Arteriosclerotic Occlusion of Cerebral Arteries: Mechanism and Therapeutic Considerations

By Walter L. Bruetsch, M.D.

The brains of 20 patients with cerebral arteriosclerosis have been studied with regard to the exact mechanism of occlusion of the arteries in encephalomalacia. The histologic material has convinced the author that the concept of "cerebral thrombosis" in its present wide application is erroneous; there is arterial occlusion but the mechanisms of its production, which are discussed, are not the usually accepted ones.

Arteriosclerosis is responsible for approximately 90 per cent of all occlusive vascular diseases of the brain occurring after the age of 50. Its dramatic clinical expression is apoplexy. In four out of five instances of an arteriosclerotic stroke, the fundamental lesion is ischemia and in its extreme form softening (encephalomalacia) due to vascular obliteration, supposedly brought about by thrombosis. For this reason, the condition has been referred to as cerebral thrombosis. In the anatomic material of this study no histologic evidence of "thrombosis" was observed. The arterial occlusions were caused by other mechanisms.

The purpose of this study is to present the histologic alterations which lead to narrowing and at times to occlusion of the arterial tree in cerebral arteriosclerosis.

A review of the literature of the past 50 years reveals few investigations which have been devoted to this subject. Foix and Ley in their excellent contribution on cerebral infarction in 1927 remarked that little if anything is found in classical neurologic text books on the exact anatomic state of the blood vessels in this condition. And this is true today.

In 1933 there appeared what is possibly the most comprehensive study dealing with arteriosclerotic changes of cerebral vessels in human material. The work was done by Wolkoff under the guidance of Anitschkow, who is known as the originator of experimental cholesterol atherosclerosis. The study emphasized the deposits of lipids in the wall of the arteries.

Anitschkow's hypercholesterolemic theory is by far the most important single contribution to the understanding of arteriosclerosis, although his concept has not remained unchallenged. In recent years this approach has gained new impetus through the studies of Gofman and his colleagues, and at present most research is being done by biochemists to the almost complete exclusion of the histologists.

However, there are certain aspects of the problem which cannot be solved by the biochemical approach or by animal experimentation and which can be advanced only by histologic study of human material.

Histology of Vascular Lesions

Broadly speaking, the human arteriosclerotic lesions in large arteries, such as the aorta, coronary arteries, and the vessels of the circle of Willis of the brain (fig. 1), and their immediate extensions, are predominantly fatty in type, due to an accumulation of cholesterol and other lipids in the arterial wall. In the small cerebral arteries, on the other hand, endothelial proliferation alone, without lipid deposits, produces occlusion. And in the smallest vessels, including the minute arterioles which give rise to the capillaries, hyalinization of the vessel wall, also called hyaline degeneration, is an
ARTERIOSCLEROTIC OCCLUSION OF CEREBRAL ARTERIES

Fig. 1. Basilar artery from a patient with severe cerebral arteriosclerosis. The grotesquely distorted vessel is completely occluded, and the customary diagnosis would be "thrombosis" of the basilar artery. Histologic analysis of serial sections reveals the occlusion to be the result of a huge deposit of lipid (A). The upper two-thirds (B) of the former lumen consist of connective tissue, containing in another level an area of bone marrow formation. In the occluding tissue there is then a gamut of connective tissue cells which have arisen from the mesenchyme and differentiated in various directions. This feature is unlike the change observed in an old organized thrombus. Toluidin blue stain.

Fig. 2. Hyalinization of arteriole from the putamen of the brain. The vessel wall is several times its normal thickness. At one side of the lumen (arrow) there is proliferation of endothelial cells, some of these exhibiting mitotic figures (see fig. 3). H.E. stain.

Fig. 3. Endothelial cell in the stage of mitosis. At A is the wall of the vessel. H.E. stain.

Important feature of the vascular alterations in arteriosclerotic encephalomalacia. Hyalinization is often associated with thickening of the vessel wall, leading at times to complete obliteration of the lumen. In addition, there may be endothelial proliferation (figs. 2, 3). The obliterative changes of the small arteries and arterioles are the cause of the "little strokes."

In the large cerebral arteries a major factor which contributes to narrowing and occlusion is the deposition of lipids. In the small cerebral arteries the occlusion is the result of endothelial proliferation. Here the histologic features suggest clearly that the endothelium is primarily involved. However, in the large cerebral arteries endothelial and fibroblastic cell proliferation may also be of some, if not of greater, importance than the deposition of lipids in causing occlusion. The lipid deposits are often walled off from the remaining lumen by relatively huge layers of fibroblastic tissue. These so-called fibroblastic cushions appear to be much more than a mere reparative reaction to the "foreign body" material represented by the lipid. There is experimental evidence that there will be no formation of atherosclerotic plaques, despite a marked hypercholesterolemia, unless the tissue has the innate ability to react to lipid infiltration.6

ETIOLOGIC CONSIDERATIONS

Furthermore, the concept of Gofman and his coworkers7 that certain classes of lipoprotein

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molecules ($S_t$ 10-20) are closely associated with the development of atherosclerosis is difficult to substantiate in human cases. In a representative group of my patients with repeated arteriosclerotic strokes, the blood cholesterol and the lipoprotein levels ($S_t$ 10-20 class), as determined by ultracentrifugal analysis, displayed little decisive change from a group of “normal subjects” of similar age. Barr is of the opinion that these tests do not deviate with sufficient constancy to permit their practical use in the clinical diagnosis of atherosclerosis or of a tendency to its development.

It has been said many times that the degree of atherosclerosis increased parallel with the quality of nutrition, being most pronounced in countries with excessive nutrition, particularly of cholesterol. The North American diet is possibly the richest in cholesterol-containing food (eggs, milk, butter, cream, cheese, etc.), yet in European countries, for instance Italy, with diets much poorer in cholesterol, cerebral and coronary arteriosclerosis are also frequent diseases. Danish vital statistics, like the statistics in the United States, rank cerebral apoplexy as the third commonest cause of death, following only coronary heart disease and cancer. These and other observations are adding to the evidence which seems to indicate that a high cholesterol intake is not the all important factor in the causation of atherosclerosis.

**MECHANISM OF OCCLUSION**

This brings us back to the other alteration in the atherosclerotic plaque, namely, endothelial and later fibroblastic hyperplasia. One will have to ask the question: What causes the fibroblastic proliferation in the plaque? Some observers feel that the fibroblastic reaction is initiated by the lipid deposit, but in many instances one has the impression that new formation of connective tissue in the plaque has been suffocated rather than stimulated by the lipid. There is usually no tendency of fibroblasts to grow toward the lipid deposit in an attempt to organize it. The fatty substance seems to lie in the tissue in an inert manner. Even after the lipid deposit has been well organized and demarcated from the remaining lumen, the tendency toward fibroblastic activity continues in places where it serves no further purpose. These observations suggest that fibroblastic proliferation is most likely an important factor in atherosclerosis. In other words, as in the small cerebral arteries, in which endothelial proliferation is the basic feature, so in plaque formation of the larger arteries, involvement of the endothelial cells and of their close relatives, the fibroblasts, may be of paramount importance.

This view receives corroboration from the presence of what the author terms “embryonic foci of cellular proliferation” in the fibrotic part of the plaque. Such foci of cellular proliferation are often located in the surface of the fibrotic cushion, being in contact with the remaining lumen where they lead to further extension of the fibroblastic obliteration of the artery. In these areas there is no normal endothelial lining but, instead, there is a wall of loosely arranged cells, from 1 to 15 cells deep, consisting of a variety of cellular elements. The cells may be young fibroblasts or lymphocytes and particularly Maximow’s undifferentiated mesenchymal cells, or a mixture of these and of still other cell types. Amitotic cell division of some of these cellular elements is often present. Such foci can be considered to

![Fig. 4. Small cerebral artery. “Focus of embryonic cellular proliferation” (arrow), sending through the lumen a syncytial-like tongue of cytoplasm containing minute hyperchromatic nuclei. In the perivascular space is an area of lymphoeytic cells. Toluidin blue stain.](image-url)
be in an embryonic state, which may erupt at any time and lead to further fibroblastic growth. The reason why the "embryonic foci of cellular proliferation" (fig. 4) have not been described previously is because they are not obvious; they consist of relatively few cells. They become particularly evident in rapidly progressive cases of atherosclerosis and in vessels which are fixed in alcohol, embedded in celloidin, and stained with toluidin blue or one of the other basic anilin dyes. These cellular foci are inconspicuous, because fibrotic narrowing of the lumen is in most instances an exceedingly slow process, going on over many years. For this reason, easily perceptible changes cannot be expected.

**Therapeutic Considerations**

In the beginning of this paper it was mentioned that the now prevailing concept of thrombosis in arteriosclerotic cerebral vascular occlusion, in its present wide application, is incorrect. It is true that gross examination of the large cerebral arteries may disclose a blood clot adhering to the vessel wall, but histologic examination fails to show lamination or any other characteristics of a true thrombus. The reason why a column of blood over a limited distance adheres to the vessel wall, suggesting a thrombus, is often due to a localized and rapid proliferation of endothelial cells which entangles red cells and thus forms an occluding mass. This observation goes well with the fact that no general disturbance of the coagulation mechanism has been demonstrated in patients with arteriosclerosis. It also explains the poor results of anticoagulants in the treatment of arteriosclerotic cerebral infarction.11 The reason for the poor results of anticoagulants has just been given. The use of a low cholesterol-low fat diet or of drugs to alter the cholesterol metabolism are being questioned by the experience that there is no good correlation of high cholesterol plasma levels with human atherosclerosis, and that the reduction of cholesterol intake has at times little or no effect on high cholesterol levels in man.12 An important phase of arteriosclerotic vascular occlusion is the proliferation of the endothelial cells and fibroblasts and the presence of "embryonic cellular foci" with mitotic activity. Therefore, the use of drugs which inhibit cell division and others which delay connective tissue formation may be advantageous in the retardation of the arteriosclerotic process.

**Summary**

An attempt was made to elucidate the mechanism by which narrowing and occlusion of arteries occurs in arteriosclerotic softening of the brain. In an extensive histologic examination of 20 brains with arteriosclerotic encephalomalacia, no evidence of the occurrence of true thrombosis was observed.

As the microscopic study progressed, emphasis shifted from the lipid deposit to the fibroblastic part of the arteriosclerotic plaque as the major factor in the obliterative sclerosis. The presence of "embryonic foci of cellular proliferation" in the plaque appear to be the source for the slow extension of the fibroblastic obliteration in the large cerebral and other vessels, such as the coronary arteries. In the small cerebral arteries, occlusion is caused by endothelial proliferation. The proliferative changes of the endothelial cells in the small cerebral vessels, as well as the proliferation of the fibroblasts in the arteriosclerotic plaques, is viewed as a morbid process occurring at a time in the individual's life, when various cell types show great propensities for abnormal growth.

**Summario in Interlingua**

Esseva studiate le cerebros de 20 patientes con arteriosclerosis cerebral. Le objectivo del studio esseva le determination del exacte mechanismo de occlusion de arterias in encephalomalacia. Le datos histologic assi colligite ha convincite le autor que le concepto de "thrombosis cerebral" in su currente application general es erronee. Il occurre occlusion arterial, sed le mechanismos de su production non es illos usualmente acceptate. Le ver mechanismos es discutite.

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