A Critical Review

THE PURPOSE OF THIS REVIEW IS to discuss the phenomenon of stenosis in extracranial cerebral arteries, its effects on normal blood flow patterns and the biological and clinical implications for the extracranial cerebral circulation. Stenosis, generally defined as a narrowing or constriction, is of particular interest because of its potential to decrease blood flow. Stenosis of the extracranial cerebral vessels is of clinical concern because the disordered flow patterns which can result may lead to exacerbation of the stenosis itself or contribute to problems in the distal vasculature. Transient cerebral ischemia, stroke, thromboembolism and post stenotic dilatation have all been reported in association with stenosis.

In this paper an introduction to the principles of normal blood flow is provided, followed by a discussion of the pathophysiological effects of stenosis. The final section considers ideas relevant to clinical aspects of extracranial cerebral arterial stenosis.

Normal Arterial Blood Flow Patterns

Flow through a blood vessel normally obeys Pousseuilles' law and proceeds in an orderly fashion as predicted by theoretical considerations derived from studies of basic fluid mechanics. Some of the principles of fluid mechanics which will be used in the discussion of blood flow through a stenosis, are reviewed here.1-5

A. Flow Through a Vessel

Blood vessels have often been considered simply as conduits for the transport of blood to the various organs and tissues of the body. The hemodynamic effects of the blood flow on the vascular wall itself are often not considered. Yet these effects play a major role in a number of pathological conditions.

The stationary vascular wall is subjected to varying amounts of stress by the blood flowing over its luminal surface. This stress is exerted in the direction of flow and is determined largely by the speed at which the blood flowing (velocity) and the viscosity of the blood. To examine more closely how that stress comes about, it is useful to consider a longitudinal section of a blood vessel (fig. 1a). Normal blood flow is conventionally described as layered or laminar in character. This means that a column of flowing blood travels in concentric layers along the vascular tube. The core layers travel at the highest velocity with each adjacent layer moving more slowly until a stationary fluid layer is encountered at the vascular wall. This decrease in velocity of blood flow from the core to the periphery of the vessel is defined as the velocity gradient.

Laminar flow is an important concept in hemodynamics for several reasons. First, it is a prerequisite for the development of a velocity gradient. This velocity gradient is important in maintaining steady flow. Second, it accounts for the typical flow profiles associated with blood flow (fig. 1). Lastly, laminar flow plays an important role in the phenomenon of shear stress.

Shear stress is best understood by examining once again the longitudinal section of a vessel with laminar flow (fig. 1a). Each fluid lamina traveling at its own speed exerts a force or forward stress on an immediate adjacent lamina traveling at a slower speed. This force is referred to as shear stress. The slower lamina exerts a backward force or drag on the faster lamina. This backward force is referred to as a resistive force. The forward stress or shear stress on any lamina must overcome the resistive forces in order to maintain steady flow. The motion of the laminae sliding past one another is called shear.

Shear stress is most pronounced at the vascular wall. The wall is stationary and the endothelial cells lining it are unable to move appreciably in the direction of flow in response to the shear stress. The greater the velocity gradient, the greater is the shear stress at the wall and the greater is the chance of endothelial injury resulting from this stress. Under normal conditions shear stress is not associated with harmful effects. However, all materials reach a limit beyond which they yield to an applied stress. This point has been termed "critical yield stress" when applied to endothelial cells and is associated with cell injury.6,7

Viscosity also influences the amount of shear stress exerted. Viscosity may be thought of as the internal friction of a fluid. Because of viscosity, a force must be exerted to cause one layer of fluid to slide over another. If the viscosity is high (i.e., the fluid is "thicker"), then greater force is required to move the fluid layer, because each layer at the periphery will have a greater tendency to retard the faster moving fluid layer adjacent to it. A more viscous fluid creates more of a pull (viscous drag) between the fluid lamina and the vascular wall itself. This effect on the wall is of particular importance with regard to vascular injury.
Figure 1. Diagrams illustrating fluid velocity profiles in various circumstances. A: The difference in velocity profile for steady (left) and pulsatile (right) flow. The length of the arrows indicates the velocity of a given lamina. B: The effect of a constriction on the velocity profile. Blunting of the profile leads to an increased shear at the wall. C: The physical reason for the blunting effect. In the tank the fluid moves toward the pipe as a solid mass (see text).

B. Steady Flow vs. Unsteady Flow

Steady or fully developed flow is the term applied to flow through straight vessels or pipes that is associated with the parabolic flow profiles (fig. 1a). In steady flow, the velocity at every point is constant with time. In other words, fast and slow areas of flow can exist at different locations but velocity at any given point always remains the same. This is not true of unsteady flow. Unsteady flow is physiologically important in that it exists in large arteries such as the aorta and is usually associated with an increased shear stress.

Flow in an entrance region can be explained in the following manner. It is characterized by a local pressure drop and therefore slowing of blood flow. Under normal conditions flow will remain steady as it slows. This situation is best visualized as fluid flowing from a large tank or reservoir, similar to a large blood vessel emptying into a smaller one (figs. 1b, 1c). The velocity of flow is the same everywhere across the area near the opening in the reservoir. Once inside the pipe, however, the velocity of the fluid near the wall slows and that in contact with the wall becomes stationary. This results in a condition of high shear at the wall. Remote from the entrance region flow again becomes fully developed or steady. Maximum velocity is once again established at the core of the vessel, decreasing to zero at the wall. Thus in the entrance region the fluid elements are undergoing acceleration. This acceleration is positive near the center of the tube and negative or retarding near the wall.

C. Boundary Layer Effects

When a fluid is viscous (as is blood) and the velocity not too high, flow will be laminar and the flow profile generally parabolic in shape. The velocity is highest in the core layers, decreasing to zero at the wall. This stagnant layer at the vascular wall is called the boundary layer, and under typical flow conditions is a thin film of fluid. The fluid a short distance from that boundary is traveling faster than the stationary layer at rest on the boundary, resulting in a non-zero shear stress at the wall. The boundary layer thins out even more in areas where a blunted flow profile is seen such as in entrance regions or at branch points and this extremely thin boundary layer is associated with an increased shear at the wall. As flow becomes fully developed, the boundary layer increases in thickness, resulting in decreased wall shear.

D. Turbulence

As long as the layering pattern of flow is maintained, flow is called "laminar" or "streamline." If the flow velocity increases beyond a critical value the layered pattern is disrupted and the fluid elements develop irregular motion and tumble. Random, irregular, local currents called vortices may be set up. Blood flow characterized by such irregular patterns of movement is called turbulent. Turbulence is seen under normal conditions in the arch of the aorta, but is not otherwise associated with normal, steady flow conditions.

Pathophysiological Effects of Stenosis

A. Flow

The description given above of flow through tubes or vessels is based on the assumption of non-pulsatile flow. Although blood flow through arteries is pulsatile, most of the same principles apply. Pulsatile flow through arteries has been extensively analyzed by McDonald.8

Arterial flow through a stenosis or constriction has been the subject of numerous studies.8-20 The following is a summary of the major points of these studies. The major characteristics of flow through a constriction include: boundary layer separation and recirculation just distal to the constriction, increased shear stress in the constricted area, and downstream turbulence (fig. 2).
Boundary layer separation can be explained in the following manner. In a straight tube or vessel, pressure diminishes in the direction of flow, and conditions are stable. In a convergent stenotic region, pressure decreases at an even faster rate, while in an expanding post-stenotic area, pressure is increasing in the direction of flow. This latter effect tends to retard flow. Centrally, the inertia of the moving fluid opposes the retarding forces but near the wall where fluid velocity is low, inertia is also low (almost negligible when compared to the viscous forces). The result is that when the adverse pressure gradient slows fluid flow enough, flow near the wall eventually reverses direction. The boundary layer at that point is no longer thin and is said to have separated, hence the term boundary layer separation (fig. 2 — between C and D). Boundary layer separation is associated with low wall shear. This boundary layer is well defined, and there is no turbulent mixing that occurs within this region.

Severe constrictions cause an increased shear stress which is proportional to the degree of stenosis and becomes maximal just before the point of maximum constriction (B — fig. 2). The streamline becomes bent and flow accelerates. The fluid velocity near the wall and orifice is quite low, resulting in what are termed "dead water zones." The flow emerging from the constriction is jet flow. Turbulence may be seen at high flow rates but the emerging jet flow is laminar at low flow rates. Downstream turbulence is a result of decelerating flow (E — fig. 2). Inertia maintains the flow going but the pressure gradient (pressure differential) develops from the wall inward, a reverse of the normal condition. This creates a situation in which pressure is higher in the outer layers than in the core, resulting in turbulence.

Pulsatile flow through a stenosis results in the same basic flow patterns as previously described: laminar flow proximal to the stenosis, increased shear stress entering the constriction, boundary layer separation after the constriction and turbulence downstream. These flow patterns are not stable in conditions of pulsatile flow, however, and all three may be observed over the period of each cardiac cycle.

The velocity profile in pulsatile flow is markedly blunted when compared to the parabolic profile seen in non-pulsatile flow. This blunted profile results in large areas of blood remaining relatively unsheared because, in effect, it is moving as a solid column (i.e., en block). In addition, an increased velocity gradient occurs at the wall which effectively means that for the same mean flow rate, shear stress is greater under pulsatile than non-pulsatile flow conditions.

While numerous theoretical studies and models have predicted disturbances in flow patterns, few in vivo studies have been done. The effect of blood flow through chronic arterial stenosis has been the subject of even fewer studies.

B. The Vessel Wall

Shear stress in arteries is directed at the single layer of endothelial cells. Shear stress causes strain or displacement in the direction of the stress, in this case, in the direction of blood flow past the endothelial cells. Endothelial cells are arranged in the direction of flow. This is supported by the observation that they are aligned with their longitudinal axes parallel the direction of blood flow. The causal nature of this relationship was confirmed experimentally by an interesting study in which a segment of dog aorta was removed and resutured in a fashion which aligned the long axis of the endothelial cells 90° away from their original orientation. Within 10 days the normal endothelial alignment with respect to blood flow was reestablished. This study also demonstrated that endothelial cells in the region of branch points were very sensitive to shear forces acting on them.

Endothelial cell injury as a result of increased shear stress was studied systematically by Fry. The term "critical yield stress" was used to designate the point beyond which an elevation in shear stress exerts pathological effects on endothelium. By inserting a grooved plug into the thoracic aorta of the dog, blood flow was diverted into a narrow stream between the plug and the aortic wall. This maneuver greatly increased blood flow velocity. Acute elevation of endothelial shear stress accompanying this increased flow velocity resulted in endothelial alterations ranging from changes in permeability to cellular injury and erosion. The results of these experiments included two findings of particular interest. First, a strong correlation was shown between sites of endothelial injury and predicted sites of highest shear stress. Second, the critical yield stress values for endothelium calculated by Fry were only slightly higher than those known to occur normally within the arterial vascular tree.

Studies of acute vasospasm, a form of localized vascular constriction, have also shown areas of endothelial injury which correspond to sites of predicted increases in shear stress and turbulence. After experimental stenosis in animals endothelial injury and restructuring occur in the area of the constriction.

Studies of acute and chronic experimental arterial stenosis have demonstrated luminal changes which are consistent with theoretical predictions. These changes include endothelial desquamation and platelet adhesion to subendothelial tissue in the area of maximal shear stress, and loss of the normal endothelial cell orientation just distal to the stenosis (fig. 3).
This area of disordered endothelial cells corresponds to the area of boundary layer separation and recirculation demonstrated in model systems. Patchy areas of desquamation were observed in areas where downstream turbulence was predicted (fig. 4). Another finding with important clinical implications was that of thrombus formation with platelets and red cells trapped in a fibrin mesh just distal to the stenosis (fig. 5). This is an area of stasis where such cells might be expected to settle out of circulation and not be washed away.

After periods of experimental arterial stenosis lasting from one month to one year, scanning electron microscopy revealed marked restructuring of the luminal surface. Such restructuring appeared to be the result of endothelial cell proliferation. After three to six months, web-like cords of endothelial cells could be seen in the vascular lumen (fig. 6). These cords arose from the endothelial surface in the region of and distal to the stenosis. Such structures apparently provide a potential nidus for thrombus formation, since scattered platelet and red blood cell thrombi were observed in these areas. Lesions in this mode of arterial stenosis which correspond to areas of high shear stress did not heal. Furthermore, they were not atherosclerotic in nature. This is supportive of a recent hypothesis of atherosclerosis, that of low mean shear stress corresponding to areas with atherosclerotic lesions.¹-⁵
In summary, the hemodynamic changes which accompany arterial stenosis have two significant effects on the vascular wall. First, they cause endothelial injury, thereby creating a thrombogenic surface. Second, such changes result in some degree of vascular restructuring which seems to cause permanently altered hemodynamic changes within and around the stenosis.

The mechanism of endothelial repair, i.e., whether endothelial cells multiply from the periphery to cover denuded areas or whether endothelial repair involves blood leukocytes has been a matter of debate. Redifferentiation of underlying smooth muscle cells has also been suggested as a possible source of endothelial repair. More recent studies, however, seem to suggest that proliferation of endothelial cells may be the predominant mechanism by which injured areas are repaired.

The extent to which an actual healing process occurs after endothelial injury remains controversial. The time period over which healing takes place and the factors which may retard or prevent healing are under study. It is clear, however, that endothelial desquamation favors platelet attachment and fibrin formation. Platelet and red cell thrombi are subsequently formed at the site of injury, attaching to the subendothelial connective tissue. Blood flowing past this area effects a shearing stress on the wall of the artery, favoring detachment of any thrombi attached to the wall. In any case, the thrombus would protrude into the path of the oncoming stream of flowing blood. If this situation is further complicated by occurring within a region of stenosis the increased shear stress, turbulence and disordered flow patterns may considerably accelerate the process of endothelial injury and greatly retard the process of endothelial repair.

C. Components of the Blood

Under conditions of steady laminar flow, a condition exists called "axial streaming," whereby cellular elements of blood travel in the center of the blood stream leaving a thin cell-free zone near the vessel wall. When turbulence exists this flow pattern is disrupted and the zone of blood flowing near the wall is no longer cell free.

Cellular elements of the blood (red cells, leukocytes, platelets) are not attracted to the normal arterial lining. They are, in fact, repelled from the intact endothelium under normal conditions because they have the same electric charge. In addition, the endothelial cell is covered with a layer of glycoproteins synthesized by the endothelial cell which are thought to prevent the activation of blood coagulation and platelets. The intact endothelial cell also releases prostacyclin which inhibits platelet aggregation. Once the endothelium is injured and subendothelial tissue is exposed the situation is drastically changed. A strong affinity exists between platelets and subendothelial collagen. Platelets adhere to the exposed collagen or microfibrils and elastin in atherosclerotic lesions, become rounded in shape and undergo a release reaction. The material released includes adenosine diphosphate (ADP), a powerful platelet aggregating agent. ADP thus causes further platelet aggregation, resulting in additional release of ADP. This reaction continues until a platelet clump of moderate size is formed. Such platelet clumps or thrombi are readily washed away and are easily disaggregated. However, at the same time plasma coagulation factors are acting and can result in a stabilized thrombus. Thromboplastin is released by the damaged vessel wall, thereby activating clotting mechanisms. This sequence of events results in conversion of prothrombin to thrombin which, in turn, converts the plasma protein fibrinogen to insoluble fibrin. Such fibrin forms the ground substance for a fully organized red blood cell thrombus. It is generally accepted that fibrin does not normally adhere to intact endothelium. The platelet aggregate usually forms the base upon which layers of fibrin and blood cells are deposited. In addition to fibrinogen conversion thrombin also acts as a stimulus for the platelet release reaction. For a comprehensive review on clotting mechanisms, the reader is referred to other sources.

The hemodynamic effects associated with stenosis — increased shear stress, turbulence and boundary layer separation — can result in a number of changes affecting the components of blood. Under conditions of laminar flow, endothelial injury and extensive platelet aggregation does not normally occur. When whole blood and platelet rich plasma have been exposed to high shear stress, however, cell aggregation, platelet and leukocyte release reactions and increased coagulability of platelets have been demonstrated. These studies and others suggest that abnormal hemodynamic flow patterns may result in platelet hypercoagulability. If such hypercoagulability exists chronically, the addition of certain other factors can enhance platelet aggregation and lead to temporary vascular occlusion. Hyperaggregability of platelets has been identified as a risk factor in transient ischemic attacks, stroke, myocardial infarction and acute peripheral arterial insufficiency. Evidence of platelet hyperaggregability has been documented in patients with thrombosis in the presence of normal bleeding times, platelet glass retention and clot retraction. Once platelet aggregates do occur the flowing blood may still carry them away or cause disaggregation. With low flow rates or stasis, such as in areas of boundary layer separation distal to a stenosis, aggregates are less likely to be carried away. In addition, stasis delays clearance of (plasma) clotting factors, thromboplastin from tissue damaged areas and soluble fibrin complexes.

Turbulence is potentially thrombogenic through its effect on red blood cells and platelets. In an interesting series of in vivo experiments, Mustard and his colleagues demonstrated that thrombi which attach to extracorporeal shunts in areas associated with turbulence are composed mostly of platelets. The deposition of particulate matter in these experiments was considered to be largely determined by hydraulic factors. Brown, using a rotational aggregometer, found...
human platelets to be particularly sensitive to increased shear stress. In turbulent flow there is an increase in the number and force of collisions between cellular components of the blood. Such collisions can result in ADP release from platelets followed by aggregation and thrombus formation. This phenomenon has been used as the basis for estimating the predilection to atheroma of the aorta and other vessels associated with turbulence. A well-documented situation where turbulence plays a major role in blood cell injury and its thrombogenic complications is that of diseased mitral and aortic valves or prosthetic heart valves. Small thrombi have been observed at the junction of a prolapsing mitral valve, and the frequency of thromboembolism has been correlated with the turbulence. In addition, thrombi have been recovered from turbulent blood flow through arteriovenous shunts. The results of such studies indicate that platelets and red cells are damaged by the mechanical effects of turbulence.

Boundary layer separation also has a potentially thrombogenic effect on the components of blood. Such separation zones which occur in stenosis have been suggested as sites where platelets and fibrin can interact to form a mesh-work which would serve to entrap lipids and contribute to formation of atheromatous plaques. In studies utilizing an aneurysm flow chamber model, there was little deposit in the central portion of the chamber where flow was relatively laminar. The dilated portion of the model where flow characteristics are analogous to boundary layer separation in a stenosis, was heavily encrusted with platelets and thrombi. As pointed out previously, prosthetic heart valves are a frequent source of thromboemboli, even with recent improvements in design and prosthetic materials. Although the role that turbulence plays in formation of such thromboemboli is well defined, some investigators attribute this phenomenon in part to the occurrence of stagnation near the valve. The available evidence suggests that both turbulence and separation zones contribute to these pathophysiological changes.

One additional potentially thrombogenic effect of turbulence may result from the disruption of the fibrinolytic system. Turbulence contributes to intravascular clotting via blood cell injury and also causes endothelial injury which leads to local platelet adhesion and formation of platelet thrombi. Injured endothelial cells release which simultaneously inhibits and controls clotting. Thus, the net effect of turbulence on fibrinolytic activity is unpredictable since it is heavily influenced by other physiological factors which might be operating at that time.

Clinical Aspects
A. Etiological Considerations

Extracranial cerebral arterial stenosis in humans is most frequently associated with atherosclerosis. This condition may be also associated with fibromuscular dysplasia, vascular injury secondary to neck manipulation, carotid dissection or as a side effect of radiation therapy in the region of the neck. These areas are considered within the context of their significance to arterial stenosis.

1. Atherosclerosis

Atherosclerosis is the most common cause of extracranial cerebral arterial stenosis in humans, a disease in which plaques composed primarily of lipid substances are deposited along blood vessel walls. Once thought to be a disease of the elderly, atherosclerosis is now recognized as an insidious disease of the blood vessels which begins early and continues over the lifetime of most individuals.

Atherosclerosis shows a predilection for specific vascular sites including the vessels of the circle of Willis and the extracranial carotid artery system. This condition is generally preceded by the appearance of fatty streaks in the vascular wall which do not extend into the lumen. Atherosclerosis ultimately results in lesions which protrude into the arterial lumen, progressively decreasing its diameter. Such lesions may lead ultimately to complete occlusion of the vessel or vessels in which they are found.

Disagreement exists regarding the underlying mechanisms responsible for the symptoms resulting from atheromatous lesions. The tendency for atheromatous plaques to occur at points of bifurcation of vessels and along areas of curvature have led investigators to seek a hemodynamic basis for sites of lesion formation. Stehbens, using glass models, demonstrated that turbulence is more likely to occur in an S-bend than along a straight segment. Moreover, areas of predicted turbulence coincide well with location of atheroma as determined at autopsy of patients with arterial stenosis. Shear stress, and pressure are the factors most frequently considered as a basis for sites of atheromatous lesion formation. Caro et al., have postulated that in regions of low wall shear stress, mass transfer to and from the vessel wall is inhibited, and it is well known that high wall shear stress is associated with mechanical damage to the endothelial lining of the vessel. Comparison of pathological data with the data obtained from glass models of the human carotid bifurcation indicates that zones susceptible to atheromatous disease are associated with low shear stress; those subjected to high shear stress are free of deposits. Such atheromatous lesions can in fact create a stenosis which may be critical or flow-limiting to the territory supplied by the affected vessel. In such cases the mechanism may be considered the flow-limiting nature of the "tight" stenosis. The explanation for the occurrence of symptoms in the territory of an affected vessel in which the stenosis is not flow-limiting is less apparent. The critical flow limiting theory argue that these symptoms must result from the thrombogenic effect of the stenosis.

Evidence of hemodynamic changes and thrombus formation have been shown in the narrowing or stenosis of vessels resulting from atherosclerotic plaques. A large plaque extending into the vessel creates an im-
pedance to normal blood flow and results in disturbed flow around the plaque. The amount of thrombus material accumulating in these areas of disturbed flow is greater than in areas where flow is laminar. Thrombus formed in such areas are not generally occlusive and, when subjected to the high shear stress and turbulence associated with stenosis, will most frequently be washed off into the distal circulation. A good example is that of thrombi formed at the carotid bifurcation fragmenting and embolizing the retinal and cerebral circulation. This phenomenon is associated with transient attacks of blindness or cerebral ischemia.

Arterial stenosis also occurs as a result of "kinking" or buckling of the artery secondary to atherosclerosis. Kinking has been defined as angulation of one or more segments of the internal carotid artery associated with stenosis of the affected segment. The association between kinking of the internal carotid artery and cerebrovascular insufficiency is reviewed by Desai and Toole in which they point out the clinical importance of this disorder. Manifestations of kinking in adults include recurrent TIAs which may be aggravated on head rotation. In many of these cases patient symptoms can be accounted for by a flow-limiting mechanism, particularly those related to rotational head movements.

The role of arterial injury in atherogenesis has been of interest since Virchow first proposed that such injury was followed by inflammation, cellular proliferation and finally degeneration and atherosclerotic plaque formation. Duguid subsequently suggested that mural thrombi became incorporated into the atherosclerotic lesion and provided the stimulus for further degenerative changes. Since that time numerous groups of investigators have contributed to the evolution of the present "response to injury" hypothesis of atherogenesis.

The initiating factor, according to this hypothesis, is injury to endothelial cells. A single, occasional injury leads to endothelial desquamation with platelet adherence, aggregation and the release reaction. This sequence of events is followed by migration of smooth muscle cells into the intima, smooth muscle proliferation and connective tissue formation. According to the proponents of this hypothesis, a single injury may be satisfactorily resolved, but repeated or chronic injury results in progressive atherosclerotic lesions. Regression of such lesions may also occur if the response to injury was not extensive and the endothelial barrier is restored. Moreover as the lesions increase in size and narrow the lumen, they are subjected to the increased shear stress and hemodynamic changes associated with a stenosis as shown in fig. 2. Under such circumstances re-endothelialization and regression of lesions is unlikely to occur. These altered hemodynamic conditions thus favor the continued formation and progression of lesions.

The amount of endothelium lost in lesion formation, determines the rate of platelet consumption and the extent to which smooth muscle cells are formed in the lesion. The amount of subendothelial tissue exposed in chronic endothelial injury is the net result of three processes: endothelial cell injury and desquamation, endothelial cell migration and endothelial cell regeneration, all of which are the subject of intensive in vitro study at present. Investigations of endothelial cell injury, in vivo, using aortic catheters and balloon catheters, all suggest that the development of acute or chronic vascular disease is related to the extent and location of the de-endothelialized surfaces.

2. Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD), a relatively uncommon cause of arterial stenosis, is defined as a segmental nonatheromatous and noninflammatory angioapathy of unknown cause. This was first described in the renal arteries in 1938. Atherosclerosis does, however, account for the vast majority of stenoses reported. Hyperplasia of the media is the most striking feature although similar pathological changes may be seen in the intima and adventitia of the affected arteries. Fibromuscular dysplasia has long been recognized as a cause of cerebral insufficiency. This condition may remain asymptomatic or may be associated with carotid artery dissections, complete occlusion, cerebral infarction or transient ischemic attacks. Of particular interest in relation to the pathogenesis of arterial stenosis are the reports of thrombi present at the site of FMD and even one published report of cerebral embolism from the site.

3. Vascular Trauma

Stenosis may also occur following a vascular injury, particularly in the vertebral arteries supplying the posterior cerebral circulation. This is an example of vascular injury which results in thrombus formation. Rotation or hyperextension of the neck accompanying trauma have resulted in vertebral artery thrombosis with signs of distal ischemia. With extreme hyperextension of the neck the vertebral artery is stretched across bony prominences in such a manner that the vessel wall may be disrupted and dissection and thrombosis can occur. Since these thrombi tend to be large and occlusive and the vessels are not examined until autopsy, it is difficult to prove the sequence of pathophysiological events. However, the torsion and temporary occlusion accompanying such neck rotation or hyperextension would have the effect of creating a transient functional arterial stenosis with the accompanying hemodynamic changes of increased shear stress and turbulence at that site. Such occlusion is also associated with chiropractic manipulation resulting in symptoms of brain stem stroke, in cases of head traction associated with posterior inferior cerebellar artery syndrome, and changes of head position. The majority of cases reported show extensive thrombosis extending from the area of injury to some distal point. Because of the extensive size of the thrombosis the symptomatology is typically attributed by inference to a hemodynamic mechanism. However, an intimal tear is generally considered a prerequisite for traumatic thrombus formation.
Nonpenetrating trauma to the internal carotid artery with associated thrombus formation has been reviewed in detail. This condition is fairly rare and may present as complete or partial occlusion with or without emboli in the partial occlusion.

4. Carotid Artery Dissection

Stenosis also occurs in association with carotid artery dissection. Dissection of the extracranial internal carotid artery can occur spontaneously13, 127-129 or in association with trauma such as penetrating neck injuries, intraoperative laceration and percutaneous carotid angiography.130-133 As described elsewhere in this paper, nonpenetrating trauma to the neck is most commonly associated with thrombosis of the internal carotid artery but can also result in dissection.134 Although now considered more frequent than previously realized, carotid artery dissection is still an uncommon occurrence carrying with it a relatively high morbidity and mortality.135, 136 First reported in 1872 by Verneilin in a patient with severe head injury, the description included an intimal tear, dissection of the cervical internal carotid artery and thrombosis extending to the middle cerebral artery.137

The pathophysiology of carotid artery dissection is generally accepted as an intimal tear. Such a tear may become the origin of complete or partial occlusion, cerebral emboli, traumatic pseudoaneurysm or dissection.138 The most common mechanism of tearing seems to be that of stretching the internal carotid artery over the upper cervical spine with the neck hyperextended and laterally flexed to the opposite side.132-137 Histological examination typically reveals that the dissection is associated with the outer layers of the media. Cystic medial necrosis, degeneration of muscle fibers and internal elastic laminae and an increase in ground substance have also been identified upon histological examination.133, 129

5. Radiation Effects

Since radiation therapy is commonly used to treat malignant tumors of the neck, its effect on extracranial vessels is important. Both the increased use of radiation therapy and the longer survival times of patients have contributed to recognition of the role of this therapy in the etiology of carotid artery stenosis and occlusion.

Vascular injury as a complication of radiation therapy was first recognized by Gassman in 1899.139 Since that time damage to large arteries in patients after radiation therapy has been described by others.140-145 In particular, narrowing or occlusion of the carotid arteries following such therapy has been recognized as an important clinical problem in recent years.144, 146-152 Such radiation-induced changes in the carotid vessels have been linked to cerebrovascular insufficiency.144, 146-147, 149

In a recent review of irradiation injury to large arteries three patterns of injury were delineated. These include: intimal damage and mural thrombosis within 5 years of therapy; fibrotic occlusion occurring within 10 years; and a predisposition to development of atheroma along with periarterial fibrosis with a latency of approximately 20 years.153

Radiation-induced atheromatous lesions which have been studied both clinically and experimentally are similar in appearance to spontaneously occurring atherosclerotic lesions.154-157 However, radiation-induced atheromatous lesions are clearly localized to vessel segments that have been irradiated, sparing nearby nonirradiated segments and are found in locations considered atypical for spontaneously occurring atherosclerosis.144, 152, 154

The specific mechanism of vascular stenosis and occlusion following radiation therapy is unknown, but experimental animal studies of the effects of radiation on the arterial wall have provided some useful information regarding vascular wall changes. An extensive study of the short- and long-term effects of radiation in large blood vessels of dogs revealed moderate to severe endothelial injury within 48 hours. This included nuclear disruption and endothelial desquamation with patchy areas of fibrin deposit. After 6 weeks reendothelialization had occurred but the endothelial cells differed in appearance from normal. After several weeks the medial layers of the arteries showed a progressive hyper trophy with subsequent fibrosis accompanied by adventitial swelling. Such findings suggest that the radiation induced injury results in slow endothelial layer repair and thickening with permanent damage to the medial and adventitial layers.155

B. Clinical Effects

1. Most Common Effects

The most common clinical effects of arterial stenosis include asymptomatic carotid artery bruits, transient ischemic attacks, stroke and post stenotic dilatation. Bruits, vibrations audible as noise with a stethoscope just distal to an arterial constriction, are of particular interest in the carotid territory. They may be asymptomatic, accompanied by TIAs or ischemic stroke, or they may remain asymptomatic. The clinical significance and natural history of asymptomatic carotid artery bruits are discussed in detail elsewhere.157, 158

Post stenotic dilatation, a weakening or bulging of the artery downstream from a stenosis, has been studied extensively, and considered secondary to the altered flow dynamics distal to a stenosis.8, 106, 107 Turbulence is considered to be of primary importance in the development of poststenotic dilatation.108

From a clinical perspective, however, the importance of arterial stenosis lies primarily in its relationship to transient ischemic attacks and stroke. The relationship between arterial stenosis of the vessels in the neck and stroke was first recognized in the mid-nineteenth and early part of the twentieth centuries169-171 but the intracranial vessels were still considered of primary importance to disease. The advent of angiography allowing visualization of the extent of extracranial vessel stenosis172 and the introduction of surgical endarterectomy173, 174 focused attention on the extracranial arter-
ies of the neck and the significance of their role in cerebral ischemia. The importance of this role has been underlined by a number of large scale clinical studies of TIA as well as case reports. Discussion of the natural history, definitions and pathogenesis of TIA are outside the scope of this review but are described in detail elsewhere. 175-178

2. General Concepts

From the preceding descriptions of the hemodynamic and cellular events which occur in the presence of stenosis, it is clear that the hemodynamic changes occasioned by a stenotic vessel narrowing may be expected to initiate thrombus formation at the site of stenosis and thrombus formation may occur at any one of three major locations. These are depicted in figure 2 and include: at the point of maximum shear stress where endothelial damage is the worst (Point B in fig. 2), in the area of boundary layer separation just beyond the stenosis (between C and D in fig. 2) or downstream if turbulence develops (E in fig. 2). Whether this proceeds to full-scale thrombosis or embolism will depend on a number of concurrent factors including blood viscosity and an effective fibrinolytic system.

An arterial stenosis is typically regarded as "critical" if it is flow limiting and "subcritical" if it is not. 179-182 Early studies suggested that arterial stenosis caused by atherosclerotic plaques led to cerebral infarction by simply decreasing cerebral blood flow. 183, 184 Others suggested that alteration of caliber was of importance for two reasons: first, by a direct effect on cerebrovascular resistance; second, by an indirect effect of producing turbulence and predisposing the vessel to local platelet aggregation. 185 Brice and others measured pressure gradient and flow in the human carotid artery and defined the degree of constriction which produced just detectable effects. They concluded that the artery must be severely constricted before there is any change of flow or pressure gradient. The amount of constriction required to limit flow corresponds to an average reduction of luminal area by about 80-85%. 186-189 Significant pressure drop does not occur distal to a stenosis of less than 72% luminal area reduction; pressure decreases occur consistently with stenosis greater than 87% luminal area, however, and may or may not occur in the presence of stenoses between these two extremes. 190

On the other hand, hemodynamic changes other than decreased blood flow associated with a stenosis of less than 80% could be expected to result in endothelial damage. We have confirmed in experimental studies of arterial stenosis that endothelial cell injury and thrombus formation occur with arterial stenosis in the range of 50-80% area reduction — clearly subcritical stenosis by accepted definition. 191, 192

The configuration of the arterial stenosis is of some interest although this factor is generally considered to be of less importance than is the degree of constriction. In clinical and experimental studies, the length of the constriction has a small hemodynamic effect; 193, 194 the proximal luminal constriction is of limited importance, while the hemodynamically dominant component of arterial stenosis is the outflow tract beyond the stenosis. 195, 196 The shape of carotid atheromatous lesions does not seem to influence the hemodynamic effects of arterial stenosis, at least in regard to pressure drop. The extent of area reduction still remains the determining factor. 197

Additional factors influence whether or not a stenosis is critical. For example, the presence of collateral circulation to the territory supplied by the affected vessel, increased metabolic demands of the tissue, drop in blood pressure or decreased cardiac output must also be considered. Such factors would modify the demand or supply of that tissue for blood and could transform a fixed subcritical stenosis to a functionally critical one.

In summary, currently available evidence suggests that no single existing theory can explain the mechanism of pathogenesis of cerebral ischemia distal to extracranial cerebral arterial stenosis. The evidence summarized in this paper suggests that either flow-limiting or thromboembolic phenomena may be operating given the appropriate conditions. Thromboembolic events seem more likely to be precipitated by a "subcritical" arterial stenosis, while a "critical" arterial stenosis may result in symptoms of distal cerebral ischemia through the mechanism of blood flow restriction and/or thromboembolism secondary to hemodynamic changes associated with blood flow through a stenosis.

Acknowledgments

Dr Ots R. Blaumanis was my collaborator in the studies of experimental arterial stenosis which led to the writing of this review. Mrs. Rene Carlyle helped to obtain the library materials and Ms. Jackie Paul typed the manuscript.

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Pathophysiology of extracranial cerebral arterial stenosis--a critical review.

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Stroke. 1984;15:224-236
doi: 10.1161/01.STR.15.2.224

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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