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THE NATURAL HISTORY OF ATHEROSCLEROSIS

THE EARLY AORTIC LESIONS AS SEEN IN NEW ORLEANS IN THE MIDDLE OF THE 20TH CENTURY*

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The real significance of atherosclerosis is the role that it plays in the production of human disease. Manipulations of diet, physical activity, or hormonal levels may alter some of the constituents of the blood, and a study of these relationships may yield useful basic information. However, the fact remains that the ultimate criterion for the effectiveness of any proposed prophylactic or therapeutic procedure must be its effect on the clinical manifestations of disease. In the variety of disorders related to atherosclerosis, the universally recognized common denominator is the characteristic arterial lesion, a structural alteration in the arterial wall which obstructs the lumen and reduces blood flow to a part of the body, thereby producing overt clinical manifestations.

Our present concept of the sequence of events in human atherosclerosis leading from lesions to clinical phenomena is diagramatically presented in Text-figure 1. The simple fatty streak is considered to represent the earliest lesion of atherosclerosis that can be recognized with facility either grossly or histologically. The fatty streak is gradually converted into a fibrous plaque, at the base of which a core of lipid usually remains. A fibrous plaque may become sufficiently large to cause slowly progressive stenosis of the lumen of a vessel, particularly if another plaque is located opposite to it. It may undergo sufficient enlargement by accretion of additional lipid on the surface so as to produce a similar effect; or it may become vascularized and

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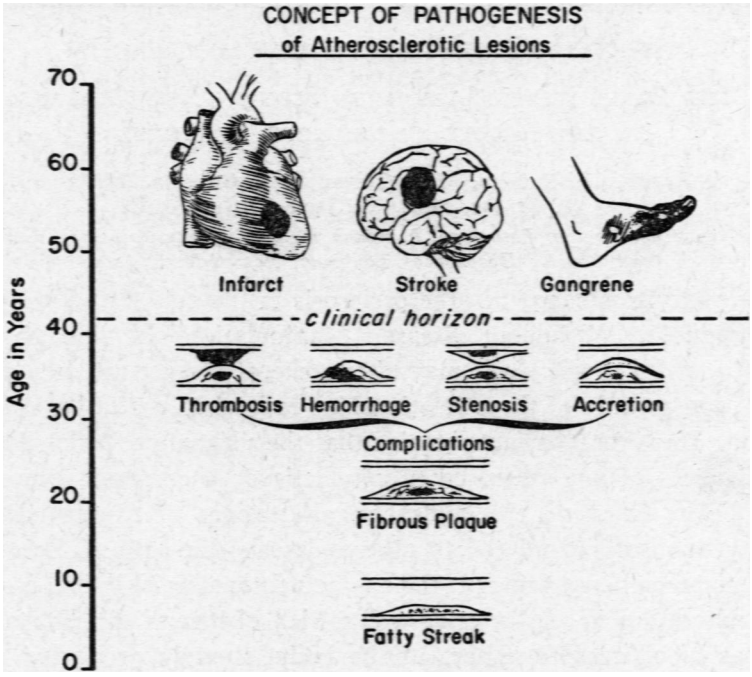
undergo hemorrhage, or ulcerated and be covered by a thrombus. In the latter instances rapid occlusion of the artery may result. Rarely, the lesion may so weaken the underlying media that an aneurysm is produced; or it may become calcified, a change probably representing a healing process.



Text-figure 1. Concept of pathogenesis of atherosclerotic lesions.

The whole gamut of these changes, and particularly those which lead to clinical recognition, have not yet been reproduced in experimental animals. Furthermore, the applicability to man of those experimental vascular lesions which have been produced in animals is not clearly established. This difficulty in correlating the lesions in experimental animals and those in man has prompted us to restudy the natural history of human atherosclerosis in the light of the concept of pathogenesis outlined above.

For this study, the aorta was selected as that part of the vascular system to be preserved and examined. The first step, previously reported in detail,[1] was the grading of 300 aortas procured from consecutive necropsies on individuals of all ages. The observations most significant with respect to the study to be reported here were that simple fatty streaks were found in children as young as 9 months of

age; that every case beyond the age of 7 years had at least minimal fatty streaks; and that only after the age of 30 years did fibrous plaques appear in appreciable numbers of cases. This early study emphasized the need for a more quantitative method of expressing the degree of severity of atherosclerotic lesions, and also demonstrated the desirability of focusing attention on the earlier age groups for more intensive consideration.

This report is based on the study of 461 essentially complete aortas (Table I) and 65 incomplete specimens from 526 patients between 1 and 40 years of age. These patients were examined at necropsy in a large general hospital and medico-legal pathology service in New Orleans over a 5-year period. The more refined methods of processing and grading atherosclerotic lesions have brought to light certain facts about their natural history that suggest important leads for future research.

TABLE I

Tabulation of 461 Cases by Age, Sex and Race

	White			Negro			Total
Age in years	M	F	Total	M	F	Total	
1–5	18	11	29	54	43	97	126
6–10	12	3	15	15	11	26	41
11–15	8	5	13	14	9	23	36
16–20	11	6	17	20	8	28	45
21–25	19	5	24	14	12	26	50
26–30	12	9	21	13	22	35	56
31–35	8	8	16	14	15	29	45
36–40	14	13	27	18	17	35	62
Total	102	60	162	162	137	299	461

MATERIALS AND METHODS

The material on which this report is based was obtained from necropsies performed on individuals between the ages of 1 and 40 years in Charity Hospital of Louisiana at New Orleans, and in the pathology laboratory of the Office of the Coroner, Parish of Orleans, in the 5-year period from 1952 to 1957. Charity Hospital is a 3,076 bed general hospital located in a metropolitan area of approximately 700,000 people, serving patients from the entire state of Louisiana. Patients suffering from all types of both acute and chronic diseases are admitted. As a general rule these patients represent the lower income groups. During the first 4 years of this study, between July 1,

1952, and June 30, 1956, Charity Hospital admitted 276,932 persons, of whom 39,776 were white males; 43,241 were white females; 67,568 were Negro males; and 126,347 were Negro females. Thus the admissions were approximately 30 per cent white and 70 per cent Negro. In this same period, there were 11,173 deaths in this hospital. Necropsies were performed on 5,973 of these cases: 1,331 white males; 825 white females; 2,051 Negro males; and 1,766 Negro females.

The Office of the Coroner in Orleans Parish performs necropsies on cases of homicide, suicide, and accidental or traumatic death occurring in this parish, and upon many patients dying without the attendance of a physician. Particular effort was made in this study to obtain aortas from persons dying suddenly from trauma or poisoning, in which any relationship between the cause of death and the arterial lesions present would be minimized.

Although the aorta was not obtained from every necropsy at either source, there was no conscious bias in selection of material on the basis of the lesions present. In rare instances, the presence of congenital heart disease led to exclusion of the specimen from the series. A few aortas were taken by the surgical staff for aortic homografts during the later years of this study, but there is no reason to believe that these specimens had more or fewer lesions than the others.

The aortas were fixed in 10 per cent formalin, stained for 15 minutes in a 0.5 per cent solution of Sudan IV dissolved in equal volumes of 70 per cent ethanol and acetone, differentiated in 80 per cent ethanol, and rinsed in running tap water for 1 hour. An example of an aorta before (Fig. 1) and after staining with Sudan IV (Fig. 2) is shown for comparison. After blocks were removed for histologic sections, the aortas were sealed in transparent plastic bags.[2] The extent of the gross lesions was estimated by two individuals without any knowledge of age, sex, race, or other clinical data. The specimens have been retained and are available for examination by any interested person.

Three types of lesions were considered: fatty streaks, fibrous plaques, and complicated lesions. "Fatty streaks," as defined in this study (Figs. 3 and 4), represented areas in the intima which stained red with Sudan IV. These may or may not have been appreciably raised above the adjacent intimal surface, but usually the elevation was minimal. Fibrous plaques (Figs. 5 and 6) were raised, pearly, glistening, firm plaques, usually containing material rich in lipid in their depths, but not staining with Sudan IV because of the thick layer of nonlipid hyaline fibrous tissue on the surface. Frequently, small lesions were encountered which appeared to be transitions between

fatty streaks and fibrous plaques, in which the lipid was only partially covered by hyaline connective tissue. The term "complicated lesion" was used to refer to any plaque in which there was additional change, such as ulceration, thrombosis, hemorrhage, or calcification.

The extent of the lesions was recorded as the percentage of the total surface area of the intima involved by each of the 3 types of lesions, as estimated by visual observation. Percentages of surface involvement were grouped into 9 different categories ranging from 0 to 100 per cent. Specimens showing degrees of involvement with fatty streaks representative of each positive category are illustrated in Figures 7 to 14. It was felt that these groups corresponded to the degree of accuracy that might be obtained by visual estimation of highly irregular surface areas.

A percentage value for each type of lesion in the entire aorta was assigned. Then, in order to study the topographic relationships, the aorta was divided into 5 different anatomic regions and an estimate of the percentage of surface involved was again made for each type of lesion in each region. The small scar at the point of attachment of the *ligamentum arteriosum* was graded separately as to the presence or absence of various types of lesions.

Hospital charts and necropsy protocols were reviewed for principal causes of death and pertinent clinical data. These data, together with the results of the grading procedure, were coded and transferred to IBM punch cards for analysis.

Results

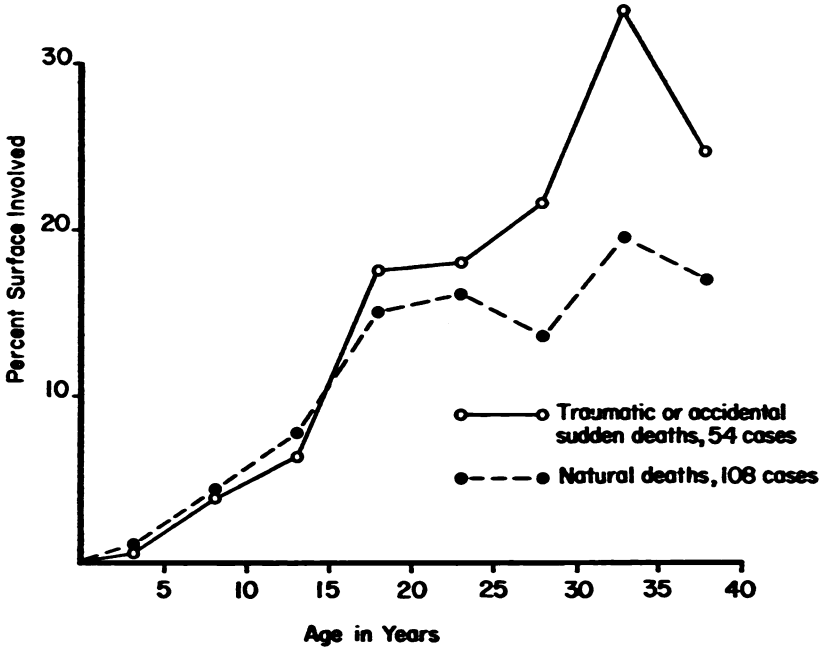
Validation of Methods

Gross Staining With Sudan IV. Gross staining with Sudan IV sharply delineated the intimal fatty streaks, and also made visible those streaks which were not apparent in the unstained specimen. Thus gross staining increased the apparent incidence and extent of fatty streaks in the early age groups. In the present study, sudanophilic material was found in the intima in every case beyond the age of 3 years.

Minimal lesions were found so frequently that some question was raised as to the significance of gross Sudan staining; i.e., whether it actually indicated an early lesion of atherosclerosis. Histologic sections were examined with this particular question in mind, and in every instance there were histologic alterations in the intima corresponding to the macroscopic sudanophilia. These alterations consisted of both intracellular and extracellular globules of lipid (as indicated

by the application of Sudan IV), and a slight increase in interstitial mucinous material. The intima in these early lesions was not always elevated, and there was little fibroblastic reaction.

Estimating Surface Area of Lesions. Visual estimation of the percentage of surface involved by the various types of lesions was tested for reproducibility and reliability by a comparison of values assigned to each of the first 311 specimens by different observers at different times. Over 50 per cent of the aortas were classified in the same

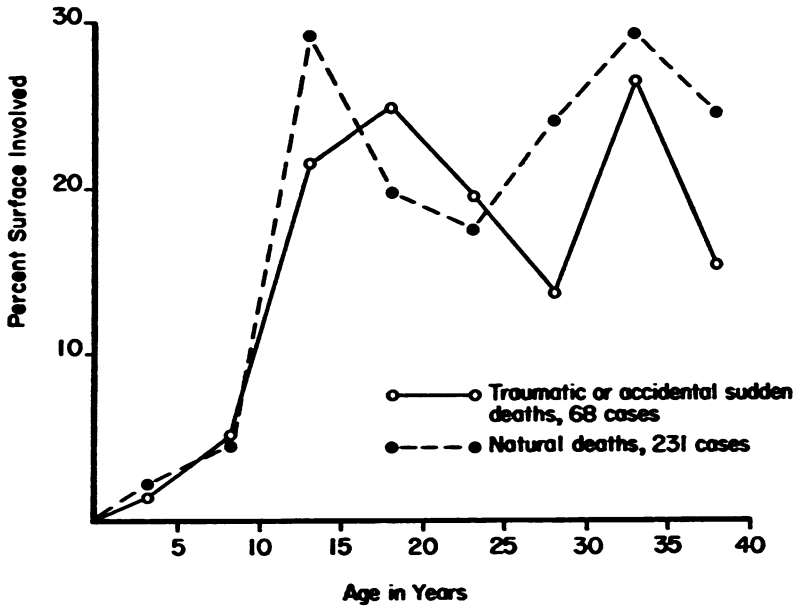


Text-figure 2. Aortic atherosclerosis, New Orleans. Fatty streaks by cause of death in 162 white cases

quantitative category by two different pairs of observers as long as 4 years apart; and only 5 per cent differed by more than 1 category. Agreement was much better between gradings performed by the same individuals at different times. It was considered desirable as a result of the analysis of methods that comparisons should be made on the basis of grading of all the specimens by the same observers. The results reported here are based on data so accumulated.

Sampling of Living Population. A serious question which arose in considering these specimens was how closely the anatomic material obtained post mortem corresponded to the living population. A post-mortem series is a highly selected group, and many factors might introduce bias into the selection. For example, the terminal illness could influence the presence or extent of early lesions. The material

thought to be least subject to any factor which might affect such lesions is that obtained from cases of accidental or traumatic death, and data from such cases were separated and compared with those obtained from the remaining cases. The comparison for fatty streaks is shown for white individuals in Text-figure 2, and for Negroes in Text-figure 3. The apparent differences in white persons after age 25 have been shown not to be statistically significant. Similar comparisons were made with respect to fibrous plaques and to a summation

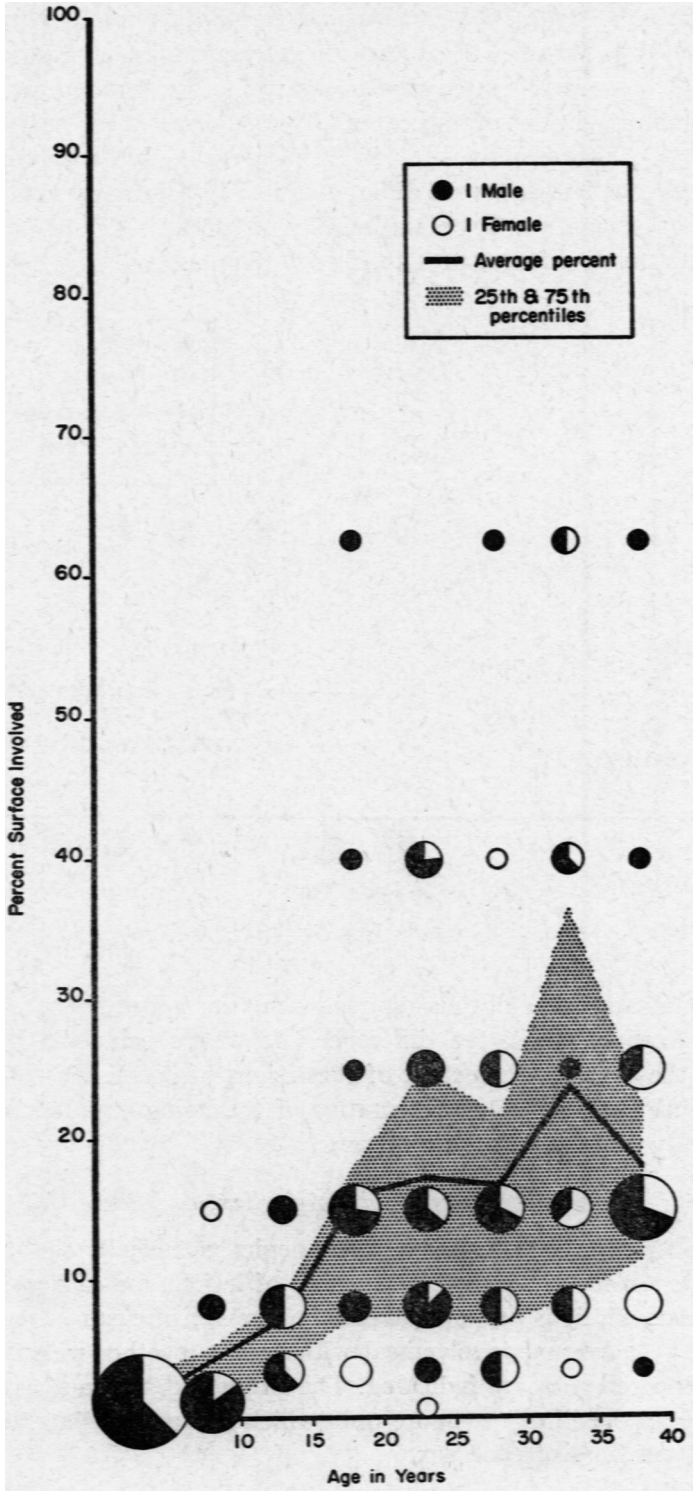


Text-figure 3. Aortic atherosclerosis, New Orleans. Fatty streaks by cause of death in 299 Negro cases.

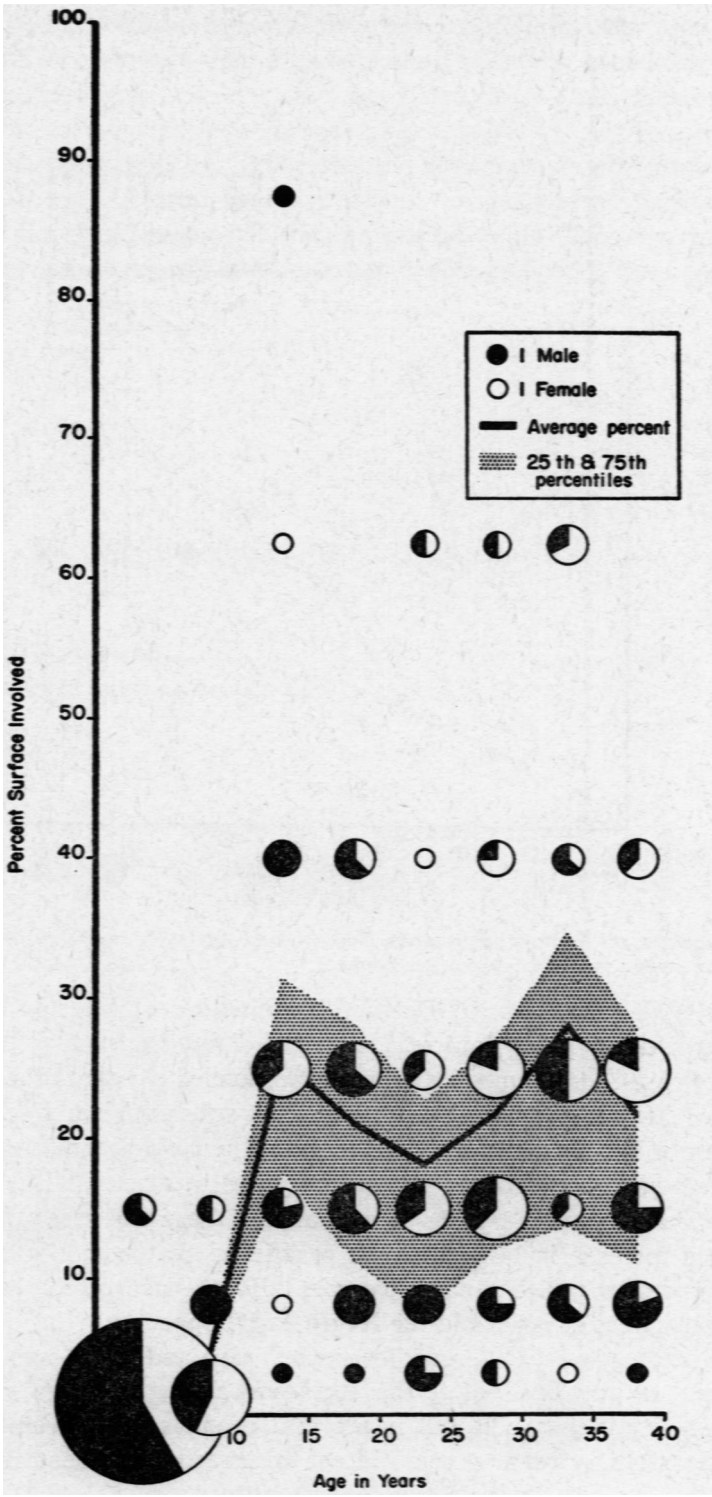
of fatty streaks and fibrous plaques, and the comparisons revealed no significant quantitative difference. It was concluded, therefore, that on the average, the extent of the lesions of aortic atherosclerosis in the entire series was representative of the living population in the community from which it was drawn.

Analysis of Lesions by Age, Sex, and Race

Fatty Streaks. Text-figures 4 and 5 depict graphically the distribution with respect to age, sex, and extent of lesions for each race. The area of each circle is proportional to the number of cases in that category, and the average involvement with lesions together with the 25th and 75th percentiles are indicated. The white and Negro averages by age are compared in Text-figure 6, in which the averages are adjusted to equal numbers of each sex.

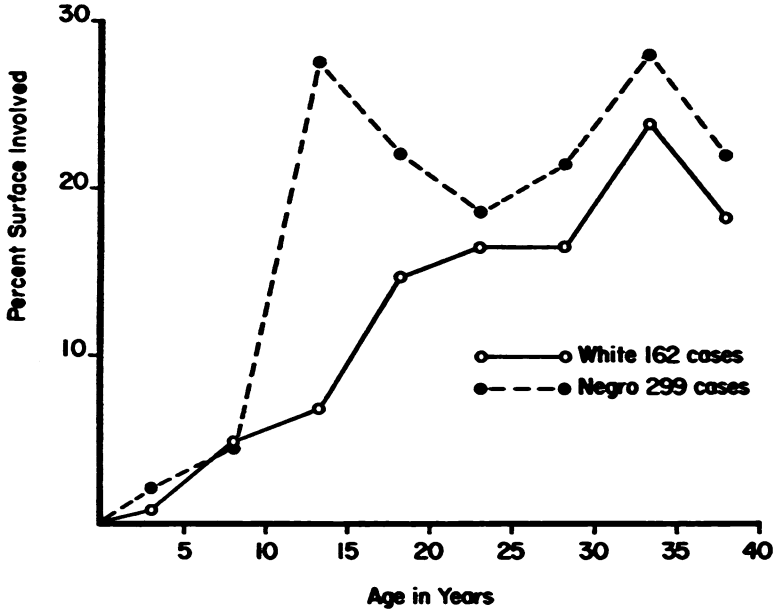


Text-figure 4. Aortic atherosclerosis, New Orleans. Distribution of 162 white cases by age, sex, and per cent of surface covered by fatty streaks.



Text-figure 5. Aortic atherosclerosis, New Orleans. Distribution of 299 Negro cases by age, sex, and per cent of surface covered by fatty streaks.

In both white and Negro, the average percentage of surface involvement proceeded gradually upward from a very low value (0.8 per cent and 2.0 per cent) to around 4 per cent for each race between 6 and 10 years of age. In the statistics covering the next 5 years of age, the most surprising phenomenon encountered in the entire study occurred. The average percentage of surface involved in the Negro cases rose to 28.1 per cent, while the average for the white cases rose only to 7.2 per cent. The probability that this difference was due to chance



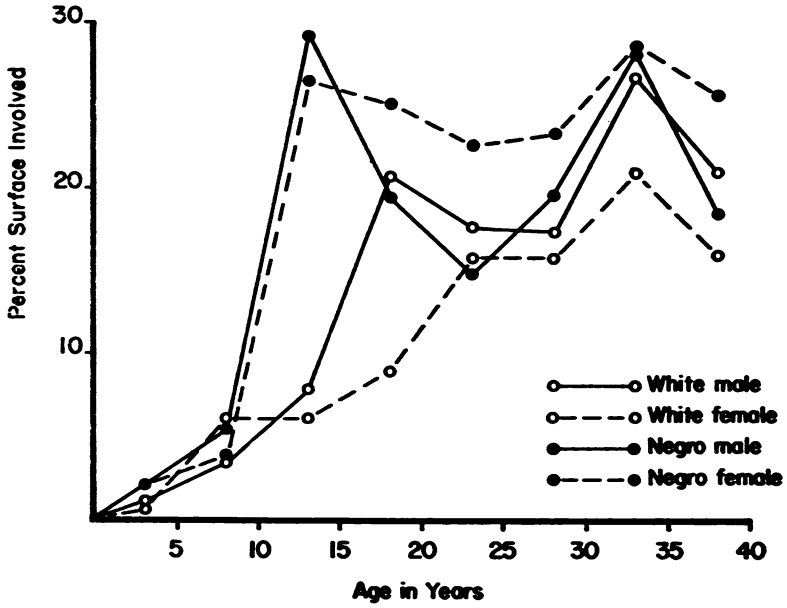
Text-figure 6. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fatty streaks, white vs. Negro, sex adjusted.

alone is less than 0.001. Detailed examination of cases in this age group disclosed no obvious reason for the difference, such as the selection of cases, for the median values corresponded closely to the average values. It was concluded that there is a substantial and significant difference in the extent of lipid streaks in the Negro race as compared to the white race between 11 and 15 years of age.

Between 13 and 18 years of age, among the white cases there was a rapid increase in lesions almost parallel to that noted for the preceding 5-year period among Negroes. By the age of 18 years, the average extent of lesions in the Negro had dropped; and in succeeding years, although the difference between Negro and white was not significant at any one point, the incidence among Negroes remained consistently higher. The fall in per cent of surface involved by fatty streaks after 33 years of age did not necessarily represent regression

of lesions, as will be seen when fibrous plaques are considered, since it may have represented conversion of fatty deposits into fibrous plaques.

When the two sexes were compared without regard to race, no difference in the percentage of surface involved by fatty streaks at any age was seen. That this similarity was artificial, however, was indicated when the sexes were further divided by race as in Text-figure 7. The development of the lesions in the Negro female was much like



Text-figure 7. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fatty streaks by age, race, and sex.

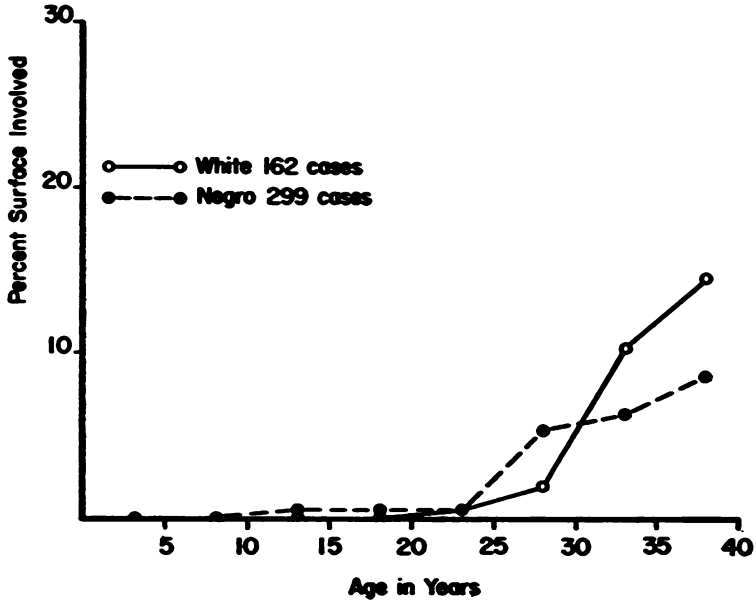
that in the Negro male, except that between the ages of 15 and 30 years in the female there was actually more surface involvement with fatty streaks. On the other hand, the extent of fatty streaks in the white female ranked consistently lower than in all other groups. Thus, the greatest contrast to be seen was that between the white female and the Negro female.

Fibrous Plaques. Fibrous plaques were first observed in cases representing the second decade, and by 20 years of age, 4 Negroes and 1 white in this group had at least minimal fibrous plaques. The frequency with which fibrous plaques were found increased steadily during the third decade of life; and after 30 years of age, 90 per cent of the aortas of each race revealed fibrous plaques to some degree.

The average percentages of aortic surface covered by fibrous plaques are charted for the two races in Text-figure 8. After age 30,

the white was consistently more severely affected, and in the last age group (35 to 40 years), the extent of these lesions in the white was almost twice that in the Negro.

Total Surface Area Affected. The average total percentage of surface covered by both types of lesions was computed by adding the average values for fibrous plaques to those for fatty streaks in corre-



Text-figure 8. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fibrous plaques, white vs. Negro, sex adjusted.

sponding age and race groups. For the whites, the apparent regression of fatty streaks after 36 years of age appeared to be largely accounted for by conversion to fibrous plaques. Attention may be called to the fact that the second stage of rapid progression of the lesions, produced by the formation of fibrous plaques, began in each race approximately 15 years after the period of rapid rise in fatty streaks.

Text-figure 9 shows the average total surface involvement for whites and Negroes, each plotted on the same graph. It may be noted that the total surface involvement among whites over 35 years of age exceeds that among Negroes.

Complicated Lesions. Complicated lesions were quite rare in this group of cases, and quantitatively were insignificant.

Topographical Relationships

The results of the quantitative estimates of the different types of lesions by anatomic region of the aorta are shown for whites in Text-

figures 10 and 11. Similar results were obtained for the Negro race for both fatty streaks and fibrous plaques.

In both races, the aortic ring was the first to be involved by fatty streaks. The sudanophilic deposits encountered in this area were scattered along a line at the upper edge of the valvular commissures.

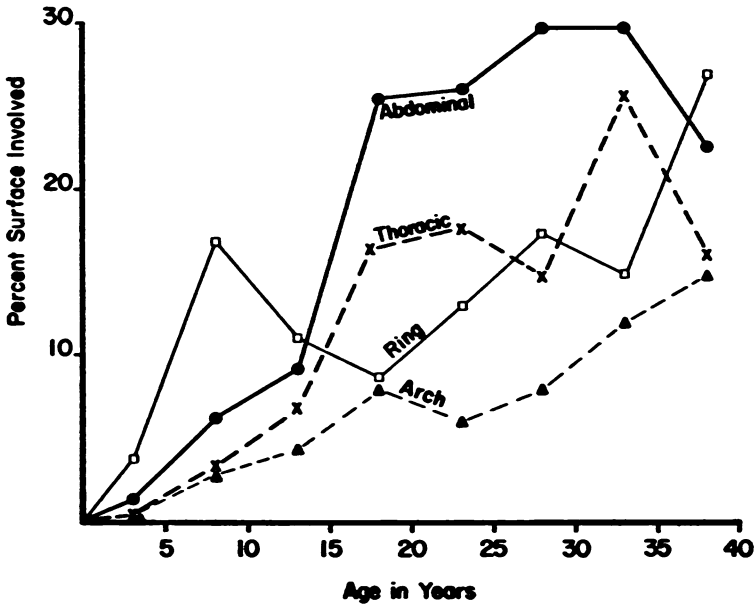
Text-figure 9. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fatty streaks plus fibrous plaques, white vs. Negro, sex adjusted. White, 162 cases; Negro, 299 cases.

The aortic valve leaflets themselves were not affected, and fatty streaks deep within the sinuses of Valsalva were rarely found. Although not sought systematically in this study, fatty deposits were frequently noted on the ventricular surface of the anterior leaflet of the mitral valve.

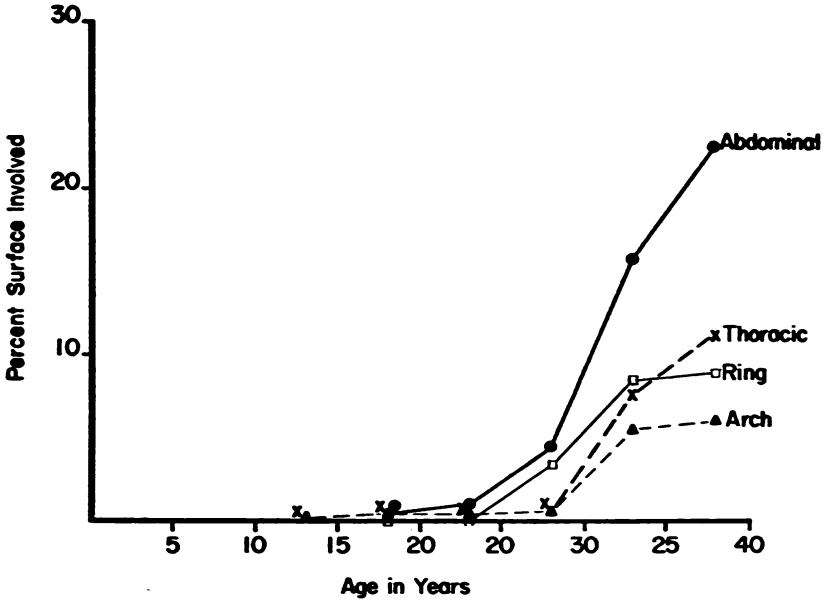
The involvement of the aortic arch was similar to that of the ring. Here the fatty deposits usually occurred in small discrete foci conforming to no particular pattern, except that they seemed to be more frequent about the orifices of the large branches arising from the arch.

The descending thoracic and abdominal portions of the aorta set the distinctive pattern of increasing lesions for each race that has been previously demonstrated in terms of total percentage of surface involved. Of the two, the abdominal aorta was consistently the more severely affected. The same relationship of the various segments of

aorta to one another was also present with respect to fibrous plaques. The abdominal segment was the most severely involved, the descending thoracic was next, and the ring and arch were the least. If the ab-



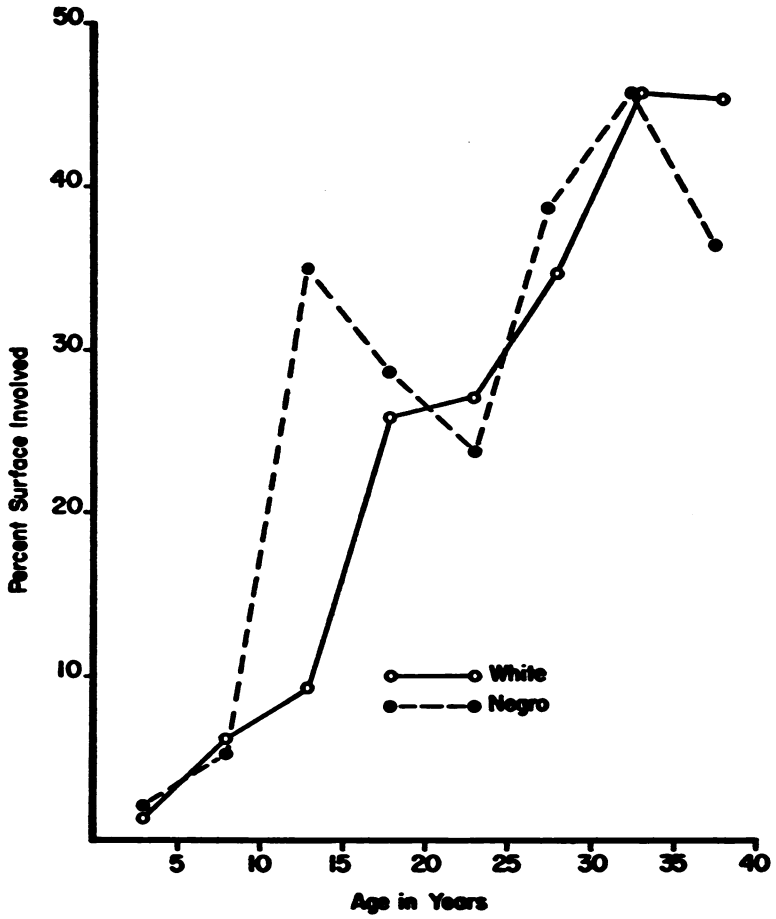
Text-figure 10. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fatty streaks by anatomic region in 184 white cases.



Text-figure 11. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fibrous plaques by anatomic region in 184 white cases.

dominal aorta alone were considered, and if the average percentage of surface covered by fibrous plaques were added to that covered by fatty streaks (Text-figure 12), the same pattern as that shown in Text-figure 6 would be reproduced, with the peaks and the difference between white and Negro at the age of 13 years accentuated.

In the descending thoracic aorta, fatty streaks—especially the extensive ones appearing in the second decade—occurred as parallel, linear, longitudinal streaks localized along the posterior portion of the aorta, between and to each side of the orifices of the intercostal vessels.



Text-figure 12. Aortic atherosclerosis, New Orleans. Average per cent surface covered by fatty streaks plus fibrous plaques in abdominal aorta only, white vs. Negro.

About each orifice there was a small area which was characteristically spared. In contrast, in the abdominal portion the fatty streaks occurred as larger irregular areas, often confluent so as to cover fairly uniformly rather extensive portions of the intimal surface.

Discussion

Concern with the very early lesions of aortic atherosclerosis is by no means new. In 1911, Klotz and Manning[3] introduced their study of the aortas from 90 cases between 1 and 73 years of age with this statement: "It is quite useless to argue the questions concerning the development of intimal scleroses if we study and discuss the late stages of the disease alone. . . . If we wish to gain a true insight into the complex question of arterio-sclerosis we must attempt to follow the lesion from its earliest beginning." Examining their specimens principally for fatty streaks, since they considered these the earliest lesions of "arteriosclerosis," they found a high incidence in individuals below 30 years of age without using any gross staining technique.

The most thorough study of aortic atherosclerosis in younger age groups that has been found reported is that of Zinserling[4] in 1925, who examined 320 aortas from children up to 15 years of age after gross staining with Sudan III. Zinserling graded these specimens into 5 groups on the basis of extent of surface involved, very much as was done in the present study except that he did not attempt quite as precise an estimation of this value. Just as we have, he found that gross staining not only enhanced the detection of lesions in the younger ages, but also increased the estimation of the extent of intimal surface involved by fatty streaks. He also found that sudanophilic deposits were present in some cases before the age of 4 years. In plotting the average degree of aortic lesions against age, Zinserling found only a steady rise in severity of lesions with age, and did not detect a more rapid rise in certain age groups. His failure to do so may have been due to the somewhat cruder method of grading and the fact that he considered cases only up to 15 years of age. As has been demonstrated for the New Orleans white, this is the midpoint of the age group in which the most rapid rise occurs.

Of particular interest in Zinserling's report are the analyses of his data on aortic lesions with respect to cause of death and the state of nutrition. He could find no single cause of death that was associated with significantly more extensive or advanced lesions. A number of the children, having died during the postwar famine, were severely emaciated as a result of starvation; these showed no difference in incidence or extent of fatty streaks as compared with the well nourished ones.

In 1938, Albert[5] reported the results of examination of 136 aortas from patients between 4 months and 25 years of age after Sudan III staining. He could detect no influence of terminal illness on aortic fatty deposits, nor could he detect any clear differences with respect

to sex. Probably for the same reasons as Zinserling, he found no rapid rise in any age period.

The remarkable feature about these earlier studies is the close similarity between the results reported from Europe approximately 30 years ago and those encountered in the present study. The additional conclusions at which we have arrived have been made possible by the larger number of cases, access to material from two races, more precise quantitation, and inclusion of cases up to 40 years of age.

Zeek[6] in 1930 made an exhaustive and critical review of the literature pertaining to juvenile atherosclerosis. Some confusion arose in her discussion because of the inclusion of cases of widespread arterial calcification in very young children, a distinctive entity that seems to be not at all related to the problem of atherosclerosis. After considering many fragmentary studies and a number of conflicting opinions on the subject, she concluded with a series of provocative questions. "Is there a real peak in the incidence of arteriosclerosis around the onset of puberty? If so, why?" Zeek asked. We may now answer with assurance that there is such a peak, and in fact that during this period of life fatty streaks advance more rapidly than at any other period under 40 years of age. Answering "Why?" is more difficult, however. The association of this rapid rise with puberty suggests a relationship to the hormonal changes of puberty.

The fact that this rapid rise during puberty occurs approximately 5 years earlier in the Negro than in the white is one of the best documented and most unexpected results of this study. It is generally recognized that at the present time, the economic status of the Negro in the southern United States is on the average inferior to that of the white. Such an environmental difference would be minimized in the selection of most of the cases studied here, since admission to Charity Hospital is largely restricted to the lower income groups of both races. Precise data concerning the diet of the Negro as compared to the white in this community is not available at the present time, but it is our impression that there exists no real difference in diet paralleling the dramatic difference in lesions in a restricted age group.

The observation that lesions are so nearly universal in young children, in which we have confirmed several previous reports in the literature, has led to serious re-evaluation of the concept of a normal aorta. It means that the existence of a "normal" patient in the sense that his aorta is completely free of structural alterations ordinarily thought of as a disease process does not occur after a very early age; consequently, the population cannot be divided into a group that has

atherosclerosis and another group that does not. All individuals have it, but simply differ in degree of involvement. This suggests that we are dealing with a process which is more or less peculiar to human subjects, the pace of which is set principally by the factors which control growth and development. Atherogenesis may be influenced to some degree in its early stages by environmental factors such as diet, but evidence accumulated in this study points to other stimuli as more important.

While we may have to accept the presence of early lesions of atherosclerosis as "normal" for humans in a statistical sense, we can never accept their presence as "normal" in an ideal sense so long as we believe that it sets the stage for crippling or fatal clinical disorders in later years. Although not every fatty streak inevitably goes through the changes eventually resulting in arterial occlusion, nevertheless the fatty streak appears to be an essential primary step in the series of alterations. Therefore, there is good reason to believe that preventing or reversing fatty streaks would avoid the later stages and thereby prevent clinical manifestations. If this perspective is maintained, there will not arise the difficulty which formerly existed when atherosclerosis was considered an inevitable result of senescence.

We believe that the data presented here are not only consistent with but actually offer considerable circumstantial evidence supporting the concept of pathogenesis described in the introduction (Text-figure 1). For example, it has been shown that there exists a base of fatty streaks sufficiently extensive and persistent to serve as a foundation for all of the fibrous plaques and complicating changes in the lesions which develop in subsequent years. It is difficult to conceive of these intracellular and interstitial lipid deposits resulting from the encrustation or imbibition of fibrin onto or into the intima as has been suggested by Duguid.[7] On the other hand, it appears quite reasonable to suspect that localized areas of tissue injury (manifested as fatty change) might be very susceptible to fibrin deposition and eventual replacement by fibrous tissue, resulting after a long period in a fibrous plaque surrounding a central core of sequestered lipid.

Our data indicate that by the age of 40 years about 20 per cent of the surface involved by fatty streaks has been converted into fibrous plaques; that it requires about 15 years for this conversion to take place; and that fibrous plaques appear in the same proportionate degree in different anatomic regions of the aorta as the fatty streaks did in younger age groups. These relationships, if they continue to hold true as the study is extended to larger numbers and other populations, are significant with respect to any future attempts

to prevent disease due to atherosclerosis. They mean that there is a period of 15 years of life in which lesions are present but are of such a nature that they do not readily produce overt manifestations, and that this period lasts until about the age of 30 years. Until this age, the lesions are almost exclusively of a type that would be much more readily reversible than those appearing later, judging from our experience with fatty degenerations and fibrous proliferative and reparative reactions elsewhere in the body.

The stepwise development of atherosclerosis, implied in the concept of pathogenesis, has also been emphasized by the present study. This feature has already been referred to in discussing the relationship of fatty streaks to fibrous plaques. The other complications occurring in atherosclerotic lesions (particularly those which finally produce sudden arterial occlusion, such as hemorrhage and thrombosis) were rarely encountered in specimens from patients up to the age of 40 years, and it appears that the fibrous plaque must undergo an additional series of changes over a period of at least several more years before the final link in the chain between subclinical lesion and clinical phenomena is forged.

Two apparent paradoxes noted in the data presented are worthy of brief comment and of careful scrutiny in the future as more data become available. The first of these has to do with the greater extent of fatty streaks (Text-figs. 5 and 6) leading to fewer fibrous plaques (Text-fig. 8) in the Negro race. There is no known explanation for this discrepancy, but it does emphasize a point of growing significance to us—namely, that factors responsible for succeeding stages of atherosclerosis (fibrous plaques, complicated lesions, and clinically recognizable disease) may be, and probably are, different from those which initiated the first stage (fatty streak). Intelligent therapeutic attempts must take cognizance of these different stages, for that treatment which is effective in one stage may be ineffective or even contra-indicated in another stage.

The second paradox is the apparent decrease in the extent of fatty streaks in the Negro race between the ages of 13 and 23 years (Text-fig. 5). It is tempting to interpret these data as evidence for reversibility of fatty streaks. It is possible, however, that a wave of environmental factors associated with World War II may have affected Negro children (1 to 5 years old) more than white children. Since the decrease in extent of fatty streaks occurred only in Negro males (Text-fig. 7), it is difficult to see how the privations or imbalances of war should have spared the Negro female. Another observation with similar implications of reversibility is demonstrated

in Text-figure 2, in which it can be seen that cases of natural death have fewer (but not statistically significant in the limited material collected thus far) fatty streaks than those dying of trauma. This suggests that the fatty streaks may have wasted along with other tissues during the terminal illness. As much as we would like to interpret these findings as evidence for reversibility of fatty deposits, prudence justifies patience and more data.

Summary

The aortas from 526 necropsied individuals between 1 and 40 years of age were obtained at a large general hospital and a medico-legal laboratory in New Orleans over a 5-year period. These specimens were examined before and after gross staining with Sudan IV, and the extent of fatty streaks, fibrous plaques, and complicated lesions (hemorrhage, ulceration, thrombosis, or calcification) was estimated for each aorta in terms of percentage of intimal surface affected by each type of lesion. Gross Sudan staining increased the ability to detect fatty streaks, and thus increased both their incidence and extent, particularly in the younger age groups.

Fatty streaks are not precipitated by terminal acute illnesses, for comparison of the average extent of lesions in cases dying suddenly as a result of trauma or poisoning with the average of lesions in natural deaths, discloses no significant difference. It is concluded that this group of specimens is as representative of the living population as it is possible to obtain at the present time.

All patients in this series 3 years of age or older had at least minimal sudanophilic intimal deposits. The percentage of surface involved rose slowly until the age of 8 years, at which time the extent of lesions began to rise precipitously in the Negro. Five years later, the extent of fatty streaks began to rise in the white, but did not reach a peak as high as in the Negro. The patterns in the Negro male and female are very much alike, with more severe involvement in females than in males at some ages. White females were consistently the group least affected.

Fibrous plaques began to appear in the second decade, but did not increase appreciably until the fourth decade. They paralleled the development of fatty streaks, but lagged about 15 years, and the relative degree of involvement of white and Negro was reversed as compared to fatty streaks. By 40 years of age, only about 20 per cent of the area covered by fatty streaks had been converted into fibrous plaques. Additional complications in the lesions were rarely seen in this series.

The aortic ring was the first region of the aorta to be the seat of fatty streaks, but it was the descending thoracic and particularly the abdominal portions which gave the distinctive pattern of increasing lesions between 8 and 18 years. Fibrous plaques also developed most extensively in the abdominal portion.

The data, in general, support the concept of stepwise development of atherosclerotic lesions, and suggest that different factors may be responsible for influencing the various steps in the progression of the lesions.

There is sufficient fatty change to serve as a basis for all the fibrous plaques encountered at later ages, and the data indicate that it requires at least 15 years for the conversion to take place. The rate of development of fibrous plaques and fatty streaks is reversed in the white as compared to the Negro, suggesting that whatever initiates the process differs from whatever carries it on to produce clinical manifestations.

These data do not support the concept of diet as the principal factor in atherogenesis. The rapid rise in lesions during the years of puberty suggests a relationship to the changing hormonal activity encountered during this period.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Unstained aorta from 32-year-old Negro female, dead of carcinoma of the cervix with metastases. Faint outlines of fatty streaks can be seen. Specimen 0-57-749. Reduced to 34%.

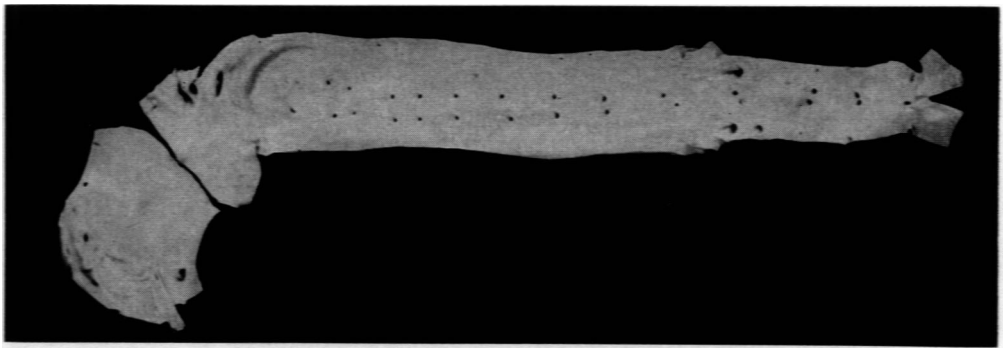
FIG. 2. Same aorta as in Figure 1 after gross staining with Sudan IV.

FIG. 3. Thoracic aorta from a 21-year-old Negro male, dead of acute lymphoblastic leukemia. Stained with Sudan IV, the fatty streaks appear black. Specimen 0-57-724. Reduced to 83%.

FIG. 4. Sudan IV stained frozen section of fatty streak from area indicated in Figure 3. The fat in this photograph appears black and is located both intracellularly and extracellularly. × 400.

FIG. 5. Abdominal aorta of 37-year-old white male, dead of ruptured cerebral aneurysm. The slightly elevated, white fibrous plaques contrast with the fatty streaks which appear black in this Sudan IV preparation. Specimen 1-56-112. Reduced to 83%.

FIG. 6. Sudan IV stained frozen section of fibrous plaque from area indicated in Figure 5. The fat appears black in this photograph. The dense layer of fibrous tissue between the endothelium and the fatty material is responsible for the failure of the lesion to stain grossly with Sudan IV. × 25.



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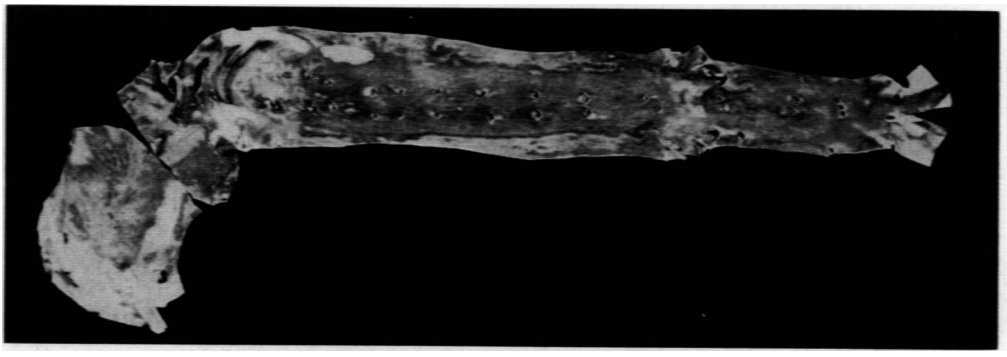

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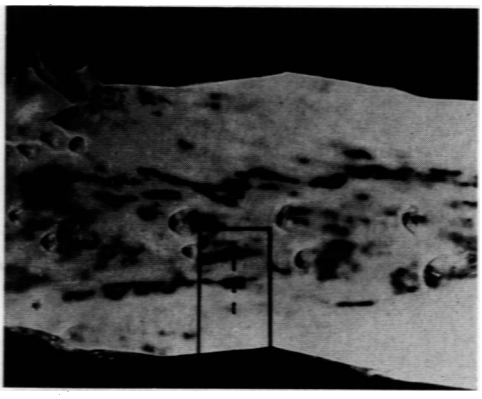

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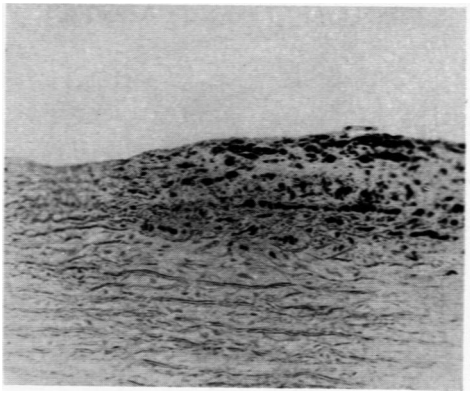

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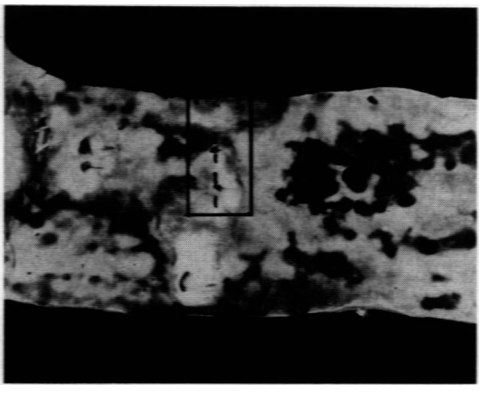

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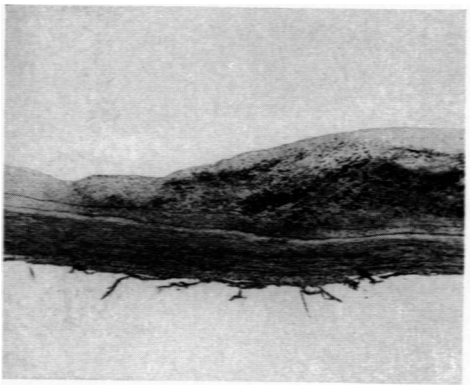

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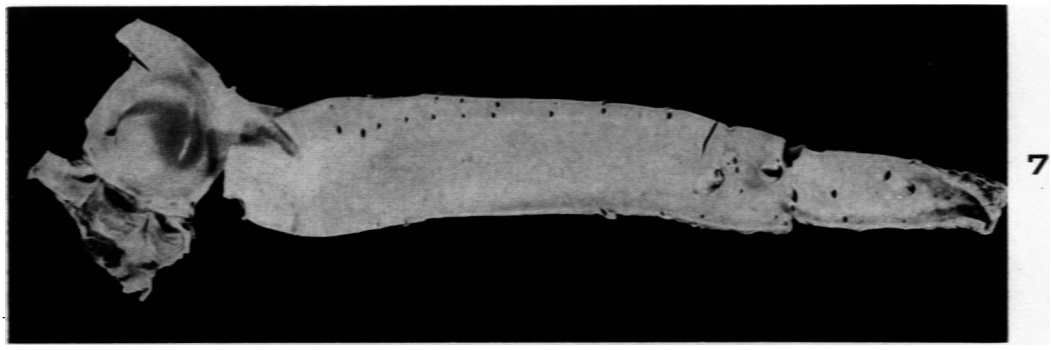
Representative examples of different degrees of involvement of aortic intimal surface by fatty streaks stained with Sudan IV.

FIG. 7. Less than 1 per cent; 4-year-old white male; death due to cardiac arrest during laparotomy for acute appendicitis and peritonitis. Specimen 0-54-1037. Reduced to 58%.

FIG. 8. One per cent to 5 per cent; 8-year-old white male; death due to acute appendicitis and peritonitis. Specimen 1-56-72. Reduced to 50%.

FIG. 9. Six per cent to 10 per cent; 15-year-old white male; death due to shotgun wound. Specimen 1-56-126. Reduced to 38%.

FIG. 10. Eleven per cent to 20 per cent; 17-year-old white female; death due to cobra snake bite. Specimen 1-56-59. Reduced to 45%.



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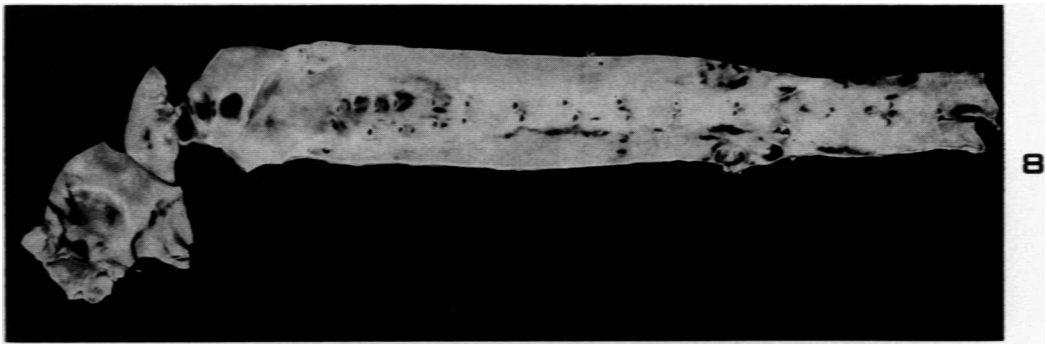

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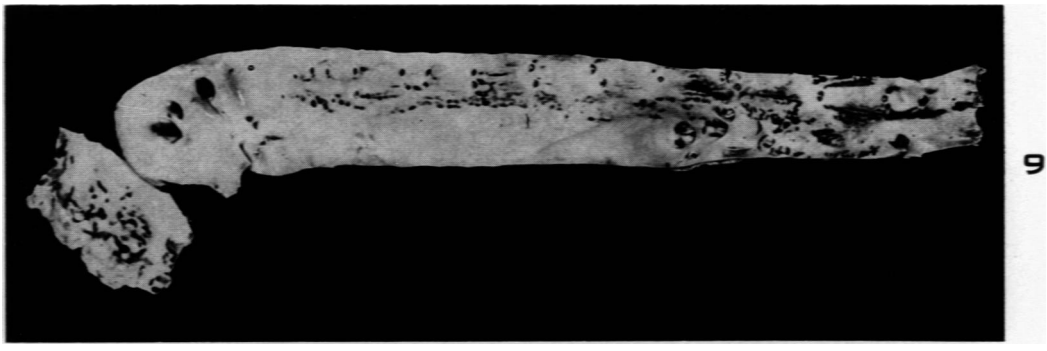

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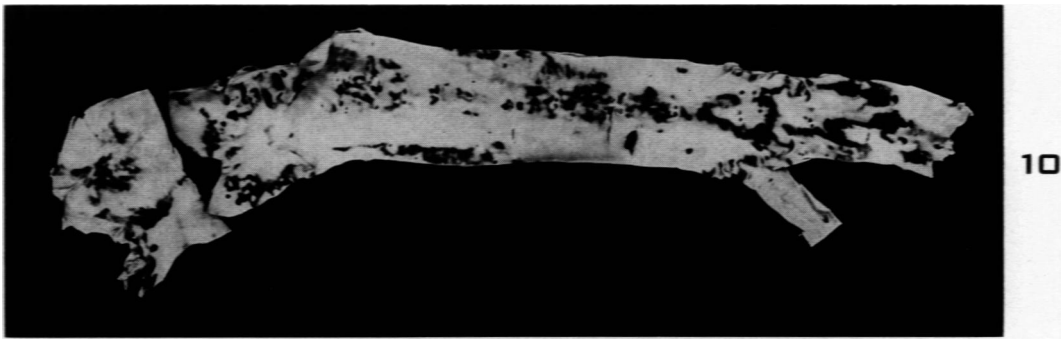

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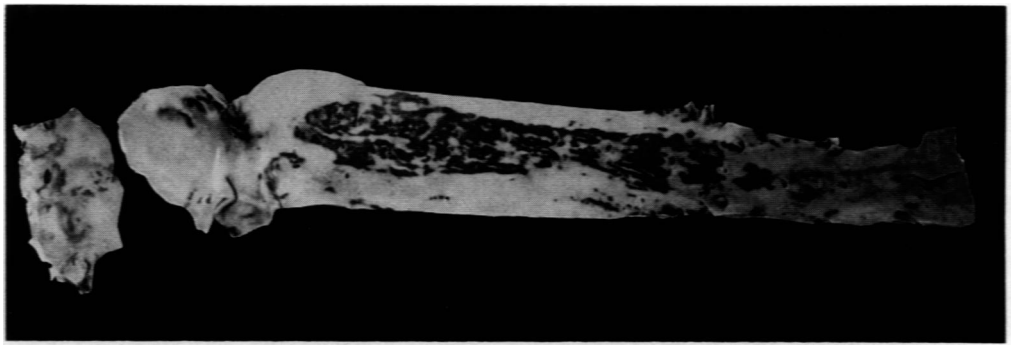
Additional examples of different degrees of involvement of aortic intimal surface by fatty streaks stained with Sudan IV.

FIG. 11. Twenty-one per cent to 30 per cent; 24-year-old Negro male; death due to suicide by hanging. Specimen 1-56-124. Reduced to 38%.

FIG. 12. Thirty-one per cent to 50 per cent; 25-year-old white male; death due to acute bulbar poliomyelitis. Specimen SBH-56-64. Reduced to 38%.

FIG. 13. Fifty-one per cent to 75 per cent; 38-year-old white female; death due to subacute bacterial endocarditis. Specimen 14.048. Reduced to 38%.

FIG. 14. Seventy-six to 100 per cent; 13-year-old Negro male; death due to tetanus. Specimen 0-55-1664. Reduced to 50%.



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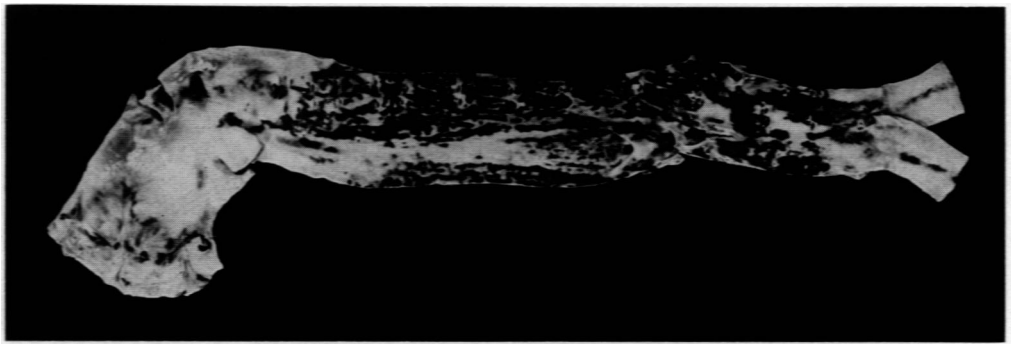

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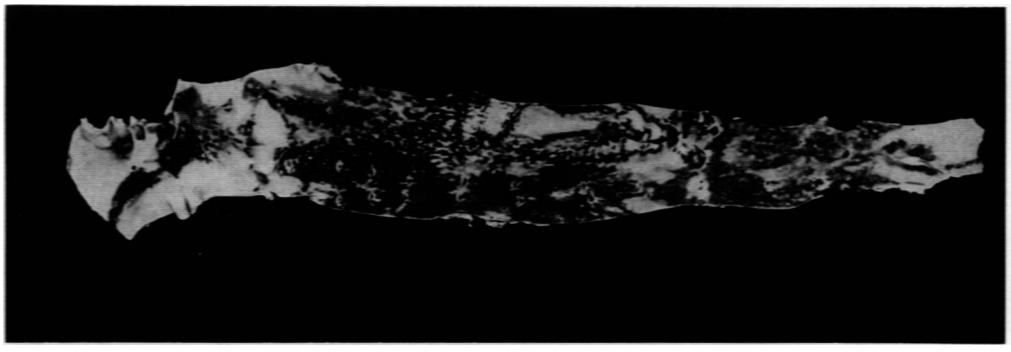

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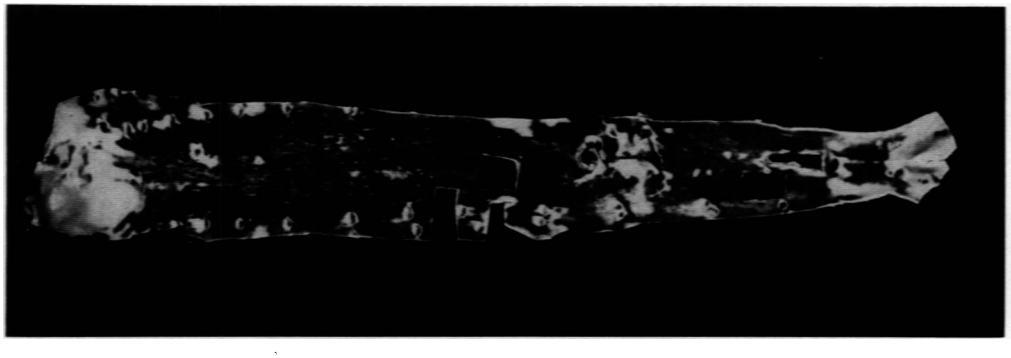

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