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THE ETIOLOGY OF ARTERIOSCLEROSIS*

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ARTERIOSCLEROSIS has been known since antiquity, though accurate knowledge of this condition has been gained only within the last seventy-five years. To Virchow we are indebted for the first careful histologic descriptions. From his time to the present, innumerable investigations have been made and, while we have detailed information concerning the anatomic changes, our knowledge of the causative factors is, in reality, meager and controversial. The importance of the condition is recognized only by consideration of its far-reaching consequences. It may be the direct cause of death by producing cerebral hemorrhage, cerebral thrombosis, or cardiac infarction. It is the underlying factor, or is associated with various other disease processes such as hypertension or nephritis.

An idea of its incidence may be gained from the registrar general's review of England and Wales for the year 1927, in which there are listed 484,000 deaths from all causes. There are 97,000 diseases of the circulatory system, of which 23,700 are directly assignable to arterial disease. These figures do not include 25,000 deaths from apoplexy, which we may assume were associated with arteriosclerosis. Thus 120,000 deaths, or 25 per cent, are more or less directly concerned with arterial disturbance. In the Berlin Krankenhaus Charité, from the years 1905 to 1912 inclusive, there were 9149 deaths from all causes, and 402 from arteriosclerosis, an incidence of 10.2 per cent of all patients over forty years of age, and 4.3 per cent of the total number. These figures are derived from autopsies and include all cases where arteriosclerosis was the direct cause of death and the basic condition. A percentage of 11.2 was found as the cause of death from autopsy material at the Peter-Paul Krankenhaus and the Marienkrankenhaus [1] in a total of 2258 persons over twenty years of age (1923-1925). Of the latter series, the incidence, according to decades, increased in frequency to 52 per cent in the seventh. Most instances were generalized and the brain, kidney, and heart were involved in descending order of frequency.

The subject has been greatly confused by the lack of agreement among investigators as to what should be included under the term "arteriosclerosis." There is the further difficulty of the application of different labels to the same conditions. We have chosen to differentiate large and small vessel sclerosis, since differences in histologic structure determine varying reactions to injury. The larger arteries are of the elastic type and are subject to changes known as senile ectasia and atherosclerosis. Small vessel alterations include hyalinization, arteriocapillary fibrosis, medial hypertrophy, and endarteritis obliterans. Arterial changes of an inflammatory nature, due directly to infectious diseases as syphilis and tuberculosis, lie outside the scope of this paper and are not considered.

PATHOLOGIC CHANGES

Senile ectasia is considered by Aschoff [2] as a normal accompaniment of old age. The aorta is primarily affected because of its large content of elastic tissue. With increasing age there is a loss of elasticity wherever this tissue is found in the body on account of a peculiar change undergone by elastin. In consequence the aorta becomes overstretched, tortuous, and dilated. Opposing this process, connective tissue increases in the intima, adding to its strength and elastic resistance. Such a vessel is strong and rigid but has lost its contractility, and in pure form is known as senile sclerosis.

Atherosclerosis is a term first used by Marchand to indicate a special type of arterial degenerative change. Aschoff considers that this is the designation for the final picture of a process that begins early in life as an atherosis or a deposition of fat in the intima. World War autopsy material has demonstrated that fatty changes occur in from 35 per cent of individuals at twenty years of age to 100 per cent over forty. It has been observed commonly in infancy and puberty, and Saltykow [3] reports the finding of lipoid flecking in the aortas of 95 per cent of infants older than three months, and in 100 per cent of children beyond eight years of age. The process is first evident as fine yellow streaks along the lines of tension of the aorta between the origins of the intercostal arteries. This occurs as a deposition of cholesterin esters in the cement substance of the elastica stria terminalis, lying between the inner elastic connective tissue layer and the outer elastic muscular layer of the intima. At first there is no change of the intima, though later by extension, fat droplets accumulate in the intimal

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cells themselves and a raised patch is formed. Regression of this change is possible in infancy and puberty.

In later years an entirely different picture is presented. The same process occurs, but this time in an aorta almost devoid of elastic tissue and thickened with connective tissue. Grossly there may be gray or yellow elevated plaques, incrustations of lime, or depressed ulcers from loss of the intimal covering. Microscopically the process begins, as in youth, with fatty infiltration, but there is concomitant or preceding hyalin degeneration of the increased connective tissue which overlies the fatty regions. Through a reactive process the connective tissue may further increase and further undergo hyalin change. With increasing accumulation of fat, the overlying tissue breaks down and atheromatous ulcers are formed. Tissue asphyxia and necrosis result from the presence of large amounts of cholesterin which subsequently splits off fatty acids with the formation of calcium soaps.

Mönckeberg has distinguished a special form of sclerosis of the muscular type, chiefly in the lower extremities, and characterized by tracheal-cartilage-like rings of calcification of the media. The calcium deposits follow necrosis and fatty change of the muscle cells. These regions may be surrounded by granulation tissue and the media may be, but usually is not, thickened. Intimal change occasionally follows. This condition is an expression of arteriosclerosis in its wider sense, though Mönckeberg considered it a separate process.

In the small vessels the changes differ somewhat from those described for the larger arteries. Hyalinization is characterized by thickening and diffuse swelling of a homogeneous highly refractile mass in the intima and media. It is commonly found in the arterioles of the spleen, uterus, kidney, and brain. It is said to be physiological in the spleen where it is present in 15 per cent of persons under the age of ten years, and in 75 per cent over sixty. Amyloid change falls in this class and may be differentiated by its special staining reactions.

The arteriocapillary fibrosis of Gull and Sutton is an exaggeration of the pathologic processes of the arteries seen with advancing age. In the arterioles of the kidney, spleen, liver, and other organs, there is a deposition of hyalin beneath the endothelium, or a hyperplasia of the internal elastic membrane with formation of many lamellae. Subsequently hyalin and fatty change and connective tissue proliferation narrow the vessel lumen. In the later stages the medium atrophies and is the site of fatty and hyalin change and ultimately connective tissue replacement. There is a dispute as to the distribution of the lesions, Gull and Sutton believing the changes to be generalized in all the arterioles and small vessels. Borchardt[4] saw no outstanding kidney involvement, whereas Fahr maintains the predominant lesions to be renal. Fishberg,[5] in seventy-two cases of essential hypertension at autopsy, found involvement of the renal vessels in all, the splenic arterioles in two-thirds, the pancreatic in one-half, the hepatic in one-third, and the cerebral in one-fifth.

Hypertrophy of the media is considered important by Albutt[6] as he believes that it may be a precursor or the first stage of arteriocapillary fibrosis. The thickening of the media may be apparent or real and may be followed by fibrous changes.

Endarteritis obliterans is a regenerative proliferation of the collagenous connective tissue fibers of the intima, without change of the elastic membrane. Physiologically this process occurs in the ovary and elsewhere as an involutionary change.

ETIOLOGY

It is apparent that it will be difficult to find a single factor responsible for a condition presenting such widespread and varying manifestations. There is disagreement as to the identity and relationship of the various processes and still further dispute as to their cause. The etiological factors may arbitrarily be grouped under the headings: mechanical; metabolic; endocrinologic; infectious; nervous; hereditary predisposition; and intoxications.

Mechanical.—Kaufmann sharply differentiates fatty change from arteriosclerosis and believes with Virchow and Orth that simple fatty change or infiltration of the intima is a separate entity and not the primary step. He reasons that the walls of the larger arteries during the ascending period of life are strengthened to meet the increasing demands by thickening of the muscular media and elastic tissue of the intima. A time may be reached when the possibility for further adjustment is exhausted, in which event, due to overstretching and the injuries of infections and intoxications, connective tissue increases. This is partly physiological, and through its insufficiency regressive changes may set in as fatty or hyalin degeneration and calcification.

Beitzke[7] supports Thoma's conception that a primary medial injury explains all the manifestations of arteriosclerosis. He likewise believes that lipoid flecking is not the first stage because of its different sites and time of appearance, capacity for regression, and lack of other intimal change. By paraffin filling, the thickened regions of the intima are demonstrated not to encroach upon the lumen of the artery. He maintains that beneath every sclerotic plaque the medium is thinned or weakened, and that the intimal thickening has developed to prevent bulging out of the arterial wall. Infectious diseases are cited as most important in causing medial injury; increased blood pressure, toxic and metabolic disturbances playing a secondary rôle.

Aschoff postulates a mechanical background in the increased infiltration of blood plasma into the intima at points of stress where there is loosening and abnormal permeability of the tissue elements.

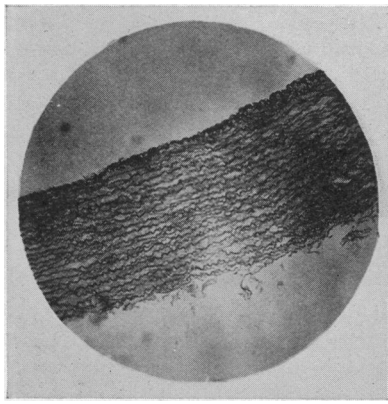

Fig. 1.—Rabbit's aorta, stained by Unna's orcein to demonstrate elastic tissue. (X100.)

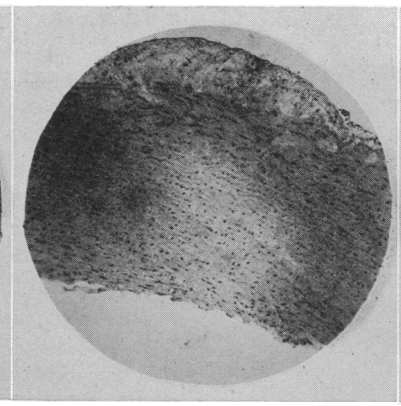

Fig. 2.—Rabbit's aorta, small intimal fatty plaque. (X100.)

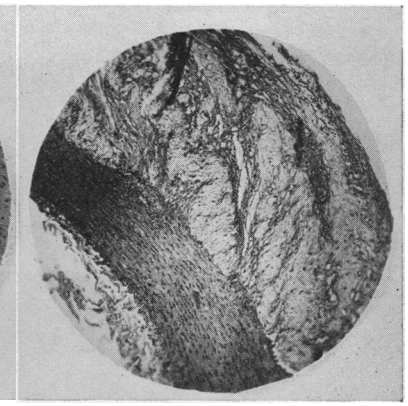

Fig. 3.—Extensive sclerosis of rabbit's aorta, produced by high protein feeding. (X100.)

Of importance in this connection are the age of the individual and the cholesterin content of the blood plasma. An increased cholesterin content of the blood has been demonstrated in infancy and puberty, an age when atherosis is prone to occur.

Moschowitz [8] seeks to prove the assumption that arteriosclerosis is the result of intravascular pressure alone, either a long-continued normal pressure, or a heightened pressure for a shorter period of time. As evidence he cites sclerosis of the vessels of the pulmonary circulation in diseases in which the pressure is raised locally as in mitral stenosis; similarly phlebosclerosis in states of chronic passive congestion. He maintains that the changes produced by cholesterol feeding are not true arteriosclerosis, but merely lipoid infiltration without other intimal change, and that such changes are not developed by carnivora.

Fishberg [5] considers arteriocapillary fibrosis as the histologic symptom of hypertension. He differentiates it from senile arteriosclerosis on the basis of the constant association with hypertension, younger age incidence, and involvement of the smaller arteries and capillaries as opposed to the large vessel distribution of the senile type. He does not believe that this condition is the cause of hypertension, as there is limited involvement of the circulatory bed and not nearly enough to increase the pressure mechanically by raising the peripheral resistance. Likewise, the limited distribution is evidence against the theory that the damage is caused by substances retained by the kidney and the anatomic changes of the kidney support this view. Moschowitz and Romberg [9] look upon the relationship of nephritis to hypertension not as one of cause and effect, but rather feel that the former is an expression of a generalized capillary disease. In addition, Romberg considers essential hypertension a comparatively rare disease, as kidney changes are always demonstrable histologically.

Metabolic.—Cholesterol, a nonatomic alcohol, nonsaponifiable by boiling alcohol, a constituent of the blood, and crystallizing in thin transparent plates, has occasioned extensive investigations. In 1913 von Wacher and Huecke [10] reported the production of atherosclerosis by feeding cholesterin to animals, with supplementary oleic acid injections. There were hypercholesterolemia and deposits of cholesterol in various organs. Kaczander [11] has pointed out that cholesterol accumulates in regions with the greatest CO_2 tensions. Schmidtmann [12] has shown that the p_H of elastic and collagenous fibers of the vessel wall is always acid, whereas the ground substance between them varies widely in both directions and tends to be alkaline in the young and acid in the aged. The chondromucin therein has been demonstrated by Anitschkow [13] to have an especial absorption affinity for lipoids. Therefore, Hueck claims that, in addition to increase of cholesterol intake and resorption relationships, the electrolyte balance of the reaction medium is one of the important associated phenomena which lead to lipoid storage in the vessel walls. Clarkson and Newburgh [14] regularly caused hypercholesterolemia and atherosclerosis in a few weeks by large amounts of cholesterol in the diet of rabbits. With high protein diets alone the same conditions were brought about and attributed by these workers to a metabolic disturbance directly referable to a protein excess and not to its cholesterol content. Lowenthal [15] found in rats that marked arterial changes may be produced by high protein and cholesterol diets. He believes that protein feeding increases the absorption and retention of cholesterol. Schmidtmann was unable to produce atherosclerosis except when chronic hypertension occurred following the high cholesterol feeding, whereas Thölldte [16] produced vessel changes in the absence of increased pressures. Anitschkow holds that without high cholesterol feeding no sclerosis can be produced.

Langstroth [17] analyzed the dietaries of five hundred patients with degenerative diseases and found that a diet containing a large percentage of nonprotective foods is conducive to early degenerative disease. As protective foods, he classifies eggs, milk, fresh-cooked vegetables, fruit, and lettuce. These contain vitamins, residue, and alkaline minerals, and constitute only 12 per cent of the average diet, the bulk being made up of

concentrated foods, high in carbohydrates and acid minerals. Nuzum[18] has produced marked atherosclerosis in rabbits by feeding high protein diets of the acid ash type. These animals secreted acid urines and developed hypertensions.

Endocrinological Influences.—The influence of the endocrine glands has been sought from several different angles. Glaser,[19] by injection of adrenalin was able to increase blood cholesterol considerably, and advanced the idea that sympathetic stimulation may lead to its deposition at the site of local vessel changes. He cautions against the transference of results of cholesterol feeding in animals to man, since it is impossible to produce, experimentally, deposition of lipoids in the vessels of carnivora, since hypercholesterolemia is present only in the earliest stages of arteriosclerosis in man, and because a long-continued high level of cholesterol in the blood of man may be present without resultant arteriosclerosis. Schmidtmann[12] found that the action of adrenalin is enhanced in Ringer's solution containing cholesterol or allied lipoid substances, as compared with the plain solution, and that a strip of muscle in such a solution gives the greatest contraction when the pH is slightly acid and becomes progressively less marked as the reaction is brought to the alkaline side. Shapiro[20] finds that the deposition of cholesterol in the aortic intima in rabbits on high cholesterol diets is hastened by thyroidectomy, splenectomy, and gonadectomy. That castration slows the excretion of cholesterol has been brought out by Lowenthal.[15] Allen[21] demonstrated a close relationship between increased functional activity of the suprarenal gland and hypertension from the increased total area of the lumina of the veins and the heightened ratio of muscle to lumina.

Medial necrosis is easily produced in animals by injections of adrenalin and the necrosis is frequently followed by calcification. This type of change of the media is often found spontaneously in rabbits. Diabetes, a disease in which there is often a disturbance of lipoid metabolism, is frequently associated with arteriosclerosis of the large vessels and the Mönckeberg type in the extremities.

Infections.—Saltykow,[22] by injecting cultures of low virulence of staphylococci into animals, produced both medial and intimal changes, the latter identical with an early stage of human arteriosclerosis. In subsequent papers, however, he feels that the changes are really due to the diets fed. From a clinical investigation Lathrope[23] concludes that there is a suggestive etiological relationship between oral sepsis and cardiovascular renal disease. Nuzum and Elliot[24] could find no such relationship in a series of two hundred and fifty patients with arteriosclerosis and a like number of controls. Virchow's idea of an inflammatory process underlying arteriosclerosis is expressed in his term "endarteritis deformans," and is not held today. It is recognized that medial injuries often result from infectious diseases as typhoid fever and diphtheria, and diphtheria toxin has been used to damage the muscular coat of the arteries of animals. Anitschkow[13] mentions that toxic influences may predispose the vessel wall to deposits of cholesterol.

Nervous Influences.—The participation of the vegetative nervous system has been mentioned in connection with the action of adrenalin. Lowenstein[25] concludes that the effect of cholesterol, calcium, or salt on the blood vessels is only secondary through their action on the vasomotor centers. Moschowitz[26] attaches great importance to the constitutional type prone to development of arteriosclerosis and hypertension. He describes such an individual as soft-muscled, overweight, tense, irritable, and an untiring worker. He believes that psychic states may affect the caliber of vessels by means of the vasoconstrictor nerves, and that continued elevation of the blood pressure eventually may lead to organic changes in the vessel walls, thus stabilizing the high pressures.

Hereditary Predisposition.—Most observers recognize the importance of the hereditary factor. O'Hare in a series of three hundred patients with arteriosclerosis found a family history of vascular disease in 68 per cent, and only 36 per cent in controls. Mortensen,[27] in a study of nine hundred persons concludes that heredity is a very positive factor in arteriosclerosis and diabetes.

Intoxications.—Alcohol and tobacco have been suspected as capable of producing arterial damage with little evidence for support. Lead, however, is known to cause vasoconstriction, and both intimal and medial injury.

SUMMARY

The experimental production of arteriosclerosis is unsatisfactory because of its spontaneous occurrence in rabbits, uncontrolled factors of the environment, and because of the difficulty in estimating the importance of the vegetative nervous system. The problem is many-sided and its solution will involve, among other things, a better understanding of the physicochemical processes of the cell. It is very likely that arteriosclerosis is the organic end stage of a beginning functional derangement, and that factors of diet, heredity, infections, etc., play important secondary rôles.

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DISCUSSION

Newton Evans, M. D. (1117 Pine Street, South Pasadena).—Doctor Evans' paper presents a review of the pathology and the possible causative factors of arteriosclerosis not only in a concise, but also a comprehensive way. He has rendered a distinct service in pointing out in his summary that spontaneous arteriosclerotic changes are liable to occur in the rabbits used as experimental animals, thus rendering them to a considerable extent unsuitable for experiments of this kind. It is evident that we have not as yet progressed very far in any real understanding of this disease.

From the standpoint of its clinical importance, vascular disease has two principal aspects, viz.:

1. Disease of the larger arteries which is for the most part of extrarenal importance and which results in such accidents as cerebral hemorrhage and thrombosis, coronary narrowing and occlusion, occlusions and hemorrhages in mesenteric vessels, vascular obstructions of the peripheral arteries resulting in gangrene, particularly of the lower extremities, and the rare arteriosclerotic aneurysms. The lesions producing effects such as these are possibly more properly called arteriosclerosis proper or atherosclerosis.

2. The more obscure group, and one more difficult to understand, of arteriocapillary changes seen in the smallest vessels of the kidneys and the capillary loops of the glomeruli. These are possibly always associated with general involvement of the capillaries throughout the body. The hypertension, which practically always accompanies this lesion, whether as cause or effect, of course is often one of the factors in the arteriosclerotic accidents encountered in the first group mentioned.

Extensive study of these capillary lesions is sorely needed and should furnish illumination for much of the obscurity which now exists in the field of vascular-renal disease.

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Emil Bogen, M. D. (Olive View).—Hardening of the arteries is one of the oldest and most widespread of the chronic disease processes, and with the increase in the average longevity of the population is becoming of everincreasing importance. It is well worth while, therefore, to examine our knowledge of this condition in the hope that new avenues of approach to the understanding of its pathogenesis may be opened.

Whatever vascular changes may occur as a normal involutionary accompaniment of old age, the arteriosclerotic process cannot be confined to geriatrics, since it is encountered to varying degrees at the earlier ages also. Despite the dictum that a man is as old as his arteries, these vessels themselves are not all of the same physiological age; hyaline changes, and even calcification occurs in certain vessels normally in quite young individuals, and pipe-stem radial arteries do not bear the same prognostic import as do corresponding changes in the vessels of the brain or coronary system.

Recent work on the calcification of blood vessels as a result of the administration of irradiated ergosterol, as well as the earlier reports of similar results from nicotin, adrenalin, high protein diets and certain particular amino-acids, and numerous other agents, even though performed on animals in which spontaneous arteriosclerosis is known to occur, cannot be entirely disregarded. Nevertheless, it may be recalled that even these known soluble agents result, not in a diffuse uniform thickening of the arterial walls, but in patchy discrete flecks and plaques, which only later tend to merge into continuous alterations of the blood vessel walls.

The etiology of arteriosclerosis involves, therefore, not only the agents responsible for the occurrence of the process at all, but also all factors concerned in its localization in vessels of a certain size, type, and position, and the particular type of lesion produced. The local factors concerned in the deposition of cholesterin and other lipoids, the accumulation of calcium salts, and the even more fundamental and mysterious hyaline and other "degenerative" changes in the tissues of the arterial walls must be elucidated before we may understand the entire mechanism involved.

We are grateful to Doctor Evans for his review of the work that has been accomplished in the past, and hope that further studies may clear up the many points that, as he has shown, still remain obscure.