Atherosclerosis

Why Do We Pretend the Pathogenesis Is Mysterious?

Additional Indexing Words:
Cholesterol Lipidemia Diet
Xanthoma Hyperlipidemia Atheroma

BETWEEN 1920 AND 1925 my teachers of pathology, in Saint Louis, Chicago, Boston, Vienna, and San Francisco, taught me that the lipid-rich intimal lesions which caused arterial obstruction were due to infiltration of plasma lipids and could be caused by hyperlipidemia due to diet.

The only rival theory — mural thrombosis — seemed to be excluded by the fact that these lesions were not present in veins and occurred in pulmonary arteries only when there was evidence of pulmonary hypertension. While the blood flow through the pulmonary arteries was the same as that through the systemic system, it had been known since 1863 that the pressure was only one fifth as high, and probably inadequate to allow infiltration of plasma lipids into the intima of the lesser circulation or the veins. Veins had far more thrombi, pulmonary arteries far more emboli than the systemic arteries. The facts contradicted the theory that mural thrombosis caused atherosclerosis.

Americans, in 1916, had confirmed the Russian reports that fatty streaks developed swiftly if rabbits were fed food enriched with egg yolk, brains, or cholesterol.1 It seemed obvious, in 1920, that the high plasma lipid infiltration theory of the causation of this form of arterial disease had been confirmed as unequivocally as Harvey’s theory of the circulation of the blood, or Koch’s theory of the etiology of tuberculosis.

In the past quarter-century, two old theories have been revived, and four new ones advanced by respected pathologists and biochemists, all of whom ignored or derided the possible relation of rich diets and intimal infiltration as primary causes of the disease. The latest theory — that the intimal lesions are due to neoplastic metaplasia caused by viruses or chemicals — was presented in leading medical journals, the latest in Science,2 with a favorable editorial in the Journal of the American Medical Association.3 Endothelial damage was the initial lesion, according to this theory; the lesion was repaired by smooth muscle cells which migrated into the intima and there synthesized or phagocytosed lipids.

Sixty years earlier the Russians who had fed cholesterol to rabbits had noted smooth muscle cells taking up lipid after severe intimal infiltrate damaged the inner elastic membrane. By 1964 the electron microscope had revealed cells containing lipid and myofibrils in the early fatty streaks in the human aorta.4 In recent studies the lining of the aorta of monkeys was mechanically injured, and the process of repair was followed with the electron microscope. The smooth muscle cells found in the intima probably had been released from the contractile strands of the media adjacent to the traumatized inner elastic membrane. No evidence was offered that these cells could detach themselves from spiral strands and migrate through intact elastica. Nor was evidence presented that endothelial injury was a prerequisite to deposition of lipid in the intima of systemic arteries. That such infiltration and deposition occurs in nursing in-

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fants was reported in several papers between 1915 and 1930 and confirmed by electron microscopic study of suckling rats. The process ends and the lipid disappears when the sucklings are weaned from their high-fat, high-cholesterol milk diet.

In American children it continues and is accelerated during adolescence. By the age of 20, over 40% of American soldiers have visible fatty streaks in coronary arteries, but no such lesions are found in the coronary arteries of Korean or Japanese men in this age group. If endothelial injury is the first step in genesis of obstructive arterial disease, we must seek the cause of this in Americans as contrasted with Orientals. Those who accept the dietary-infiltrative theory find support in the fact that blood cholesterol in American soldiers averages about 240 mg/dl, while in young men in Japan and Korea the figure is 30% lower — 160 mg/dl. In the Orientals life habits and diet are as important in the incidence of coronary disease as in other races. The incidence of heart attacks in people over 40 years of age is only 0.6% among Chousan fishermen, but it is 7% among Shanghai factory workers and 20% in Sinkiang herdsmen, living on meat and milk. Genetic predisposition is worldwide; incidence is determined primarily by diet.

Erupting and regressing xanthomas of the skin of diabetics were biopsied at the same institution that demonstrated intimal disease following experimental lesions. In the xanthoma study the subendothelial cells taking up chylomica are called pericytes. They contain myosin and seem to play the same role as similar cells and macrophages in tubercles, lepromas and other granulomas. They are related not to causation but to the defense of the tissues. They play a major role in the regression of xanthomas when hyperlipidemia is controlled and in regression of fatty arterial plaques when animals are taken off experimental diets. Triglyceride disappears faster than cholesterol. Studies of the source and of the molecular biology of such cells will shed light on the body’s defense against granulomas due to infection or to deposition of poorly soluble material in disturbances of lipid or carbohydrate metabolism. These studies confirm rather than alter our concepts of pathogenesis of any disease.

There is no mystery about the pathogenesis of a disease which can be evoked regularly by experiments on some species of mammal, even if most species are immune. Even birds have been useful in studies of pathogenesis of malaria, beriberi, and lipid infiltrates of the systemic arteries. Guinea pigs fortunately were not immune to human tuberculosis, as were most laboratory animals. Rabbits are peculiarly susceptible to cholesterol feeding, but animals or birds of many species develop intimal infiltrate if their plasma lipids are raised by appropriate diets or drugs. Histologically, chemically, and in their distribution (sparing veins and rarely occurring in pulmonary arteries), there is a close resemblance between arterial lesions in man and those evoked by feeding diets rich in animal fat and cholesterol to other mammals or birds. Histologically, chemically, and in its relation to hyperlipidemia, there is also a close relationship between xanthomas and early fatty streaks in the human aorta. In patients with severe familial hyperlipidemia, xanthomas, and intermittent claudication, marked reduction of plasma lipids not only resolved the xanthomas but raised the maximal blood flow to the legs 60%. Flow was measured after 5 minutes ischemia, in these observations at the National Institute of Health. As of 1970, the pathogenesis, and the reversal of xanthomas and of human or experimental intimal lipoidoses seemed proved beyond all question.

One fascinating aspect of the arterial lesions which will kill or disable so many physicians this year is why the lesions are called atheromas and the disease atherosclerosis. In 1740 von Haller was struck by the resemblance between yellow arterial plaques and the skin lesions the ancient Greeks had named atheromas, but we call sebaceous cysts. By 1904, when Marchand introduced “atherosclerosis,” the histology of sebaceous cysts was known to be unlike that of arterial lesions. Now we know it is identical with that of xanthomas, and that people with familial xanthomatosis have a high incidence and early onset of arterial lipoidosis, often fatal before they are 20. It is high time pathologists, editors, and the medical index reject the errors of the eighteenth century. We should speak of the intimal lesions as xanthomas and the disease as xanthosclerosis. This will save us a syllable and correctly identify the nature of the process.

Xanthomas localize at sites of tissue stress — over elbows, knees, buttocks, and in the upper eyelid. Vascular permeability may have been altered at these sites. Histamine injected into the skin of rabbits with hyperlipidemia due to diet elicited florid lesions, but had no effect on the skin of rabbits fed normal diets.

In arteries, xanthomas also localize at sites of vascular injury; this was most striking in syphilitic aortitis and is seen in surgical anastomoses. But neither in the skin nor arteries do these lesions appear at such sites unless plasma lipids are high. Cholesterol over 180 mg/dl seems to be the threshold for arterial lesions, over 400 mg for eruptive xanthomas in the skin, where intravascular pressure is lower. In the tissues of infants, intimal lesions occur with cholesterol levels under 120 mg/dl but the triglyceride levels are high. The variations in in-
dividual susceptibility and tissue susceptibility to lipid granulomas is no more remarkable than individual and tissue susceptibility to tuberele bacilli, histoplasmosis, or coccidioides, or the deposition of metabolites in gout, or in glycogen and lipid storage diseases. Although some hypotheses on localization have been offered, none are as firmly supported by facts as the hypothesis on pathogenesis. There is no mystery about why the incidence of vascular disease, like that of bronchial cancer and of venereal disease, continues to rise for many decades after pathogenesis is established. Human beings, including physicians and informed laymen, are eager for excuses not to face annoying facts and so they continue to do things which are agreeable but hazardous. Like most of my fellow students, I ignored the facts on xanthosclerosis in daily life long after I accepted them as proved. Osler, in 1896, had pointed out the great difference in the incidence of xanthosclerosis in the carnivorous rich and the vegetarian poor of Montreal, Philadelphia, and Baltimore, just as Ignatovsky had noted in Russia. This led to the experiments on rabbits and to Osler’s concluding that “angeiosclerosis is the Nemesis through which Nature exacts retributive justice for the violation of her laws.” He considered diet as the most important feature of management, but few heeded the wisdom of the world-famous Hopkins professor.

Our incidence of coronary disease will continue to rise as long as our professors seek and expound ephemeral theories of pathogenesis and our profession denies the importance of “stuffing, sitting, smoking and sipping” in the pathogenesis of xanthosclerosis. The young men feel that “where ignorance is bliss, 'tis folly to be wise” (T. Gray, On a distant prospect of Eton College), and surely the diet of our youth cannot hurt us. Some of the old men think: “Why should I do without the things I like in order to do without them longer?” This logical query does not justify fallacious teaching of pathology or medicine, but it helps to explain why we pretend that the pathogenesis of our arterial occlusions is mysterious. It is human to reject new ideas, even when they do not impose any change in our way of life. It is almost impossible for most men to accept any suggestion that it might be wise to give up agreeable habits such as smoking or eating favorite foods. That is why we call xanthomas of the arteries “atheromas.” Every textbook points out how easily xanthomas can be cured, but we long to believe our arterial disease is a hopeless enigma. That is why we who had been shown exactly how to produce it a half a century ago continue to pretend “atherosclerosis” is mysterious.

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References

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Circulation. 1974;50:647-649
doi: 10.1161/01.CIR.50.4.647
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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