Plasma Lipid Levels and the Diagnosis of Coronary Arteriosclerosis in England

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Although each of the different plasma lipids has, at some time, been proposed as an index of the time when symptoms of coronary heart disease will appear in apparently healthy people, none has yet gained indisputed approval. This has been due partly to the discordant results produced by different groups working in similar societies, but also, as Page et al. (1957) pointed out, because it was not known what concentration of plasma lipid could be regarded as abnormally high. In particular, they questioned whether it was appropriate to adopt, as a "normal" level, the average for a North American (or European) population. Later, it was deduced by Keys and Fidanza (1960) that their studies of the inhabitants of Minneapolis and Naples did "not support the idea that there is a 'normal' serum cholesterol level for clinically healthy middle-aged men in general, or that there is some kind of a critical level that distinguishes all average coronary patients."

The present note describes an analysis of lipoprotein measurements in men born and bred in this country, which confirms and extends this opinion.

METHODS

Definition of Disease. This discussion will be restricted to coronary arteriosclerosis, which will be assumed to be a major cause of heart disease arising through obstruction of the coronary lumen. The term "diseased" will be applied only to subjects in whom symptoms of this disease have become manifest, i.e. those who are suffering from angina pectoris, cardiac ischemia, myocardial infarction, or who have a characteristically changed electrocardiogram. All other subjects will be termed "healthy".

Nomenclature. Where the discussion refers to the level of plasma cholesterol, it will be convenient to distinguish between those measurements in which cholesterol esters were hydrolysed, and those in which they were not. The former, true estimate will be designated as: CHOLESTEROL, while the latter will be written, cholesterol. Where measurements made in these two units have been compared, the factor 0-85 has been used to convert unhydrolysed to absolute values.

In addition, the following abbreviations will be used:

TC—Total plasma cholesterol.

α-cholesterol—The constituent cholesterol of the α-lipoprotein. The corresponding notation will be used for β-lipoprotein cholesterol.

A.I.—The atherogenic index defined by Gofman et al. (1956).

S_f-n—An interval in flotation rate between n and m Svedberg units which defines a group of lipoproteins. In all cases the values have been corrected (deLalla and Gofman, 1954) for the effects of concentration dependence.

[ ]—This symbol will be used for "concentration of", e.g. [S₀-12] reads: "the concentration of S₀-12 lipoproteins" (cf. Dodds and Mills, 1959). The letters s and r will be used to indicate the statistical standard deviation and correlation coefficient, respectively.

Specimens. Blood samples were obtained from a total of 748 healthy male volunteers, between the ages of 14 and 94, who had no clinical symptoms of coronary artery disease. Most of these men had been bred in the British Isles and the few who were of foreign extraction had lived for many years in England. The technique of collection was that described by Dodds and Mills (1959).

Samples were obtained in the same way from 97 male patients (aged from 40 to 80 years; mean 58) under treatment in hospital for unequivocal myocardial infarction, and subjected to the same analyses as those from the healthy men. In addition, total cholesterol

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levels in 362 cases of coronary artery disease in men aged from 23 to 80 years were extracted from the records of the Middlesex Hospital between 1956 and 1962. The cholesterol level in these specimens was determined by the method used in the other cases, but no other estimations were made on them.

Analytical Methods. The methods of fractionation used were those of deLalla and Gofman (1954) and of Cohn et al. (1950). All other techniques were those described by Dodds and Mills (1959). The concentration of lipids or lipoproteins in plasma has always been quoted in mg./100 ml. plasma (mg./100 ml.). The technical errors of each analysis were as follows:

\[
TC = \pm 4.7; \quad \beta\text{-cholesterol} = \pm 5.6; \quad \alpha\text{-cholesterol} = \pm 3.0; \quad S_{0-12} = \pm 15; \quad S_{12-20} = \pm 4.7; \quad S_{20-100} = \pm 8.8; \quad S_{100-400} = \pm 8.5.
\]

All "Cohn fractionations" in which the sum of \(\alpha\)- and \(\beta\)-cholesterol differed from the TC by more than \(\pm 5\) per cent were discarded. Moreover, the result of each fractionation was compared with the lipoprotein pattern obtained in the ultracentrifuge. In cases of evident disagreement the analyses were repeated.

Statistical Methods. The authorities followed are Fisher (1938) and Snedecor (1946). In the deduction of Fig. 1, it was first shown that the observed frequency distribution of [TC], in both healthy and diseased subjects, was not significantly different from normal, when the observed values were averaged over intervals of 10 mg./100 ml. It was then assumed that the distribution of [TC] could properly be expressed by a smooth curve of the normal form, having the calculated values of \(\sigma\) and mean [TC]. This curve, shown in Fig. 1, was plotted for an arbitrary population of 100,000 using the frequencies given in the tables of ordinates of the normal distribution. The same procedure was employed for the diseased men, using the data for the group of 357 men with coronary heart disease. For the purpose of preliminary calculation this number has been treated as if it was the approximate annual rate of incidence of the disease in 100,000 apparently healthy men.

In the derivation of the curve shown in Fig. 2 the numbers of both healthy and diseased men having each value of [TC] were determined by inspection of Fig. 1. For example, the number of men in these categories who would be expected to have a plasma cholesterol of 270 mg./100 ml. was found to be 763 and 2, respectively. Thus, the annual incidence of the disease in Englishmen with this value of plasma cholesterol would be expected to be approximately 260 per 100,000. Points were plotted in this way, at successive values of [TC], to yield a curve which exhibited a shallow minimum at 200 mg./100 ml. T.C. By making the value at this point the unit in which the incidence rate was expressed, the generalized curve shown in Fig. 2 was then constructed. It should be observed that this curve, which is logarithmic in form, describes the connexion between plasma cholesterol and the relative rates of incidence of manifest coronary heart disease. It is independent of the actual

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**Fig. 1.**—The smoothed frequency distributions of total plasma cholesterol in healthy men and in men with atherosclerotic coronary heart disease. The medians and standard deviations used in the calculations were those determined experimentally. The healthy curve was calculated for a group of 100,000 men and the diseased curve for 357 men. The vertical line marks the point 256 mg./100 ml. cholesterol, which is midway between the medians of the two curves.
incidence rate, but is only exactly applicable to a population with the same characteristics as the one from which it was derived, namely, one in which the healthy and diseased groups differ in mean [TC] by 45 mg./100 ml. and have σ of ±43 mg./100 ml. and ±69 mg./100 ml., respectively.

The results observed for the whole group of healthy men are summarized in Table I, together with their distribution according to age, taken by decades.

It will be seen that the average plasma level of all the β-lipoproteins rises with age until about 40, they then remain almost unchanged through middle life, and finally show a tendency to decline once the age of 70 is passed. The last stage is particularly noticeable in the case of the S₄₁₂–400 substances. These changes are reflected in the distribution of the mean [β-cholesterol], which can be conveniently described statistically (0·02 < p < 0·05) by the equation:

$$[\beta\text{-cholesterol}] = 162·4 + 0·89A - 0·006A^2 \quad (1)$$

where A is the age in years.

By contrast, the mean [α-cholesterol], after an initial fall, rises steadily throughout life according to the equation:

$$[\alpha\text{-cholesterol}] = 25·4 + 0·31A + 0·002A^2 \quad (2)$$

where p < 0·001. Thus the slight fall in [β-cholesterol] during old age is offset by the rise in [α-cholesterol] and the mean total plasma cholesterol increases slightly, even in the ninth decade. This correlation is represented, to a high degree of significance (p < 0·001), by:

$$[\text{TC}] = 178·5 + 1·65A - 0·009A^2 \quad (3)$$

The plasma lipid levels for the diseased subjects have been presented in two groups. Those for the 97 men whose plasma was fractionated have been averaged and are included in Table I. All differ significantly from the mean levels in healthy men of the same age. The 362 cases of coronary heart disease for which only cholesterol was determined, have been divided into classes by decades of age for which the mean cholesterol levels are shown in Table II. In contrast to the healthy men, the mean [TC] in these cases falls continuously with age according to the relationship:

$$[\text{TC}] = 311 - 0·07A - 0·007A^2 \quad (4)$$

### TABLE I

<table>
<thead>
<tr>
<th>Mean age</th>
<th>Total cholesterol (mg./100 ml.)</th>
<th>β-cholesterol (mg./100 ml.)</th>
<th>α-cholesterol (mg./100 ml.)</th>
<th>S₁₀–₁₂</th>
<th>S₁₂–₂₀</th>
<th>S₂₀–₁₀₀</th>
<th>S₁₀₀–₄₀₀</th>
<th>A.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–0</td>
<td>194 ± 40</td>
<td>131 ± 44</td>
<td>66 ± 13</td>
<td>175 ± 75</td>
<td>12 ± 11</td>
<td>30 ± 23</td>
<td>3 ± 7</td>
<td>25 ± 18</td>
</tr>
<tr>
<td>25–9</td>
<td>212 ± 42</td>
<td>175 ± 45</td>
<td>31 ± 14</td>
<td>268 ± 88</td>
<td>36 ± 19</td>
<td>84 ± 56</td>
<td>65 ± 99</td>
<td>59 ± 32</td>
</tr>
<tr>
<td>35–4</td>
<td>228 ± 48</td>
<td>189 ± 46</td>
<td>35 ± 10</td>
<td>320 ± 89</td>
<td>47 ± 25</td>
<td>93 ± 63</td>
<td>66 ± 88</td>
<td>68 ± 30</td>
</tr>
<tr>
<td>44–7</td>
<td>239 ± 43</td>
<td>192 ± 30</td>
<td>44 ± 14</td>
<td>329 ± 76</td>
<td>57 ± 35</td>
<td>93 ± 51</td>
<td>57 ± 57</td>
<td>69 ± 25</td>
</tr>
<tr>
<td>55–1</td>
<td>243 ± 38</td>
<td>195 ± 37</td>
<td>49 ± 8</td>
<td>325 ± 84</td>
<td>54 ± 31</td>
<td>82 ± 44</td>
<td>49 ± 57</td>
<td>65 ± 23</td>
</tr>
<tr>
<td>63–3</td>
<td>248 ± 42</td>
<td>194 ± 62</td>
<td>54 ± 17</td>
<td>329 ± 86</td>
<td>53 ± 36</td>
<td>72 ± 49</td>
<td>33 ± 46</td>
<td>61 ± 25</td>
</tr>
<tr>
<td>76–2</td>
<td>196 ± 30</td>
<td>143 ± 36</td>
<td>58 ± 12</td>
<td>280 ± 67</td>
<td>33 ± 12</td>
<td>83 ± 39</td>
<td>42 ± 56</td>
<td>56 ± 20</td>
</tr>
<tr>
<td>83–3</td>
<td>240 ± 41</td>
<td>162 ± 39</td>
<td>60 ± 11</td>
<td>264 ± 75</td>
<td>29 ± 13</td>
<td>65 ± 37</td>
<td>20 ± 23</td>
<td>47 ± 14</td>
</tr>
</tbody>
</table>

| 52       | 239 ± 43                        | 192 ± 44                      | 47 ± 17                     | 321 ± 83 | 53 ± 34 | 83 ± 51 | 49 ± 63 | 64 ± 26 |
| 58       | 273 ± 62                        | 228 ± 53                      | 45 ± 12                     | 385 ± 128 | 68 ± 47 | 143 ± 90 | 76 ± 93 | 88 ± 36 |

Note: Upper 8 lines of the table show the mean values for 748 apparently healthy men, taken by decades of age. The 9th line shows the mean for this group taken as a whole. The 10th line quotes the mean levels for 97 patients with atherosclerotic coronary heart disease: each differs significantly (p < 0·01) from the corresponding values in healthy men. The units are mg./100 ml. plasma and each value is followed by its standard deviation.
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It is important to note that, whereas eqn. 3 represents the progressive change in mean total cholesterol with age, eqn. 4 relates the total cholesterol level to the terminal age at which manifest symptoms of disease appear. These two equations clearly summarize the observation that, whereas young diseased men tend to have much higher levels of TC than young healthy men, the values of TC converge with age until, at 65 years, the difference is barely significant (p=0.05). Above this age the two categories of men are virtually indistinguishable by measurements of cholesterol.

### TABLE II

<table>
<thead>
<tr>
<th>Mean age (yr.)</th>
<th>Total cholesterol (mg./100 ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-0</td>
<td>310 ± 30</td>
</tr>
<tr>
<td>36-7</td>
<td>309 ± 80</td>
</tr>
<tr>
<td>45-5</td>
<td>297 ± 66</td>
</tr>
<tr>
<td>55-1</td>
<td>293 ± 65</td>
</tr>
<tr>
<td>65-3</td>
<td>261 ± 63</td>
</tr>
<tr>
<td>73-0</td>
<td>259 ± 59</td>
</tr>
<tr>
<td>85-0</td>
<td>257 ± 17</td>
</tr>
</tbody>
</table>

*Note: Mean value for whole group = 284 mg./100 ml. ± 69.*

### DISCUSSION

The method of separating plasma lipoproteins used in British laboratories has almost invariably been that of paper electrophoresis. Consequently, there are no British data exactly comparable with those given in Table 1, which must accordingly be collated with analyses from American sources.

The levels of low density lipoproteins reported by deLalla and Gofman (1961) are up to 35 per cent higher than those presented here, the greatest divergence being observed for the triglyceride-rich substances of lowest density. In both countries the mean level of each β-lipoprotein species shows a prominent maximum in middle-age: it occurs, however, at about the age of 45 in Englishmen, whereas in Americans it is at 55 (Glazier et al., 1954), a difference that arises because the decline in [S₅,20-100] and [S₅,100-400] begins at 35-45 in the former, but is some 10 years later in Americans. Thus, the elderly American has substantially more plasma triglycerides than his British counterpart.

In the diseased Englishman, the average level of all the lipoprotein species was greater than in healthy subjects. Although this formally confirms the observations of the Donner Laboratory, the values for diseased Englishmen are little higher than those of healthy Americans, and are notably less than in Americans who have manifest disease. Moreover, the difference between [S₅,0-12] in healthy and diseased Englishmen is twice as great as in Americans, while the divergence in [S₅,12-400] is one-third more. The two categories of Englishmen, can, therefore, be more easily distinguished by lipoprotein measurements than is the case with Americans. This suggests that Gofman’s AI may not be directly applicable to societies other than that from which it was derived.

This comparison of β-lipoprotein levels suggests that the [β-cholesterol] should also be higher in Americans than in Englishmen. However, the results of earlier surveys have not always supported this conclusion. Thus, when Russ, Eder, and Barr (1951) fractionated the plasma from 45 healthy men by the Cohn procedure, they found levels of β-cholesterol that were closely similar to those of the English, ranging from 137 mg./100 ml. between 18 and 35 years of age, to 170 mg./100 ml. between 45 and 65. By contrast, the level of α-cholesterol was observed to be from 14 to 24 mg./100 ml. greater (i.e. about 50% more) than the equivalent in the English. Similar observations were made by Searcy et al. (1960a, b), who measured cholesterol in electrophoretically separated α- and β-lipoproteins. In these experiments also, the mean [β-cholesterol] was found to rise until, near 40 years of age, it reached a maximum of about 210 mg./100 ml., which is little more than in the English. The [α-cholesterol], on the other hand, was almost constant from the age of 20 to 50, at a level of 65-70 mg./100 ml., which is at least 50 per cent more than the value in Englishmen. Between the ages of 50 and 70, however, the level showed a tendency to decline. These two surveys suggest, therefore, that Americans have about the same β-lipoprotein levels as Englishmen, but that the former have much more α-lipoprotein. The experiments of Keys and Fidanza (1960) lead to the opposite conclusion, however, namely that Americans have about 40 mg./100 ml. more β-cholesterol than Englishmen, and that it is the [α-cholesterol] which is the same in both. In contrast to these American surveys, Carlson (1960), who determined cholesterol in chromatographically separated lipoproteins, found that Scandinavians had more of both the α- and β-forms than the English. Unfortunately, there is no ultracentrifugal confirmation of this. Nonetheless, this survey offers strong support for the age relationships observed in the English. Thus, whereas Carlson found that [α-cholesterol] was age dependent to a highly significant degree, he could find no correlation between age and [β-cholesterol]. In the English, the
relatively weak correlation noted in the latter case probably results from the larger group under study.

The observation, expressed by eqn. 4, that coronary disease is associated with a higher [TC] in the young than in the elderly, has been so well established by others as to need no further discussion (cf. Faber, 1946; Oliver and Boyd, 1953; Lawry et al., 1957; Björck, Blomquist, and Sievers, 1957; Dodds and Mills, 1959; Carlson, 1960). However, the evidence for an increase of plasma cholesterol levels with age in healthy men has been more contradictory. Thus, Sperry (1937) suggested that the [TC] remains at a characteristic constitutional level throughout life, and this received support from a number of laboratories (Turner and Steiner, 1939; Peters and Man, 1943; Sperry and Webb, 1950; Enos, Holmes, and Beyer, 1953; Oliver and Boyd, 1953; Adlersberg et al., 1956). There is also, however, considerable evidence for the opposite view that [TC] increases with age, at least up to the middle years (Bürger and Möbius, 1934; Keys et al., 1950; Jones et al., 1951; Schettler, 1953; Malmros, Björck, and Swahn, 1956; Lawry et al., 1957; Albrink, Meigs, and Man, 1961). Moreover, the values in Americans are from 25-40 mg./100 ml. higher than those found for the Englishmen, when compared in the same units. In particular, Lawry et al. (1957) found that [TC], like the lipoprotein measurements of Glazier et al. (1954), reached a maximum at about 50 years of age and, with the difference that the maximum occurs near the age of 60, it is with these results that those recorded in Table I show the most satisfactory agreement.

Despite the evident lack of agreement between different laboratories concerning the level of lipids in both fractionated and un fractionated plasma, there is little doubt that the average healthy American has a higher plasma cholesterol level than the corresponding Englishman. The most consistent interpretation of the remaining evidence is that, in both English and Americans, there is a tendency for the β-lipoprotein level to rise with age and that the level in Americans exceeds that in Englishmen by an amount almost equivalent to the difference in their respective values of [TC]. The mean level of α-lipoprotein in these two societies is probably nearly the same however, and in the healthy population it increases slowly with advancing years.

The only British survey comparable with that reported here appears to be that of Oliver and Boyd (1953), who determined CHOLESTEROL in 149 men between the ages of approximately 30 and 80 years. In a second investigation (1955), using the electrophoretic technique, these workers also determined the α:β ratio in 50 healthy men. It is evident, on inspection, that these results differ from ours in two respects: first, in the unusually low levels of [TC] recorded (mean 171 mg./100 ml.), and secondly, in the high estimates of [α-cholesterol] which average about 28 per cent of the total cholesterol level. These values are similar to those reported for unsophisticated rural societies such as the Navajo Indians (mean [TC] = 175-178 mg./100 ml.; Page, Lewis, and Gilbert, 1956), Ugandans (mean [TC] = 164 mg./100 ml.; Shaper and Jones, 1959), Yemenites (mean [TC] = about 180 mg./100 ml.; Toor et al., 1960), or even Somali shepherds (mean [TC] = 148 mg./100 ml.; Lapicciarella et al., 1962), and we are unable to confirm that Englishmen are so unlike their urban counterparts of Europe and America as this comparison would imply (cf. also Straus, Wurm, and Kositchek, 1964).

It is important to note that, in Englishmen, the [TC] is increased mainly through the elevation of [β-cholesterol], as was also reported for other nationalities by Keys (1957), Keys et al. (1957, 1958). In the case of Englishmen, the relationship can be represented by the regression equation:

\[
[\beta\text{-cholesterol}] = 0.94 [\text{TC}] - 32.25 (r = 0.93) \quad (5)
\]

whereas the corresponding expression for the α-lipoprotein is:

\[
[\alpha\text{-cholesterol}] = 0.071 [\text{TC}] + 29.8 (r = 0.18) \quad (6)
\]

The overwhelming influence of [β-cholesterol] in changes of [TC] can be seen by comparing the coefficients of [TC] in these equations.

It is also significant in this context, that [α-cholesterol], in rural or peasant communities from countries with a low standard of living, is little or no different from that observed in urban English, Americans, or the members of other rich societies (cf. Neapolitans (41 mg./100 ml.), Keys and Fidanza, 1960; Fidanza, Mancini, and Cioffi, 1960; Yemenites (44 mg./100 ml.), Brunner and Lobl, 1958; Malayans (44 mg./100 ml.), Chong, 1964). By contrast, [β-cholesterol] in the members of these poor societies may fall as low as 75 mg./100 ml. It therefore appears to be a fundamental defect of plasma lipoprotein metabolism that the α-lipoprotein level cannot be raised above a fairly well-defined limit which, in healthy men, is equivalent to 45-55 mg./100 ml. cholesterol. Moreover, the lowest [β-cholesterol] with which this level of α-cholesterol normally coexists is from 80-100 mg./100 ml. Any [β-cholesterol] greater than this can accordingly be regarded as a measure of hyper-
lipoproteinæmia which, as Tables I and II show, may correspond to conditions favouring athero-
sclerosis. However, the Tables also show that,
not only did the cases of infarction have a mean
[β-cholesterol] substantially higher than that of
healthy men of the same age, but their [α-chol-
esterol] was significantly lower (p < 0.001). Ana-
lyses that illustrate this effect may also be found in
the earlier work of Dodds and Mills (1959) and of
Keys and Fidanza (1960). The presence of
actively developing atherosclerotic coronary heart
disease is, therefore, statistically associated both
with a raised [β-cholesterol] or [β-lipoprotein] and
a depressed [α-cholesterol], and not, as has been
claimed, for example by Gofman et al. (1954) or by
Brunner et al. (1962), with one of these variables to
the exclusion of the other.

It can be seen from Table I that, by comparison
with healthy men, the diseased subjects have a
mean [α-cholesterol] that is depressed by about 10
per cent and a [β-cholesterol] that is raised by
about 17 per cent. By contrast, both Russ et al.
(1951) and Oliver and Boyd (1955) observed
changes of up to 100 per cent in both these fractions,
and were thus able to distinguish healthy from
diseased subjects with an ease which the present
survey suggests was exaggerated. This view is
supported by the studies of the inhabitants of
Minneapolis and Naples, made by Keys and Fida-
za (1960), who also found changes in the chol-
esterol fractions which did not exceed 17 per cent.
Moreover, the [β-cholesterol] in the healthy Ameri-
cans (232 mg./100 ml. cholesterol) was almost
the same as that of the diseased Englishmen studied
here, whereas in the diseased Americans it was
much higher (260 mg./100 ml. cholesterol). These
observations are, therefore, consistent with those
on the β-lipoprotein levels measured by ultra-
centrifugation, which were discussed earlier. It is
also interesting to note that the situation is reversed
when Neapolitans and Englishmen are compared,
the diseased Italians having β-cholesterol levels
which are similar to those of healthy Englishmen,
i.e. 210 and 195 mg./100 ml., respectively.

Englishmen thus have plasma lipid levels that are
intermediate between those of Neapolitans and
Americans. Since Englishmen also suffer from
atherosclerosis to an intermediate extent (Lew,
1962), these observations satisfy the established
correlation between lipid levels and disease rate
which is considered in more detail below.

By means of the method described in the previous
section, a relationship has been deduced between
[TC] and the relative rate of incidence of coronary
disease, which is illustrated in Fig. 2. This calcu-
lated incidence rate increases very slowly as the
[TC] rises from 180 to 220 mg./100 ml. but, above
this level, it rises with increasing rapidity.
Thus, the change of [TC] from 240 to 340 mg./
100 ml. is accompanied by a fivefold increment in
incidence of the disease. The general form of this
curve is well confirmed by the direct observations
of Kagan et al. (1962) on the population of Framing-
ham, Massachusetts, and also with the analysis
of those observations made by Cornfield (1962).
There is also a satisfactory quantitative agreement
with these results, if allowance is made for the
different methods of presentation used. It may,
therefore, be concluded that Englishmen who have
the same [TC] as Americans are also equally sus-
cetable to coronary heart disease and that the
greater incidence among the latter is the result of
their higher average [TC].

It is important to note, however, that at any given
value of [TC], the members of the population who
develop manifest disease within a set time are
heavily outnumbered by those who still appear
healthy. This may be exemplified in the following
way. Adopting the suggestion of Straus et al.
(1964), a datum is set halfway between the medians
of the two curves of Fig. 1, i.e. at 256 mg./100 ml.
cholesterol, to distinguish the potential coronaries
above from the apparently healthy below. Under
these circumstances, the tables of cumulative normal
frequency (Snedecor, 1946) show that 34.5 per cent
of the healthy population would be estimated as
“high risk” and 39 per cent of the diseased as
“low risk” (false negative.). Thus, in an
apparently healthy population from which an
annual incidence of 500 coronaries/100,000 might
be expected, this criterion would lead to 34,500
men being suspected as potential cases. But only
305 of these would become ill within 12 months,
and the suspect population is 100 times larger than
the annual rate. Thus, statistical analyses of the
type proposed by Straus et al. (1964) are misleading,
partly because they use a “normal” population of
artificial size, but also because the disease process
of which [TC] is the proposed index is, in general,
too slow for its status to be judged by this measure-
ment alone. It has been insufficiently emphasized
in earlier studies that, if [TC] is a measure of the rate
of atherogenesis, at least two other measurements
are needed to define the condition of coronary
arteriosclerosis in each subject, namely, an estimate
of the existing extent of atherosclerosis (cf. Corn-
field, 1962), and also of the critical extent of the
disease at which the latent process becomes mani-
fest. In the absence of this information it is
evident that casual determinations of plasma
cholesterol can be of little or no practical value in
the prognosis of coronary heart disease.
The same deductive process can be equally well applied to the \([\beta]\)-cholesterol], but the other factors referred to in Table I are less tractable, because their frequency distributions are not normal. Nonetheless, the argument is valid to a first approximation and leads to the conclusion that no measurement of plasma lipids is of practical use in deciding when coronary arteriosclerosis is likely to reach its climax.

SUMMARY

Analyses of plasma lipoproteins by both the ultracentrifugal and the Cohn techniques have shown that the average level of \(\alpha\)-lipoprotein in healthy Englishmen is very similar to that found in other societies, whereas the level of \(\beta\)-lipoprotein, though rather less than that of the average American, is substantially more than is found in communities with a lower standard of living. The concentration of both lipoprotein species increases with the age of the subject. Moreover, it has been shown that, when the total plasma cholesterol level increases, it is almost entirely the result of a rise in \(\beta\)-cholesterol level, the concentration of \(\alpha\)-cholesterol remaining almost unchanged.

In subjects suffering from atherosclerotic coronary heart disease there is a significant depression of \(\alpha\)-cholesterol levels below, and an increase of \(\beta\)-cholesterol levels above those in healthy men.

By combining the frequency distributions for healthy and diseased men, a relation between plasma cholesterol and the incidence of disease has been deduced. This strongly favours the view that the rate of incidence in a society can be related to the mean plasma lipid level of its members. In particular, a level of \(\beta\)-cholesterol above about 100 mg./100 ml., or of total cholesterol more than 150 mg./100 ml., may be considered as abnormal. It can be shown, however, to be impracticable to estimate the status of atherosclerotic coronary heart disease in an individual from plasma lipid measurements alone.

It is a pleasure to acknowledge the help and encouragement of Sir Charles Dodds during these investigations, and also the support of the Medical Research Council and the British Heart Foundation. Our thanks are also due to Major-General R. A. Bennett, M.D., and the pensioners of the Royal Hospital, Chelsea, who provided many of the samples from elderly men, and also to the M.R.C. Social Medicine Research Unit, by whose efforts many other samples were provided. We are especially grateful to our many colleagues who have patiently undertaken the tedious experimental work.

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