An enigma for the 1980s is the continuing diet-heart controversy. Over 60 years ago, the cholesterol-fed rabbit model of atherosclerosis was discovered, and coronary atherosclerosis was linked to the clinical syndrome of myocardial infarction. Over 30 years ago, the role of dietary fat in the etiology of atherosclerotic disease was suggested, and epidemiologic evidence linking diet to atherosclerotic disease began to accumulate. The number of scientific papers on diet and atherosclerosis is now enormous. On the one hand, believers assemble these reports into an argument for dietary cholesterol and saturated fat being major causative agents for the high levels of atherosclerosis in the technically developed countries. On the other hand, skeptics contend that inconsistencies, gaps, and paradoxes in the evidence do not permit one to infer a causative relationship between these dietary components and atherosclerosis. When conservative interpretations of the diet-heart issue \(^1\) are contrasted with recommendations such as those of the American Heart Association, \(^2\) it is no wonder that the public is confused.

Why is this issue so difficult to resolve? In this review, we will examine selected aspects of the diet-heart relationship that may be responsible for some of the gaps in the evidence linking diet to atherosclerotic disease. The first of these, the apparent contradiction between correlation coefficients based on group means and correlation coefficients based on individual values within groups, has been cited frequently as a gap in the epidemiologic evidence for an association of diet with atherosclerotic disease. Our analysis of this incongruity suggests that the true correlation coefficient is somewhere between.

A second issue, the possibility that dietary cholesterol and saturated fat may have different effects on one of the lipoprotein species, could lead to a more precise definition of the steps between diet and atherosclerotic disease, and could help to relate the rapidly developing knowledge of lipoprotein-cellular interactions to nutritional effects on lipoprotein metabolism. Finally, the observation that several species of animals fed a diet enriched in cholesterol and saturated fat frequently adapt to that diet suggests that humans also may adapt to similar diets. If adaptation does occur in humans, it may account for some of the inconsistencies encountered in testing fat-modified diets.
The Problem of Correlations

Most comparisons of population groups have found a strong positive association between the average dietary cholesterol or saturated fat intakes of these groups with average plasma cholesterol concentrations, average severity of atherosclerosis, or mortality or morbidity rates for the atherosclerotic diseases. In contrast, most surveys of individuals within groups have found a weak association, or none, between dietary lipid intake and either plasma cholesterol concentrations or probability of developing clinically manifest atherosclerotic disease. This failure to find strong positive associations based on individual values has been interpreted as a major gap in the evidence for a relationship of diet to atherosclerosis. The reasons for this discrepancy may be found by considering the difficulties in obtaining accurate estimates of the degree of association between two variables.

To examine the correlation coefficients applicable to these two different situations, we will use mathematical models to simulate the correlation of two variables, X and Y, among population groups and among individuals within these groups. The two variables could represent pairs of variables such as dietary intake of a lipid and an indicator of atherosclerotic disease.

Associations Based on Group Values

Robinson first discussed the differences between correlation coefficients computed using group means and correlation coefficients computed using individual values. Different values of correlation coefficients obtained by these two different approaches are not necessarily contradictory.

Let us suppose that a population is subdivided into subpopulations. Within each subpopulation, the values of the two variables X and Y for individuals have a correlation coefficient \( \gamma \). The means of X and Y in the various subpopulations are different, and the correlation coefficient between the subpopulation means is \( \rho \).

The correlation in the overall population (Appendix A) is

\[
\text{Corr} (\bar{X}, \bar{Y}) = \frac{\rho \sigma_x \sigma_y + \gamma \delta_x \delta_y}{\sqrt{(\sigma_x^2 + \delta_x^2)(\sigma_y^2 + \delta_y^2)}}
\]

where \( \bar{X} \) and \( \bar{Y} \) indicate that we have averaged over the values of the X and Y variables for the subjects within the subpopulations.

Thus, in using the group means to examine the relationship between X and Y, the terms containing the within-subpopulation variances are divided by the sample size m, thereby reducing the effect of the within-subpopulation correlation and variances. If m is large, within-subpopulation effects are negligible.

So far, we have dealt with the true relationship among the variables, that is, the parameters, and have not considered the effect of the sampling plan on estimation of a correlation coefficient. In most experiments or surveys, individuals within subpopulations are selected randomly. In contrast, the subpopulations are almost always selected purposively because of practical considerations or because the investigator wishes to obtain a wide range. The true correlation coefficient cannot be estimated when levels of one variable are selected purposively. When purposive selection is used and a correlation coefficient is computed, we have no way of knowing how the computed coefficient relates to the true underlying parameter. The wide range deliberately selected by the investigator aggravates the uncertainty. To explain this uncertainty, we examine the relationship between the correlation coefficient and the variances.
If the regression of Y on X is linear with constant variance about the regression line, the square of the correlation coefficient of X and Y is related to the variances and conditional variances by

\[ (\text{Corr}(X, Y))^2 = 1 - \frac{\text{Var}(Y|X)}{\text{Var}(Y)}. \]

\text{Var}(Y) \text{ is the variance of variable } Y \text{ and } \text{Var}(Y|X) \text{ is the variance of } Y \text{ for any given value of variable } X. \text{ If there is a relationship between } X \text{ and } Y, \text{ when the investigator chooses the levels of } X, \text{ no proper estimate of } \text{Var}(Y) \text{ can be obtained. } \text{Var}(Y|X) \text{ can be estimated by the variance about the linear regression line. Suppose that the variance of } Y \text{ were estimated as if the } Y \text{ values were from a random sample, even though the distribution of } Y \text{ values was affected through its relationship to the } X \text{ values which were selected. If levels of the } X \text{ variable were chosen to achieve a wide range, the variance of } Y \text{ will be overestimated because extreme values of } Y \text{ are represented to a greater degree than actually exists in the population. As the calculated } \text{Var}(Y) \text{ becomes artificially large because of being overestimated, the second term on the right side of the equation becomes small and the square of the correlation coefficient approaches 1. Even if the true coefficient is close to zero, this selection has the potential to make the calculated correlation coefficient appear to be close to 1 or to -1.}

When the subpopulations are selected purposely, relationships are more properly examined by regression techniques.\(^6\) Because tests of a correlation coefficient being zero and the slope of a linear regression line being zero are algebraically equivalent (although not conceptually equivalent), we may interpret a significant correlation coefficient as evidence for a relationship. The statistical test result may be valid, but the numerical value of the correlation coefficient may not be a good estimate of the underlying parameter, and is likely to be higher (that is, closer to 1 or to -1) than the true coefficient.

Although in practice purposive selection of subpopulations is necessary, it usually is feasible to select subjects within subpopulations randomly. Thus, a correlation coefficient between two variables within any subpopulation (previously designated \(\gamma\)) can be properly estimated.

**Associations Based on Individual Values**

As mentioned previously, correlation coefficients between diet and disease endpoints estimated from individual values within subpopulations usually have been quite low in comparison to those based on group means.\(^2\)^\(^4\) In this section we show how within-subject variability makes it difficult to detect relationships based on observations on individuals within subpopulations. The effects of within-subject variation and of measurement error, and these effects on the association between dietary intake and serum cholesterol, have been discussed by Liu et al.\(^8\) and Jacobs et al.\(^9\)

A mathematical model similar to that used in the foregoing section will be useful (Appendix B). Following the previous notation, consider subjects within the \(i^\text{th}\) subpopulation. The correlation among the observations \((X_{ij}, Y_{ij})\) in the subpopulation is

\[ \text{Corr}(X_{ij}, Y_{ij}) = \frac{\gamma}{\sqrt{(1 + \frac{\epsilon^2}{\delta^2})(1 + \frac{\epsilon^2}{\delta^2})}}. \]

\(X_{ij}\) and \(Y_{ij}\) are the values of the \(X\) and \(Y\) variables for the \(k^\text{th}\) observation on the \(j^\text{th}\) subject in the \(i^\text{th}\) subpopulation; \(\epsilon_x\) and \(\epsilon_y\) are the within-individual standard deviations; and, as before, \(\delta_x\) and \(\delta_y\) are the within-subpopulation standard deviations. Within-subject variability is due to both biologic variation and methodologic error.

This equation shows that the correlation coefficient for \(X\) and \(Y\) is not the true coefficient, but a value less than the true coefficient because we divide the true coefficient, \(\gamma\), by a number that is greater than 1. If within-subject variability \((\epsilon_x\) or \(\epsilon_y\)) is large, the observed correlation coefficient can be quite small, even though the true values are highly related.

The degradation of the correlation coefficient by within-subject variation can be illustrated by some examples. If \(\gamma = 0.75\) (the true correlation), the observed correlation is reduced to 0.5 if \(\epsilon^2 = 0.5\) and \(\delta^2 = 0.25\). If \(\epsilon^2\) and \(\delta^2\) are increased to 1, then the observed correlation between \(X\) and \(Y\) is reduced to 0.375. If \(\gamma\) is 0.5, the observed correlation coefficient is reduced to 0.33 and 0.25, respectively, under the same assumptions for within- and between-subject variation.

If, instead of single observations, we had \(I\) observations on each subject, the correlation among the means is

\[ \text{Corr}(\bar{X}_{ij}, \bar{Y}_{ij}) = \frac{\gamma}{\sqrt{(1 + \frac{\epsilon^2}{I\delta^2})(1 + \frac{\epsilon^2}{I\delta^2})}}. \]

where \(\bar{X}_{ij}\) and \(\bar{Y}_{ij}\) indicate we have averaged over the \(I\) observations on each subject.

As \(I\) increases, the correlation coefficient among the means of several observations approaches the true coefficient \(\gamma\) since we are diminishing the effect of the within-subject vari-
The within-subject variation has the potential for affecting the within-subpopulation correlation greatly, but has less potential for affecting the group correlation. If subjects per subpopulation are randomly selected and \( I \) observations made on each subject, the correlation among the subpopulation means is

\[
\text{Corr}(\bar{X}_l, \bar{Y}_l) = \frac{p + \gamma \frac{\delta_x \delta_y}{\sigma_x \sigma_y}}{\sqrt{(1 + \frac{\delta_x^2}{\sigma_x^2} + \frac{\delta_y^2}{\sigma_y^2}) (1 + \frac{\delta_x^2}{\sigma_x^2} + \frac{\delta_y^2}{\sigma_y^2})}}
\]

where \( \bar{X}_l \) and \( \bar{Y}_l \) indicate we have averaged over the multiple observations on each individual and over the subjects within the subpopulations. The terms involving the within-subject variation are reduced by dividing by the product of \( I \) and \( m \).

**Some Examples**

In the International Atherosclerosis Project, 19 geographic-racial groups were ranked on the basis of advanced atherosclerotic arterial lesions, percentage of dietary calories from fat, and serum cholesterol concentration.10 A rank correlation coefficient of 0.688 was calculated between percentage of calories from fat and raised lesions, and a rank correlation coefficient of 0.741 was calculated between percentage of calories from fat and serum cholesterol. The selection of geographic-racial groups was not random but was based on practical considerations and a desire to obtain extremes. Thus, the computed correlation coefficient cannot be regarded as an estimate of \( p \) in our model, that is, the correlation among subpopulation means.

In the Seven Countries Study, Keys11 reported a correlation coefficient of 0.84 between the average percentage of calories from saturated fat and the 10-year coronary heart disease mortality rate; and a correlation coefficient of 0.73 between the average percentage of calories from saturated fat and the 10-year coronary incidence rate. The dietary intake values were derived from averages of intakes of saturated fat in 16 cohorts of men. This correlation coefficient clearly represents a group correlation in which the effects of within-subgroup variation have been reduced by averaging. Because these cohorts were selected purposively, and not randomly, we do not know to what extent the computed correlation coefficients reflect the true relationships among subpopulation means.

In the same Seven Countries Study, a correlation coefficient of 0.90 was found between the mean serum cholesterol concentrations of the cohorts and the serum cholesterol concentrations predicted from the fat composition of the diets. The serum cholesterol concentrations were predicted by a formula obtained from multiple regression analysis of controlled dietary experiments. However, no significant association was found between serum cholesterol concentration and dietary fat intake for individuals within the cohorts. Keys interpreted this discrepancy as a natural consequence of the large within-subject variation, which was similar in magnitude to between-subject variation. That is, even if a true relationship existed within the cohorts between fat composition of diet and serum cholesterol concentration, the within-subject variability would make this relationship difficult to detect.
Studies using other measurements of dietary intakes and disease endpoints also have failed to detect strong associations. For example, in a longitudinal study of 7705 men of Japanese ancestry living in Hawaii, Yano et al.\textsuperscript{12} found no relationship between fat intake and myocardial infarction or death from coronary heart disease. From dietary data obtained in interviews with next of kin of deceased persons whose arteries were graded for atherosclerotic lesions at autopsy, Moore et al.\textsuperscript{13} found an association between animal fat intake and percent intimal surface area involved with advanced atherosclerotic lesions in the coronary arteries. However, they found no association of dietary cholesterol intake with arterial lesions. These results are typical of those obtained in many other studies involving diet, plasma cholesterol concentrations, and various indicators of atherosclerosis and the atherosclerotic diseases.

In the Western Electric Study, a longitudinal study of 1885 men, Paul et al.\textsuperscript{14} found no differences in dietary intake between noncoronary cases and coronary cases after 5 years of follow-up. However, after 20 years' follow-up, Shekelle et al.\textsuperscript{15} reported a small but significant association between mean diet score and 19-year risk of death from coronary heart disease. The mean diet score was the average of the diet scores obtained at the initial examination and at a reexamination 1 year later. The averaging of these two scores reduced the effects of within patient variability.

In this same study, Shekelle et al. also reported a significant correlation between diet score and serum cholesterol concentration. The coefficient was 0.124, much less than the 0.90 found by Keys\textsuperscript{11} on the basis of between-group correlation. This contrast is another example suggesting that the individual correlation coefficient may be underestimated, while the between-group correlation coefficient may be overestimated.

**Evaluation of Group and Individual Correlations**

The foregoing discussion suggests several reasons why group correlations between dietary lipid intake and serum cholesterol concentration, or between dietary lipid intake and coronary heart disease mortality, seem to be much greater than the individual correlation. The true correlation among the subpopulation means actually may be much greater than the individual correlation within subpopulations. The group correlation may simply appear to be larger than individual correlations because averaging reduces the effects of within-subpopulation variation, because the group correlation coefficient may be overestimated due to purposive selection, and because within-subject variability causes the individual correlation coefficient to be underestimated.

We suggest that the limitations of each type of analysis be considered when examining the strength of the hypothesized relationship between diet and heart disease. A balanced evaluation of the evidence probably will indicate that the strength of the true relationship between diet and heart disease is somewhere between the values computed from group data and those computed from individual data.

**Response of High Density Lipoprotein Cholesterol to Dietary Factors**

Shortly after intensive investigation of the relationships of serum lipids and lipoproteins to atherosclerotic disease began in the 1950s, Gofman et al.\textsuperscript{16} suggested that the lipoprotein profile might be more predictive of disease than the total serum cholesterol concentration. This idea fell out of favor until epidemiologic evidence accumulated in the 1970s indicated that high density lipoprotein (HDL) cholesterol was inversely associated with atherosclerotic disease\textsuperscript{17,18} and with atherosclerosis.\textsuperscript{19,20} Meanwhile, most investigators studying the effects of diet components on serum lipids measured serum cholesterol as an endpoint because it had been firmly established as the major independent risk factor for the atherosclerotic diseases and appeared to be the major intervening variable linking diet to atherogenesis.

As knowledge of lipoprotein metabolism developed, as the specific functions of each lipoprotein class became known, and as the contrasting relationships of low density lipoprotein (LDL) and HDL to atherosclerosis became apparent, investigators returned to the issue of diet and hyperlipoproteinemia. A number of reports now indicate that each dietary lipid may affect the plasma lipoprotein profile differently and may also alter the structure and composition of some lipoproteins. Dietary effects on LDL were reviewed by Grundy.\textsuperscript{21} There is now evidence which suggests that HDL cholesterol, previously thought to be unaffected by diet,\textsuperscript{22} may be influenced along with LDL cholesterol by some dietary components.

Several cross-sectional epidemiological studies have examined the relation of HDL cholesterol levels to nutrient intake. In the Princeton School District Study, Morrison et al.,\textsuperscript{23} using correlation analysis, found that total fat, saturated fat, polyunsaturated fat, and cholesterol intake had no association with HDL levels. There was a small but significant (p < 0.05) negative association of sucrose, protein, and calories with HDL cholesterol. On the other hand, deciles of HDL
cholesterol levels showed a significant ($p < 0.05$) difference in saturated fat and polyunsaturated fat intake and P/S (polyunsaturated to saturated fat) ratio.

The Lipid Research Clinic Program examined the relation of nutrient intake based on 24-hour recalls to HDL cholesterol concentrations. In 4855 subjects from 10 clinics, they found a strong positive association between alcohol intake and HDL cholesterol level, and a negative association between total carbohydrate, sucrose, and starch intake and HDL cholesterol. In another analysis of the Lipid Research Clinic subjects, Beagliehle et al. found cholesterol intake positively correlated with HDL cholesterol in 11- to 17-year-old males. Total carbohydrate and sucrose intake were negatively correlated with HDL in 18- to 25-year-old females. Otherwise, they found no association between nutrients and HDL cholesterol in 6- to 25-year-old subjects.

In view of the limitations (discussed in the preceding section of this review) afflicting all surveys that search for associations between nutritional factors and their suspected effects within single population groups, it will be difficult for additional studies of this type to resolve the question of diet and HDL cholesterol.

Experiments that alter dietary cholesterol or fat and measure the resulting changes in plasma lipoproteins have greater capability to detect effects due to dietary components, but usually are limited to relatively short-term exposures. Those that have examined HDL cholesterol responses in humans are summarized in table 1. Most of the studies altered saturation of fat, but some simultaneously changed the cholesterol intake and several changed the total fat intake. Six of the 15 reports describe a significant decrease in HDL cholesterol when subjects were changed to a diet lower in saturated fat, either by increasing the P/S ratio or by lowering total fat. HDL cholesterol in some groups of subjects in two other studies also decreased with less saturated fat; but HDL cholesterol in other groups in the same studies showed no significant change with less saturated fat. Three studies found an increase in HDL cholesterol with less saturated fat in the diet. The trend, therefore, seems to be for HDL cholesterol to decrease as saturation of dietary fat decreases. However, the results are not consistent and an unequivocal conclusion cannot be drawn from current information.

Some investigators have proposed that the level of HDL cholesterol itself is less important in determining cardiovascular risk than the LDL/HDL ratio. We calculated these ratios for each study in table 1 and found the results also to be inconsistent. Changes in LDL/HDL ratio with dietary changes ranged from $-2.4$ to $+1.1$. There was no consistent relationship between either the direction or the magnitude of change in HDL cholesterol and the LDL/HDL ratio. For example, a decrease in HDL cholesterol was associated in one study with a decrease, in another with an increase, and in others with no change in the LDL/HDL cholesterol ratio.

Although high levels of HDL cholesterol and low LDL/HDL ratios are associated with less cardiovascular risk and less severe atherosclerosis, the relative importance of these two variables and whether manipulating them by diet actually changes a person's risk status are not known. However, we no longer can assume that plasma HDL cholesterol concentration is unresponsive to dietary lipid intake. In particular, some experiments indicate that it is influenced by dietary saturated fat. As knowledge of the functions of HDL and its interactions with arterial wall cells continues to grow, more precise definition of the effects of each dietary component on HDL should provide more insight into the diet-heart relationship.

Adaptation to Diet

The idea of adaptation is common in biology, but adaptation to diet, and particularly to an atherogenic diet, has not often been considered in regard to disease caused by overnutrition. A phenomenon similar to adaptation was suggested by Reiser and Sidelman in speculating on the function of cholesterol in mother's milk. However, the hypothesis that a high intake of cholesterol in infancy, as experienced by breast-fed infants, induces a tolerance for dietary cholesterol later in life has not been supported by observations on humans.

We have become aware of a phenomenon that appears to represent adaptation to diets enriched in cholesterol and saturated fat. Among investigators working with diet-induced experimental atherosclerosis, it is common knowledge that, in animals fed a high-cholesterol saturated fat diet, the serum cholesterol concentration rises and...
Table 1. Effects of Dietary Cholesterol and Fat on HDL Cholesterol In Humans

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Description</th>
<th>Subjects</th>
<th>Diet</th>
<th>Period (days)</th>
<th>Cholesterol (mg/day)</th>
<th>%Kcal Fat Saturation†</th>
<th>HDL cholesterol (mg/dl) Change†</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farquhar and Sokolow 1958</td>
<td>15</td>
<td>14 M, 1 F, 36-63 years, clinical evidence of arteriosclerosis</td>
<td>A. Habitual diet</td>
<td>26-960</td>
<td>56</td>
<td>620</td>
<td>33-53</td>
<td>95% S</td>
<td>40 ± 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Habitual diet with safflower oil substituted for saturated fat</td>
<td></td>
<td></td>
<td>496</td>
<td>33-53</td>
<td>59 g P</td>
<td></td>
</tr>
<tr>
<td>Spritz and Mishkel 1968</td>
<td>12</td>
<td>6 M, 6 F, 21-70 years, 6 Type II, 6 normolipemic, 10 with occlusive vascular disease</td>
<td>A. Formula with butter or coconut oil</td>
<td>21-136</td>
<td></td>
<td>40</td>
<td>P/S &lt; 0.1</td>
<td>33 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Formula with corn oil or safflower oil</td>
<td></td>
<td></td>
<td>40</td>
<td>P/S = 4.9 or P/S = 8.1</td>
<td>32 ± 2</td>
<td></td>
</tr>
<tr>
<td>Schonfeld et al. 1976</td>
<td>16</td>
<td>10 M, 6 F, 18-32 years, normolipemic</td>
<td>A. Habitual diet</td>
<td></td>
<td>4-5</td>
<td>4</td>
<td>&lt; 1</td>
<td>43 ± 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Formula containing 80% carbohydrate, 20% protein</td>
<td></td>
<td></td>
<td>4</td>
<td>&lt; 1</td>
<td>32 ± 8</td>
<td>-11</td>
</tr>
<tr>
<td>Blum et al. 1977</td>
<td>4</td>
<td>1 M, 3 F, 18-23 years, normolipemic</td>
<td>A. Mixed food</td>
<td>14</td>
<td>≥ 14</td>
<td>&lt; 300</td>
<td>P/S = 0.2</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Mixed food</td>
<td></td>
<td></td>
<td>&lt; 3</td>
<td>21</td>
<td>-10 &lt; 0.02</td>
<td></td>
</tr>
<tr>
<td>Mahley et al. 1978</td>
<td>6</td>
<td>2 M, 4 F, 27-40 years, normolipemic</td>
<td>A. Habitual diet plus 4-6 eggs/day</td>
<td>28</td>
<td>≥ 28</td>
<td>&gt; 1000-1500</td>
<td>&lt; 3</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Habitual diet</td>
<td></td>
<td></td>
<td>&lt; 3</td>
<td>43</td>
<td>-7 NS</td>
<td></td>
</tr>
<tr>
<td>Shepherd et al. 1978</td>
<td>4</td>
<td>19-22 years, normolipemic</td>
<td>A. Mixed food</td>
<td>35</td>
<td>35</td>
<td>400</td>
<td>P/S = 0.3</td>
<td>46 ± 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Mixed food</td>
<td></td>
<td></td>
<td>400</td>
<td>P/S = 4.0</td>
<td>31 ± 3</td>
<td>-15</td>
</tr>
<tr>
<td>Von Lossonczy et al. 1978</td>
<td>42</td>
<td>19 M, 23 F, 24-76 years</td>
<td>A. Habitual diet with 150 g Gouda cheese/day</td>
<td>21</td>
<td>21</td>
<td>&lt; 3</td>
<td>S</td>
<td>56 ± 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Habitual diet with 200 g mackerel/day</td>
<td></td>
<td></td>
<td>&lt; 3</td>
<td>P</td>
<td>59 ± 16</td>
<td>+3</td>
</tr>
<tr>
<td>Hjermann et al. 1979</td>
<td>23</td>
<td>M, 40-49 years, hypercholesterolemic, selected for good diet response</td>
<td>Habitual diet</td>
<td>~ 1460</td>
<td></td>
<td>~ 527</td>
<td>44</td>
<td>P/S = 0.4</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lipid lowering diet</td>
<td>~ 1460</td>
<td></td>
<td>~ 289</td>
<td>28</td>
<td>P/S = 1.0</td>
<td>50</td>
</tr>
</tbody>
</table>

Note: The table presents the effects of dietary and fat on HDL cholesterol in humans. The reference numbers indicate the sources of the data. The description of the subjects includes details about age, sex, and medical conditions. The diet section describes the type of diet used, including the period of observation and the cholesterol content. The HDL cholesterol level is also reported along with the change and statistical significance (P†).
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Description</th>
<th>Subjects</th>
<th>Diet</th>
<th>HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%Kcal Saturation†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P†</td>
</tr>
<tr>
<td>Applebaum-Bowden et al. 1979</td>
<td>3</td>
<td>2 M, 1 F, 29–59 years, 2 normo-</td>
<td>A. High cholesterol formula</td>
<td>30</td>
<td>5016 45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lipemic, 1 hypercholesterolemic</td>
<td>B. Habitual diet</td>
<td>-</td>
<td>-    328</td>
</tr>
<tr>
<td>Ernst et al. 1980</td>
<td>9</td>
<td>M, Type II, mean age 39 years</td>
<td>A. Habitual diet</td>
<td>11-15</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>F, Type II, mean age 49 years</td>
<td>B. Weighed mixed food</td>
<td>11-15</td>
<td>-</td>
</tr>
<tr>
<td>Shepherd et al. 1980</td>
<td>7</td>
<td>M, normolipemic, mean age 22 years</td>
<td>A. Habitual diet</td>
<td>11-15</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>F, normolipemic, mean age 19 years</td>
<td>B. Weighed mixed food</td>
<td>11-15</td>
<td>-</td>
</tr>
<tr>
<td>Vessby et al. 1980</td>
<td>9</td>
<td>3 M, 6 F, 44–70 years, hyper-</td>
<td>A. Habitual diet</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lipemic</td>
<td>B. Weighed mixed food</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3 M, 4 F, 23–69 years, Type IIa</td>
<td>A. Mixed foods</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Mixed foods</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3 M, 2 F, 40–71 years, Type IIb</td>
<td>A. Mixed foods</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Mixed foods</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>12 M, 6 F, 39–78 years, Type IV</td>
<td>A. Mixed foods</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Mixed foods</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Tan et al. 1980</td>
<td>6</td>
<td>2 M, 4 F, 26–35 years, normo-</td>
<td>A. High cholesterol, high saturated fat</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lipemic</td>
<td>B. Habitual diet</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C. Low cholesterol, high polyunsaturated fat</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>

*Change in HDL cholesterol from a more cholesterolemic diet to a less cholesterolemic diet.
†S = saturated; P = polyunsaturated; P/S = polyunsaturated-to-saturated fat ratio; P = probability.
‡HDL cholesterol values calculated from original data.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects Description</th>
<th>No.</th>
<th>Period (days)</th>
<th>Diet Description</th>
<th>Cholesterol (mg/day) Range</th>
<th>Period (days)</th>
<th>Fat %Kcal Saturation</th>
<th>HDL cholesterol mg/dl Change* Pf ± so (mg/dl) %Kcal Saturation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brussard et al. 1980°</td>
<td>37 M, 23 F, 18-30 years, normolipemic, divided into 4 groups</td>
<td>15</td>
<td>17</td>
<td>A. Weighed mixed food, moderate fat</td>
<td>302</td>
<td>16</td>
<td>30/30</td>
<td>P/S = 1.1 +2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>56</td>
<td>A. Weighed mixed food, moderate fat</td>
<td>284</td>
<td>16</td>
<td>30/30</td>
<td>P/S = 1.1 +3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>56</td>
<td>A. Weighed mixed food, low fat</td>
<td>257</td>
<td>17</td>
<td>30/30</td>
<td>P/S = 0.4 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>56</td>
<td>A. Weighed mixed food, moderate fat</td>
<td>302</td>
<td>17</td>
<td>30/30</td>
<td>P/S = 1.1 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>17</td>
<td>A. Weighed mixed food, moderate fat</td>
<td>302</td>
<td>17</td>
<td>30/30</td>
<td>P/S = 1.1 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>56</td>
<td>A. Weighed mixed food, low fat</td>
<td>257</td>
<td>17</td>
<td>40/22</td>
<td>P/S = 1.7 +4</td>
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<tr>
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<td>15</td>
<td>56</td>
<td>A. Weighed mixed food, low fat</td>
<td>302</td>
<td>17</td>
<td>40/22</td>
<td>P/S = 0.2 0</td>
</tr>
</tbody>
</table>

*Change in HDL cholesterol from a more cholesterolemic diet to a less cholesterolemic diet.
†HDL cholesterol values calculated from original data.
‡S = saturated; P = polyunsaturated; P/S = polyunsaturated-to-saturated fat ratio; P = probability.
after about 1 year begins to decline. In a recent experiment, baboons were maintained on a high-cholesterol, high-saturated fat diet for 2 years. The total serum cholesterol concentration rose to about 225 mg/dl within 4 months after the start of the diet, and began to fall about 8 months later (figure 1). At the termination of the experiment after 27 months on the diet, the serum cholesterol concentration had declined to about 180 mg/dl. All of the decline after the peak elevation occurred in LDL cholesterol. We observed an even greater decline in another experiment in which baboons were maintained on a similar diet for 3½ years (unpublished observations). In that experiment, the total serum cholesterol rose to about 250 mg/dl and fell to about 160 mg/dl at the end.

A similar decline in serum cholesterol occurs in other species of nonhuman primates that respond to the atherogenic diet with much greater elevations in LDL cholesterol than does the baboon. For example, in a long-term experiment designed to test regression of diet-induced lesions, rhesus monkeys developed a peak level of plasma cholesterol of about 900 mg/dl after 4 months on an atherogenic diet. In the 97 animals continued on the same diet, plasma cholesterol began to decline after 14 months and reached 550 mg/dl at 35 months (figure 2; personal communication from M.G. Bond, Winston-Salem, North Carolina). A similar pattern of response to diet was also observed in rhesus monkeys by DePalma et al., and in patas monkeys by Mahley et al.

A decline in plasma cholesterol concentration after prolonged feeding of an atherogenic diet has also been observed in rabbits but usually has been attributed to the massive cholesterylisis that develops in the liver and other organs of this species. However, the response of serum cholesterol to atherogenic diets in baboons is modest and the animals develop no lesions resembling those of cholesterol storage disease. Therefore, it appears that the decline in serum cholesterol in the baboon cannot be attributed to a toxic effect on the liver or other tissues.

We have found no observations that directly demonstrate a similar adaptation to diet in humans. To detect adaptation in humans would require that subjects consume a basal diet low in cholesterol and saturated fat until their serum cholesterol levels had stabilized, and then consume a diet high in cholesterol and saturated fat for several years. Such an experiment has not been performed.

If adaptation does occur in humans, it may be partially responsible for the failure of diet modification to reduce serum cholesterol to the degree predicted. Most studies designed to test the effects of added dietary cholesterol and fat have compared serum cholesterol levels of subjects on a diet low in cholesterol and saturated fat with those of the same subjects on the test diet. The results were then used to predict changes in serum cholesterol when subjects were placed on serum cholesterol-lowering diets.

For example, in the National Diet-Heart Study, the observed decline in serum cholesterol was only about 60% of the decline predicted from the equations. This discrepancy was attributed to failure of subjects to adhere to the prescribed diet and to inadequacy of the diet records.

If the subjects, whose baseline values were determined while on their habitual diets, were a
mixture of persons who had adapted to their diets and those who had not adapted, another explanation for the failure to achieve the anticipated reduction might be offered. Subjects who had adapted would have only a limited capacity to reduce their serum cholesterol levels. The ability to achieve a reduction in serum cholesterol may have been limited further by the exclusion of subjects with serum cholesterol levels over 350 mg/dl, and it seems likely that these subjects would include a high proportion of nonadaptors.

Adaptation to an atherogenic diet has been seen in animal experiments frequently enough to indicate that it is real, and to suggest that it is likely to occur also in humans. However, we can only speculate as to its mechanism. If it involves primarily LDL cholesterol, as suggested in our experiments with baboons, the atherogenicity of a diet would be greatest during the first year or two of exposure. This phenomenon deserves exploration in humans and animal models, since any insight into the mechanism of the phenomenon would suggest means to control hyperlipidemia.

Conclusion

It appears likely that the hypothesized relationship of dietary cholesterol and saturated fat to atherosclerosis will be modified as interpretation of epidemiologic findings is refined, as knowledge of dietary effects on lipoproteins grows, and as evidence for an adaptive phenomenon accumulates. These are only a few highly selected examples of how intensive investigation of inconsistencies can lead to the discovery of hidden relationships, and resolution of paradoxes can lead to new insights.

Meanwhile, focusing on inconsistencies does not deprecate the judgment, based on evidence now available, that many Americans are likely to reduce their risk of atherosclerotic disease by modifying their diet. This judgment can be upheld while, at the same time, improved knowledge is developing the basis for more specific and possibly more effective dietary recommendations.

Appendix A

Let the true mean for the ith subpopulation be \( \alpha_i \) for the X variable and \( \alpha_j \) for the Y variable. The true values for the jth individual within the ith subpopulation, labeled \( X_{ij} \) and \( Y_{ij} \), are assumed to be

\[
X_{ij} = \alpha_i + \tau_{xij} \\
Y_{ij} = \alpha_j + \tau_{yij}
\]

where the \( \tau_{xij} \) and \( \tau_{yij} \) represent deviations of the individual from the subpopulation mean. Let \( \tau_{xij} \) have mean 0 and variance \( \delta_x \), and \( \tau_{yij} \) have mean 0 and variance \( \delta_y \). The correlation between \( \tau_{xij} \) and \( \tau_{yij} \) (the within subpopulation correlation coefficient) is \( \gamma \).

We assume the \( \alpha_i \) have a mean of \( \mu_i \) and a variance of \( \sigma_i^2 \) and the \( \alpha_j \) have a mean of \( \mu_j \) and a variance of \( \sigma_j^2 \). The correlation between \( \alpha_i \) and \( \alpha_j \) (the between subpopulation correlation coefficient) is \( \rho \).

We further assume the deviations in different individuals are independent of each other and of the subpopulation means.

In the population, the correlation between \( X_{ij} \) and \( Y_{ij} \) is

\[
\text{Corr} (X_{ij}, Y_{ij}) = \frac{\rho \sigma_x \sigma_y + \gamma \delta_x \delta_y}{\sqrt{(\sigma_x^2 + \delta_x^2)(\sigma_y^2 + \delta_y^2)}}
\]

Appendix B

In Appendix A we considered the true value of an individual to be a sum of a subpopulation mean and a deviation from the mean. Suppose repeated observations on this individual yielded different results, that is, there was within subject variation. We assume this additional variation is represented by an additive deviation from the true value. Let the kth observations on the jth individual in the ith subpopulation be

\[
X_{ijk} = \alpha_i + \tau_{xij} + \eta_{xijk} \\
Y_{ijk} = \alpha_j + \tau_{yij} + \eta_{yijk}
\]

where the \( \eta_{xijk} \) and \( \eta_{yijk} \) represent the deviation from the true values for the individual. Let \( \eta_{xijk} \) have mean 0 and variance \( \epsilon_x^2 \) and \( \eta_{yijk} \) have mean 0 and variance \( \epsilon_y^2 \). We assume \( \eta_{xijk} \) and \( \eta_{yijk} \) are uncorrelated. Other conditions remain as stated in Appendix A. We assume the deviations in different individuals and within individuals are independent of each other and the subpopulation means. Within a particular subpopulation

\[
\text{Corr} (X_{ijk}, Y_{ijk}) = \frac{\gamma}{\sqrt{(1 + \frac{\epsilon_x^2}{\delta_x^2})(1 + \frac{\epsilon_y^2}{\delta_y^2})}}
\]

and in the overall population

\[
\text{Corr} (X_{ijk}, Y_{ijk}) = \frac{\rho + \gamma \delta_x \delta_y}{\sqrt{(1 + \frac{\delta_x^2}{\sigma_x^2} + \frac{\epsilon_x^2}{\delta_x^2})(1 + \frac{\delta_y^2}{\sigma_y^2} + \frac{\epsilon_y^2}{\delta_y^2})}}
\]

Index Terms: dietary cholesterol • dietary fat • coronary heart disease • atherosclerosis • high density lipoprotein • correlations • adaptation
Unresolved problems in the diet-heart issue.
H C McGill, Jr, C A McMahan and J D Wene

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