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THE PEDIATRIC ASPECTS OF ATHEROSCLEROSIS

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SUMMARY

Atherosclerosis begins in childhood with the appearance of aortic fatty streaks. Aortic fatty streaks of some degree are present in practically all individuals from every human population that has been studied. The average amount of aortic intimal surface involved with fatty streaks does not differ much among human populations.

Coronary fatty streaks begin to form in adolescence. Most persons 20–29 years of age have coronary fatty streaks of some degree, even if they are from low socioeconomic strata.

While fatty streaking is clinically harmless and potentially reversible, the progression of fatty streaks to more advanced lesions is a critical stage of atherosclerosis. This conversion takes place at earlier ages in populations with high morbidity and mortality from coronary heart disease.

The development of fibrous plaques begins in the twenties. Therefore, even though control programs which attempt to reduce coronary heart disease by preventing atherosclerosis may meet some success when applied to middle-aged persons, these programs should be directed toward individuals in the twenties and thirties for maximum benefits. Dietary habits that retard atherosclerosis should be established in childhood.

Key words: *Atherosclerosis – Fatty streaks – Raised atherosclerotic lesions – Geographic pathology – Fibrous plaques – Prevention of atherosclerosis – Atherosclerosis in children – Prevalence of atherosclerosis*

INTRODUCTION

The late RUSSELL L. HOLMAN in 1961 raised the question, "Atherosclerosis—a Pediatric Nutrition Problem?"[1] The basis for the concern of pediatricians with this

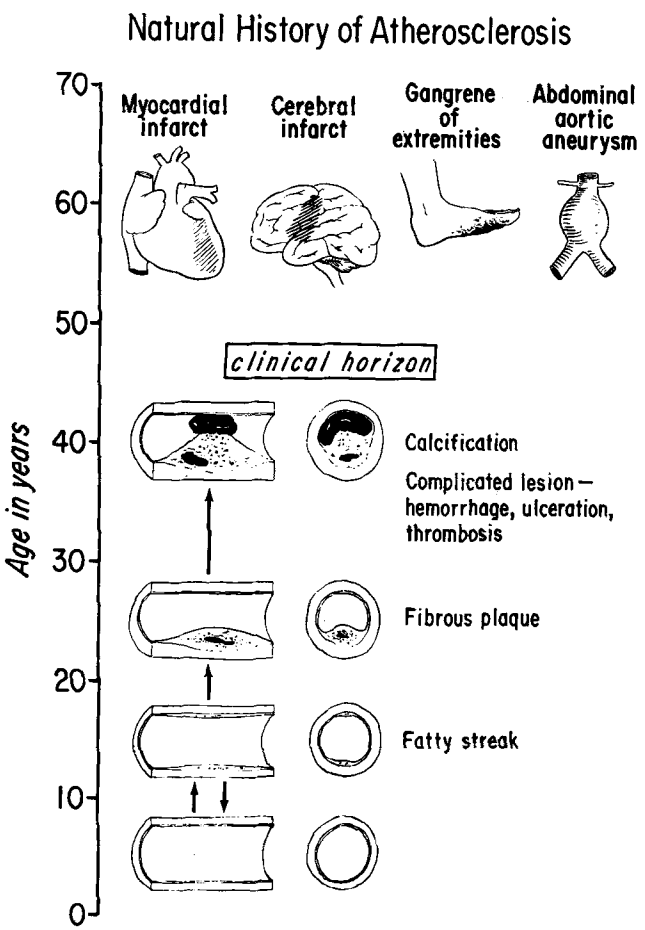

Fig. 1. Diagrammatic concept of the natural history of atherosclerosis. With permission of Academic Press reprinted with slight modification from McGILL JR., H. C. *et al.*, Natural history of human atherosclerotic lesions. In: M. SANDLER AND G. H. BOURNE (Eds.), *Atherosclerosis and its Origin*, Academic Press, New York, 1963.

disease is illustrated in Fig. 1. Clinical manifestations of atherosclerosis appear during middle age, but the mural arterial lesions begin in childhood. The purpose of this article is to review data concerning the early stages of atherosclerosis in children, adolescents, and young adults.

Fatty streaks begin in the arteries of children as accumulations of fat in a slightly thickened intima. Pathologists long ago noted that fatty streaks occur frequently in the aortas of children[2-5]. From data on more than 1600 autopsied persons, we have found that aortic fatty streaks are present in many children under age 3, and in all children over age 3 (refs. [6,7]). Later, we found that coronary artery fatty streaks are rare before age 10, but become much more frequent in the second decade of life and are nearly always present after age 20 (ref. [8]).

Data from New Orleans cases were compared with similar data from autopsied

young persons from Guatemala, Costa Rica, Colombia, Puerto Rico, and Durban, South Africa[9–12]. Fatty streaks began in the first decade of life in all these populations, first restricted to the aortic ring and the aortic arch and later appearing in the descending thoracic and abdominal aorta. All aortas were involved to some degree, but the average extent of intimal surface involved was small.

After 10 years of age the extent of intimal surface involved by fatty streaks increased rapidly in succeeding age groups from all locations. There was no consistent difference in aortic fatty streaks among groups from different geographic locations, but, there was a racial difference. The Negro groups from New Orleans and Durban had more extensive fatty streaks between the ages of 15 and 25 years than other groups. Aortic fibrous plaques and other more advanced atherosclerotic lesions tended to parallel differences in incidence of coronary heart disease in middle aged adults from the same populations. New Orleans white cases were most extensively involved with fibrous plaques.

These studies led to the International Atherosclerosis Project (IAP), a more broadly ranging investigation of the geographic pathology of atherosclerosis[13]. A group of cooperating pathologists examined aortas, coronary arteries, and (in some laboratories) cerebral arteries collected from autopsied persons in 14 countries. Evaluations of the 23,000 sets of coronary arteries and aortas form the basis of the data in the IAP. The racial and geographic comparisons among these populations have been described in previous reports[14], and this article will, as the title implies, discuss the implications of the data for the pediatric aspects of atherosclerosis.

MATERIALS AND METHODS

This report specifically deals with aortic and coronary artery lesions in 4737 autopsied cases, of both sexes, ages 10–39, from 6 location-race groups in the IAP. The 6 geographic and ethnic groups were selected because they have relatively large numbers of cases and because they represent populations in which the extremes (high to low) of advanced atherosclerosis are found in older persons. The 6 groups are New Orleans white, New Orleans Negro, Santiago, Costa Rica, Guatemala, and Durban Bantu. The distribution of cases by age, sex and location-race groups is shown in Table 1. Certain demographic characteristics of these and other groups in the IAP have been described by McMahan[15].

The material in this report, therefore, is a subsample of the material in the IAP. Guzmán *et al.*[16] have described the methodologic aspects of the IAP; only a summary of the methods of collection and evaluation of specimens will be described here.

In each laboratory, coronary arteries and aortas were dissected "uniformly" at necropsy, labeled with coded numbered tags, and shipped to a central laboratory. The central laboratory staff stained the specimens grossly with Sudan IV and packed them in plastic bags identified by code numbers. A team of 5 pathologists estimated the percent of intimal surface area covered by different types of lesions. Interobserver variation was reduced by developing explicit criteria and by training.

TABLE 1

NUMBER OF CASES BY AGE, SEX, AND LOCATION-RACE GROUP

Location-race groups	*Age (years)*													
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*		*Totals*	
	male	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*
New Orleans white	5	3	27	11	39	19	35	16	63	17	66	34	235	100
New Orleans Negro	18	10	23	17	80	21	72	24	70	34	78	46	341	152
Santiago	58	28	146	75	221	124	266	121	303	135	309	120	1303	603
Costa Rica	29	22	44	28	47	32	38	22	56	42	67	53	281	199
Guatemala	40	29	57	41	64	52	66	46	72	65	88	52	387	285
Durban Bantu	20	24	26	47	59	60	96	74	106	84	148	107	455	396
Totals	170	116	323	219	510	308	573	303	670	377	756	412	3002	1735

The operational definitions of the different types of atherosclerotic lesions were as follows:

Fatty streak: Any intimal lesion that is stained distinctly by Sudan IV and that does not show any other change underlying it.

Fibrous plaque: A firm, elevated intimated lesion which in the fresh state is pale gray, glistening, and translucent. After staining, it may be partially or completely covered by sudanophilic deposits. If a lesion shows hemorrhage, thrombosis, ulceration, or calcification, that portion is classified under that category.

Complicated lesion: A lesion in which there is hemorrhage, ulceration, necrosis, or thrombosis with or without calcium.

Calcified lesion: A lesion in which there is calcium visible or palpable without overlying hemorrhage, ulceration, or thrombosis.

Raised atherosclerotic lesion: Fibrous plaques, complicated lesions, and calcified

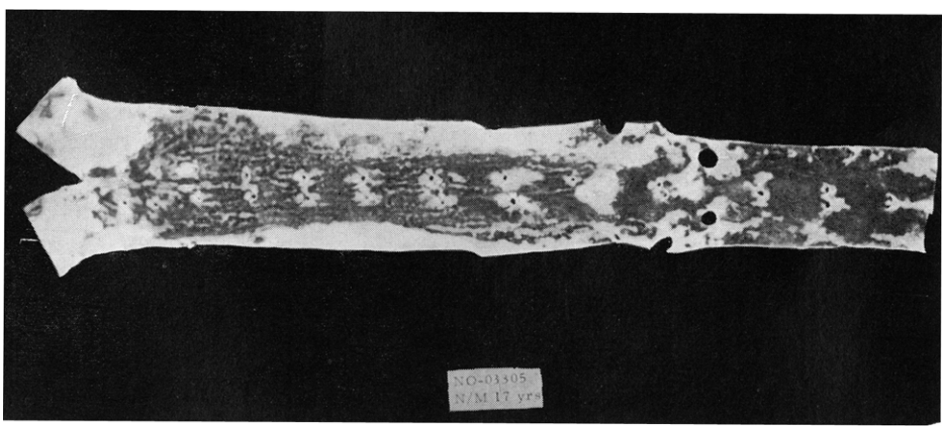

Fig. 2. Descending thoracic and abdominal aorta of a 17-year-old New Orleans Negro male. The aorta has been opened longitudinally and stained grossly with Sudan IV. Fatty streaks appear black in this photograph.

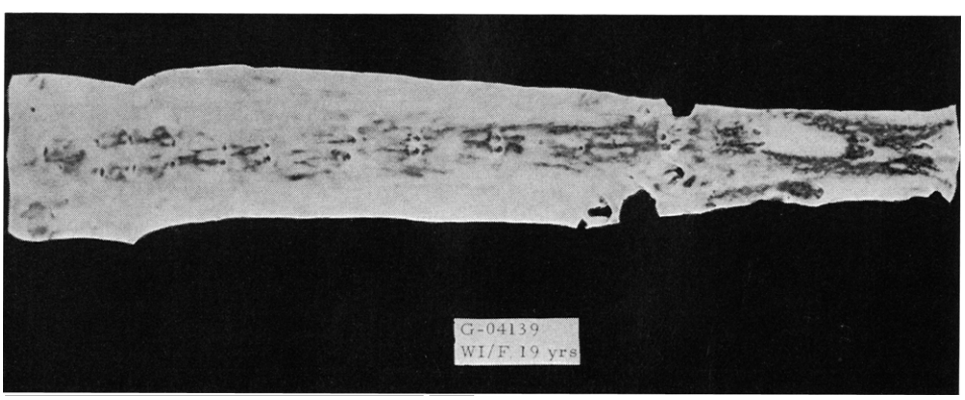

Fig. 3. Descending thoracic and abdominal aorta of a 19-year-old Indian-white Guatemalan female prepared similarly to specimen in Fig. 2.

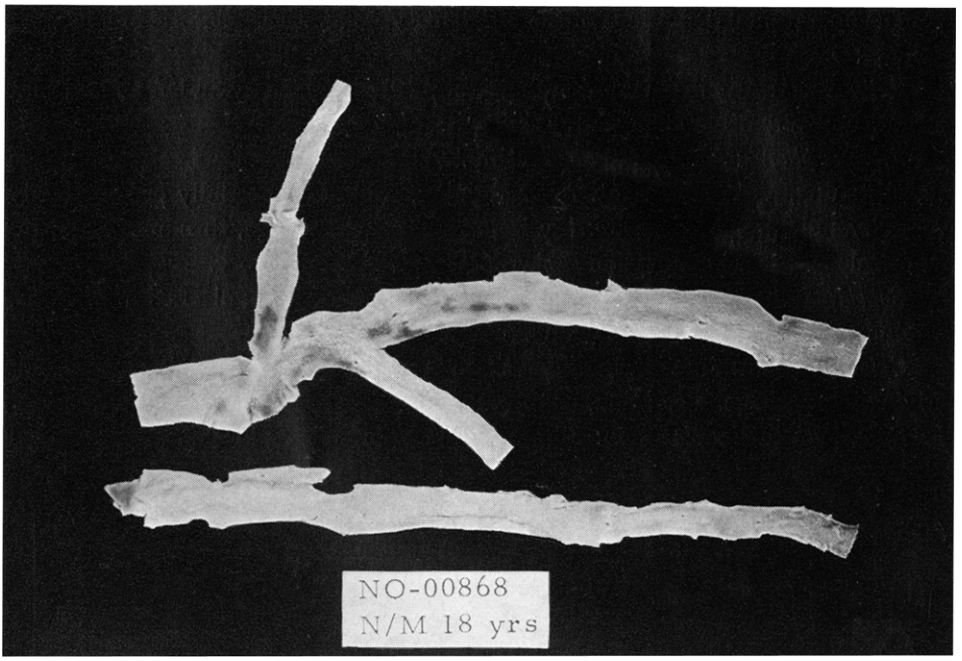

Fig. 4. Longitudinally opened coronary arteries of an 18-year-old Negro male from New Orleans. These arteries have been stained grossly with Sudan IV. Scattered fatty streaks are present in the left coronary artery.

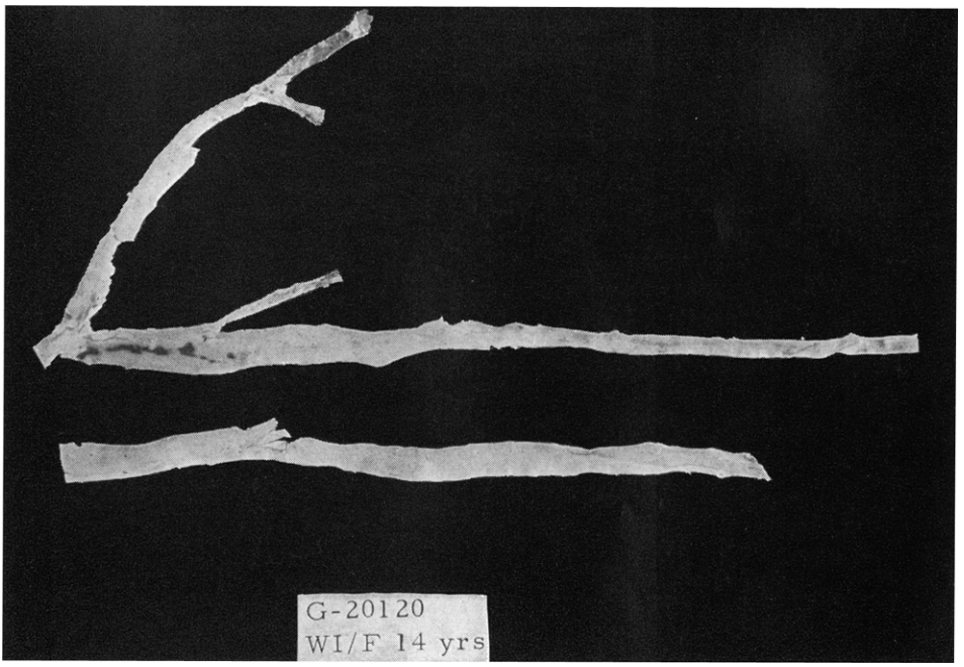

Fig. 5. Longitudinally opened and Sudan-stained coronary arteries of a 14-year-old Indian-white male from Guatemala. Fatty streaks are present in the anterior descending branch of the left coronary artery.

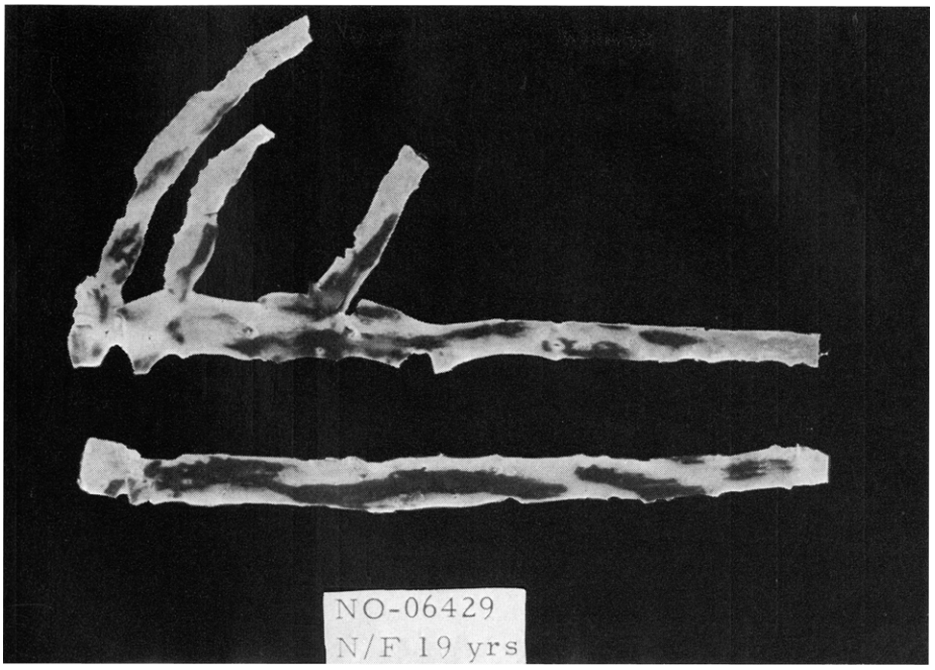

Fig. 6. Sudan-stained coronary arteries of a 19-year-old Negro female from New Orleans. Extensive fatty streaks are present in all major branches. A small fibrous plaque is present at one of the bifurcations of the anterior descending branch.

lesions computed by adding the individual estimates of the three types of lesions.

Figs. 2–6 show examples of specimens from young persons with varying degrees of lesions.

RESULTS

Prevalence of lesions

Table 2 compares the percent of aortas positive for fatty streaks in these 6 location-race groups. Almost all aortas from all groups are positive for aortic fatty streaks. Thus, by age 10, it is impractical to compare populations by the prevalence of aortic fatty streaks.

Table 3 shows the prevalence of coronary artery fatty streaks in these groups. Coronary fatty streaks are not as frequent as aortic fatty streaks, but they occur in some cases from each location-race group even in the 10–14 year age group. Fatty streaks of some degree are present in practically all persons over age 20 in New Orleans, and are present in approximately 90 % of persons in the other groups by age 30.

Tables 4 and 5 show the percentages of aortas and coronary arteries positive for any of the raised atherosclerotic lesions. Raised lesions begin in some cases from each group before age 20 and increase rapidly in the 2 decades following. New Orleans cases are usually most frequently involved. Sex differences in prevalence of coronary raised

TABLE 2

PERCENT OF CASES POSITIVE FOR FATTY STREAKS IN THE AORTA BY LOCATION-RACE GROUP, AGE AND SEX

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	male	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*
New Orleans white	100	100	100	100	100	100	100	100	100	100	100	100
New Orleans Negro	94	90	100	100	100	100	100	100	100	100	100	100
Santiago	100	100	100	100	100	100	100	100	100	100	100	100
Costa Rica	100	100	100	100	100	100	100	100	100	100	100	100
Guatemala	100	100	100	100	100	100	100	100	100	100	100	100
Durban Bantu	95	100	100	100	100	100	100	100	100	100	100	99

TABLE 3

PERCENT OF CASES POSITIVE FOR FATTY STREAKS IN THE CORONARY ARTERIES BY LOCATION-RACE GROUP, AGE AND SEX

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	male	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*
New Orleans white	40	33	78	82	95	89	100	94	98	94	100	100
New Orleans Negro	67	60	83	71	94	100	99	96	100	100	100	100
Santiago	34	46	59	72	81	84	91	88	96	92	96	96
Costa Rica	31	41	66	64	72	63	92	86	88	90	96	100
Guatemala	18	24	47	68	64	85	79	70	86	75	91	79
Durban Bantu	25	25	65	64	81	82	91	97	95	92	97	97

TABLE 4

PERCENT OF CASES POSITIVE FOR RAISED ATHEROSCLEROTIC LESIONS IN THE AORTAS BY LOCATION-RACE GROUP, AGE AND SEX

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	male	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*
New Orleans white	0	0	7	0	5	5	40	38	67	76	80	71
New Orleans Negro	6	0	0	6	9	14	26	42	47	59	76	76
Santiago	0	7	3	1	7	3	11	15	29	20	39	38
Costa Rica	3	14	2	11	2	13	8	23	36	26	40	49
Guatemala	0	3	2	2	9	17	17	15	26	17	36	48
Durban Bantu	0	4	12	9	19	10	26	19	52	36	56	45

TABLE 5

PERCENT OF CASES POSITIVE FOR RAISED ATHEROSCLEROTIC LESIONS IN THE CORONARY ARTERIES BY LOCATION-RACE GROUP, AGE AND SEX

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	male	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*
New Orleans white	0	0	7	18	44	11	71	38	78	41	86	65
New Orleans Negro	22	0	22	12	34	43	44	38	54	44	81	67
Santiago	0	7	10	4	18	7	29	12	53	23	57	36
Costa Rica	0	0	7	7	15	13	21	18	43	17	60	38
Guatemala	0	0	7	2	23	12	21	11	35	15	38	42
Durban Bantu	5	0	12	13	17	10	31	18	54	38	45	45

TABLE 6

MEAN PERCENT OF INTIMAL SURFACE INVOLVED WITH AORTIC FATTY STREAKS (FS) AND RAISED ATHEROSCLEROTIC LESIONS (RL) IN MALES BY LOCATION-RACE GROUP AND AGE

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	FS	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*
New Orleans white	7	0	17	1	25	0	28	3	27	8	25	17
New Orleans Negro	19	0	31	0	28	1	27	2	24	5	25	10
Santiago	9	0	15	0	18	0	20	1	21	2	20	3
Costa Rica	9	0	15	1	19	0	23	0	22	2	24	3
Guatemala	12	0	16	0	21	1	24	0	24	2	25	3
Durban Bantu	9	0	16	1	21	1	25	2	26	6	26	6

TABLE 7

MEAN PERCENT OF INTIMAL SURFACE INVOLVED WITH AORTIC FATTY STREAKS (FS) AND RAISED ATHEROSCLEROTIC LESIONS (RL) IN FEMALES BY LOCATION-RACE GROUP AND AGE

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	FS	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*
New Orleans white	5	0	19	0	29	0	31	2	30	6	33	12
New Orleans Negro	13	0	32	0	42	1	45	4	33	11	30	9
Santiago	14	0	19	0	22	1	25	1	29	2	31	3
Costa Rica	13	0	19	2	24	0	30	1	30	2	35	6
Guatemala	14	1	21	0	26	1	25	2	29	1	36	7
Durban Bantu	14	0	22	1	29	1	30	2	30	4	28	6

TABLE 8

MEAN PERCENT OF INTIMAL SURFACE INVOLVED WITH CORONARY FATTY STREAKS (FS) AND RAISED ATHEROSCLEROTIC LESIONS (RL) IN MALES BY LOCATION-RACE GROUP AND AGE

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	FS	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*
New Orleans white	1	0	2	1	5	3	10	11	11	16	11	24
New Orleans Negro	2	0	3	0	6	2	9	4	14	6	16	13
Santiago	1	0	1	0	3	0	4	1	6	3	8	6
Costa Rica	0	0	2	0	2	1	5	1	6	3	6	4
Guatemala	0	0	1	0	2	1	3	1	5	2	5	4
Durban Bantu	1	0	3	0	7	0	9	2	16	3	15	4

TABLE 9

MEAN PERCENT OF INTIMAL SURFACE INVOLVED WITH CORONARY FATTY STREAKS (FS) AND RAISED ATHEROSCLEROTIC LESIONS (RL) IN FEMALES BY LOCATION-RACE GROUP AND AGE

Location-race groups	*Age (years)*											
	10–14		*15–19*		*20–24*		*25–29*		*30–34*		*35–39*	
	FS	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*	*FS*	*RL*
New Orleans white	0	0	2	0	4	1	7	2	10	4	14	7
New Orleans Negro	1	0	8	0	13	1	14	2	16	4	19	11
Santiago	2	0	2	0	3	0	5	1	5	1	7	2
Costa Rica	1	0	1	0	4	0	7	1	5	1	8	4
Guatemala	0	0	3	0	3	0	3	0	3	0	6	3
Durban Bantu	1	0	4	0	5	0	9	1	14	3	15	3

lesions are present to a variable degree. Raised lesions are much more frequent in men than in women in the New Orleans white and in the cases from Santiago and Costa Rica.

Extent of lesions

The mean percent of aortic intimal surface involved by fatty streaks and raised atherosclerotic lesions is shown for males in Table 6. On the average, fatty streaks involve from 7–19 % of the aortic intima in cases 10–14 years of age, and from 20–28 % in the cases 20–24 years of age. Aortic fatty streaks show no clear pattern of geographic or ethnic differences except for the greater than average involvement of the New Orleans Negro. Aortic raised lesions show geographic and ethnic differences by age 30 with the New Orleans white most extensively involved.

Table 7 shows similar data for females. There are minor differences in the absolute percentages, but the early development of fatty streaks and the rapid increase in extent during adolescence are present. The pattern of development of aortic raised lesions is not much different from that in the male (Table 6).

Table 8 compares the extent of coronary artery fatty streaks and raised lesions in males among the 6 location-race groups. The 2 Negro groups (the New Orleans Negro and the Durban Bantu) and the New Orleans white have the greatest average involvement with coronary fatty streaks. Raised atherosclerotic lesions begin in the coronary arteries by age 20 and soon become most extensive in the New Orleans white. Cases from Santiago, Costa Rica, Guatemala, and the Durban Bantu have much less of the coronary intimal surface involved by raised atherosclerotic lesions at all ages. Coronary involvement with raised lesions in the New Orleans Negro is intermediate.

Fatty streaks in females from these same groups (Table 9) are more extensive in the New Orleans cases and the Bantu. The New Orleans Negro females have the most extensive raised atherosclerotic lesions. The New Orleans white females have only slightly less raised lesions.

DISCUSSION

Almost all persons have aortic fatty streaks by age 10 and most persons have coronary artery fatty streaks by age 20 regardless of geographic or ethnic origin. Raised atherosclerotic lesions may appear in both aorta and coronary arteries before age 20, and their prevalence and extent parallel the frequency of clinical manifestations of atherosclerosis in later life.

Few will question the relevance of raised atherosclerotic lesions to clinically manifest disease since these lesions may narrow the arterial lumen and set the stage for thrombosis and occlusion. Some investigators question the relation of coronary artery fatty streaks to raised lesions and to clinical disease. The relationship of fatty streaks to more advanced atherosclerotic lesions was investigated by three different methods in arteries collected in the cooperative study.

In the first, sections from a standardized location in the coronary arteries were

examined microscopically[17]. This microscopic study indicated that musculoelastic thickening of the coronary intima is present even before lipid accumulation occurs. No sharp distinction could be made histologically between the pure fatty streak and the typical fibrous plaque. This finding suggests that there is a gradual transition from the fatty streak to the fibrous plaque. Microscopically, more intimal lipid and greater intimal cellular infiltration occurred in the New Orleans cases than in the other location-race groups. Thus the microscopic characteristics of the early lesions in New Orleans coronary arteries were different from those of other populations in which atherosclerosis was less precocious.

Another analysis focused on the predictive value of coronary artery fatty streaks in childhood for advanced atherosclerotic lesions in middle age[18]. Young Negro populations had as much or more extensive fatty streaks than other populations of the same age group despite the fact that the Negro populations characteristically develop less extensive advanced lesions at older ages. This racial discrepancy and its possible explanations are discussed in the report[18]. If Negro and non-Negro groups were considered independently, however, populations with extensive coronary artery fatty streaks in childhood tended to have more extensive raised atherosclerotic lesions in middle age. This parallel relationship did not hold for aortic fatty streaks, as there were practically no population differences in aortic fatty streaks. From this study we concluded that the data were consistent with the hypothesis that advanced atherosclerotic lesions develop by progression and transformation of fatty streaks and that the degree to which the transformation takes place appears to vary among arteries and among racial groups.

The topographical distribution of atherosclerotic lesions along the coronary arteries was compared in another investigation of the relation of fatty streaks and fibrous plaques[19]. The axial distribution of fatty streaks and fibrous plaques was approximately the same within each major branch of the coronary arteries at all ages. This close topographic association between fatty streaks and fibrous plaques at different ages is consistent with the hypothesis that fibrous plaques are derived from fatty streaks.

The reliability of estimating fatty streaks in blood vessels that contain advanced atherosclerotic lesions has been discussed by GUZMÁN *et al.*[16]. For practical purposes, the extent of fatty streaks in persons under age 20 may be a realistic estimate of amount of intimal lipid. However, after this age, when other lesions are also present, one should interpret findings concerning quantitative evaluations of fatty streaks with caution.

The time sequence for the pathogenesis of each of the typical stages of coronary atherosclerosis is summarized for New Orleans white males in Table 10. Prevention or treatment of atherosclerosis could be undertaken at any one of several points. If terminal complications leading to clinical disease could be prevented, clinical manifestations might be averted even if the basic mural atherosclerotic lesions were not altered. There is hope, for example, that environmental conditions associated with a predisposition to thrombosis may be identified. It may also be possible to prevent

TABLE 10

PATHOGENESIS OF CORONARY ATHEROSCLEROSIS IN NEW ORLEANS WHITE MALES

Lesion	*Appears in decade*
Musculoelastic intimal thickening	1
Fatty streak	2
Fibrous plaque	3
Complicated lesion	4
Clinically manifest disease	5

complications in fibrous plaques, or to prevent the transformation of fatty streaks into fibrous plaques. Much circumstantial evidence indicates that the simple amount of lipid in the fatty streak determines whether it is converted into a fibrous plaque. If this stage becomes the point of attack, the data presented here suggests that the time to begin the attack is at the latest in the third decade; probably in the second decade; and perhaps in the first decade.

The prevalence and extent of atherosclerosis and its sequelae differ greatly among different populations. Differences in lesions of the coronary arteries appear even in adolescence. This observation encourages the belief that the process is not inevitable but is environmentally determined. Preventive measures undertaken before fibrous plaques become extensive should control permanently the epidemic of coronary heart disease. Other clinical manifestations of atherosclerosis, such as abdominal aneurysm, stroke and peripheral vascular disease, may likely be controlled at the same time. To test such concepts of prevention, a longer trial period than the usual 5 years must be planned and the preventive measures must be taken early in life.

To return to HOLMAN's provocative remarks, atherosclerosis, at least in part, is a nutritional problem. Overwhelming evidence from human and experimental animals relates serum lipids, dietary habits, atherosclerosis, and coronary heart disease. Clinical disease related to atherosclerosis may not be a pediatric problem, but the seeds of the problem are undoubtedly sown in childhood, adolescence, and young adulthood. Preventing fatty streaks or preventing the progression of fatty streaks to more advanced lesions seems to be the key to the problem. Programs to control the progression of atherosclerosis should be directed toward persons in the twenties and thirties, and perhaps earlier. If the programs include changes in dietary patterns, it is reasonable to propose that these beneficial dietary patterns be established in childhood. Thus, atherosclerosis is almost certainly a pediatric as well as a nutritional problem.

ACKNOWLEDGEMENTS

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