ADOLESCENCE AND THE ONSET OF ATHEROSCLEROSIS*

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INTRODUCTION

THE chief interest in atherosclerotic vascular disease has traditionally focused on males in their forties, fifties, and older—the time of life when thrombotic coronary and cerebrovascular complications become serious medical and public health problems. Yet recent autopsy studies[1, 2] have shown that atherosclerosis, at least among American males, has its onset in the second decade of life—about 20 to 25 years before the rapidly increasing frequency of clinical sequelae. By the age of 20 disease of the artery wall among American males is surprisingly advanced, already differentiating our population from others in which mid-life atherosclerosis and clinical complications are infrequent or unknown.

Countless epidemiologic studies have repeatedly associated several environmentally determined factors with atherosclerosis and its superimposed clinical phenomena. The importance of these associations has been strengthened by their consistency with our present knowledge of the induction of atherosclerosis in laboratory animals, including subhuman primates. Many of these factors are traceable in onset to the first and second decades of life.

Some years ago, Schilling[3] collected and summarized a vast array of cross-sectional data on blood cholesterol at various ages and in various world populations. Among American males a marked age-related increase in the concentration of this lipid begins in the late second decade of life. At this period, average levels diverge from the stable or slightly

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rising values found in many other populations;[3-5] by age 40 to 50, virtually every adult American male is hypercholesterolemic by worldwide norms.

The second decade of life also marks the onset of habits and practices which affect the regulation of blood lipids and which in other ways may influence the course of atherosclerosis: dietary habits, in terms of type and amount of fats as well as the over-all level of calories consumed; habits of expenditure of energy; and cigarette smoking.

It has proved next to impossible to separate out the independent effects of these factors (which in themselves may be interrelated); other factors too, such as blood pressure and disordered carbohydrate metabolism, have been associated with thrombotic vascular disease. Nonetheless more and more attention has been turned to the idea of preventing this disease through favorable alteration of environmentally determined risk factors. Impetus has been provided as much by appreciation of the universality, the gloomy clinical course, and the impotence of current medical management of these diseases as it has been by recent demonstrations that many risk factors *can* be altered practically and on a large scale.

But a better understanding of the relatively long course of time in the progression of underlying atherosclerosis and of the uncertainties in influencing the lesion at a time of life when fibrosis and calcification are setting in must ultimately lead to the paying of more attention to regulation of risk factors not in middle or old age but in the teens or twenties.

In order to attempt a better understanding of dietary habits, blood cholesterol, and balance of energy throughout adolescence we set out several years ago to study a group of high school students in our area, some of whom were followed into college.

Materials and Methods

A total of 1,236 boys aged 12.0 through 17.9 years of age volunteered, with parental permission, to enter these studies. One hundred and seventy-eight were recruited from a private day school located in the Boston area, 393 from a Boston public high school, and 665 from a Boston parochial high school. These numbers represented 95, 70, and 50% respectively of the populations of the specified age range enrolled in these schools. Information on ethnic background, except for the observation that more than 98% were Caucasian, was not known. Annual examinations were carried out during the 1965-1966 academic year,

and for three subsequent years; all boys who were willing to participate were included, and these follow-up examinations were performed within one month of the date of the initial encounter. After the second round of examinations, boys still remaining in the parochial school were not resurveyed in order to direct attention to the time-consuming task of contacting and examining those boys from all three schools who had graduated and were attending college in the Boston area.

Age on the date of the first examination was calculated to the nearest tenth of a year and, for purposes of analyses, boys were kept in their initial cohort, since the examinations were performed at 12 monthly intervals.

At each annual examination measurements were made of height without shoes (to the nearest 0.1 cm.), stripped weight (to the nearest 0.1 kg.), and of triceps and subscapular skinfold thickness (to the nearest 1 mm. with Lange calipers). Sexual maturation was assessed according to the method of Greulich;[13] this one-to-five scale for rating maturity is based on growth of genitalia and of pubic, axillary, and facial hair. For the first three years of the study, these measurements were all made by a single observer, a trained graduate student in physical anthropology. On the fourth year of the survey they were made by myself. Free-flowing capillary blood, from either the lobe of an ear or puncture of a finger, was collected in heparinized hematocrit tubes and the total cholesterol was measured in the plasma.[6]

In order to assess current dietary habits a self-administered screening questionnaire was developed for use in surveying small groups of boys 10 to 15 in number, in which a nutritionist* explained, supervised, and checked each form. These forms were obtained on every boy in the initial year of the study. Analysis of this questionnaire was directed largely at making estimates of the sources, type, and quantity of dietary fats. More detailed research dietary interviews were completed on 182 boys during the first two years of the investigation. Both types of dietary data were augmented by a home questionnaire directed at information on the types of fats used in the home. Coding and computer analyses of nutrient intakes were done by the same schemes developed for the National Diet-Heart Study.[7]

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Results and Discussion

Cross-sectional. Anthropometric measurements as recorded at the initial examination are shown in Table I. Within each age group, there were no significant differences in any of these characteristics among the three schools. In comparison to currently used American standards[8] mean heights are about 1 cm. greater and mean weights greater by about 3 kg. at age 12, to 7 kg. by age 17. The trends in both triceps and subscapular skinfold thickness from age 12 to 14 reflect the marked "thinning out" associated with the rapidly changing maturity rating and the concomitant burst of linear growth. At the completion of sexual maturity, by age 15 to 16, increasing skinfold measurement reflects the adipose component of the weight gain which will continue on into adult life. Using Seltzer's published criteria[9] of obesity in males over this age range, its prevalence rises from 9.2% at age 15 to 17.4% by age 18.

Since there were significant differences in the mean levels of plasma cholesterol at various age groups among the three schools, these values are separated by school in Table II. Within each school there can be noted a tendency of this lipid to be lowest at the termination of sexual maturation, higher both before and afterwards. In order to assess possible seasonal influences on plasma cholesterol, blood samples in 107 15-year-old boys from the public and parochial schools were measured in November, in January, and in April (the period over which almost all examinations were carried out). Mean and standard deviations were respectively 166.7 ± 29.0, 169.3 ± 33.1, and 168.1 ± 31.2 mg. %. While possibly reflecting either seasonal or secular trends, these differences are not large enough to account for differences between schools.

Nutrient data derived from the screening questionnaire are presented in Table III, and from the research interviews in Tables IV and VI. There were no statistically significant differences among the three schools in terms of any of the computed nutrients. The great increase in the intake of mean daily calories from age 12 to 14 is a dramatic reflection of the needs to support growth as well as the relatively greater energy expenditure at this time of life.

Whether estimated by questionnaire or detailed interview, the percentage of calories contributed by total, saturated, and polyunsaturated fat are similar over the entire age range. In comparison with counterpart estimates on intakes of middle-aged men[7, 10] the percentage of fat calories is higher (42 to 45 versus 40%), the percentage of saturated fat calories

TABLE I. ANTHROPOMETRIC CHARACTERISTICS AT INITIAL EXAMINATION

	Age groups					
Measurement	*12.0-12.9*	*13.0-13.9*	*14.0-14.9*	*15.0-15.9*	*16.0-16.9*	*17.0-17.9*
Number	*72*	*100*	*388*	*321*	*198*	*157*
Height, cm.	153.4* ± 8.6	162.3 ± 7.2	167.0 ± 8.1	171.9 ± 7.2	175.0 ± 6.1	175.9 ± 6.3
Weight, kg.	46.8 ± 9.6	53.8 ± 10.4	58.3 ± 10.9	64.3 ± 10.5	66.9 ± 8.9	71.8 ± 11.5
Triceps, mm.	15.5 ± 7.4	11.5 ± 5.7	10.7 ± 4.7	9.9 ± 4.2	9.2 ± 4.4	10.1 ± 5.4
Subscapular, mm.	9.7 ± 7.7	7.7 ± 4.8	7.6 ± 3.8	7.9 ± 3.6	8.2 ± 3.4	9.4 ± 5.1
Maturity rating	2.3 ±0.92	3.4 ± 0.91	4.2 ± 0.86	4.7 ± 0.41	4.9 ± 0.08	5.0 ± 0.02

*Mean ± S.D.

TABLE II. PLASMA CHOLESTEROL AT INITIAL EXAMINATION

	Age groups					
	12.0-12.9	*13.0-13.9*	*14.0-14.9*	*15.0-15.9*	*16.0-16.9*	*17.0-17.9*
Private	187.5* ± 36.5 (31)†	178.9 ± 34.8 (37)	166.4 ± 28.0 (29)	176.6 ± 30.3 (29)	185.7 ± 32.9 (28)	194.3 ± 31.7 (24)
Public	165.4 ± 29.2 (31)		163.7 ± 30.2 (119)	162.1 ± 28.5 (109)	169.8 ±32.1 (48)	174.7 ± 31.8 (51)
Parochial		172.9 ± 30.0 (55)	168.9 ± 31.3 (232)	169.1 ± 29.7 (147)	175.6 ± 33.4 (107)	178.0 ± 32.2 (63)

*Mean ± Standard Deviation, mg. per 100 ml.
†Sample size.

TABLE III. DAILY INTAKE OF SPECIFIED NUTRIENTS, MEAN AND STANDARD DEVIATION*

			Total fat		*Saturated fat*		*Polyunsaturated fatty acids*			
Age group	*Number*	*Total calories*	*(gm.)*	*Total calories (%)*	*(gm.)*	*Total calories (%)*	*(gm.)*	*Total calories (%)*	*P/S ratio*	*Cholesterol (mg.)*
12.0-12.9	72	3280 ± 770	153 ± 39.8	42.0	67 ± 19.1	18.4	7.2 ± 3.2	2.0	.11	517 ± 155
13.0-13.9	100	3549 ± 823	173 ± 50.2	43.9	75 ± 21.0	19.0	11.9 ± 5.1	3.0	.16	659 ± 144
14.0-14.9	388	3770 ± 832	183 ± 53.8	43.7	79 ± 25.5	18.9	13.4 ± 4.8	3.2	.17	674 ± 170
15.0-15.9	321	3744 ± 821	178 ± 51.7	42.8	76 ± 22.7	18.3	13.0 ± 5.3	3.1	.17	648 ± 163
16.0-16.9	198	3761 ± 855	183 ± 50.9	43.8	78 ± 22.4	18.7	12.9 ± 5.0	3.1	.17	656 ± 155
17.0-17.9	157	3818 ± 843	186 ± 56.0	43.8	79 ± 23.8	18.6	14.0 ± 5.8	3.3	.18	680 ± 157

*Screening questionnaire.

TABLE IV. DAILY INTAKE OF SPECIFIED NUTRIENTS, MEAN AND STANDARD DEVIATION*

			Total fat		*Saturated fat*		*Polyunsaturated fatty acids*			
Age group	*Number*	*Total calories*	*(gm.)*	*Total calories %*	*(gm.)*	*Total calories %*	*(gm.)*	*Total calories %*	*P/S ratio*	*Cholesterol (mg.)*
14.0-14.9	36	3491 ± 768	175 ± 43.7	45.2	73.3 ± 19.2	18.9	15.2 ± 5.5	3.9	.21	578 ± 139
15.0-15.9	56	3641 ± 772	172 ± 40.5	42.4	70.3 ± 17.0	17.4	13.9 ± 4.9	3.4	.20	600 ± 115
16.0-16.9	43	3529 ± 741	174 ± 41.8	44.4	74.7 ± 17.9	19.0	11.3 ± 4.1	2.9	.15	603 ± 133
17.0-17.9	47	3908 ± 832	189 ± 44.8	43.5	79.4 ± 19.2	18.3	13.1 ± 4.7	3.0	.16	646 ± 129

*Research interview.

TABLE V. PER CENT CONTRIBUTIONS OF MAJOR FAT-CONTAINING FOOD GROUPS IN BOYS 14.0 TO 17.9 YEARS OLD

	Total fat		*Saturated fat*	
Meats and poultry	27.1	(31.8)*	30.4	(34.1)*
Dairy foods (except butter)	28.5	(18.0)	33.9	(25.1)
Baked goods and candy	11.3	(14.7)	8.1	(11.7)
Fats and oils (including butter)	12.1	(11.0)	12.6	(12.1)
All others	21.0	(24.5)	15.0	(17.0)

*Comparable percentages, *National Diet- Heart Study*.[7]

is higher (18 to 19 versus 15 to 16%), and the percentage of polyunsaturated fat calories is slightly lower. Dietary intake of cholesterol among middle-aged men is estimated at 533 mg. per day, about 100 mg. less than in these boys. Thus, in light of our knowledge of the regulation of plasma cholesterol in adults, these diets must be judged even more atherogenic than diets of typical adult American males.

In Table V, the major sources of total and saturated fat from groups of food are compared in adolescent boys and middle-aged men. It appears that the adolescents' reliance on dairy products is the most remarkable difference in patterns of eating between these age groups.

Estimates of the intake of protein and various micronutrients (Table VI) must be judged adequate in comparison with current recommended dietary allowances.[11] On the other hand, calculation of micronutrient intake on a "per calorie" basis, as shown in Table VI, shows that these boys are not achieving high calorie intakes by merely consuming more of all the usual foods consumed by adults. Except for calcium (from dairy products), the nutritional quality of adolescent diets is diluted out by snack and high-fat items and the micronutrient per calorie intakes are lower than in adults.

As stated above, comparison of dietary intakes at specific age groups among the three schools showed that there were no statistically significant differences among the schools in regard to type or amount of dietary fats. Nonetheless, at each age group the estimated percentage of calories from both total and saturated fat was 5 to 10% higher among the private school boys than among the other two groups, a trend at least consistent with the generally higher levels of plasma cholesterol in that school.

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TABLE VI. DAILY INTAKE OF SPECIFIED NUTRIENTS, MEAN AND STANDARD DEVIATION*

Age group	*Number*	*Protein (gm.)*	*Calcium (mg.)*	*Iron (mg.)*	*Vitamin A (I.U.)*	*Thiamine (mg.)*	*Riboflavin (mg.)*	*Niacin (mg.)*	*Ascorbic acid (mg.)*
14.0-14.9	36	133 ± 30.0	1580 ± 569	16.2 ± 4.7	8264 ± 5801	1.37 ± .44	2.35 ± .78	21.6 ± 6.3	106 ± 70
15.0-15.9	56	138 ± 30.4	1675 ± 606	16.5 ± 4.8	8700 ± 6438	1.53 ± .39	2.50 ± .85	21.4 ± 6.1	100 ± 72
16.0-16.9	43	146 ± 31.0	1670 ± 603	16.7 ± 4.9	8700 ± 6212	1.51 ± .41	2.39 ± .77	21.5 ± 6.1	97 ± 68
17.0-17.9	47	155 ± 34.3	1685 ± 615	16.8 ± 4.8	8794 ± 6370	1.57 ± .42	2.54 ± .76	21.4 ± 5.7	103 ± 66

*Research interview.

TABLE VII. INTAKE OF SELECTED NUTRIENTS PER 1,000 CALORIES

Nutrient	*15-yr.-old boys*	*45 to 54-yr.-old men*	*Ratio boys/men*
Calcium, mg.	459	320	1.43
Iron, mg.	4.54	5.34	0.85
Vitamin A, I.U.	2392	2627	0 91
Thiamine, mg.	0.42	0.47	0.89
Riboflavin, mg.	0.69	0.74	0.93
Niacin, mg.	5.88	6.98	0.84
Ascorbic acid, mg.	27.50	34.71	0.79

TABLE VIII. PAIRED CHANGES IN PLASMA CHOLESTEROL AFTER SPECIFIED INTERVALS

Initial age	*No.**	*One year*	*No.*	*Two years*	*No.*	*Three years*
12.0-12.9	52	+0.38† ± 3.22	47	+4.29 ± 2.96	45	+ 7.97 ± 3.13‡
13.0-13.9	52	+3.41 ± 3.08	30	+4.60 ± 4.07	29	+11.12 ± 3.72‡
14.0-14.9	248	+4.90 ± 1.32‡	112	+8.97 ± 1.87‡	101	+12.51 ± 1.83‡
15.0-15.9	202	+6.68 ± 1.33‡	109	+9.28 ± 1.72‡		
16.0-16.9	128	+3.59 ± 1.92	93§	+7.81 ± 3.10‡		
17.0-17.9	97§	+5.80 ± 1.83‡	92§	+9.98 ± 2.50‡		

*Number of pairs.
†Mean change ± standard error, mg./100 ml.
‡Significant at $p > 0.05$.
§Most of these boys were in college.

Correlation analysis by specific age groups showed that the variability in the level of plasma cholesterol was also not accounted for by type or quantity of dietary fats. That is, boys in the top quartile of the serum cholesterol distribution did not eat differently from boys in the lowest quartile. Intakes of specific nutrients, at least as best we can measure these, do not account for variability among individuals in homogeneous population groups. Precisely the same thing has been reported from descriptive studies on adults. [5, 12]

Neither height nor weight achieved statistically significant association with plasma cholesterol in age group-specific correlations. On the other hand, both triceps and subscapular skinfold thickness were related with plasma cholesterol at the $p < 0.05$ level of confidence in each age group;

but even here, significant correlation coefficients, on the order of r = 0.20 to 0.30, in fact account for only 5 to 9% of the variance in plasma cholesterol. Again, this is similar to the situation in adult males.[7]

Longitudinal. The interval changes, classified by age group at the time of the initial examination and calculated on the basis of paired values, are shown in Table VIII. These mean changes represent pooled data from boys in all three schools in each age group. This was done because, even though the initial, baseline mean levels were not the same, paired interval changes were not significantly different by school, nor could interval changes be related to initial levels. Thus individuals at the upper end of the cholesterol frequency distribution at the first examination remained in the upper end of the new (and rising) distribution one, two, or three years later; the same was true for boys with low levels. Except for the initially youngest age group (12.0 to 12.9 years) mean annual increments range from 2 to 5 mg. % per year, a rate of increase which apparently continues throughout the third decade of life.[3] When measured serially in groups of this size, increments of this magnitude reached a high degree of statistical confidence after two or three years of follow-up.

Conclusion

Thus it appears that environmentally-determined forces strongly associated with atherosclerotic vascular disease in middle life begin to operate during adolescence. Both duration as well as intensity of exposure to these forces must be responsible for the net accumulation of atherosclerosis in middle-aged American males. If prevention is ever to achieve its maximal benefit, attention must be turned to much younger groups.

Further, both qualitative and quantitative aspects of diets as well as the level of energy expenditure may be more easily manipulated at a time of life when habit patterns are still being established and may thus be more amenable to practical alteration.

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