Physical Factors in the Pathogenesis of Cerebral Atherosclerosis

BY JOSEPH A. RESCH, M.D., RUTH B. LOEWENSON, PH.D., AND A. B. BAKER, M.D., PH.D.

Abstract:
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This report consists of an analysis of autopsy material from 5,031 cases. The cerebral vessels, as represented by the circle of Willis, were scored for severity and extent of atherosclerosis. The effect of physical factors on this process was considered. It is concluded from our data that Laplace's law best explains the mechanical stress leading to injury of the vessel wall. The literature concerning this and other hypotheses is reviewed.

ADDITIONAL KEY WORDS
autopsy  circle of Willis  Laplace's law
mechanical stress

Atherosclerosis is due to a variety of factors which in all probability are mutually interrelated. Among these are the vascular filtration pressure, the composition of the blood, the permeability of the endothelial membrane, the hydrodynamic effects of blood flow, hormones, lipid metabolism, nutritional state, hypertension, sex, age, and race. This communication addresses itself to the various factors of a physical nature which exert an effect on atherogenesis in cerebral vessels.

Review of the Literature
It is apparent that the focal, discrete distribution of atherosclerotic lesions must depend on local differences in the arterial wall or physical effects thereon since the composition of the plasma is, for all practical purposes, uniform. That physical effects on atherogenesis are considered important is generally reflected in the literature. They were considered as early as 1864 by Rindfleisch. There are a number of interesting hypotheses, and this review will be directed to their examination.

MECHANICAL FACTORS
Strain Hypertrophy
Adami in 1909 promulgated the theory of "strain hypertrophy" as the cause of atherosclerosis. He suggested that there is a local weakness of the media which gives way under pressure. This defect in turn produces an increased strain on the overlying intima, which undergoes a certain amount of stretching as it is pushed outward to cover the bulging media. Intimal proliferation continues until the volume of new tissue and the resistance it affords balance the loss of substance by the weakened media. Boucek, more recently, reported on his theory of strain on the arterial wall and came to the conclusion "that a relation exists between the structural-mechanical properties of the artery wall, its functional role, and discrete intimal hyperplasia."

Shearing Force
Allbutt in 1915 advanced a concept in which a "shearing" effect was the cause of the early intimal change. The distention and contraction of the artery during pulsation result in a slight displacement or slipping of the intima.

Loosening of Ground Substance
Virchow in 1856 and Aschoff in 1924 felt that the intravascular pressure caused a "loosening" of the connective tissue increases with resultant local intimal thickening and subsequent imbibition of lipids from the blood.

Fixation
Duguid called attention to the location of...
atherosclerotic lesions about the mouths of branch arteries. He theorized that a loss of elasticity in the intima occurred with advancing age. The loss of elasticity causes the intima to fold inward, particularly during the contraction of the vessel, and this infolding of the intima results in splits separating the intima from the media. Intimal proliferation and finally fatty infiltration occur at such points of separation. The amount of stress on intimal folding is dependent on the range of diastolic recoil. The above changes occur at points where such movement is likely to be the greatest, for example, the area surrounding the origin of branches.

**Intimal Hemlatlon**

Krafka advanced an interesting concept. He postulated that there were interstices between the media and elastic tissue of the intima. These fenestrae are points of tensile weakness which under pressure may lead to microscopic intimal herniation with intimal proliferation as a consequence of the irritative effect.

**Trauma**

A number of investigators have suggested that intimal change and subsequent lipid deposition occur in response to some type of trauma to the vessel wall. Such trauma may result from repetitive pulsatile stress. An attempt to repair the injury in the presence of hypercholesterolemia may lead to atherosclerosis. Stephenson utilized hypercholesterolemic dogs as his experimental subjects. He produced trauma to the aorta by means of periaortic fibrosis with asbestos, aortic autografting, and coarctation and found segmental concentration of the atheromata in the zone of the operative trauma in each of these procedures. It was concluded that in the presence of the hypercholesterolemia, trauma to the arterial wall was the predisposing factor for the focal deposition of lipid and subsequent formation of atheroma.

**HEMODYNAMIC FACTORS**

**Hydraulic Effect of Velocity Energy and Static Energy**

Texon has been an exponent of the application of the laws of fluid dynamics to explain the focal nature of atherosclerotic lesions. In his hypothesis the velocity of blood flow, the caliber of the vessels, and the anatomical pattern of the arteries have a composite hydraulic effect which determines the site of predilection and the progression of atherosclerotic lesions. In his opinion Bernoulli's theorem can account for the fact that lesions have a tendency to occur at points of converging boundaries, branching, bifurcation, abrupt curves, and fixation. Bernoulli's theorem states that "fluid in motion possesses velocity energy as well as static or lateral energy and that the sum of these energies is constant at any two points of flow." Diminished lateral pressure in the vicinity of curves, branching, and points of fixation, coupled with an associated increase of velocity energy in these areas, results in a "suction"-like action which tends to draw the wall of the vessel inward toward the center of the lumen. The intima is subjected to a lifting or pulling effect on the endothelial layer. The earliest reparative process is the thickening of the intima due to proliferation of endothelial cells and fibroblasts. Subsequently, lipid changes occur as droplets within the fibroblasts in the basement zone of the intimal plaque. It is Texon's belief that atherosclerosis, whether natural or induced, is consistently found at sites of diminished lateral pressure. He produced alterations in the femoral arteries of dogs and demonstrated that the intimal changes conformed to the laws of hemodynamics described above.

Forbus studied hemodynamic effects in a model consisting of rigid tubes in which bifurcations were placed at various angles simulating the situation in cerebral arteries. He concluded that pressure within such a system was not exerted equally in all directions but was greatest at the points perpendicular to the axis along which the pressure was initially applied. In this observation he did not differ from Gubner and Ungerleider who thought that increased lateral pressure was responsible for the formation of lesions. It should be kept in mind that Forbus was using a rigid rather than a pulsating tube system. Gubner and Ungerleider state that arterial blood pressure has two components, static or lateral pressure and a velocity pressure. However, it was their suggestion that in large arteries and in areas of fixation or bifurcation, the velocity head component was transferred to an increased static or lateral pressure which was then exerted against the arterial wall. This increased...
lateral pressure initiates the atherosclerotic process in these special areas of the vascular tree. Although they agree with Texon in the matter of the two types of energy characterizing the blood flow through a vessel, they take rather the opposite view concerning the way in which these forces are applied.

**Turbulence**

Schwartz and Mitchell\(^2\) performed an autopsy study on the distribution of arterial plaques. They observed that plaques were more frequent in areas of bifurcation and in curvatures. They suggested that turbulence occasioned by blood flow was the mechanical factor responsible for the lesion. They considered turbulence to be most common at the origin of the larger arterial branches, and suggested that this may account for the increased prevalence of atheromatosis in the terminal intracranial carotid segment as opposed to the lesser prevalence in the cervical and petrous portion of the internal carotid.

Sako\(^2\) and Wesolowski et al.\(^2\) also subscribe to the turbulence theory. Sako demonstrated that atheromatous changes were more severe in an artery immediately proximal to an experimental arteriovenous fistula, probably because of the turbulence at this site. Wesolowski described two possible mechanisms by which turbulence may lead to an atheromatous lesion: (1) critical injury to the vessel wall as a result of high-frequency vibrations or (2) local changes in the vessel wall due either to suppression of secretion or increased filtration of lipids. Stehbens,\(^2\) utilizing glass tube models for the study of flow effects, observed that the velocity of flow in the vascular system was sufficiently high for turbulence to occur. He thought that such turbulence might be a factor in initiating lesions at the sites of branching of cerebral vessels.

**Hypertension**

There is considerable evidence from experimental, clinical, and pathological studies to show that hypertension is associated with acceleration of the atherosclerotic process. By inference then, the blood pressure under any circumstance can be considered to have a profound effect on the pathogenesis of this condition.\(^2\) Burton\(^2\) in 1951 discussed the physical equilibrium of small blood vessels on the basis of LaPlace’s law.\(^2\) Wil-

\(^{2}\)The equation is expressed as \(T = P \times R\), where \(T\) is the tension in dynes/cm, \(P\) is the excess of hydrostatic pressure inside the vessel over the outside, expressed in dynes/cm\(^2\), and \(R\) is the radius in cm.
CHARACTERISTICS OF LESIONS IN MAN AND ANIMALS

There is general agreement that the larger arteries are more likely to be atherosclerotic. Young et al. studied a large number of sections of coronary and cerebral arteries and quantitatively assessed the degree of atherosclerosis. He noted an almost linear relationship between the degree of atherosclerosis and the radius of the artery. Blumenthal subsequently observed that the incidence of plaque formation was higher in arteries of larger lumens than in those with smaller lumens. Willis found that bifurcations of arteries were common sites of atherosclerosis. His conclusion was that this was due to a local increase in the vessel radius existing at these bifurcations. Moschcowitz pointed out that patches of aortic atherosclerosis occur earlier and are more extensive at or near the origin of the intercostals which fix the posterior wall of the aorta. He therefore suggested that the fixation and impaired expanse of motility played a role in atherosclerosis, observing that the anterior aspect of the aorta, which is free, is much less subject to atheromatosis. Leary also noted that lesions were more commonly found at the oriﬁces of the vessels and theorized that the waves of dilatation and contraction of the free wall as it came up against the relatively ﬁxed oriﬁces of the vessels lead to internal disturbance, resulting in the atherosclerotic process along the circle of Willis.

Insofar as severity is concerned, there is not complete unanimity of opinion as to exact pattern of the vessel involvement. However, there is general agreement that the internal carotid, basilar artery, and middle cerebral artery are most involved and that the smaller caliber vessels, such as the vertebral, posterior and anterior cerebral, and the communicating arteries, are less severely involved. This would be in agreement with LaPlace’s law which, it will be recalled, states that tension in the vessel wall increases directly with the radius.

Taylor and Fontaine et al. made a study of the location of early atherosclerotic lesions in hypercholesterolemic rabbits. Taylor showed that early lesions were in the shape of a delta with the apex pointing downstream and with the base about the oriﬁce of branching vessels. Fontaine et al. found the earliest lesions on the convex surface of the arch of the aorta. The abdominal segment was next involved and ﬁnally the visceral arteries. Stehens examined intimal changes of the cerebral arteries in sheep and steers. Intimal proliferation was observed at the sites of branching on the face and on the dorsum of each vessel bifurcation. In some bifurcations there was an increase of ground substance deep in the intima. Lipid was often present in the involved areas. The location of lesions at bifurcations suggests a hemodynamic factor.

Methods

The material was obtained from routine autopsies at the University of Minnesota Hospitals and the Hennepin County General Hospital during the period of 1961-1965. Certain characteristics of the autopsy populations have been described previously. It was found that deaths in younger individuals are more frequently autopsied than those in older persons and that male deaths come to autopsy in slightly larger proportions than females.

The autopsy rates for the two hospitals in 1965 were as follows: in University of Minnesota Hospitals 87% for males and 80% for females, in Hennepin County General Hospital 70% for either sex. In the same year circles of Willis were obtained from 81% of the male autopsies and from 76% of the female autopsies at the University of Minnesota Hospitals, and the corresponding percentages were 85 and 93 from Hennepin County General Hospital.

SCORING

The method of scoring the extent and severity of cerebral atherosclerosis was that of Baker. The scoring is on a numerical basis with the grades of involvement from 1 to 4 at each of 22 sites, which are indicated in ﬁgure 1.

The scores for a given site are deﬁned as follows:

Grade 1—Opacity involving only a small part of the vessel circumference. No lumen narrowing.

Grade 2—(A) A diffuse, thin plaque that does not involve the entire vessel circumference with minimal lumen narrowing. (B) A small thick plaque that produces less than 25% lumen narrowing.

Grade 3—(A) A diffuse, thin plaque involving the entire vessel circumference with mild lumen narrowing. (B) A localized, thick plaque producing 25 to 50% lumen narrowing.

Grade 4—(A) A thick plaque involving the entire vessel circumference with moderate or
marked lumen narrowing. (B) A localized thick plaque resulting in over 50% lumen narrowing.

Figure 2 illustrates this scoring system in a diagrammatic manner.

RELIABILITY STUDIES

Two types of reliability studies on the scoring method were conducted between the two investigators who had been involved in the coding of cerebral atherosclerosis. The first study dealt with the reliability of the total score for the whole circle of Willis, whereas the second study was concerned with the scoring of single lesions. The second reliability study is particularly relevant to the analysis of single vessel involvement presented in this report.

In the second study 80 vessel pieces were independently scored twice by each coder. The specimens were chosen from different caliber arteries of the circle of Willis and showed varying degrees of atherosclerotic involvement, including some without lesions. The vessel pieces were about 3 cm long, they were stapled onto a piece of cardboard, and a cut was then made through the middle of the specimen for scoring. The results of the study are presented in Table 1. The differences in scores between the two coders were distributed symmetrically, indicating no systematic discrepancy in coding. Furthermore, the size of the vessel did not seem to have any effect on the inter-coder agreement in scores. The intra-coder differences revealed a tendency toward higher scores on the second scoring.

DATA ANALYSIS

Mean vessel scores were obtained for the individual scoring sites by ten-year age groups. A comparison of the means and variances revealed no differences between corresponding scoring sites of the two hemispheres; thus, it was possible to combine the data for the scoring sites in identical right and left arteries. The same analysis was applied to the data obtained from the group of clinically diagnosed hypertensive cases and the group of nonhypertensive cases. Values of standard deviations are given for selected age groupings.

<table>
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<th>Total</th>
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<th>No hypertension</th>
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<td>15</td>
<td>737</td>
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<tr>
<td>10-19</td>
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<td>183</td>
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<td>20-29</td>
<td>250</td>
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<td>30-39</td>
<td>332</td>
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<td>292</td>
</tr>
<tr>
<td>40-49</td>
<td>618</td>
<td>71</td>
<td>547</td>
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<tr>
<td>50-59</td>
<td>861</td>
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<td>60-69</td>
<td>896</td>
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<td>727</td>
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<tr>
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<td>814</td>
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<td>80+</td>
<td>311</td>
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<td>248</td>
</tr>
<tr>
<td>Total</td>
<td>5,031</td>
<td>693</td>
<td>4,338</td>
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TABLE 1

Reliability Study on Single Vessels (80 Specimens)

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<tr>
<th>Coder</th>
<th>Total agreement No.</th>
<th>Agreement within ± 1 point No.</th>
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</thead>
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<td>A with B</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>A with himself</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>B with himself</td>
<td>61</td>
<td>76</td>
</tr>
</tbody>
</table>

TABLE 2

Number of Cases in Study
groups to indicate trends in variability. The age distribution of the cases is presented in table 2.

**Results**

**DISTRIBUTION OF SINGLE LESIONS**

A single lesion is, in a sense, presumptive evidence of the site of origin of atherosclerosis in a given case. This certainly would be the case where the criterion is a macroscopic lesion. Figure 3 shows the location of the 289 single lesions found in this autopsy series. It should be noted that the sites of predilection are the upper and lower basilar artery, the internal carotid artery, the middle cerebral artery, the posterior cerebral artery, the anterior cerebral artery, and the communicating arteries in that order.

**SINGLE VESSEL ANALYSIS**

For purposes of this analysis, we chose three vessels of different size, all originating at the internal carotid trunk (fig. 4), and, similarly, three vessels which are part of the vertebral basilar system (fig. 5). We noted that the severity of atherosclerosis is greatest in the vessels with the largest radius. Whether the anterior or posterior circulation has a greater risk for atherosclerotic involvement is a moot point. Unfortunately, the vessels available for comparison are not precisely of the same caliber; however, there seems to be little difference in the two systems between vessels of approximately the same radius.

The possibility that hypertension might affect the distribution of vessel involvement led to an analysis of vessel scores in hypertensive
and nonhypertensive cases. The results in figures 6 and 7 show that the scores for any given segment are higher in the hypertensive cases than in the normotensive cases. The pattern of involvement remains essentially the same, the vessels with a larger radius having a proportionately greater involvement than the vessels with the smaller radius.

VARIABILITY
Table 3 indicates that the variability of vessel scores increases with age. However, a comparison of the standard deviations between the hypertensive and nonhypertensive groups shows that larger standard deviations are concurrently associated with higher values of mean vessel scores. Since the scores increase with age, it is not certain whether the increase in variability is correlated with age, or with higher scores (indicating greater severity), or with both. Previous analyses of total vessel scores revealed similar trends.42

Discussion
The data on single lesions would agree with the observations of Blumenthal32 and others28, 81, 82, 42 that the caliber of the vessel is an important factor in the occurrence of atherosclerosis. This observation lends support to LaPlace's law, whereas Texon's hypothesis,15-16 based on his interpretation of Bernoulli's theorem, does not seem to give an adequate explanation for our data on single lesions. From figure 3 it is quite apparent that the highest frequency of single lesions occurs in the rather straight vessels, that is, in the internal carotid and the basilar artery. Curved sections, such as the proximal portion of the middle cerebral artery and the posterior cerebral artery, have a definitely lower frequency of single lesions. Fisher,48 in commenting on Texon's work,18-19 did not concur in the observation that atheromata formed along the inner aspect of a curving vessel. In fact, he says "there are more exceptions to this rule than confirmations."

When the data of the single vessel analyses are considered, LaPlace's law pro-

TABLE 3
Variability in Vessel Scores for Given Arteries and Selected Age Groups

<table>
<thead>
<tr>
<th></th>
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<td>30-39</td>
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<td>0.51</td>
<td>0.65</td>
<td>0.18</td>
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<tr>
<td>50-59</td>
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<td>0.76</td>
<td>0.68</td>
<td>1.17</td>
<td>1.03</td>
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<td>70-79</td>
<td>1.37</td>
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<td>1.11</td>
<td>1.53</td>
<td>1.41</td>
<td>0.77</td>
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<td>0.92</td>
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<td>0.47</td>
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<td>1.37</td>
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<tr>
<td>70-79</td>
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<td>1.42</td>
<td>1.36</td>
<td>1.33</td>
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Stroke, Vol. 1, March-April 1970
vides an explanation. From figures 4 and 5 it can be seen that severity of involvement increases with the radius of the vessel. On the other hand, in figures 6 and 7 it is apparent that hypertension definitely increases the severity of involvement throughout the decades. The variable factor is now increased pressure since the diameters of the vessels remain the same. LaPlace’s equation clearly implies that an increase in radius, or in pressure, or in both would increase the tension which produces the injury to the vessel wall.

That there are other factors responsible for atherosclerosis is quite readily acknowledged. For example, once a vessel has undergone a certain amount of luminal encroachment, particularly if it is extensive, the effect of LaPlace’s law should tend to decrease the amount of stress on the vessel wall since the radius is reduced. At this point, however, other factors undoubtedly become operative because of the roughened vessel wall, e.g. turbulence or platelet thrombosis.

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Stroke. 1970;1:77-85
doi: 10.1161/01.STR.1.2.77

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