Atherosclerosis—A Pediatric Nutrition Problem?

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We certainly recognize any condition that is responsible for 54 per cent of the deaths in the United States as being a problem. I think it is a pediatric problem; but whether it is a nutritional problem, I am not too certain at the present time. I do think that pediatricians have definite responsibilities if we are ever to make progress in stopping the ravages of this disease. I wish to present to you what we have seen in studying the natural history of this disease, and then take up some of the basic questions with which we need help.

Figure 1 illustrates our concept of the pathogenesis of atherosclerosis. We believe that atherosclerosis develops in a series of definite stages. It starts in infancy as a fatty streak, and continues as a relatively simple fatty streak for the first two decades of life. Without the fatty streak we believe that there would be no second stage or fibrous plaque, which is produced by the laying down of connective tissue about the fat. Fat becomes concentrated at the base of the fibrous plaque, leaving a yellow core of grumous material covered by a cap of connective tissue. Blood vessels grow into the margins of this plaque. In the fourth and later decades of life various complications take place in these fibrous plaques, such as thrombosis, hemorrhage, necrosis, ulceration or accretion, any one of which may encroach upon the lumen of the artery and produce stenosis. If this stenosis develops rapidly in an artery to a vital organ beyond the capacity of collateral circulation, there then develops the fourth stage of atherosclerosis, clinical episodes—myocardial infarct, stroke, gangrene and the like.

I would like to discuss that portion of the process below the clinical horizon and to emphasize the fact that three important stages occur in the arterial wall before clinical disease becomes manifest: fatty streak, fibrous plaque and complication. I also wish to emphasize that different factors may be responsible for each of these stages in the development of atherosclerotic lesions, and that still other factors may be responsible for determining the occurrence of clinical disease.

The methods we have used to study the natural history of atherosclerosis are quite simple.[1,2] They consist of collecting aortas, coronary arteries and cerebral arteries from unselected autopsies on patients of all ages in a large general hospital and in a medicolegal laboratory. We fix these arteries in formalin, stain them in Sudan IV to delineate the intimal lipid, and preserve them in plastic bags. We then estimate the percentage of intimal surface involved by each of these types of atherosclerotic lesions. Figure 2 shows a set of arteries from one patient prepared in this manner. The dark streaks in the specimens are fatty streaks which have been stained with Sudan IV.

Figure 3 shows the results of our study of aortas collected in the New Orleans area from subjects under forty years of age.[1] It was surprising to find that many children under the age of three had fatty streaks in the aorta;

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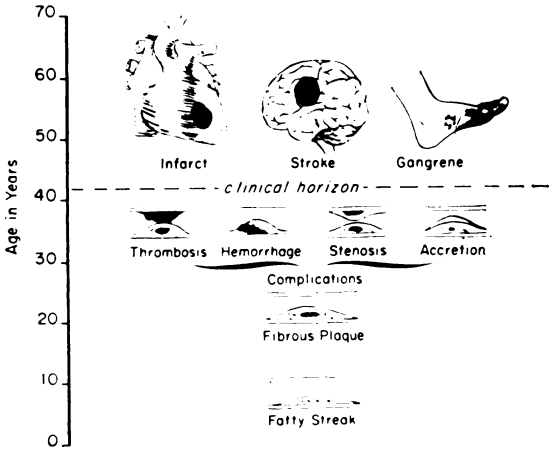

FIG. 1. Concept of pathogenesis of atherosclerotic lesions. The fatty streak is pictured as developing in childhood, being converted into a fibrous plaque in young adulthood. In the thirties and forties, these fibrous plaques undergo changes that produce rapid occlusion of the lumen and thereby precipitate clinical disease in middle life. From HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P. and GEER, J. C. *Am. J. Path.*, 34: 209, 1958.[1]

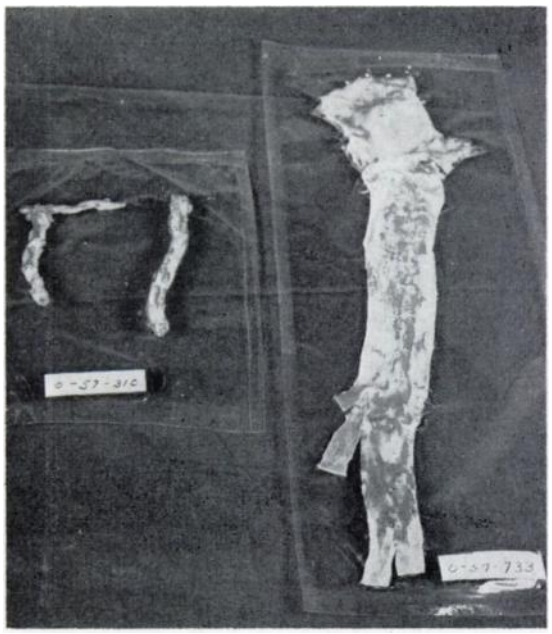

FIG. 2. Aorta and coronary arteries that have been stained with Sudan IV and packaged in transparent plastic bags. Extensive fatty streaks in both specimens show up here as dark areas on the intimal surface. From HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P. and GEER, J. C. *Lab. Invest.*, 7: 42, 1958.[2]

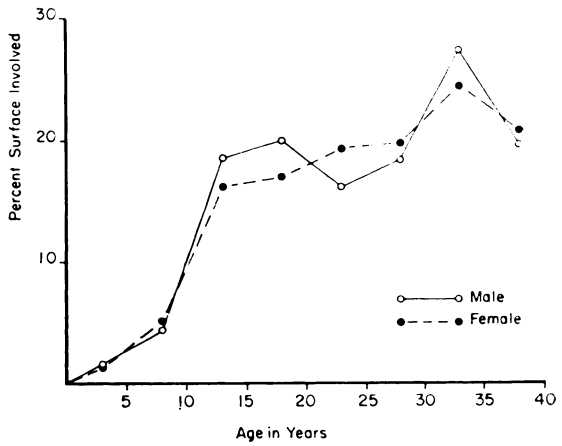

FIG. 3. Average percentage of aortic intimal surface involved with fatty streaks in New Orleans subjects from one to forty years of age.

and furthermore, that every person beyond the age of three years had some degree of fatty streaking. By ten years of age the average percentage of aortic intimal surface involved was approximately 5 per cent. In the second decade, the average percentage of intimal involvement was 20 per cent. Thereafter, the average extent of the fatty streaks remained about the same.

After defining the base line of expectancy for fatty streaks in young persons in the New Orleans area we began to examine specimens from people in other parts of the world, hoping to find some area of the world in which the aorta remains uninvolved. However, specimens collected from Spain, Puerto Rico, Guatemala, Costa Rica,[3] Colombia[4] and even from Bantu in South Africa[5] turned out to have approximately the same frequency and average extent of intimal surface involvement with these same fatty streaks. Some of these groups are shown in Figure 4. This pattern has turned out to be monotonously similar in all parts of the world, regardless of the incidence of clinical heart disease as determined from vital statistics. How are we going to define "normal" if everyone shows these changes?

We have also been concerned with the question of whether the patient's terminal illness has anything to do with the extent of these fatty streaks. As you may know, it

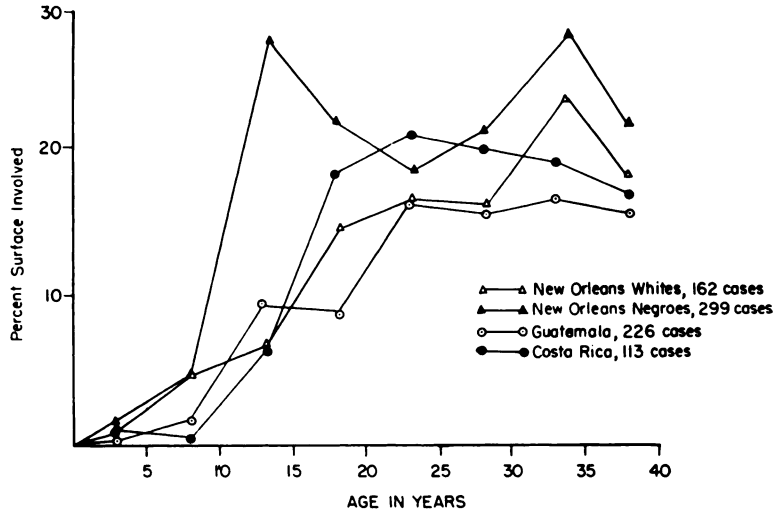

FIG. 4. Comparison of aortic fatty streaks by age and geographic location in subjects from one to forty years of age. From STRONG, J. P., MCGILL, H. C., JR., TEJADA, C. and GEER, J. C. *Am. J. Path.*, 34: 731, 1958.[3]

has been suggested that these lipid deposits are due to infection. Therefore, we compared cases of traumatic death with cases of natural death, most of the latter being due to infection. If anything, the patients involved in accidental deaths showed more involvement, as seen in Figure 5. Since these latter patients represent the best possible sample of the living human population that can be obtained, we conclude that the figures on the extent of aortic fatty streaks in necropsy cases approximates the degree of these lesions in the respective living populations from which they were selected by death.

There is another feature of the results of these studies that has not been demonstrated in the preceeding illustrations, that is, the marked individual variation from one case to another. The differences between two persons of the same age, of the same sex and race, and from the same geographic area may be forty- or fiftyfold. Furthermore, the individual variation in any given geographic area always exceeds the inter-area variation. This is where we need help.

When we go on to the second stage of atherosclerosis, the fibrous plaque, we find some differences that begin to correlate with incidence of clinical disease as indicated by vital statistics. The average white person in New Orleans ends up at age forty with about 15 per cent of the aortic surface covered with fibrous plaques. These fibrous plaques seldom occur before the age of twenty; they develop to a slight degree during the third decade of life; and they grow rapidly during the fourth decade.

In Guatemalans, Costa Ricans and in the Bantu, however, fibrous plaque formation is much less conspicuous. By age forty, aortic fibrous plaques are only one-fifth as extensive in these groups as in the white

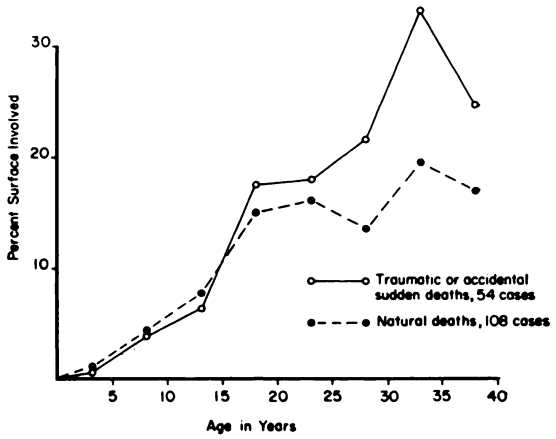

FIG. 5. Comparison of aortic fatty streaks by age and cause of death in white persons in New Orleans. From HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P. and GEER, J. C. *Am. J. Path.*, 34: 209, 1958.[1]

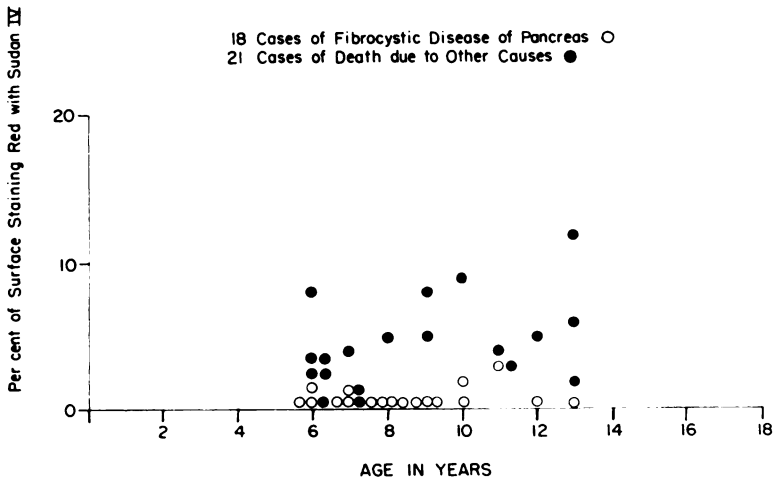

FIG. 6. Comparison of aortic fatty streaks by age and cause of death in eighteen cases of fibrocystic disease of the pancreas and twenty-one cases of death due to other diseases. From HOLMAN, R. L., BLANC, N. A. and ANDERSON, D. *Pediatrics*, 24: 34, 1959.[7]

population of New Orleans, corresponding to the widely recognized differences in frequency of coronary heart disease.[3–5]

We have also conducted similar studies on the coronary and cerebral vessels. We will not go into the details of these results here, but only say that the same process takes place in the other segments of arterial system. It develops in the coronary arteries about twenty years later than in the aorta; and in the cerebral arteries about twenty years later than in the coronary arteries.

What does all this mean? What is the source of this fat? It could arise from increased filtration from the lumen. It could be due to increased local formation, decreased local removal or any combination of these events that would produce a net increase in local lipid content. Studies of the metabolism of intact arteries[6] indicate to us that filtration has been overemphasized and that local formation under hormonal control has been underemphasized. If the pathogenesis of atherosclerosis is to be understood, we believe that the arterial wall should be considered a metabolic factory in its own right.

We have recently described a decreased amount of atherosclerosis associated with one condition, a finding which may yield a clue to the factors influencing the development of these fatty streaks in infancy and childhood.[7] Figure 6 shows a comparison of fatty streaks in eighteen cases of fibrocystic disease of the pancreas with those in twenty-one cases of deaths due to other causes. We do not believe that the differences in body weight are responsible for these differences, for other studies have shown that there was no correlation between body weight and the amount of fatty streaking in the aorta. In fact, obese children may have none and even severely malnourished children may have an average or greater amount.

SUMMARY

To recapitulate the natural history of aortic atherosclerosis, the first two decades of life are taken up with the formation of fatty streaks which we believe are primarily due to local formation. In the second two decades the arterial wall reacts to certain lipids with the proliferation of connective tissue elements. Later complications may precipitate one or more of the well known clinical manifestations.

The pediatric component of the problem is the development of aortic fatty streaks beginning in infancy and accelerating during puberty. Aortic fatty streaks are universal in all parts of the world so far studied and appear to be independent of diet.

An important consideration is the marked individual variation in extent of these lesions, which could be genetic; it does not appear to be ethnic.

Fibrocystic disease of the pancreas is associated with a decreased amount of fatty streaking in the aorta and might be investigated as a possible clue to the etiology and pathogenesis of this lesion.

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