RELATION OF SERUM LIPOPROTEIN LEVELS AND SYSTOLIC BLOOD PRESSURE TO EARLY ATHEROSCLEROSIS

The Bogalusa Heart Study

WILLIAM P. NEWMAN III, M.D., DAVID S. FREEDMAN, PH.D., ANTONIE W. VOORS, M.D., DR.P.H.,*
PAUL D. GARD, M.D., SATHANUR R. SRINIVASAN, PH.D., JAMES L. CRESANTA, M.D.,
G. DAVID WILLIAMSON, M.S., LARRY S. WEBBER, PH.D., AND GERALD S. BERENSON, M.D.

Abstract We assessed the relation of risk factors for cardiovascular disease to early atherosclerotic lesions in the aorta and coronary arteries in 35 persons (mean age at death, 18 years). Aortic involvement with fatty streaks was greater in blacks than in whites (37 vs. 17 percent, $P<0.01$). However, aortic fatty streaks were strongly related to antemortem levels of both total and low-density lipoprotein cholesterol ($r = 0.67$, $P<0.0001$ for each association), independently of race, sex, and age, and were inversely correlated with the ratio of high-density lipoprotein cholesterol to low-density plus very-low-density lipoprotein cholesterol ($r = -0.35$, $P = 0.06$). Coronary-artery fatty streaks were correlated with very-low-density lipoprotein cholesterol ($r = 0.41$, $P = 0.04$). Mean systolic blood-pressure levels also tended to be higher in the four subjects with coronary-artery fibrous plaques than in those without them: 112 mm Hg as compared with 104 ($P = 0.09$). These results document the importance of risk-factor levels to early anatomical changes in the aorta and coronary arteries. The progression of fatty streaks to fibrous plaques is uncertain, but these data suggest that a rational approach to the prevention of cardiovascular disease should begin early in life. (N Engl J Med 1986; 314: 138-44.)

ATHEROSCLEROSIS begins early in life. Fatty streaks are seen in the aortas even of three-year-olds[1] and appear in the coronary arteries during the second decade of life.[2] More advanced coronary atherosclerosis was seen in a majority of young adults in whom autopsies were performed during the Korean and Vietnam wars.[3,4] Fibrous plaques are closely related to clinical coronary heart disease,[5] and the extent of raised lesions in the coronary arteries among populations parallels the prevalence of clinical disease.[6] However, the importance of fatty streaks and their transition to more advanced atherosclerotic lesions is less certain.[7-9]

Experimental, epidemiologic, and clinical studies in adults have identified serum lipid, lipoproteins, and blood-pressure levels and smoking as predictive of coronary heart disease. Atherosclerosis and coronary heart disease probably share at least some of the same risk factors, but few autopsy studies have related antemortem risk-factor data to postmortem lesions in adults.[10-15] The relations of previously collected risk-factor measurements to the extent of arterial lesions, measured at postmortem examination, have not yet been documented in children and young adults.

Several epidemiologic studies have described the distributions and interrelations of risk factors and the persistence of elevated blood pressures and blood lipid levels in early life.[16-21] This report examines the relations of risk factors for cardiovascular disease in the young to the extent of fatty streaks and fibrous plaques in persons in whom autopsies were performed. Most important, it relates lesions in both the aorta and the coronary arteries to antecedent risk-factor measurements in a biracial sample of adolescents and young adults.

From the Departments of Pathology, Medicine, Public Health and Preventive Medicine, Biochemistry, and Biometry and Genetics, Louisiana State University Medical Center, New Orleans. Address reprint requests to Dr. Berenson at Louisiana State University Medical Center, 1542 Tulane Ave., New Orleans, LA 70112.

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METHODS

Population

The Bogalusa Heart Study is an epidemiologic study of risk factors for cardiovascular disease from birth through the age of 26 years in a biracial (64 percent white and 36 percent black) population. The risk factors studied included the levels of serum total cholesterol, serum triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and systolic and diastolic blood pressure, as well as obesity and cigarette smoking.

Between 1973 and 1983, four comprehensive cross-sectional surveys, each with a high level of participation,[22] were conducted in Bogalusa, Louisiana (Ward 4 of Washington Parish). (The populations of Ward 4 and Washington Parish are approximately 22,000 and 42,000, respectively.) The first survey was restricted to children 2½ to 14 years of age, and the subsequent three included persons between the ages of 5 and 23 years. Each survey included over 3000 children; to date, data from over 8000 persons have been collected. Risk-factor information has also been obtained during exploratory studies conducted in Franklinton, Louisiana, a nearby community in Washington Parish.

In 1978, a local information system was developed to obtain the family's or coroner's consent to conduct an autopsy on any resident of Washington Parish who died between the ages of 3 and 26 years in Washington or an adjacent parish. Since that time, autopsy specimens have been collected in 88 persons, representing 87 percent of all the known eligible deaths. Autopsies have been conducted in local funeral homes or hospital morgues, and selected tissues (including heart and coronary arteries, aorta, kidneys, adrenals, and blood) have been sent to the Department of Pathology and to the core lipid laboratory of the National Research and Demonstration Center–Arteriosclerosis at Louisiana State University Medical Center.

Of the 88 deaths, 90 percent were the result of accidents, homicides, or suicides; the remainder were related to clinical diseases including renal, neoplastic, and infectious diseases. Thirty-five persons (40 percent of all those in whom autopsies were performed) had previously been examined as part of the Bogalusa Heart Study. Twenty were examined more than once: six were examined twice;

*Deceased.

four, three times; four, four times; and six, five times. The ages at death ranged from 7 to 24 years (mean, 18). The ages at the last risk-factor examination ranged from 3 to 18 years (mean, 14). The longest interval between the last examination and death was 10 years; the shortest, three weeks.

Risk-Factor Data

Procedures for obtaining anthropometric, blood-pressure, and serum lipid and lipoprotein measurements have been reported in detail. Height was measured to the nearest 0.1 cm, weight to the nearest 0.1 kg, and triceps skin-fold thickness to the nearest 1 mm.[23] The ponderal index (weight/height^3) was used as a measure of obesity.[24]

Fasting venous blood was collected and shipped in cold packs to New Orleans. Serum total cholesterol, triglycerides, and lipoprotein cholesterols were measured in a standardized laboratory as previously reported.[25-27] (For several analyses, the high-density lipoprotein ratio was calculated as follows: high-density lipoprotein cholesterol/low-density lipoprotein cholesterol + very-low-density lipoprotein cholesterol.) Blood pressure was measured in the right arm, with the patient in a relaxed sitting position.[28] The average of six measurements with a mercury sphygmomanometer was used in all analyses. A smoking history was obtained by questionnaire from a parent or the subject in the last three risk-factor examinations.[29]

Serum lipid and lipoprotein levels were not measured in two subjects. Two values for triglyceride and very-low-density lipoprotein cholesterol were excluded from the analyses because the children were not fasting at the time of the examination. The smoking habits of nine subjects were unknown; most of these children were examined only in the first risk-factor examination.

Grading Procedures for Lesions

Aortas and coronary arteries were opened longitudinally, Sudan stained, and intermixed with specimens from other research projects. The vessels were then evaluated visually for the extent of intimal-surface involvement with fatty streaks and fibrous plaques by procedures developed in the International Atherosclerosis Project[30] and currently being used by the Department of Pathology. Three pathologists graded all the vessels independently; the mean grade was used. Aortas were available in 32 cases, and coronary arteries in 29. In most of the cases in which specimens were unavailable, the vessel had been destroyed by gunshot or other traumatic cause.

Statistical Analyses

All the analyses included only the 35 subjects with previously measured risk-factor levels. Study-specific and age-specific Z-scores were used to eliminate the effects of age and possible laboratory drift[31,32] on the risk-factor levels. Except in the case of three age groups containing 91, 60, and 48 persons, all Z-score calculations were based on groups of more than 200 persons. The Z-scores were then reconverted into original risk-factor units, with 14-year-old children from the first survey used as a reference population. Except for systolic and diastolic blood pressure, which show the most marked age-related changes, adjustments did not substantially alter the risk-factor values. In addition, since blood pressure in childhood is highly correlated with height,[33] Z-scores based on 5-cm increments of height were also calculated. Both height-adjusted and age-adjusted blood-pressure levels were highly correlated; only the results based on age-adjusted blood-pressure levels are presented.

For the 20 persons with multiple risk-factor measurements, adjusted levels were averaged. These average levels were highly correlated with the levels at both the first and the last examination. In addition, average levels and levels measured at either the first or last examination all showed similar associations with lesions.

Polynomial regression (using age, age^2, and age^3 as independent variables) was also used to adjust risk-factor levels for age.[34] Because values transformed by Z-scores and regression showed similar associations with the lesions, only the Z-score–transformed results are shown. In addition, since the extent of fatty streaks was only weakly associated with the age at death, unadjusted fatty-streak levels are used.

Because the sample sizes were small and the distributions were not normal, nonparametric statistical tests were used in the analyses. Associations between risk-factor levels and lesions were examined with use of Spearman correlations; this nonparametric analysis is based on ranks and is therefore not influenced by outliers. Jonckheere's test[35] was used to examine the increasing trend in the extent of aortic fatty streaks according to the level of low-density lipoprotein cholesterol. (This nonparametric test is more powerful than analysis of variance because it is directed against a prespecified [one-sided] alternative hypothesis.) Stratified analyses were performed to eliminate the effects of race, sex, and age at death. Additional linear-regression analyses, allowing for interaction between the race–sex group and the risk-factor level, confirmed these results. Wilcoxon rank-sum tests[36] were used to examine differences in risk-factor levels between subjects with and without fibrous plaques. Unless otherwise stated, all the statistical tests were two-sided.

Results

Description of Study Population

Table 1 shows the race, sex, and age distribution of the dead persons who had antecedent determination of levels of risk factors. Overall, the mean age at death was 17.9 years; the mean age at death according to race–sex group ranged from 16.4 (black males) to 19.0 years (white males). Sixty-three percent of all the deaths occurred between the ages of 15 and 19 years. Eight persons, six of them white males, smoked cigarettes.

Males were overrepresented in the study population as compared with the reference population, whereas black females, and, to a lesser extent, white females were underrepresented. Table 2 shows mean levels of risk factors in the study and reference populations, after covariance adjustment for race and sex. The autopsy series had slightly lower mean levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and blood pressure, but slightly higher triglyceride and very-low-density lipoprotein cholesterol levels and high-density lipoprotein ratios than did the reference population. Only for systolic blood pressure was the lower mean level in the autopsy series statistically significant ($P = 0.03$).

Intimal-surface involvement with aortic fatty streaks was extensive, ranging from 1 to 61 percent. The one subject having only 1 percent aortic-surface involvement died at the youngest age (seven years). (The aortic ring, the most common site of fatty streaks

Table 1. Race, Sex, and Age Distribution of 35 Patients Examined at Autopsy.

Age at Death	White		Black		Total
	Male	Female	Male	Female	
yr	*number (percent of race–sex group)*				
5–9	0	1 (11)	0	0	1 (3)
10–14	0	2 (22)	1 (14)	0	3 (9)
15–19	11 (65)	3 (33)	6 (86)	2 (100)	22 (63)
20–24	6 (35)	3 (33)	0	0	9 (26)
Total	17	9	7	2	35

Table 2. Comparison for Mean Age-Adjusted Risk-Factor Levels of Autopsy Series and Reference Population.*

Risk Factors†	Autopsy Series (N = 35)	Reference Population (N = 337)
White (%)	74	61
Male (%)	69	55
	mean ±SD‡	
Total cholesterol (mg/dl)	150±33	158±27
Triglycerides (mg/dl)	79±36	74±29
Lipoprotein cholesterol (mg/dl)		
LDL	79±25	85±21
HDL	59±20	63±19
VLDL	11±9	10±7
HDL ratio	0.75±0.32	0.71±0.30
Blood pressure (mm Hg)		
Systolic	104±8§	107±9§
Diastolic	65±6	67±7
Ponderal index (kg/m^3)	12.3±1.6	12.3±2.2

*The reference population consisted of 14-year-olds examined in 1973-1974. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and VLDL very-low-density lipoprotein. The HDL ratio is calculated as HDL-C/(LDL-C + VLDL-C).

†Serum lipid and lipoprotein levels, blood pressure, and ponderal index are adjusted by analysis of covariance for differing race–sex distributions.

‡To convert cholesterol and triglyceride values to millimoles per liter, multiply by 0.026 and 0.011, respectively.

§$P<0.05$.

in the very young,[1] was not included among the standard evaluated segments.) Blacks had approximately twice as much intimal-surface involvement with aortic fatty streaks as did whites (37 vs. 17 percent, $P<0.01$); this racial difference was seen in both sexes and for both the thoracic and abdominal aortas. Although fatty streaks were present in the coronary arteries in all but six cases, these lesions averaged only about 1 percent of the intimal surface, with a maximal surface involvement of 6.2 percent. No racial difference was noted in the extent of coronary-artery fatty streaks.

Fibrous plaques were observed in six males (four whites and two blacks), in no case covering more than 1.5 percent of the intimal surface (Table 3). (No fibrous plaques were seen in any of the nine female subjects.) Two of the three aortic fibrous plaques were in the thoracic aorta, whereas the left anterior descending artery was the most common site of fibrous plaques in the coronary arteries. Analyses showed that aortic fatty streaks were not associated with fatty streaks in the coronary arteries, aortic fibrous plaques, or age at death. However, persons with extensive fatty streaks in the coronary arteries also tended to have coronary-artery fibrous plaques.

Relations between Cardiovascular Disease Risk Factors and Lesions

The associations of fatty streaks with the risk factors are shown in Figure 1. Rankings for total cholesterol and low-density lipoprotein cholesterol were strongly associated with rankings for aortic fatty streaks ($r = 0.67$ for each correlation coefficient). The extent of aortic fatty streaks was not related to triglycerides, high-density lipoprotein cholesterol, systolic blood pressure, or diastolic blood pressure, but tended to be inversely associated with the high-density lipoprotein ratio ($r = -0.35$, $P = 0.06$). Although the associations between risk factors and coronary-artery fatty streaks tended to be weaker, all correlations were in the expected direction. However, only very-low-density lipoprotein cholesterol was significantly associated with these lesions ($r = 0.41$, $P = 0.04$).

Fatty streaks were not related to smoking or obesity. In the aorta, mean surface involvement with fatty streaks was slightly greater for white male nonsmokers than for white male smokers (20 vs. 16 percent). The corresponding mean levels of coronary-artery surface involvement with fatty streaks according to smoking status were 1.0 and 1.5 percent, respectively. There was no relation of the ponderal index, Quetelet index (weight/height^2), or triceps skin-fold thickness to the extent of fatty streaks at either site.

Figure 2 shows the extent of aortic-surface involvement with fatty streaks, according to low-density lipoprotein cholesterol level. The overall trend of increasing mean surface involvement with fatty streaks according to increasing level of low-density lipoprotein cholesterol was impressive ($P = 0.0003$ by a one-sided Jonckheere's test). In the various low-density lipoprotein cholesterol groups, mean surface involvement increased from 10 to 41 percent. Within each such group, the standard deviation of aortic fatty-streak involvement ranged from 6.3 percent (low-density lipoprotein cholesterol, 40 to 60 mg per deciliter [1 to 1.6 mmol per liter]) to 17.9 percent (120 to 140 mg per deciliter [3.1 to 3.6 mmol per liter]).

To eliminate the possible effects of race, sex, and age on the statistically significant associations shown in Figure 1, stratified analyses were performed (Table 4). Although associations of both total cholesterol and low-density lipoprotein cholesterol to the extent of aortic fatty streaks persisted in male subjects of both races, the relations were weaker in white female subjects. Almost no difference in the magnitudes of associations was observed according to age at death. The extent of fatty streaks in the coronary arteries was associated with the level of very-low-density lipoprotein cholesterol in both age groups and in whites. The lack of association in black males may be due to reduced variation in levels of very-low-density lipopro-

Table 3. Characteristics of Six Male Subjects with Fibrous Plaques.

Race	Age at Death (Yr)	% Total Surface Involvement with Fibrous Plaques (Fatty Streaks)*	
		Aorta	Coronary Arteries
Black	11	0.1 (41)	0 (0.5)
White	21	1.5 (27)	0 (0)
Black	17	0 (28)	0.2 (3.4)
White	17	0 (24)	0.3 (6.2)
White	21	0 (28)	0.5 (2.8)
White	23	0.3 (12.8)	1.4 (0.7)

*Values are the percentage surface involvement with fibrous plaques (percentage surface involvement with fatty streaks).

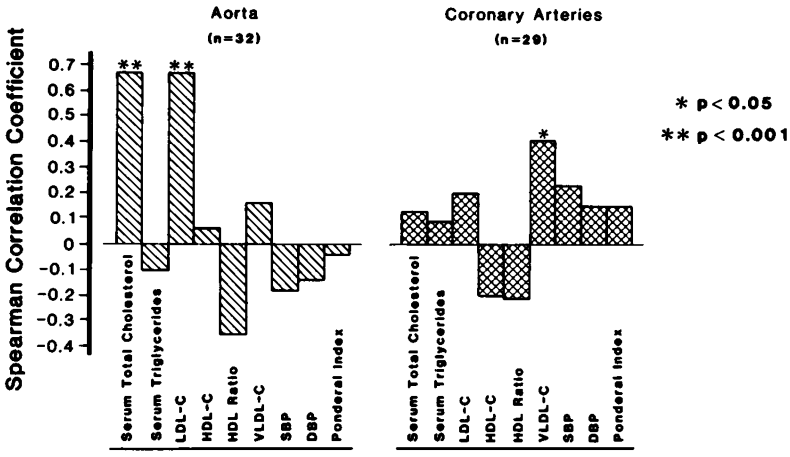

Figure 1. Associations between the Percentage of Fatty-Streak Involvement and Risk-Factor Levels.

Total cholesterol and low-density lipoprotein cholesterol (LDL-C) are related to aortic fatty streaks (r = 0.67 for each correlation); very-low-density lipoprotein cholesterol (VLDL-C) is related to coronary-artery fatty streaks (r = 0.41). HDL-C denotes high-density lipoprotein cholesterol, HDL high-density lipoprotein, SBP systolic blood pressure, and DBP diastolic blood pressure. The HDL ratio is calculated as HDL-C/(LDL-C + VLDL-C).

tein cholesterol: the standard deviation was 6.4 mg per deciliter (0.17 mmol per liter) for white males, but only 3.8 mg per deciliter (0.10 mmol per liter) for black males. Strong associations of coronary-artery fatty streaks with both systolic and diastolic blood pressure were also noted in white males: r = 0.56 and 0.57, respectively; P = 0.02 for each correlation coefficient (data not shown).

The four persons with gross evidence of coronary-artery fibrous plaques tended to be older at death (range, 17 to 23 years; mean, 19.5) than the autopsy series in general, and three were white males. In addition, three males (two whites and one black) had aortic fibrous plaques. Cigarette smoking was not related to the presence of fibrous plaques at either site, and no associations between risk factors and aortic fibrous plaques were observed. However, coronary-artery fibrous plaques tended to be associated with elevated risk-factor levels (Table 5), and the difference in mean systolic blood-pressure levels approached statistical significance (P = 0.09). In addition, when comparisons were restricted to white males, 17 years of age or older at death (to control for the possible confounding effects of race, sex, and age), differences between those with (n = 3) and those without (n = 11) coronary-artery fibrous plaques were significant for systolic blood-pressure levels (115 vs. 102 mm Hg, P = 0.04) and approached significance for triglycerides (115 vs. 71 mg per deciliter [1.3 vs. 0.8 mmol per liter], P = 0.08).

Discussion

Although clinical cardiovascular events attract the most attention from the public and practicing physicians, it is important to understand the development of atherosclerosis in early life. Studies of the natural history of human atherosclerosis support the longitudinal development of lesions in adults.[37] However, considerably less is known about the progression of early lesions to more advanced fibrous plaques. This study was undertaken to evaluate the relation of antemortem risk factors for cardiovascular disease to the atherosclerotic lesions commonly seen in adolescents and young adults.

The results show that risk factors for cardiovascular disease are related to even the earliest stages of grossly visible atherosclerotic lesions in the young. The extent of aortic fatty streaks is very strongly related to the levels of both total cholesterol and low-density lipoprotein cholesterol, and tends to be inversely associated with the high-density lipoprotein cholesterol ratio. Fatty streaks in the coronary arteries are significantly related to antemortem levels of very-low-density lipoprotein cholesterol and tend to be associated with levels of serum lipids, other lipoprotein cholesterols, and blood pressure. (The low prevalence of fatty streaks in the coronary arteries may explain their weaker associations with the risk factors.) Grossly discernible fibrous plaques in the coronary arteries, which may progress to obstructive disease, tend to be associated with elevated levels of both triglyceride and systolic blood pressure. The associations are independent of race, sex, and age. Obesity is related neither to fatty streaks nor raised lesions, in agreement with the results of the International Atherosclerosis Project.[38]

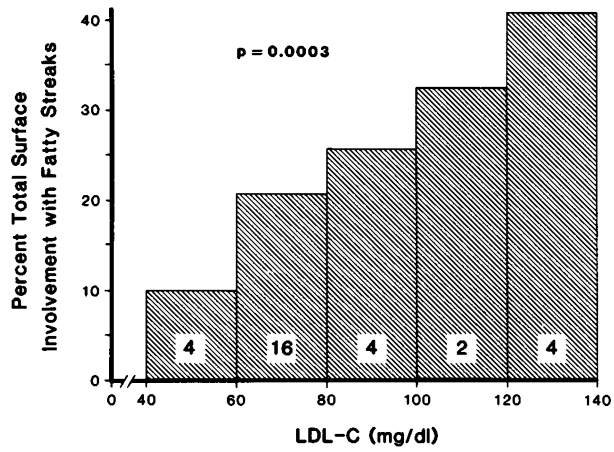

Figure 2. Atherosclerotic Fatty-Streak Involvement of the Aorta Related to Levels of Low-Density Lipoprotein Cholesterol (LDL-C) in 30 Young Persons.

Increasing LDL-C levels are significantly related to increasing amounts of aortic fatty streaks. To convert values for cholesterol to millimoles per liter, multiply by 0.026.

Table 4. Associations between the Percentage of Total Surface Involvement with Fatty Streaks and Selected Cholesterol-Related Risk Factors, According to Race–Sex Group and Age at Death.*

CHOLESTEROL	AORTA					CORONARY ARTERIES				
	WHITE MALES (N = 15)	WHITE FEMALES (N = 6)	BLACK MALES (N = 7)	AGE AT DEATH (YR)		WHITE MALES (N = 15)	WHITE FEMALES (N = 5)	BLACK MALES (N = 6)	AGE AT DEATH (YR)	
				<18 (n = 11)	*≥18 (n = 19)*				*<18 (n = 9)*	*≥18 (n = 18)*
Total	0.66†	0.31	0.41	0.78†	0.61†	0.10	0.87	0.14	0.11	0.10
Low-density lipoprotein	0.55‡	0.31	0.79‡	0.71‡	0.57†	0.14	0.87	−0.14	0.16	0.23
Very-low-density lipoprotein	0.03	0.40	0.04	0.57	−0.09	0.57‡	0.80	0.03	0.57	0.41

*Black females have been omitted (n = 2). †P<0.01. ‡P<0.05.

The results also show more extensive aortic-surface involvement with fatty streaks in blacks than in whites — a finding consistent with earlier reports.[1,8,39] McGill[8] found that up to age 19, blacks from New Orleans had approximately two to three times as much aortic-surface involvement with fatty streaks as did whites. Thus, although black children have elevated values for high-density lipoprotein cholesterol,[27,40] they may be especially susceptible to arterial lipid deposition without the later formation of fibrous plaques.[6] Future studies should examine the hypothesis that racial differences in risk-factor levels could account for the different extents of aortic fatty streaks; levels of low-density lipoprotein cholesterol and blood pressure may be the most important factors in the early development of atherosclerotic lesions.[41-43]

Several studies have evaluated the relation of fatty streaks to more advanced atherosclerotic lesions. In the International Atherosclerosis Project, the axial location of fatty streaks in the coronary arteries was very similar to that of raised lesions,[44] and the mean extent of coronary-artery fatty streaks in young persons was related to the extent of raised lesions in middle-aged persons from the same population.[8] In addition, intimal thickening of the proximal portion of the left anterior descending coronary artery occurs early in life and is followed by monocyte and macrophage infiltration.[45] Therefore, most investigators accept the idea that coronary atherosclerosis begins in childhood.[9] (In the current study, fibrous plaques were found in 33 percent of the 88 subjects with fatty streaks in their coronary arteries.) However, evidence of fatty-streak progression to fibrous plaques in the aorta is not as convincing.[46] Anatomical, racial, and sex differences in the extent of aortic fatty streaks are the opposite of those observed for aortic fibrous plaques in adults,[9] and in a group, the extent of fatty streaks in youth does not predict the extent of raised lesions in later life.[8] However, over a greater range of surface involvement, as seen among individuals rather than populations, aortic fatty streaks may be related to more advanced lesions. In support of this view, endothelial denudation and fatty streaks precede the appearance, at similar anatomical sites, of fibrous plaques in the nonhuman primate *Macaca nemestrina*.[47]

The observed associations of risk factors for cardiovascular disease in childhood and adolescence with early atherosclerotic lesions extend the findings of studies of adults in Honolulu,[10] Framingham,[11] Sweden,[12] Oslo,[13] Puerto Rico,[14] and Japan.[15] In these adult autopsy studies, elevated total cholesterol and systolic blood pressure (but not triglyceride) levels

Table 5. Age-Adjusted Levels of Risk Factors According to the Presence or Absence of Fibrous Plaques in the Coronary Arteries.

RISK FACTOR*	CORONARY-ARTERY FIBROUS PLAQUES†		P VALUE‡
	ABSENT (N = 25)	PRESENT (N = 4)	
Total cholesterol (mg/dl)	146±32‡ (91–210)	151±27 (113–174)	0.66
Triglycerides (mg/dl)	70±28 (43–170)	97±37 (45–131)	0.25
Lipoprotein cholesterol (mg/dl)			
LDL	78±24 (48–133)	85±25 (57–112)	0.66
HDL	59±21 (21–127)	52±20 (33–78)	0.57
VLDL	9±6 (2–26)	14±10 (3–27)	0.25
HDL ratio	0.76±0.32 (0.2–1.6)	0.62±0.34 (0.3–0.9)	0.66
Blood pressure (mm Hg)			
Systolic	104±7 (95–124)	112±8 (103–121)	0.09
Diastolic	66±6 (58–82)	64±9 (50–71)	0.73
Ponderal index (kg/m^3)	12.4±1.7 (9.4–17.0)	12.0±2.0 (10.0–14.5)	0.73

*LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and VLDL very-low-density lipoprotein. The HDL ratio is calculated as HDL-C/(LDL-C + VLDL-C).

†Values are means ±SD; minimal and maximal values are given in parentheses. To convert values for cholesterol and triglycerides to millimoles per liter, multiply by 0.026 and 0.011, respectively.

‡Based on two-sided Wilcoxon tests.

have been found, with few exceptions, to be related to the presence of advanced atherosclerotic lesions.[48] In the Oslo Heart Study,[13] the only study measuring levels of high-density lipoprotein cholesterol, an inverse relation was found between the presence of advanced coronary-artery lesions and the high-density lipoprotein ratio ($r = -0.35$). In some but not all of these studies in adults, cigarette smoking has been found to be related to the presence of raised lesions. Although cigarette smoking may not influence the development of atherosclerosis, the lack of association in the current study may be due to some persons classified as nonsmokers having started smoking before death, or a tendency of adolescent smokers to smoke less heavily than adults.

Although other lipoprotein cholesterols were not measured in the adult autopsy studies, the very strong relation of childhood levels of low-density lipoprotein cholesterol to aortic fatty streaks was of particular interest in the current study. Apolipoprotein B, the chief protein component of low-density lipoprotein, and intact complexes of low-density lipoproteins with sulfated glycosaminoglycans have been found in lesions from both humans[41] and nonhuman primates.[42] Further studies are needed to verify the importance of other risk factors for cardiovascular disease, such as the levels of very-low-density lipoprotein cholesterol and triglycerides, the high-density lipoprotein ratio, and systolic blood pressure, in the development during childhood of fatty streaks and fibrous plaques in both the aorta and coronary arteries.

The results of this community-based study show the importance of cardiovascular risk factors to the earliest grossly discernible lesions of atherosclerosis in childhood and adolescence. Documentation of these anatomical substrates is necessary for an understanding of the early natural history of atherosclerosis. Furthermore, the correlation of clinically measurable risk-factor levels with anatomical changes in early life can help to define abnormal risk-factor levels in childhood and adolescence. This understanding will result in a more rational approach to the prevention of cardiovascular disease.

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VIDARABINE VERSUS ACYCLOVIR THERAPY IN HERPES SIMPLEX ENCEPHALITIS

RICHARD J. WHITLEY, M.D., CHARLES A. ALFORD, M.D., MARTIN S. HIRSCH, M.D., ROBERT T. SCHOOLEY, M.D., JAMES P. LUBY, M.D., FRED Y. AOKI, M.D., DANIEL HANLEY, M.D., ANDRE J. NAHMIAS, M.D., SENG-JAW SOONG, P.D., AND THE NIAID COLLABORATIVE ANTIVIRAL STUDY GROUP*

Abstract We randomly assigned 208 patients who underwent brain biopsy for presumptive herpes simplex encephalitis to receive either vidarabine (15 mg per kilogram of body weight per day) or acyclovir (30 mg per kilogram per day) for 10 days. Sixty-nine patients (33 percent) had biopsy-proved disease; 37 received vidarabine, and 32 acyclovir. The mortality in the vidarabine recipients was 54 percent, as compared with 28 percent in the acyclovir recipients (P = 0.008). Six-month mortality varied according to the Glasgow coma score at the onset of therapy. For scores of >10, 7 to 10, and ≤6, mortality was 42, 46, and 67 percent in the patients treated with vidarabine, as compared with 0, 25, and 25 percent in those treated with acyclovir. A six-month morbidity assessment using an adapted scoring system revealed that 5 of 37 patients receiving vidarabine (14 percent) as compared with 12 of 32 receiving acyclovir (38 percent) were functioning normally (P = 0.021). Eight vidarabine-treated patients (22 percent) and three acyclovir-treated patients (9 percent) had moderate debility. Patients under 30 years of age and with a Glasgow coma score above 10 had the best outcome with acyclovir treatment. We conclude that acyclovir is currently the treatment of choice for biopsy-proved herpes simplex encephalitis. (N Engl J Med 1986; 314:144-9.)

IN 1977, the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group demonstrated that mortality from biopsy-proved herpes simplex encephalitis was decreased significantly six months after treatment with vidarabine (adenine arabinoside) — from 70 percent in placebo recipients to 44 percent in drug recipients.[1] A subsequent study verified an improved mortality of 39 percent and revealed a return to normal function in nearly one third of the treated patients.[2] Age and the level of consciousness at the time of therapy initiation had the greatest influence on outcome. A return to normal function occurred most frequently in young patients (<30 years of age) who had been lethargic

From the Departments of Pediatrics, Microbiology, and Biostatistics, University of Alabama at Birmingham; the Department of Medicine, Massachusetts General Hospital, Boston; the Department of Medicine, University of Texas Health Science Center at Dallas–Southwestern; the Department of Medicine, University of Manitoba, Winnipeg, Manitoba; the Department of Neurology, Johns Hopkins University, Baltimore; and the Department of Pediatrics, Emory University, Atlanta.

Address reprint requests to Dr. Whitley at the Department of Pediatrics, Suite 653, Children's Hospital Tower, 1600 Seventh Ave. S., University of Alabama at Birmingham, Birmingham, AL 35294.

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*The members of the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group were M. Myers (project officer), NIAID, National Institutes of Health; R. Whitley, C. Alford, S. Soong, G. Caddell, C.G. Cobbs, J. Gnann, R. Morawetz, J.W. Benton, O. Snead, Central Unit, University of Alabama at Birmingham; M.S. Hirsch, R.T. Schooley, Massachusetts General Hospital, Boston; R. Dolin, R. Betts, R. Reichman, University of Rochester; L. Corey, University of Washington; F. Aoki, G.W. Hammond, University of Manitoba, Winnipeg; M. Levin, R. Andersen, University of Colorado; A. Nahmias, H. Keyserling, S. Schwartzmann, Emory University, Atlanta; J. Wolinsky, University of Texas–Houston; D. Hanley, The Johns Hopkins University; J. Connor, S. Spector, M. Oxman, D. Richman, University of California, San Diego; F. Hayden, J. Greenlee, University of Virginia; S. Greenberg, L. Taber, Baylor University, Houston; J. Luby, University of Texas Health Science Center at Dallas–Southwestern Medical School; M. Myers, C. Linnemann, University of Cincinnati; D. Powell, Ohio State University, Columbus; D. Durak, Duke University; R. Pollard, University of Texas,