

*Serum cholesterol levels of 1,938 men and 2,306 women in Metropolitan New York City were determined and interpreted in relation to sex, age, and weight. The means of serum cholesterol were studied in relation to the pathogenesis of coronary heart disease. A concept of rate of increase and cumulation of serum cholesterol is proposed and applied to some observed epidemiologic aspects of coronary heart disease.*

## **STUDIES OF SERUM CHOLESTEROL IN 4,244 MEN AND WOMEN: AN EPIDEMIOLOGICAL AND PATHOGENETIC INTERPRETATION**

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IN 1937 Sperry<sup>1</sup> stated, "the use of the term normal concentration of total cholesterol in the serum in the customary general sense is without definite meaning." This has been borne out by reports from many parts of the world demonstrating that serum cholesterol levels may vary in relation to sex, race, diet, nationality, and so forth. It is, therefore, understandable that the physician is in a state of confusion when appraising the serum cholesterol of his individual patient.

Though the literature was surveyed<sup>2-26</sup> in order to summarize studies reporting serum cholesterol level according to age and sex, few series tabulated their results in a manner permitting valid comparisons. It is apparent that the reporting of serum cholesterol by different age ranges and the lack of standardizations among methods of determining serum cholesterol concentrations are serious interpretive limitations. Tables 1 A-B-C represent a composite of the significant series reviewed.

The Framingham Study<sup>27,51</sup> indicates that the development of coronary heart

disease is associated with obesity, hypertension, LVH, and hypercholesterolemia. Well documented standards exist for the evaluation of obesity, hypertension, and electrocardiographic abnormalities. However, there is an impressive lack of available data of serum cholesterol values reported by sex and specific age, especially from concentrated population areas of the United States. The U. S. Public Health Service survey<sup>28</sup> has located areas of high coronary heart disease incidence. These areas are the South Atlantic seacoast stretching from Delaware to Central Georgia, most of the northeastern and Great Lakes regions, the Mississippi River Delta region, and the greater part of the area west of the Rockies. It has been observed that in metropolitan counties the coronary heart disease rates were 37 per cent higher for males and 46 per cent higher for females than in nonmetropolitan counties. The same survey suggests that these areas might be thought of as "natural laboratories." New York City ranks within the first 20 per cent of 163 leading metropolitan areas in death rate



from coronary disease. In New York City the death rate from arteriosclerotic heart disease for men from 50 to 59 years of age was 616 per 100,000 in 1957 (ICS420). According to the 1960 United States census, the official population figures of Metropolitan New York City is 14,759,429. Large series of cholesterol studies are lacking from areas of high coronary incidence in the United States.

The purpose of this study was to determine the level of serum cholesterol in both sexes residing in a large metropolitan area such as New York City, and correlate their total cholesterol to age and body weight.

Sample

The sample of our population study consisted of a multiracial group of office personnel of various nationalities employed in an insurance group located in

Metropolitan New York City. Single serum cholesterol values were determined in office employees aged from 16 to 65 (2,306 female, 1,938 male). No effort was made to categorize the group into echelons of authority or responsibility. Bricker<sup>29</sup> in 1961 performed a dietary analysis of the personal and family food habits of a subsample of our present study sample consisting of 113 18- and 19-year-old unmarried women workers. Bricker concluded: "The food habits and patterns of eating within the total group seemed to mirror each other. At the same time, according to the data from the subjects in the random sample and their mothers, the food habits of the mothers were mirrored closely, especially at breakfast, evening meal, evening snack and when entertaining friends."

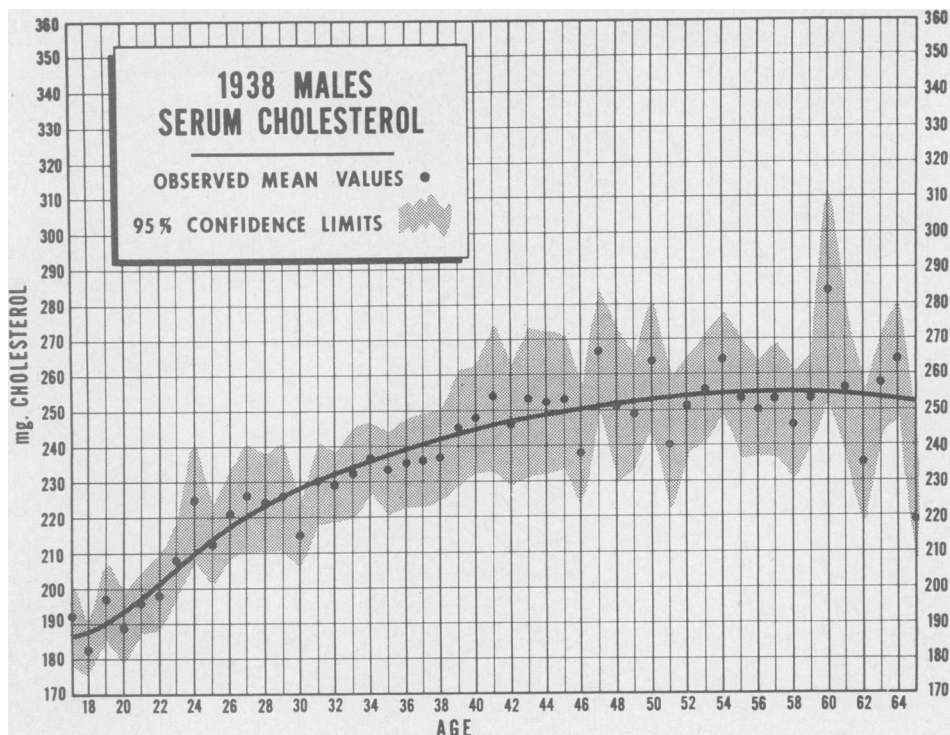
All the individuals in the study were examined at the time of cholesterol determinations. The examination consisted

Table 1C

Ethnicity Racial and Occupational Characteristics		Sample No.	AGE RANGE																
			6-10	11-14	15-18	20-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80		
GEORGIA, U.S.A., white	( 9)	393	156-170	171-189	191-191														
GEORGIA, U.S.A., non-white	( 9)	225	137-177	178-177	196-197														
VARIOUS CITIES, U.S.A., white	(13)	3,404				200	210	216	215	230	236	253	273	261					
VARIOUS CITIES, U.S.A., white	(14)	212				196		209		225		252							
NEW YORK CITY, U.S.A. white Italian	(11)	301								213	231	232	232	229	251				
NEW YORK CITY, U.S.A. white, Jewish	(11)	208								233	264	269	274	265	257				
NEW YORK CITY, U.S.A., white (at age indicated)	(10)	549	3-7 209	8-12 196	13-17 183	18-22 193	23-27 202	28-32 200	33-37 207	38-42 225	43-47 239	48-52 250	53-57 286	58-62 264	63-67 260	68-72 242			
SWISS, BLATTEN	(22)	45		157					168		185		195		197		187		
BASEL		85	172	171	197		196		192		224		238		247		232		
POLYNESIANS, RAROTONGA	(24)	71	192	192		192		215		250		239		226		190			
ATIU-MITIARO		151	201	208		235		243		263		294		293		255			
GUATEMALA, Urban	(25)	70				172		200		208		222							
RURAL		57				147		156		172		138							
Comparative U.S.A. Group		250				189		203		219		247							
			6-10	11-14	15-18	20-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80		

Numbers in parentheses indicate referances

Graph 1



of a medical history and physical examination, inclusive of urinalysis, blood sugar, hemoglobin or complete blood count, serology, and chest x-ray. A 12-lead electrocardiogram was obtained from males 30 years and over, and from females 35 years and over. Comprehensive biochemical studies and other diagnostic procedures were performed to assure the absence of disease affecting the serum cholesterol level. Those individuals with evidence of diabetes mellitus, familial hypercholesterolemia, essential hyperlipemia, thyroid disease, Laennec's cirrhosis, nephrosis, and coronary heart disease were excluded from the study. The blood specimen was drawn two hours postprandial up through 39 years of age and 9 to 14 hours fasting, 40 years and over.\*

\* No significant difference was observed between two- and four-hour postprandial (breakfast), and 10- to 14-hour fasting values of serum cholesterol in a series of 20 subjects.

## Method

The Schoenheimer-Sperry method, or its modification, which is time-consuming and costly is regarded by many as the standard method of cholesterol determination. The validity of other methods of cholesterol determination are often compared to the Sperry method or an equivalent. The McGavak-Pearson method<sup>30</sup> for the determination of serum cholesterol was used in our laboratory. It was substantiated by comparing it with the Sperry method.† Blood samples of 132 healthy subjects were simultaneously appraised by both methods. The mean of the individual differences was 0.01 mg with a standard deviation of 5.7 mg. This observed difference is nonsignificant at the 5 per cent level.

† Schoenheimer-Sperry determinations were performed under the direction of Louis B. Dotti, Ph.D., assistant director of the Clinical Pathology Department, St. Luke's Hospital, New York, N. Y.

Results

A. Relationship of Serum Cholesterol to Age and Sex

Graph 1 represents the mean of single serum cholesterol determinations of 1,938 males stratified according to age. No fewer than 18 nor more than 64 individuals comprised each specific age category. Ninety-five per cent confidence limits for the observed mean values are shown for each age.

The greatest rate of increase in serum cholesterol occurs between ages 19 and 24. This is followed by a diminished rate of increase at age 31 to 44. The curve then assumes a broad curvilinear configuration at age 45 followed by a plateau or decrease to age 65.

Single serum cholesterol determinations of 2,306 females by age are shown in Graph 2. Each specific age category

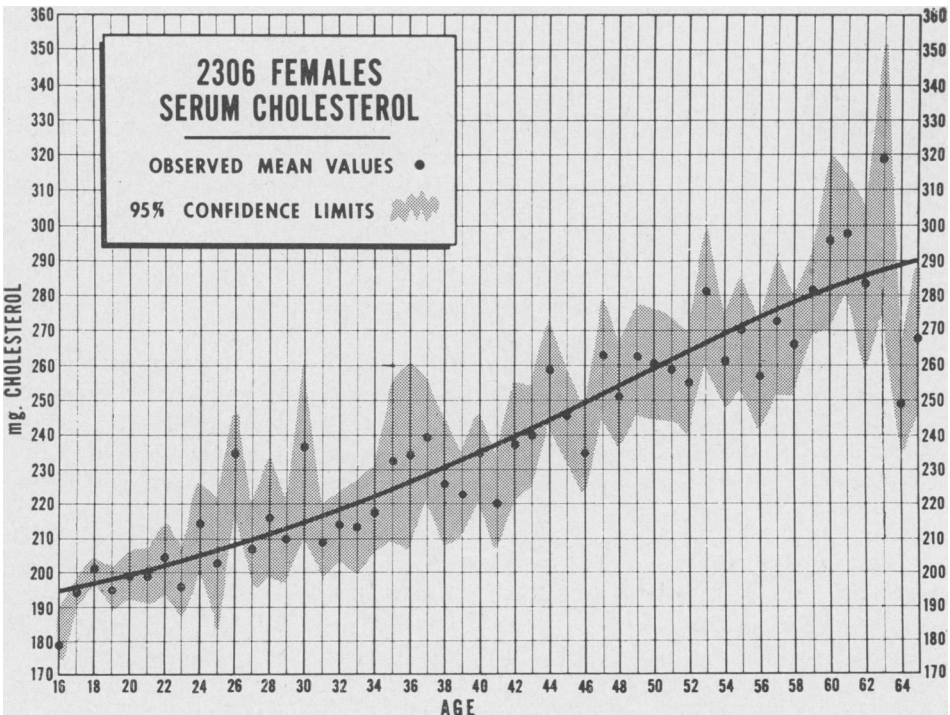
is comprised of a minimum of 15 and a maximum of 256 individuals. This graph is characterized by a markedly flattened sigmoid curve and is accompanied by 95 per cent confidence limits.

Graph 3 is an overlay of Graphs 1 and 2. The two curves intersect at age 22 and 48 years. From 23 to 47 years the serum cholesterol level of the male subjects is higher than that of the female. The range of greatest difference is from age 30 to 36. There is a divergence of direction of the means at age 48; the average serum cholesterol levels of males tend to plateau or drop slightly, while that of the female continues to rise to age 65, the age limit of our sample.

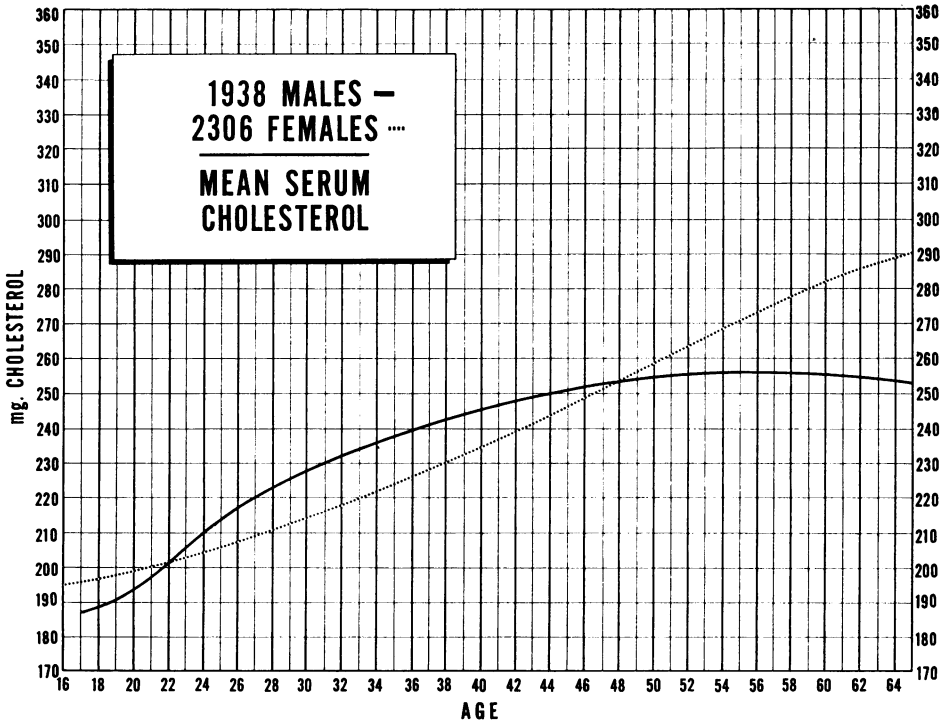
B. Relationship of Serum Cholesterol to Weight

One thousand one hundred and twenty males and 1,288 females comprising a

Graph 2



Graph 3



total of 2,408 subjects were weighed with indoor clothing, measured with shoes, and compared to the average weight within their respective age groups.<sup>31</sup> From this comparison (actual weight/average weight) was derived the relative weight factor which was matched with the serum cholesterol of the individual.

Scattergrams depicting serum cholesterol and relative weight are represented in Figures 1 and 2. The plotted points for age groups indicate the paired values of relative weight and cholesterol levels. No relationship between weight and cholesterol was found. Cholesterol-actual weight scattergrams (not shown) were plotted and display the same random characteristics and lack of relationship.

The correlation coefficient was computed for females age 17 and 18. The

coefficient for age 17 was 0.009 and for age 18 was 0.001. Both are of the order of zero correlation. Because other age groups showed similar characteristics this study was discontinued after evaluating 2,408 individuals.

### Discussion

Gofman<sup>32</sup> noted a significant correlation between obesity and serum Sf 35-100 lipoprotein level but observed that the relationship between total cholesterol and obesity was only of borderline significance. In a review of 465 males and 535 females Walker<sup>33</sup> indicated that there was an increase in the mean cholesterol level with increasing weight, more marked for males than for females. At Johns Hopkins Medical School,<sup>34</sup> a group of 159 male medical students whose mean age was 22, showed

no significant correlation between serum cholesterol level and weight or thickness of the fat shadow. Keys and Fidanza<sup>35</sup> noted that if socioeconomic classes were disregarded, various relationships between relative weight and

serum cholesterol might be indicated, depending upon the groups and the numbers comprising them. Lewis<sup>13</sup> observed that the correlation of the Sf 20-100 lipoproteins with relative weight is higher, whereas the correlation of cho-

Figure 1

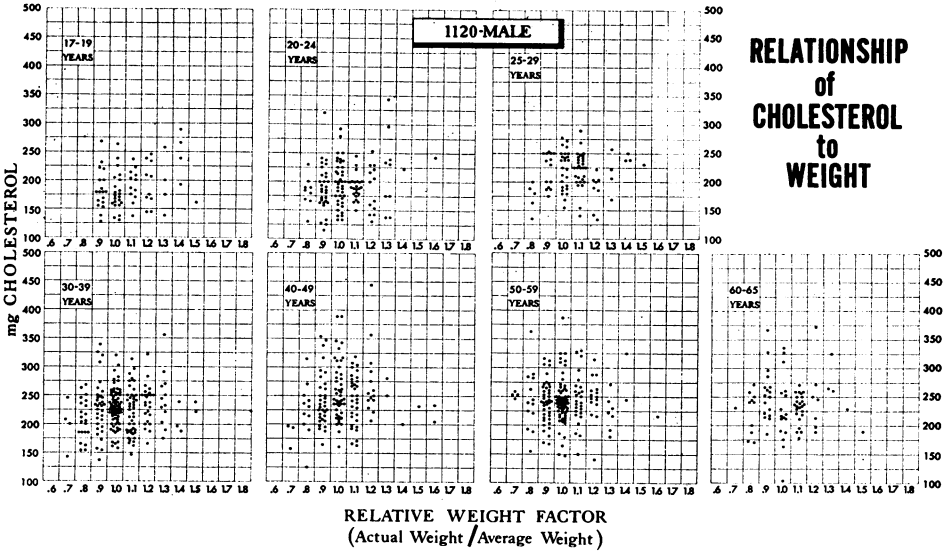
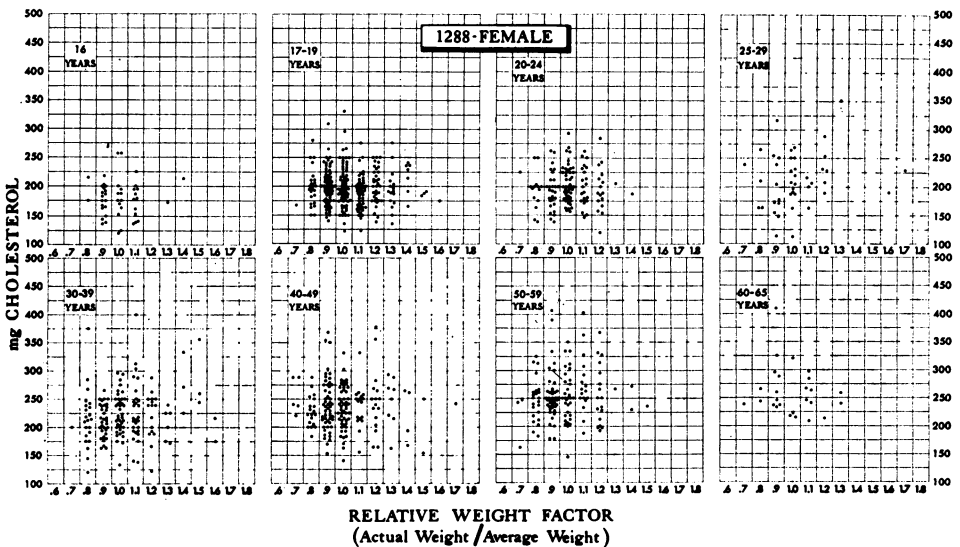
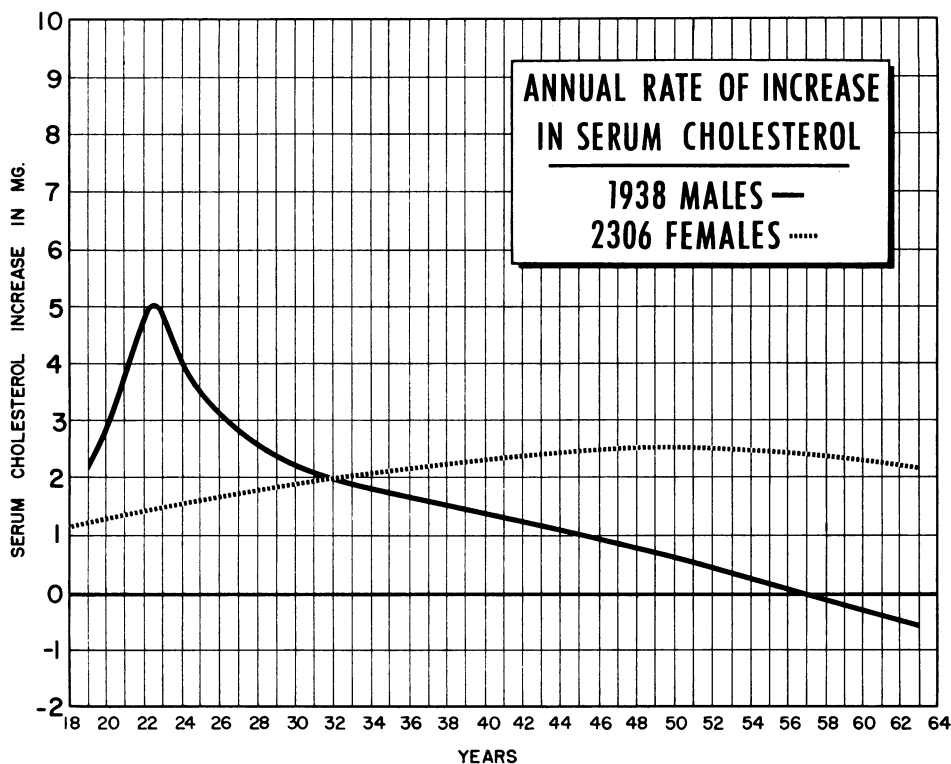


Figure 2



Graph 4



lesterol with relative weight is low. The excessively overweight 20-39-year-old male subjects of Hunter's<sup>23</sup> study demonstrated a significantly higher mean total cholesterol than the normal weight subjects of this group. This was in contrast to his findings in the 40-59-year-old samples in which both the overweight and the normal weight subjects had identical serum cholesterol levels. Jolliffe<sup>36</sup> reported that the average benchmark cholesterol level for 111 obese men from 50 to 59 years of age was 261 mg per 100 ml compared to 251 mg per cent in the group of normal weight subjects of similar age, but the difference was not considered statistically significant.

In interpreting our results, it is apparent that serum cholesterol values in

relation to age may reflect the sum total of variables which influence the level of serum cholesterol in an American metropolitan community. The curve of the levels of serum cholesterol by age in the female (Graph 2) beyond the fifth decade rises sharply and has been interpreted as associated with the menopause. While the configurations of these graphs are similar to those given by Lewis,<sup>13</sup> the means are somewhat uniformly higher for all age groups of both sexes. A prominent feature of Graph 3 is the divergence of the curves beyond the fourth decade. In order to determine the ultimate directions of the curves of mean serum cholesterol levels, it would be necessary to study a healthy population group beyond 65 years of age.



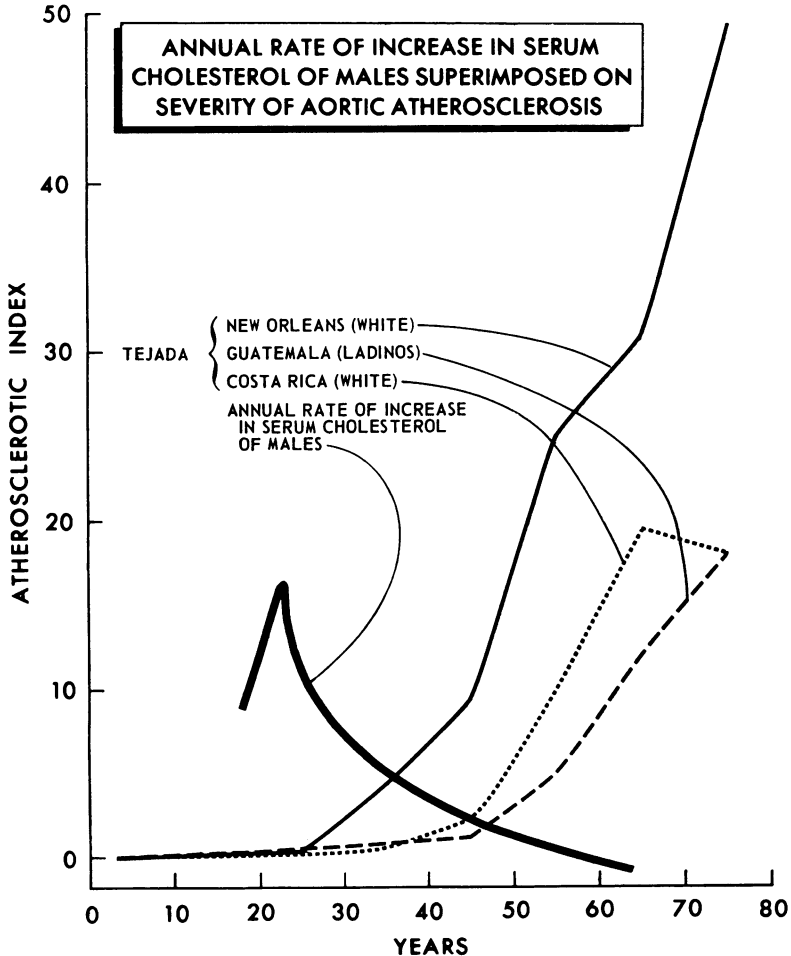
After the fourth decade the configuration of Graph 1 (male) may be due to: (1) a physiological concomitant of age; (2) an increased absorption of serum cholesterol within a specific tissue compartment, with resultant decrease in serum cholesterol; (3) some therapeutic attempt to lower serum cholesterol, i.e., diet, medications; (4) deaths from coronary heart disease in patients having higher serum cholesterol values.

Our study sample is derived from a population with a known high incidence of coronary heart disease. Since this

disease is believed to be associated with abnormal lipid metabolism, it would seem appropriate to relate the pathogenesis of this condition with changes in the serum cholesterol level which occur within specific age groups for both sexes.

In order to focus on those parts of the graphs which might be associated with known epidemiologic facets of coronary heart disease, rates of annual increase in milligram of serum cholesterol were plotted by age for males and females as shown in Graph 4. This

Graph 5



graph shows a sharp rate of increase of serum cholesterol levels in the male which reaches a peak at age 23, followed by a rapidly diminishing rate of increase from ages 23 to 29. From age 35 to 57 there is a decrease to below zero. This reflects the absolute decrease in mean serum cholesterol after age 58 shown in Graph 1.

In contrast, the rate of increase of serum cholesterol for the female reveals a gradual curvilinear configuration reaching its maximum at age 46 followed by a plateau until age 53, then declining more rapidly to age 63. It is possible that the rapid rate of increase in serum cholesterol present in the male from ages 20 to 30 may be associated with the sharp rise in coronary artery intimal thickness of American males of the same age group.<sup>37</sup>

In order to explore the possible pathogenetic significance of our data, we have taken the liberty of superimposing the rate of increase in serum cholesterol in the male, upon the graph developed by Tejada, et al., which indicates the severity of aortic atherosclerosis of the New Orleans white male by age<sup>38</sup> (Graph 5). The rapid rise in the rate of increase of serum cholesterol before the advent of aortic atherosclerosis may represent an important stage in the metabolic pathogenesis of cardiovascular atherosclerosis. The potential validity of the association of aortic atherosclerosis and coronary heart disease, however, remains to be proved.

We are also tempted to use the apparently rapid rate of increase in the male as a possible explanation of the development of coronary heart disease in younger age groups.<sup>39</sup> Furthermore, exposure to the metabolic events represented by a climbing serum cholesterol level may be a factor in explaining the increased incidence of coronary heart disease reported in some northern European countries after World War II.<sup>40</sup> Thus a concept associating coronary

heart disease with rate of increase of serum cholesterol is suggested by this interpretation.

Doyle<sup>41</sup> of the Albany Study states that in association with other variables investigated, a total serum cholesterol of 275 mg or more appeared to be associated with an increased risk of coronary heart disease. The Framingham Study<sup>27</sup> reveals that men with a serum cholesterol over 244 mg have more than three times the incidence of coronary heart disease than those with cholesterol levels 210 mg or less. Moreover Cornfield<sup>42</sup> points out that a 1 per cent difference in the average serum cholesterol of population groups is associated with a 2.66 per cent difference in risk at all levels of serum cholesterol as determined by discriminant function analysis.

It is apparent that the incidence of clinical coronary heart disease is less in the presence of low serum cholesterol. If a direct relationship between coronary heart disease and level of serum cholesterol is presumed, an elevation above 180 mg per cent may represent the cumulative effect of a lipid disorder which may be associated with the development of this disease. Thus, a "safe" or "desirable" limit of serum cholesterol for males should be proposed.

In approaching a definition of desirable levels or ranges and interpreting the graph of the male from this viewpoint, three interpretations appear possible as illustrated in Graph 6:

A. That the means of our data represent the normal physiological increase in serum cholesterol with age.

B. That a physiological increase of serum cholesterol occurs with age to a specific limit, perhaps approximately 220 mg at age 58 years in the male. Such "desirable levels" would approximate curve A but would exhibit a more gradual slope. Therefore, according to this definition the means of curve A are abnormally elevated.

C. That once the mean serum cholesterol reaches 180 mg per cent at 12 weeks of age,<sup>7</sup> it has attained what may be considered a physiological limit in that any increase of

serum cholesterol above this level may be of pathologic significance.

A limit of 220 mg was used in interpretation B since 220 mg of serum cholesterol has been shown to be associated with a moderately low incidence of coronary heart disease.<sup>27</sup> Interpretation C also has some basis, since Milch,<sup>15</sup> Keys,<sup>43</sup> and Mann<sup>44</sup> have studied population groups in which the serum cholesterol did not increase with age.

These three concepts of "desirable levels" may be compared in terms of a theory of "cumulative excess serum cholesterol." We define the concept of "cumulative excess serum cholesterol" as that amount of serum cholesterol above 180 mg per cent per year. Accordingly, an excess of serum cholesterol totaling 180 mg is equivalent to a "cholesterol year." For example, on the basis of hypothesis C, a male of our population

group who is 40 years of age has accrued 954 mg per cent of excess serum cholesterol. He can be said to be 5.3 years older, having been exposed to five added "cholesterol years."

If hypothesis B is presumed to be correct, he has accrued 564 mg per cent of excess serum cholesterol, or approximately one-half that accumulated under hypothesis C, and has aged three "cholesterol years." On the other hand, an individual maintaining a serum cholesterol below 180 mg per cent will be younger in terms of "cholesterol years" than his chronological age. It is of interest that Mattingly<sup>50</sup> states that, "The age of the vascular system frequently differs from the chronological age of the patient."

The area subtended from curve A to B and curve A to C of Graph 6 may be computed for inclusive age groups. These areas represent "cumulative excess

Graph 6

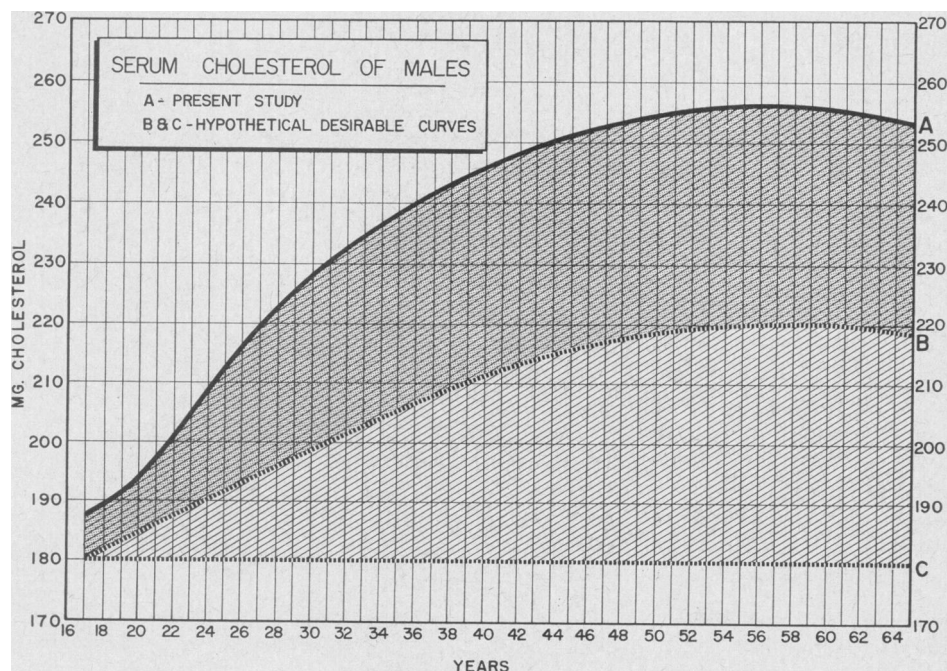


Table 2

EXCESS SERUM CHOLESTEROL  
COMPUTED FROM GRAPH VI BY AGE

AGE	CUMULATIVE EXCESS SERUM CHOLESTEROL	CHOLESTEROL YEARS	CUMULATIVE EXCESS SERUM CHOLESTEROL	CHOLESTEROL YEARS
19	25	.1	20	.1
22	75	.4	53	.3
25	161	.9	108	.6
28	284	1.6	188	1.0
31	427	2.4	274	1.5
34	588	3.3	368	2.0
37	764	4.2	466	2.6
40	954	5.3	564	3.1
43	1157	6.4	668	3.7
46	1365	7.6	768	4.3
49	1621	9.0	871	4.8
52	1803	10.0	976	5.4
55	2028	11.3	1081	6.0
58	2250	12.5	1183	6.6
61	2476	13.8	1289	7.2
64	2694	15.0	1389	7.7

serum cholesterol" accrued by our study population (curve A) based on hypothetical "desirable" curves B and C. Table 2 shows the cumulative excess serum cholesterol computed from Graph 6 in relation to various ages of males.

The clinical aspects of myocardial infarction appear to integrate well with the concept of a combined effect of rate of increase and cumulative excess serum cholesterol in both sexes. The incidence of myocardial infarction by male to female ratio is 6.9 by the fourth decade, 2.1 by the sixth decade, and continues to decrease to 0.9 by the eighth decade.<sup>45</sup> As indicated in Graph 4 the annual rate of increase in serum cholesterol in the male rises rapidly over a relatively short period of time. The male is also exposed to considerable cumulative excess serum cholesterol by the fourth decade (see Table 2), whereas in the female the combined annual rate of increase and cumulative excess cholesterol demonstrate a slower gradual increase.

In addition to correlating the data presented with metabolic and pathologic aspects of coronary heart disease, we are provoked to speculate whether Graphs 1 and 2 actually represent "desirable levels."

The concept of the normalcy of any physiological variable infers a need for criteria which define the many different influences that may act upon it. Thus the following factors must be considered in attempting to define normal ranges of serum cholesterol: (1) The population studied should be free of diseases affecting the variable under study. (2) The population should be homogeneous as to specific characteristics, such as sex, race, type of occupation. (3) Cognizance be taken that variables such as psychic stress, or the anticipation of stress, smoking and exercise have been implicated as affecting serum cholesterol levels. (4) The laboratory method employed in determining the serum cholesterol level may exhibit

specific inherent errors. (5) Among the "normal" populace studied, there may be a physiological pattern of diurnal, monthly or seasonal variation of serum cholesterol. (6) "Normal" may be defined on a purely statistical basis, or may be defined epidemiologically. Just as "normal" or "desirable" body weight may be defined on the basis of a large population sample whose height and weight are known, or may also be defined in terms of the effect of excess body weight on increased mortality, so may serum cholesterol be defined on the basis of means obtained from a large populace, or in terms of the function of increased risk in developing coronary heart disease. In considering normal values Lewis<sup>13</sup> indicated two important considerations which also apply to this investigation. First, it is difficult to study a population group which reflects all the ecologic heterogeneity of the general population; second, while the mean serum cholesterol level of any two age groups may vary significantly, large areas of overlap may exist. Thus it is tenuous to compare any single serum cholesterol level to that of any given population group even if the series is large.

In spite of these difficulties, various

authors have speculated on levels of normal serum cholesterol. Stamler<sup>46</sup> has suggested that the upper limit of normal for serum cholesterol should range from 200 to 225 mg per cent. Dock<sup>47</sup> and Kinsell<sup>48</sup> consider 180 mg per cent as the upper limit of "desirable." Jolliffe<sup>49</sup> believed that 200 mg per cent was the upper limit of desirable cholesterol level for the adult.

On the basis of the metabolic and pathologic significance of hypercholesterolemia, and of the current knowledge of the relationship of serum cholesterol and incidence of coronary heart disease derived from many populations studied, it appears reasonable to suggest that "desirable levels" for any age group beyond adolescence are in the range of 180-220 mg of serum cholesterol, preferably under 200 mg per cent.

The data of Tables 3 and 4 are presented in terms of 80, 90, and 99 percentiles to indicate the distribution of an individual patient's serum cholesterol value when matched to the characteristics of our population sample. As can be seen from this table, it is certain that those individuals lying in the 1 per cent and 10 per cent upper ranges are within the area of abnormality in relation to our sample. They should be considered

Table 3—Serum Cholesterol Distribution by Age Group—Male

AGE GROUP	80% OF THOSE TESTED WILL RANGE BETWEEN:		10% WILL HAVE A VALUE EQUAL TO OR:		1% WILL HAVE A VALUE EQUAL TO OR:	
	MINIMUM	MAXIMUM	LESS THAN	MORE THAN	LESS THAN	MORE THAN
17 - 19	142 MG.	233 MG.	141 MG.	234 MG.	106 MG.	270 MG.
17 - 18	142	233	141	234	105	270
19 - 21	147	239	146	240	110	276
20 - 24	153	249	152	250	114	288
22 - 24	156	254	155	255	117	294
25 - 27	166	268	165	269	123	311
25 - 29	168	272	167	273	125	315
28 - 31	173	280	172	281	128	325
30 - 34	177	287	176	288	132	332
35 - 39	184	296	183	297	137	345
40 - 44	188	306	187	307	141	354
45 - 65	192	310	191	311	143	360

**Table 4—Serum Cholesterol Distribution by Age Group—Female**

AGE GROUP	80% OF THOSE TESTED WILL RANGE BETWEEN:		10% WILL HAVE A VALUE EQUAL TO OR:		1% WILL HAVE A VALUE EQUAL TO OR:	
	MINIMUM	MAXIMUM	LESS THAN	MORE THAN	LESS THAN	MORE THAN
16 - 19	150 MG.	242 MG.	149 MG.	243 MG.	112 MG.	281 MG.
20 - 24	154	249	153	250	115	288
25 - 29	160	259	159	260	119	299
30 - 34	166	270	165	271	124	312
35 - 39	174	282	173	283	130	326
40 - 44	182	296	181	297	136	342
45 - 49	192	310	191	311	143	359
50 - 54	201	326	200	327	150	377
55 - 59	211	341	210	342	157	395
60 - 65	219	355	218	356	163	411

candidates for preventive therapy and constitute a target population for public health action if we are to accept the premise that hypercholesterolemia is a risk factor in the development of coronary heart disease.

**Summary**

The serum cholesterol level of 1,938 males and 2,306 females were determined and interpreted in relation to sex, age, and weight.

A sharply rising curve was found to be present in the male with a maximum level of serum cholesterol reached at age 58, followed by a tendency to plateau or decrease beyond this age.

The serum cholesterol level of the female exhibited a gradual rise to age 65.

Ranges of serum cholesterol levels by sex and age were constructed.

No relation was found to exist between serum cholesterol levels and weight in 2,408 subjects studied.

A comparison of the male and female curves reveals that the mean serum cholesterol of the male is lower than that of the female until age 22 at which time it rises sharply above that of the

female until the age of 50. Following age 50 the mean serum cholesterol of the female continues to rise until the age of 65 while that of the male reaches a plateau or decreases slightly after the age of 59.

The means of serum cholesterol were treated in terms of possible relationships to the pathogenesis of coronary heart disease. A concept of rate of increase and cumulation of serum cholesterol was proposed and applied to some of the observed epidemiological and pathological aspects of coronary heart disease.

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## "The Fate of Pesticides"

The Public Health Service has announced the beginning of a five-year study to determine what happens to pesticides after completing their tasks of killing insects. The research will be undertaken by scientists at Rutgers, the State University, at New Brunswick, N. J.

The Rutgers grant, entitled "The Fate of Pesticides," will include studies of how pesticides are retained or released in various types of clays and other soils, the interactions between pesticides and soil microorganisms, behavior in water, retention by fish, absorption and accumulation in plants and the possible formation of tumors or other cellular changes in animals. The work will be coordinated by Dr. Billy Ray Wilson, chairman of the recently established Bureau of Conservation and Environmental Science at Rutgers.