurysm by moving through any point in space and acquiring views at any angle in real time. It thus becomes possible to "enter" the aneurysm through the parent vessel and assess therapeutic options. Using data for the three-dimensional image as geometric boundaries for numerical simulations, one can also ascertain the three-dimensional distribution of pressure and blood flow and use this hemodynamic information to simulate, plan and predict the outcome of therapeutic procedures.

The primary objective in the treatment of cerebral aneurysms is to minimize the effects of the hemodynamic forces on the aneurysm wall. This can be accomplished through neurosurgical intervention, endovascular occlusion or a pharmacological regimen of hypotensive agents.

Neurosurgical intervention is typically reserved for problematic aneurysms, because it is the most invasive of the procedures and poses the greatest risk to patient safety. The surgeon enters into the cranial cavity and closes or clips the aneurysm so that blood flow is once again directed through the parent artery into the daughter arteries without imposing further damage to the aneurysm wall. Even if postoperative infection and recovery time are minimal, a major disadvantage of neurosurgical intervention is the possibility of incomplete clipping of the aneurysm. This exposes the remaining portion to further hemodynamic stresses, making it susceptible to the development of a residual aneurysm that must also be corrected.

Endovascular occlusion is a minimally invasive procedure in which the aneurysm is embolized, or filled, preventing blood from impinging on the aneurysm wall. One either uses mechanical (balloons, coils[20]) or chemical (biocompatible adhesives, plastics[21]) agents to occlude the aneurysm physically or uses lasers to induce photocoagulation of the blood within the aneurysm.[22] In either approach, the embolization agent is delivered via a cathe-



ANEURYSM CRITICAL RADIUS, the radius at which the aneurysm is in imminent danger of rupture, can be predicted by Laplace's law. These contours show the calculated dependence of the critical radius on blood pressure for typical aneurysm wall thicknesses (**a**) and on wall thickness over a typical range of blood pressures (**b**), in each case assuming a constant elastic modulus of 1.00×10^7 dynes/cm^2 for the aneurysmal material. FIGURE 5

ter that can easily be threaded and guided through the major arteries to the aneurysm.

Pharmacological therapy involves administering a regimen of hypotensive medications designed to reduce the systemic blood pressure and has been shown to effectively decrease the probability of rupture.[23] However, this approach represents a short-term solution to the problem, since in principle other biological or biochemical systems could act to increase the blood pressure even under the influence of medication, thereby increasing the probability of rupture.

At the University of California at Los Angeles and many other institutions, the prevailing form of therapeutic treatment for cerebral aneurysms is an endovascular embolization procedure in which platinum coils are guided into the aneurysm through major vessels using a catheter.[24] Electric current is then applied to the coils, causing them to detach within the aneurysm and causing blood within the aneurysm to thrombose, or clot. The aneurysm is thus "packed" with the coils and the clot, protecting the stressed aneurysm wall from further hemodynamic damage and imminent rupture. Figure 6 shows the results of this procedure. The outcome for patients with aneurysms following this procedure has been extremely encouraging, and research is under way to further improve this technique from both a technical and clinical standpoint.

Prognosis for the future

The immense complexity of blood flow and its role in the development of cerebral aneurysms cannot be overemphasized. From a theoretical standpoint the "simple" case of blood flowing through a normal artery involves the pulsatile flow of a non-Newtonian fluid through a tapered, viscoelastic tube and requires the solution of a time-dependent nonlinear differential equation with variable boundaries. The presence of an aneurysm introduces another level of complexity into the problem. Still, application of elementary physical principles gives us a qualitative (and to a lesser extent a quantitative) understanding of the hemodynamic processes involved. Indeed, while this article has dealt with cerebral aneurysms, the biophysical treatment presented here is also applicable to the most common type of aneurysm—the abdominal aortic aneurysm—as long as its fusiform or ellipsoidal geometry is taken into account. The physical principles outlined in this article affect all aspects of the development of an aneurysm, from its initiation to its diagnosis and treatment, and they remain a fundamental basis for gaining further knowledge about and insight into this form of cerebrovascular disease.

However, the aneurysm is a very complex disease, in whose origin, development and rupture a number of factors are believed to have significant roles. The predominant factor is widely believed to be, as in most cerebrovascular diseases, a familial predisposition based on a genetic abnormality.[25] Congenital hypotheses have not been substantiated with evidence other than clinical observations and cannot be considered proven until a gene unique to the presence of aneurysms has been identified and isolated. Other possible factors that have been investigated include biochemical disorders of collagen metabolism, enzymatic destruction of the arterial tissue and preexisting health conditions such as hypertension, obesity and diabetes.

Advancing technology promises to provide the tools necessary for measuring the physical variables relevant to various stages of aneurysmal development and for developing more elaborate and realistic models and *in vitro* simulations that will help us to better understand how and why cerebral aneurysms occur. Research has been particularly active in the therapeutic treatment of aneurysms. With continuing advances in our knowledge of the physics and hemodynamics involved in each stage of aneurysm development, new treatments will substantially improve the therapeutic outcome and overall quality of life for patients with cerebral aneurysms.

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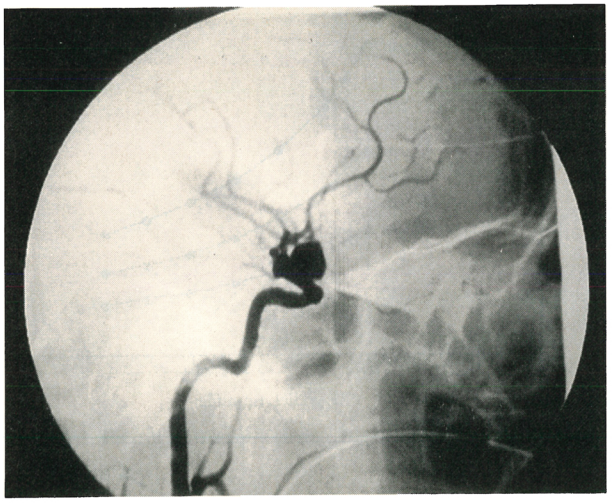

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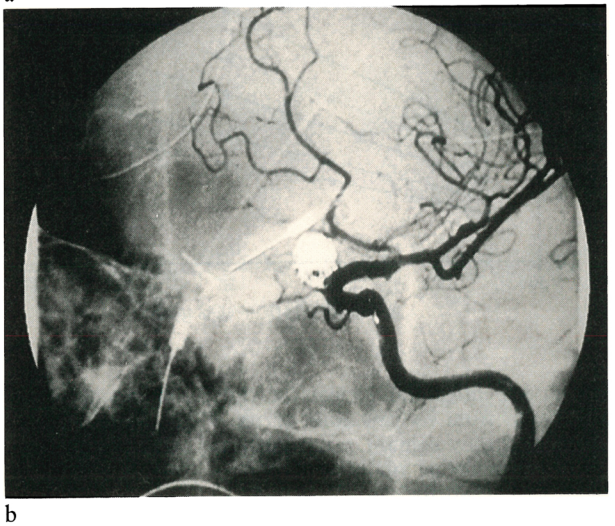

b

DIGITAL-SUBTRACTION-ANGIOGRAPHY radiographic projections of the cerebrovasculature of a patient with a cerebral aneurysm at diagnosis (a) and following successful endovascular therapy (b), as evidenced by the complete packing of the aneurysm. FIGURE 6

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