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ISCHEMIC HEART DISEASE AND LIPIDS IN BLOOD AND DIET[1]

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INTRODUCTION

The number of individual and environmental characteristics correlated with the frequency of ischemic heart disease is large (39) and growing. Among the host of variables related to variations in the risk of ischemic heart disease, the associations with diet and serum lipids have attracted the greatest attention and

[1]In this article, the term calories refers to dietary Calories or kilocalories, equal to 1,000 heat calories.

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stimulated the greatest controversy. The controversy is engendered not just by conflict between epidermiological data and other research findings, but also by the apparent contradiction between different sets of epidemiological findings. Some studies present strong and consistent support for the hypothesis that diets high in saturated fat contribute to the causation of ischemic heart disease, and others offer no support at all. The intent of this review is not to resolve the controversy, but to clarify the basis for it.

Because the variables associated with ischemic heart disease are interrelated, to treat matters of diet and serum lipids in isolation from the other correlates ignores interactions that may help to explain patterns of the disease in populations. However, a truly holistic treatment is not possible here. In most instances the variables were investigated in separate studies, and integration of them must be largely inferential. Therefore this review has an almost entirely univariate focus.

The relation between diet and ischemic heart disease has been stated and modified many times, and not all forms of the hypothesis have been addressed appropriately in epidemiological studies. Indeed some of the modifications of the hypothesis have occurred as evolutionary adaptations to the failure of epidemiological data to support the proposition in its then existing form. Many of the intricacies of current knowledge of lipid metabolism and atherogenesis cannot be accommodated in epidemiological studies, since those studies must be economically feasible and employ procedures that are acceptable to healthy, free-living people. Further, new information usually cannot be assessed in antecedent studies, so that, for example, most of our data on population serum cholesterol values cannot be partitioned into high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions, as desirable as that would be. Therefore, the form of the hypothesis that can be evaluated epidemiologically is overly simple in biochemical terms; it does, however, include the elements essential to the formulation of a dietary program for the prevention of ischemic heart disease.

The hypothesis is that excessive ingestion of saturated fat leads to elevation of LDL-cholesterol in serum; this causes atherosclerosis, which in turn brings about clinical manifestations of myocardial ischemia.

In population-based research, total fat in the diet must often be used as an index of saturated fat; total serum cholesterol must usually be used as an index of LDL-cholesterol; and clinical diagnoses must be used as an index of atherosclerosis. The program is simplified by ignoring dietary cholesterol for the most part, and serum triglycerides entirely—exclusions that are dictated by the paucity of epidemiological data, and that are justifiable (40, 67), perhaps (10).

The evidence linking diet and ischemic heart disease may be divided into five categories.

1. Animal experiments. This field of inquiry has a long and distinguished history, and, despite the problems of determining what animal species are reasonable surrogates for humans, the findings offer strong evidence that dietary manipulation can cause atherosclerotic lesions to develop and to recede.
2. Experiments on individual human beings in tightly controlled environments. Data from these studies have demonstrated that dietary manipulation can cause serum cholesterol values to rise and fall in a predictable manner and in predictable quantity.

These fields of study are outside the realm of epidemiology, and are not considered further in this review. However, the strong evidence cannot be dismissed and must influence the evaluations of epidemiological evidence.

3. Comparative studies of populations and subsets of populations. Extensive bodies of data have been accumulated, ranging from national statistics of ischemic heart mortality and dietary fat to determinations of diet and serum cholesterol values for a considerable array of peoples exhibiting great cultural variation.
4. Observations of individuals in communities, sometimes extending over protracted periods of time. From these longitudinal studies, quantitative estimates of the risk of ischemic heart disease have been derived to measure the strength of the association between disease and a number of characteristics of study subjects ascertained at the beginning of the study.
5. Experiments involving modification of diets comparing the subsequent occurrence of ischemic heart disease between individuals within communities, and between communities. Direct experimental dietary intervention should represent the most stringent test of the hypothesis that the composition of diet affects the risk of ischemic heart disease.

The latter three categories of research lie within the purview of epidemiology, and are the subject of this review. The associations that can be explored in observational epidemiological research data are those between *(a)* serum cholesterol and ischemic heart disease; *(b)* diet and serum cholesterol; and *(c)* diet and ischemic heart disease. The diet modification experiments are reviewed as a separate category.

SERUM CHOLESTEROL AND ISCHEMIC HEART DISEASE

Little doubt exists that among middle-aged men living in Western, industrial societies the risk of ischemic heart disease rises as serum cholesterol increases over most of the serum cholesterol range. Following many reports of series of cases of ischemic heart disease in which the case profile included elevated

serum cholesterol, and a few case/comparison studies (28, 29, 88) in which the cases had higher mean values for serum cholesterol than did the noncases, cohort studies have been initiated. These prospective studies, in which serum cholesterol and other characteristics of the study subjects were measured prior to prolonged periods of observation, have consistently confirmed that serum cholesterol concentration strongly predicts subsequent ischemic heart disease. The association persists when other characteristics of study subjects are taken into account; that is, serum cholesterol makes an independent contribution to the prediction. Although the association has been expressed in many ways, the data extracted from the pooling project report (81) are fully illustrative (Table 1).

The eight studies show some variation, some of which is related to small numbers of observations; but generally, except in quintiles 1 and 2, the relative incidence rises monotonically as cholesterol values increase. The fact that the lowest quintile so often had higher mortality from ischemic heart disease than did the next higher quintile is troubling. This was observed among men in the middle of the age distribution, and in these studies in the United States, the serum cholesterol values for the lowest quintile were well above those measured in other populations with very low risk of ischemic heart disease. The association diminishes sharply above 60 years of age, and is not as strong for women as for men. Similar findings were obtained in Stockholm (10), the Western Collaborative Group Study (86), male garment workers in New York City (20), the Seven Countries Study (50), and the NIHONSAN Study (63). In a small prospective study in Scotland (4), however, cases of ischemic heart disease occurring over a five-year period showed no association with serum cholesterol concentration (nor with smoking or blood pressure).

Table 1 Relation of serum cholesterol determinations to subsequent incidence of ischemic heart disease in selected cohort studies.

	Standardized incidence ratios							
Quintile of serum cholesterol distribution	Albany	Chicago Gas Company	Western Electric Company	Framing-ham	Tecumseh	Los Angeles	Minnesota Business	Minnesota Railroad
1	72	100	62	74	10	37	64	47
2	67	61	57	50	83	46	78	50
3	72	89	70	88	56	116	117	77
4	129	124	99	160	145	73	117	96
5	177	118	159	167	242	143	189	194
All	100	100	100	100	100	100	100	100

The value of serum cholesterol measurement in a quantitative prediction of ischemic heart disease has been investigated, commonly as one element of a multivariate prediction model. The predictions have been said to be stunning successes or abysmal failures, and the difference seems more a matter of philosophy than of mathematics. Attempts to discriminate between persons with or destined to acquire manifest ischemic heart disease and those free of the disease are constrained by the reciprocal relation between sensitivity and specificity. Thus improving the sensitivity of a predictive index by lowering it to include more of the cases decreases the specificity as more noncases are included. The only escape from this trap is to modify the structure of the index, and this should be possible in the case of serum cholesterol by partitioning the measure into HDL and LDL components. However, data from previous studies (19, 32), in one of which only total serum cholesterol determinations were available, yielded estimates of sensitivity of about 25% when the specificity was acceptably high (98%) for application to free-living populations. Increased sensitivity in one study (14) of 35% was accompanied by a specificity of 75%; to misclassify one quarter of a healthy population as positive is too fine a screen for most public health programs.

Still another approach to the prediction of ischemic heart disease was taken by Cornfield (15), who analyzed the joint dependence of the disease on serum cholesterol and systolic blood pressure measurements, using Framingham data. He found the relation of serum cholesterol to disease to be a function of the serum cholesterol value to the 2.66 power. The implication of this is that a reduction of serum cholesterol of 1% would result in a reduction of 2.66% in the risk of ischemic heart disease across the entire range of serum cholesterol values; therefore the effective reduction in risk would rise rapidly as the effectiveness of serum chlolesterol reduction increased, and the absolute reduction in risk would be greater in the upper range of the serum cholesterol distribution. This notion is of importance in evaluating the experimental trials of diet modification.

DIET AND SERUM CHOLESTEROL

Comparisons Among Communities

Figures 1 and 2 represent an interpretive summary of a large array of population survey data. (6, 9, 13, 26, 35, 42, 45, 47, 48, 50–55, 60, 61, 66, 69, 70, 71, 78, 82, 84, 89, 90, 91, 94, 96, 98, 102, 103). The ages of the study subjects were grouped differently in different studies, so some of the points represent an interpolation of the data reported. For both men and women, serum cholesterol values are strongly related to the percent of total calories derived from fat, across broad ranges on each axis. The strength of this association has impressed

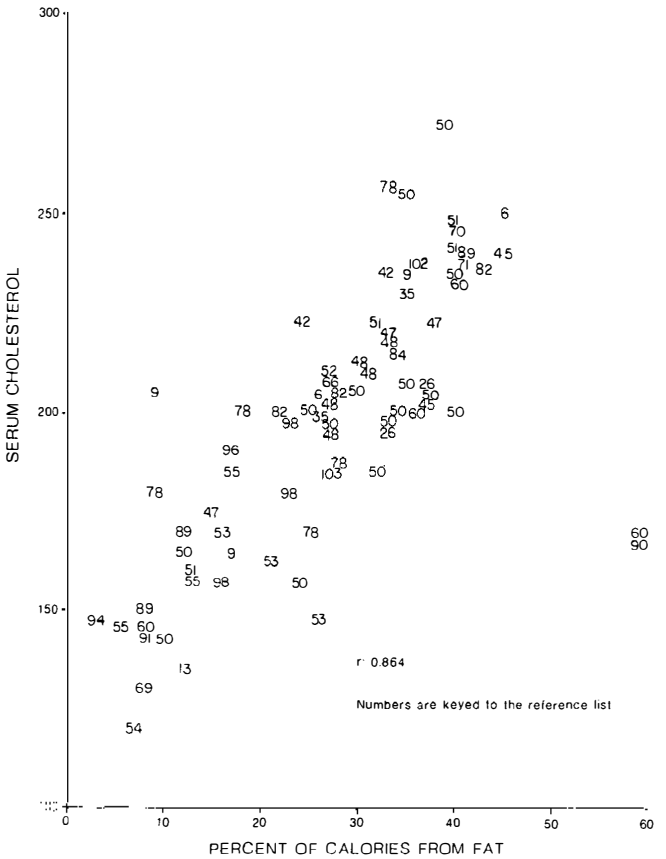

Figure 1 Scatter plot of dietary fat against serum cholesterol in males approximately 50 years of age; selected population groups.

epidemiologists for years, and it is all the more remarkable given that the studies were done over decades, using many study methods and laboratories, that each of the variables is subject to substantial measurement error, and that both variables are surrogates for the measurements we would prefer. The only impossible outliers in the distribution are the observations of the Masai and Samburu, which will probably never be explained away. Taking the studies at face value, the correlation between population mean values for serum cholesterol and percent of calories derived from fat is high (0.86 for males and 0.79 for females, excluding the Masai and Samburu).

The percent of calories derived from fat has been used here because it is the statistic related to dietary fat most commonly available from these studies. In some instances the dietary measurements were made on samples of the groups whose serum cholesterol was determined. Often the dietary assessments were

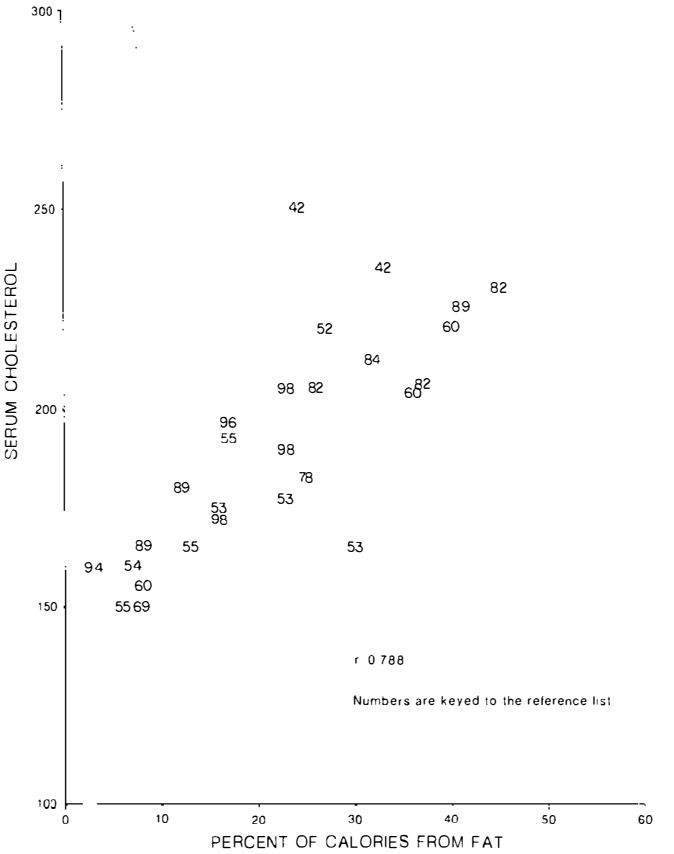

Figure 2 Scatter plot of dietary fat against serum cholesterol in females approximately 50 years of age; selected population groups.

presented without regard for gender; this surely overstates the total caloric intake for women and understates it for men, and the percent of calories from fat should be more resistant to this bias.

Comparisons Among Individuals Within Communities

In sharp contrast to those of the relation between communities, studies of the association between dietary constituents and serum cholesterol concentration in individuals have been bleak (Table 2). Except in the Tarahumara Indians, the variation in serum cholesterol values in the populations studied has not been significant correlated with the recorded variation in dietary intake. This observation has distressed some epidemiologists almost as much as the population surveys delighted them, and considerable effort has been spent on a campaign to save the hypothesis.

Table 2 Correlation coefficients for the relations between serum cholesterol concentration and various dietary measurements; selected population studies

	London Bankmen (71)	Israeli (48)	Framingham (31) 50–59 yrs.		NIHONSAN (49)			Tecumseh (75a)	Tarahumara (13)
			M	F	Hiro	Haw	SF		
Number of study subjects	99	8829	133	153	1717	7949	178	1621	103
Cholesterol vs.									
Calories/day	–0.07	–0.10	–0.20	0.05	–0.02	–0.02	–0.07		0.06
Fat, g/day	–0.04	–0.01	–0.11	0.15	0.11	0.06	0.00	–0.11	0.55
Fat, percent cal.	0.04		0.11	0.26	0.13	0.12	0.12		
Saturated fat		0.03			0.15	0.07	0.07		
Animal fat	–0.04								0.59
Polyunsaturated fat					0.14	0.02	–0.11		

Three major explanations have been offered to extend the life of the hypothesis: that the observations reflect a threshold effect, that the dietary patterns of people in the same community are too homogeneous to provide an appropriate range of variation, and that the variation in measurement of the variables is so great that it obscures a true and meaningful association. If the third explanation is accepted, the first two are not needed, which is fortunate because they are not tenable. The threshold notion declares that the residents of the communities studied virtually all subsist on diets so high in fat that everyone is at high risk. Neither this nor the homogeneity proposal is supported by observations in the United States, where variation is seen over a considerable range, and the studies of Japanese in Japan and Hawaii and of other populations with dietary customs markedly different from those in the United States clearly eliminate these explanations.

The third hypothesis requires more careful consideration. It states in effect that the noise in the information system drowns out the signal. Two reports have approached the problem from a mathematical perspective. The first (58) presented the relation between the number of dietary measurements and the magnitude of the correlation between dietary variables and serum cholesterol concentration, and the second (44) gave a model and applications of the model for evaluating the degree of attenuation of correlation coefficients caused by intra-individual variation in these measurements. The point is demonstrated that such variation can greatly reduce a postulated strong correlation. Therefore, the argument proceeds, the group mean values derived from population surveys represent truth, whereas in the measurements of individuals the truth is

buried too deeply to be seen. This thesis is rational, and who can argue with a model?

However, a model is not a reality, but an abstraction of reality, and it may be mathematically impeccable but biologically flawed. Data are available that indicate this explanation may not totally resolve the issue. For example, in the Evans County, Georgia, Study (97), 25 white males were selected whose serum cholesterol values were 160 mg/dl or less (mean = 159) and 26 with values of 260 mg/dl or more (mean = 274). In these samples drawn from the extremes of the cholesterol distribution, none of the dietary variables differed significantly; in the low and high groups total intake was 2885 and 2940 cal respectively, total fat intake was 145 and 146 g; calories derived from fat were 45 and 45%; and saturated fat intake was 47 and 48. Similarly, sorting the men and women of the Tecumseh Study (75) into tertiles by serum cholesterol concentration did not establish a gradient of the dietary variables for either gender; the percent of calories derived from fat and the polyunsaturated to saturated fatty acid ratio did not differ among the categories of serum cholesterol measurements. In the NIHONSAN Study (49), however, men in the lowest quartile of the serum cholesterol distribution had lower values for dietary saturated fat than the persons in the highest quartile.

Other analyses have employed the converse of this method. Padmavati's data (78) on serum cholesterol and dietary intake were divided into dietary classes covering a range of fat intake from less than 25 to more than 200 g per day, and the mean values of serum cholesterol showed no association. Yet in these same data a distinct difference existed between the serum cholesterol values of persons in different socioeconomic groups. A similar analysis (D. Reed, unpublished data) of Japanese-Americans enrolled in the Honolulu Heart Program showed little variation in serum cholesterol for persons whose percent of total calories derived from fat varied from less than 10% to more than 60%; when arrayed by grams of fat ingested per day, serum cholesterol did not vary in the groups from 75–200 g. The London Bankmen (71) were analyzed both ways, and no trends for serum cholesterol were seen in the quartiles of dietary fat measurements, and no trends in dietary fat values were seen in the quartiles of the serum cholesterol distribution.

If the mean values derived from population surveys light the path to truth, then no obvious reason exists to explain why the mean values in these studies do not similarly enlighten. Especially troubling are the Indian data in which variation in dietary fat does not affect serum cholesterol, but socioeconomic class does. These computations are not truly the equivalent of mean values calculated for separate populations, and they are surely subject to serious errors of classification in the class intervals; but the range of fat intake is so great that to invoke measurement error as an explanation of the failure to find an association is tantamount to declaring that the dietary observations are worth-

less. If measures of dietary intake are worthless, then the dietary hypothesis may be preserved but the information presented in Figures 1 and 2 cannot be used to support it.

A study of European and Maori Seventh Day Adventists in New Zealand (23) used the quantity 2S-P (two times the saturated fat intake minus the polyunsaturated fat) as a dietary index, and computed the (Spearman's) correlations between this index and serum cholesterol concentration. Spearman's rank order correlations in the four groups—European male, European female, Maori male, Maori female—were, in order, 0.19, 0.01, 0.29, and 0.17. How these computations might compare with Pearson's correlation coefficients is not clear, but in multiple regression analyses, only the European males generated a significant regression coefficient for 2S–P as a predictor of serum cholesterol. Seventh Day Adventists eat differently from other people, and Maoris may eat differently and may metabolize fats differently from Europeans, but none of this explains why European females showed no relation between dietary fat and serum cholesterol. If the difficulty in detecting a true association is due to the variation inherent in the measurement of these variables, all four of the groups in this study should have suffered pretty much the same variation.

The measurement of diet and serum cholesterol performed at the beginning of the Western Electric Study did not show any important association between the two (80), but the measurements were repeated a year later and this made possible an analysis of the effects of change (92). Keys's dietary score was used as the index of dietary fat. It showed a correlation coefficient of 0.078 with serum cholesterol at the first examination; the correlation was modestly higher (0.124) between the change in Keys's score and the change in cholesterol from the first to the second examination.

The conclusion that intra-individual variation in measurements of serum cholesterol and dietary constituents contributes to the finding of near zero correlations between them is strongly supported. Further, the theory predicts that the correlation between change in dietary fat and change in serum cholesterol should be greater than the single survey values, and it is. However, in none of the observations except those of the Tarahumara Indians have we any indication that the fat composition of the diet accounts for much of the great differences in serum cholesterol seen among individuals. However statistically significant, the highest correlations reported are low, and among the New Zealand Seventh Day Adventists of European heritage only 6% of the variance in serum cholesterol could be explained by the recorded variations in diet. Somehow these seem meager rewards for such insightful mathematical modelling and sophisticated computation. The strong correlation between fat and serum cholesterol in the between-community comparisons may, indeed, represent the true nature of the relation between the two variables; but an alternate hypothesis can be suggested—i.e. that the high correlation is due to the

correlation between ordered clusters, with that ordering determined by variables related to, but other than, dietary fat. Perhaps the problem calls for a biological rather than a statistical solution.

DIET AND ISCHEMIC HEART DISEASE

Comparisons Among Communities

The data concerning the association between diet and ischemic heart disease in communities are derived primarily from national statistics and from longitudinal studies conducted in the United States, Europe, and Japan. The report by Yerushalmy & Hilleboe (105) is exemplary of the use of national data. They related mortality for males aged 55–59 years in the period 1951–1953 from 21 countries with data on food availability published by the Food and Agriculture Organization of the United Nations. The correlation coefficient between death rates for arteriosclerotic and degenerative heart disease and percent of calories derived from fat was high, 0.66. A more recent similar analysis (65) of data from 37 countries, for the mid-1960s, found a correlation coefficient of 0.74 between dietary fat as a percent of total calories and arteriosclerotic and degenerative heart disease mortality for men aged 55–64 years. Comparisons of cause-specific mortality for different populations pose a special dilemma: the broader the category of cause of death, the more reliable are the data, but the less the cause category represents a specific disease. Further, most national data on food are not based on surveys of food consumption; the information on food availability is derived from production, export, and import figures.

The Seven Countries Study (50), begun in 1947 by Keys and colleagues, reported ten-year incidence and mortality from ischemic heart disease in 16 communities. The studies were carefully designed and conducted, and the data derived from them are much more defensible than national statistics. The major limitations of this research effort are that the communities studied were small (~ 500–1000 persons) and were selected to present sharply contrasting experience with ischemic heart disease. The selection procedure may have carried in selection biases of many kinds that may be confounded with the relation between diet and disease. However, the association between dietary fat and the occurrence of disease is impressive, with a correlation coefficient of 0.84 for the relation between ischemic heart disease mortality rates and the percent of calories derived from saturated fat.

Comparisons Among Individuals Within Communities

The comparisons of communities give rise to an expectation that dietary measurements of individuals should have value in predicting subsequent occurrence of ischemic heart disease, but this expectation has not been fulfilled (Table 3). In six studies in the United States and one in the United Kingdom in

Table 3 Dietary variables for ischemic heart disease cases and noncases; middle-aged men; selected longitudinal population-based studies

	North Dakota (106)		Western Electric (80)		Western Collaborative Group (87)		Honolulu Japanese (104)	
	Cases	Noncases	Cases	Noncases	Cases	All subjects	Cases	Noncases
Number of study subjects	162	324	88	1797	70	3182	179	7411
Calories/day	2831	2782	3082	3174	2100	2280	2125	2290
Fat, g/day	141	140	148	152	—	—	85	86
Fat, percent calories	45	45	43	43	43	44	35	33
Saturated fat	—	—	—	—	—	—	31	32
Animal fat	—	—	116	118	—	—	—	—
P/S	—	—	—			—	—	—
Dietary cholesterol	—	—	721	757	585	668	521	549

	Puerto Rico (27)				London Bank and Bus Men (64)		Framingham (33)	
	Urban		Rural					
	Cases	Noncases	Cases	Noncases	Cases	Noncases	Cases	Noncases
Number of study subjects	213	5585	73	2347	50	287	79	780
Calories/day	2305	2413	2241	2353	2656	2869	2488	2622
Fat, g/day	98	99	81	86	118	129	112	114
Fat, percent calories	38	37	32	32	40	40	41	39
Saturated fat	36	37	33	33	—	—	43	44
Animal fat	—	—	—	—	—	—	—	—
P/S	0.54	0.50	0.32	0.33	0.15	0.16	0.41	0.39
Dietary cholesterol	449	442	335	358	516	566	534	529

which dietary assessment was done at the beginning of a period of observation, the persons who subsequently developed overt ischemic heart disease either differed not at all in their total caloric and fat consumption patterns from the persons who remained well or they differed slightly in the direction opposite to that projected by the hypothesis.

Food habits and customs are so intimately involved with other components of the cultural environment that any comparison of one group with another that

is based on dietary measures must, of necessity, be confounded with many other cultural characteristics. Therefore, to attribute differences in disease frequency to observed differences in dietary composition is to select the dietary variable arbitrarily from among a complex of interrelated variables, and the arbitrary nature of the choice is not lessened if information about the other variables was not collected. This raises at least a possibility that mean values of dietary constituents and of serum cholesterol may correlate well with the incidence and mortality rates for ischemic heart disease for communities if the disease rates of communities are determined by some other variable or variables that are correlated in a general way with diet. Suppose, for example, that some unidentified factor caused high, intermediate, and low frequencies of ischemic heart disease in populations, and that these groups within populations overlapped. If the unidentified factor were associated with dietary fat, then the association of fat and disease would be high between communities and could be low within communities. Although the puzzling observations might theoretically be explained by such a mechanism, no obvious candidate variable presents itself.

We might ask whether the information presently available to us suggests the operation of unknown variables. In cosmolgy, another observational science, the perturbations of planetary movements have led to the postulation of the existence of bodies before they were identified. Epidemiological data are not as orderly as planetary orbits and the laws governing disease behavior are not so explicitly defined, but some interesting possibilities exist. The vast popularity of multiple regression analysis and preoccupation with the statistical significance of regression coefficients have somewhat obscured the fact that in the most carefully conducted studies only a small part of the variance in the occurrence of ischemic heart disease can be accounted for by the variation in associated characteristics. Many reasons for this can be adduced, but the possibility remains that important determinants of ischemic heart disease may not presently be incorporated in our researches.

Since a multivariate regression equation estimates regression coefficients that provide the best fit to the data set used for the computation, the coefficients reflect the vagaries of those data. Therefore, applying an equation to another population would be expected to be less perfectly predictive than the original analysis suggests. Despite this, Gordon et al (34) allocated cases and noncases of ischemic heart disease for the second ten-year period of the Framingham study into deciles of a risk score computed from the experience of the first ten-year period, and found approximately as good agreement between actual and expected distribution in the predicted as in the fitted computations. In contrast, in the Seven Countries Study (50), equations computed from the observations in Southern Europe predicted ischemic heart disease frequencies in Northern Europe about half as great as were recorded, and the Northern

European equations overestimated the Southern European experience by a factor of about two.

Mathematical models of disease may have inherent interest, but their utility in epidemiology depends upon their contributions to our understanding of the population dynamics of disease. Multivariate regression models have severe limitations (95).

1. The equations explain variance in the dependent variable, which may or may not be related to explanations of disease occurrence. As Gordon et al point out (34), "the phrase 'proportion of variance explained' sometimes is taken to mean more than it says. The proportion of variance explained—whether it is large or small—does not cast any light on whether the variables considered are explanatory in a mechanistic sense or whether there are other important factors involved. Even where R^2 is non-trivial it is entirely conceivable that a completely different set of factors could be found that had an equal 'explanatory' power to those under consideration."

2. Community environmental characteristics are not easily incorporated into the equations along with the measurements of individuals. This might, for example, have something to do with the dissonance between Northern and Southern Europe.

3. The quantitative relations among the independent variables that are established by the regression coefficients imply a depth of understanding of the structure of the risk of ischemic heart disease that we do not possess.

The differences found in different applications of multivariate regression equations are explicable if variables other than those included in the analyses influence the risk of ischemic heart disease. Thus within-community variations are accounted for as well as the information will permit, but large between-community differences remain unexplained. Therefore we are in about the same situation in evaluating the association between diet and ischemic heart disease as we were with diet and serum cholesterol. The failure of measures of diet to discriminate between people who will or will not manifest ischemic heart disease may be due in large part to variability in the dietary measurement, but other explanations might be entertained.

EXPERIMENTAL TRIALS OF DIET MODIFICATION

As we have seen, the proposition that modification of dietary lipids can reduce the risk of coronary heart disease is remarkably robust and has withstood assaults that would have destroyed many worthy hypotheses. Among the possible explanations for this peculiar phenomenon is, of course, that the proposition is correct. The results of research aimed at testing the hypothesis experimentally have been used to support opposed positions. Perhaps we could

have been spared this ambiguity. In 1960, the National Diet-Heart Feasibility Study was initiated (74); designed expertly and conducted with care, it is one of the few projects in this field to achieve its modest goals. In 1963, centers were established in five cities and a state mental hospital, and a total of 2000 male urban residents between 45 and 54 years of age, and 400 male hospital inmates aged 40 to 59 years were recruited to the study. In the main part of the study, three diets were employed (summarized in Table 4; these are the average intakes recorded, deviating modestly from the diets prescribed). Different methods of meeting the dietary constraints were tested, including purchases on the open market and processing of foods specifically for the trial. Of 1211 subjects who entered the first year of study, 1062 (88%) remained loyal, and 553 (89%) persons finished the second year from among 624 who began. Persons assigned to the first diet, marked by fat and cholesterol restriction, had an average reduction of serum cholesterol of 12%; the second diet, with cholesterol restriction and a high ratio of polyunsaturated to saturated fats, showed a mean reduction of 13%; and the third, more or less normal American diet group had a reduction of 3%. Adherence was evaluated and was judged generally satisfactory, and cholesterol reduction was proportional to the assessment of faithfulness of adherence to the diet. Many of the participants lost weight; some reduction in blood pressure was noted; and a gratifying proportion stopped smoking cigarettes—all in all a pleasant denouement. The research group reported that a more definitive study to assess the effectiveness of dietary intervention in reducing the frequency of coronary heart disease was feasible and should be initiated. The report was treated as though it were contaminated; the proposed sample size, nearly 60,000 persons, and the price tag, from 50 to 250 million dollars, were judged to render the feasible unfeasible. Since that judgment was made, a number of studies of less definitive character have been reported and others are still under way. The costs of those done in the United States far exceed the amount required for the study originally

Table 4 Selected data from the National Diet Heart Feasibility Study

	Experimental diet 1	Experimental diet 2	Control diet
Calories/day	2154	2262	2228
Fat, percent of calories	30	34	35
Polyunsaturated/saturated fats	1.4	1.8	0.4
Cholesterol, mg/day	282	289	322
Baseline serum cholesterol, mg/dl	230.1	229.9	226.9
Change in serum cholesterol, mg/dl	–25	–28	–7

proposed, and the decade required for that study has dribbled away along with the money and the opportunity. In any case, we are left with what we have, and what we have contains the seeds of conflict.

The studies abstracted here have been classified into three groups, further subdivided according to whether the study subjects had or had not experienced a myocardial infarction prior to the study.

More-or-less Controlled Experiments

POST-INFARCTION Beginning as early as the mid-1940s, studies of the effect of dietary modification on the likelihood of recurrence among patients with prior myocardial infarction were carried on. These were more extensions of clinical practice than experiments, and the work of Morrison (72) and From Hansen (25) is typical of them. Morrison allocated an alternate 50 cases of a 100-patient series to a stringent diet; 1500 total cal, 25 g of fat, and 50–70 mg of cholesterol. He reported a reduction of 30% from the mean baseline cholesterol of 312 mg/dl. At the end of 12 years of observation 19 of the 50 patients under treatment were still alive, compared with none of the untreated group. From Hansen arranged for 133 patients to be served a 2000 cal diet with about 40 g of corn or soya oil, while 132 other patients continued a usual diet. After an average period of observation of 4.7 months, five myocardial infarcts were recorded in the untreated group, and none in the patients on the diet.

Bierenbaum's study (7) was more elaborate. One hundred men, aged 30–50 years, with prior myocardial infarctions, were recruited and assigned to one of two diets. Both restricted fat to 28% of total calories, but one had a polyunsaturated-to-saturated (P/S) ratio of 2.6 and the other 0.3. Serum cholesterol reductions of 9.7 and 7.3%, respectively, were reported for the two diet groups. A control group was assembled belatedly, from among post-infarction industrial employees. During 10 years of observation, 16 fatal myocardial infarctions occurred in the experimental diet group, and 28 in the untreated persons, with a larger advantage in the younger than in the older subjects.

These studies have often been cited favorably but perhaps more often criticized. Much of the criticism is based on applying criteria for tightly controlled experiments, which, of course, these were not. Viewed as anecdotal data, the results are interesting and certainly compatible with the hypothesis that modification of fats in diet is beneficial.

PRE-INFARCTION The New York Anti-Coronary Club (NYAC) study (11) also suffers from the appendage of a control group after the study had been underway for a couple of years; although the treated and control groups were both comprised of volunteers, the recruitment procedures differed, and so did the recruits. An attempt was made to accommodate the differences by post-stratification for religion and occupation, and by adjustment for age. The

experimental diet consisted of approximately equal quantities of saturated (S), monounsaturated (M), and polyunsaturated (P) fats totalling 30–33% of calories, and with a P/S ratio of 1.25–1.5. The diet group had a reduction in serum cholesterol of 13.5% from an initial mean of 260 mg/dl. After seven years of observation, among men aged 40–49, the incidence of ischemic heart disease events was 2.0 per 1000 in the treated group and 3.8 in the untreated; for men aged 50–59, comparable rates were 6.4 and 13.3.

Post-stratification and matching do not provide protection against selection biases equivalent to that offered by random assignment. However, if the beneficial effects noted in the NYAC and in Bierenbaum's study were due to bias, we should try to identify the bias, bottle it, and market it.

Controlled Experiments Allocating Individuals Randomly (Table 5)

POST-INFARCTION In three studies oil was added to the diet to increase the P/S ratio, and in the fourth the experimental diet was low in fat. In all four, the test groups achieved reductions in serum cholesterol, some of them handsome. These experiments involve a strikingly small number of study subjects; the numbers commonly recommended for studies of this kind in the United States have been 8,000–21,000.

None of the studies in Great Britain offered a glimmer of hope, and the one in Norway has been variously interpreted. Leren concluded that his findings in Oslo supported the proposition that dietary modification protected study subjects under the age of 60 years from subsequent relapse. The Committee of the British Medical Research Council directing the Soya Oil Study compared their results with those of Leren and concluded that they were "remarkably similar"—i.e. both negative. Attention has been drawn to the fact that the most favorable results in Oslo I were observed in the category of acquired angina pectoris (although these differed little from those in the category of fatal myocardial infarction), and that the persons evaluating angina pectoris were not blinded to the assignment to the treated and control groups. Deducting the angina pectoris cases from the total ischemic heart disease events leaves 56 and 70 cases in the treated and control groups respectively, which represents a 20% reduction, appreciable though not satisfying for those who believe that truth is to be found only in associations with p values less than 0.05.

Proponents of the diet-heart hypothesis have argued that all of these picky points are irrelevant, since an effective dietary regimen may have limited (or no) value in men who have already experienced severe ischemic heart disease.

PRE-INFARCTION Two studies have been conducted in which persons without prior infarction have been allocated randomly to test and control groups, the

Table 5 Controlled diet modification experiments with random allocation of individuals

	London corn oil (85)[a]			Oslo I (56)[b]		London soya oil (68)[c]		London low fat (83)[d]		LAVA (18)[e]		Oslo II(38)[f]	
	Exper.	Cont. 1 (Olive Oil)	Cont. 2	Exper.	Cont.	Exper.	Cont.	Exper.	Cont.	Exper.	Cont.	Exper.	Cont.
Study population													
Number of subjects	28	26	26	206	206	199	194	123	129	424	422	604	628
Age (mean or range)	53	55	59	56	56	<60	<60	<65	<65	65	66	45	45
Diet													
Calories/day	2070	2045	1933	2387		2380	2274	2000	2400	2496	2496	2248	2331
Fat, g/day	116	105	70	104		ca. 120	ca. 115	44	112	108	111	70	114
Fat, percent of calories	50	46	33	39		ca. 45	ca. 45	20	42	30	40	28	44
P/S	—[g]	—	—	—		2.0	0.2	—	—	—	—	1.0	0.4
Cholesterol, mg/day	—	—	—	264		258	588	—	—	365	653	289	527
Serum cholesterol (mean)	—	—	—										
Baseline, mg/dl	263	262	253	296	296	272	273	263	266	233	234	328	329
Achieved, mg/dl	—	—	—	239	283	229	255	223	239	—	—	263	341
Percent change	−7.9	0.0	−1.1	−17.6	−3.7	−15.8	−6.6	−15.2	−10.2	−20.0	−7.3	−19.8	+3.6

Disease events													
Angina pectoris	--	---		8	20	—	—	—	—	16	16	—	—
Non-fatal myocardial infarction	7	6	5	24	31	25	25	31	34	36	44	13	22
Fatal myocardial infarction	2	1	0	10	23	15	14					3	2
Sudden death	3	2	1	22	16					18	27	3	12
Total IHD events	12	9	6	64	90	62	74	46	48	54	71	19	36
Total IHD deaths	5	3	1	37	50	25	25	—	---	—	—	6	14
Total deaths, all causes	—	—	—	—	—	28	31	20	24	174	177	16	24

[a]Two years of observation.
[b]1958–1963
[c]1960–1967
[d]1957–62
[e]1959–1967
[f]1972–1977
[g]—: Not reported

Los Angeles Veterans Administration (LAVA) study, and a second study in Norway (Oslo II).

LAVA showed an apparent reduction (24%) in the frequency of ischemic heart disease events in the treated group but no decrease in total deaths. It is curious that most of the study subjects (average age 65) were well past the age at which serum cholesterol ceases to be predictive of ischemic heart disease. If cholesterol is not associated with the disease, any benefit that derives from reduction in cholesterol is difficult to explain. Oslo I showed benefits only below age 60, Bierenbaum's study showed a greater differential in younger persons, and in the Faribault study all the benefit accrued to persons less than 50 years of age. Of course, these arguments assume that some biological significance is attached to the findings of those three studies, for one can only apportion benefit if benefit exists.

By far the strongest evidence for a beneficial effect of diet modification is found in Oslo II. The reduction in total ischemic heart disease events was 47%, and deaths due to conditions other than ischemic heart disease were equally distributed between the test and control groups. Three fatal myocardial infarcts occurred in the diet group and only two in the control group, but these are small numbers about which to quibble in the presence of the other findings. The most notable design feature of this study was the selection of study subjects with high serum cholesterol values; the mean of two determinations had to exceed 290 mg/dl, and the average for all study subjects was over 320. This was a confounded trial in which reduction of cigarette smoking was recommended as well as change in diet. The authors calculated that 60% of the reduction in ischemic heart disease could be attributed to reduction in serum cholesterol, and 26% to reduction in smoking.

Controlled Experiments Allocating Groups

Both studies in this group were conducted in mental hospitals, in Helsinki, Finland, and Faribault, Minnesota. The Finnish study (99) employed a cross-over design, using one hospital for the treatment and one for the control for the period 1959–65, and then reversing this designation for the years 1965–71. The various cells in the cross-over design contained from 196 to 248 study subjects. The treatment diet differed from the normal diet primarily in substitution of unsaturated fats, changing the P/S ratio from 0.25 to about 1.5. Use of the diets was accompanied by a reduction in serum cholesterol of 19% in one hospital and 12% in the other. Coronary deaths were 54% lower in the treated group during the first time interval, and 47% lower in the second.

In Faribault (22), through five years of observation, a favorable effect of a cholesterol-lowering diet was seen only in men less than 50 years old, who exhibited a 72% reduction in the (combined) rate of myocardial infarcts, sudden deaths, and stroke.

Other Experiments

Additional relevant information is available from MRFIT (73), a multifactor intervention study of individuals, and the North Karelia, Finland, project (12), an uncontrolled community-wide intervention program. Both of these incorporated diet change in the study design, but in both any diet effects are thoroughly confounded with smoking cessation and treatment of hypertension.

In 1968, Frederickson wrote (24), "A tiny boat . . . mismanaged sinks silently. When a major field trial dismasts, it spills a vast cargo for all to see; and the mournful note of the Lutine bell clamors on and on in our consciences." This quotation might be judged an apt obituary for the MRFIT trial were it not for the suspicion that the vast cargo was put to sea in a derelict, stripped of masts and rudder before it left the dock. This judgment is no harsher than the opinion expressed in the *Wall Street Journal* of 6 October 1982. Having launched a purposefully confounded study design, at its conclusion the investigators had the unenviable task of picking through the flotsam to see if subset analysis could save any part of the investment. Sherwin (93) wrote in 1978, "it [MRFIT] tests the effect on the incidence of coronary heart disease of intervention directed toward the reduction of serum cholesterol, cigarette smoking, and hypertension. It does *not* test the hypothesis that any one of these factors (or even all of them together) is causally related to coronary heart disease. . . ." Therefore, based on the design specifications, the significant results from MRFIT are as follows: In the experimental group the deaths from coronary heart disease numbered 115 (17.9 per 1000) while the deaths from all causes numbered 165 (41.2 per 1000). In the control group these figures were 124 (19.3 per 1000) and 260 (40.4 per 1000), respectively. The evidence declares that the experimental group fared no better than the control group.

In North Karelia, a community-wide program was begun in 1972, planned to effect modifications of diet and reductions in serum cholesterol, cigarette smoking, and high blood pressure. An adjacent county was chosen as a reference area. The results of mortality analysis are shown in Table 6. Here again the evidence shows no benefits.

Cornfield & Mitchell (16) reviewed the dietary modification experiments in 1969 and concluded, "There are good grounds for believing that certain potentially modifiable risk factors may have an important influence on the amount of coronary disease. The problem is complicated, however. It does not appear as if, despite considerable effort, we have been successful in surmounting difficulties and actually demonstrating the possibility of such reduction or of estimating its magnitude." Although the present review includes data published since 1969, the situation has not changed appreciably. One may still choose to discard the negative or the positive studies on grounds of inadequate study design or irrelevance. The magnitude of reduction in serum cholesterol noted in the trials is not clearly correlated with reduction in risk of ischemic

Table 6 Controlled experiments allocating individuals randomly

	Age-adjusted death rates per 1000 for persons aged 30–64 years			
	Cardiovascular Disease		All causes	
	Men	Women	Men	Women
1970–71				
North Karelia	7.7	2.5	13.8	4.8
Reference area	7.7	2.5	14.0	4.9
1977–78				
North Karelia	6.1	1.5	11.5	3.9
Reference area	5.9	1.3	11.8	3.7

heart disease. Perhaps Oslo II does indicate that manipulation of diet is most effective for persons with especially high baseline serum cholesterol values, and benefits are probably greater among younger men who have not yet experienced their first myocardial infarctions. Even these hesitant inferences have as much a flavor of theology about them as of science. By the rule of strong inference, a single well-designed and carefully conducted experiment that demonstrated no benefit would serve to invalidate the hypothesis. Unfortunately, none of the studies has the force either to drive a stake through the heart of the hypothesis or to provide it the sustenance it needs.

INTERPRETATIONS OF THE EVIDENCE

The Official Word

By 1960, research on diet, serum cholesterol, and coronary heart disease had convinced many scientists of the causal role of dietary fat. Dr. Irvine Page, addressing a hearing on research in cardiovascular disease (79), recommended weight reduction for obese persons and dietary modification for people with hypercholesterolemia. But, he said, "when you talk about the problem of changing the fat content of the diet of the entire American public, I think you are talking about something else. . . . I think the whole problem simply deserves more careful consideration [rather] than any wholesale recommendation at the present time." An ad hoc committee of the American Heart Association issued a statement in 1961 (1) that almost exactly echoed Dr. Page's recommendations, and that view was presented again in 1962 by the Council on Foods and Nutrition of the American Medical Association (17): " . . . despite the promise of diet in therapy, there is not sufficient information available at the present time to warrant a change in the American diet aimed at preventing heart disease in the general population."

A decade later, a divergent view had emerged in the recommendations of some authoritative groups. In 1970, the Intersociety Commission for Heart Disease Resources (43) advised substantial dietary modification for the public at large, incorporating the principles of what has come to be called the prudent diet: weight control, dietary cholesterol intake below 300 mg per day, and fat ingestion less than 35% of total calories with saturated fat intake below 10% of total calories. That this position was not universally held is illustrated by the report of the Task Force on Arteriosclerosis of the National Heart and Lung Institute, published in 1971 (5). It adhered fairly closely to the earlier pronouncements, saying, "Intuitively, it would seem prudent to decrease the incidence of hyperlipidemia in the population of the United States by controlling diet. However, this would be a formidable venture if it were to involve changing the diet of the entire nation. Indeed, before advocating such a major revolution in diet, the Task Force concluded that convincing evidence should be sought that lowering the levels of lipids in blood reduces morbidity and mortality from arteriosclerosis." The pivotal term is, of course, "convincing evidence," for the existing evidence seemed amply convincing to some panels of experts and not to others.

In the years since, despite the accumulation of formidable masses of data bearing on this issue, statements emanating from various more or less official bodies have continued to differ. In 1976, the Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society on Prevention of Coronary Heart Disease published a cautious affirmation of the desirability of general public adoption of the prudent diet (46). The Nutrition Committee of the American Heart Association was also cautious in its statement of 1978 (77): " . . . it appears prudent for the American people to follow a diet aimed at lowering serum lipid concentrations. . . . There is substantial evidence that the diets recommended . . . will aid in the control of serum lipid levels in man. Diets similar to those recommended here have been consumed by many persons in the United States for periods of more than 15 years without any evidence of harmful effects." This is not exactly a ringing call to man the battlements, and the assurance that the prudent diet is likely not to be harmful seems curiously defensive.

The Senate Select Committee on Nutrition and Human Needs was neither cautious nor defensive (101). The Committee's dietary goals for the United States included reduction of dietary fat to 30% of total calories, divided equally between saturated, monounsaturated, and polyunsaturated fats, and a cholesterol intake of about 300 mg per day. The report stimulated considerable discussion but did not reflect or engender a consensus among the experts. The report of the Surgeon General of the United States Public Health Service on Health Promotion and Disease Prevention (36) recommended a prudent diet without specifying exactly the extent of modification: "Premature heart disease is unequivocally associated with elevated blood cholesterol levels. . . . Direct

evidence from animal studies supports the linkage of atherosclerosis with high levels of fats (particularly saturated) and cholesterol in the diet." The statement is most remarkable for its citation of evidence from animal studies and total silence on the great volume of research on people. According to a pamphlet for the general public, issued jointly by the United States Departments of Agriculture and Health, Education, and Welfare (100), "There is controversy about what recommendations are appropriate for healthy Americans. But for the U.S. population *as a whole,* reduction in our current intake of total fat, saturated fat, and cholesterol is sensible."

The opposing views emerged clearly in two publications in 1980. The Food and Nutrition Board of the National Research Council released a report entitled *Toward Healthful Diets* (21) according to which "Intervention trials in which diet modification was employed to alter the incidence of coronary artery disease and mortality in middle-aged men have been generally negative. . . . There was a marginal decrease in coronary disease incidence but no effect on overall mortality. . . . The Board recommends that the fat content be adjusted to a level appropriate for the caloric requirements of the individual. . . . It does not seem prudent at this time to recommend an increase in the dietary P:S (polyunsaturated to saturated fats) ratio except for individuals in high risk categories." Given the same data, a Committee of the American Heart Association (3) concluded that life-long adoption of the prudent diet should be promoted, for "although all the . . . studies were flawed in some aspect of experimental design, they are uniform in revealing a favorable trend towards decreasing CHD risk on cholesterol-lowering diets" (76).

In summary, prestigious panels of experts have, since 1970, recommended mass changes in the food consumption practices of the American public, and equally prestigious groups have argued that the existing information was not sufficient to support such recommendations. The proponents include people who urge dietary change unreservedly and others who argue that because the dietary change proposed are wholly innocuous they might as well be adopted, even if definitive evidence of benefit is lacking.

Blackburn, reviewing the recommendations (8), emphasized the consistency of the expert committee reports from many countries over the decade of the 1970s. However, at least in the United States, the statements of various boards and panels are not fully independent, because of overlapping memberships and respect for precedent. Nevertheless, despite the position of the Food and Nutrition Board and an equivocal report from the AMA, the dominant opinion has indeed favored promotion of the prudent diet as a matter of national policy.

The Individual Heavies

Individual scientists, many of whom have served on the advisory boards, panels, and committees cited earlier, have not been loath to speak out on this

issue, and, not surprisingly, their judgments vary widely. From among many judgmental statements, a smaller number can be selected, each of which included specific references to the diet modification experiments designated LAVA, Oslo I, and Helsinki. Therefore, we can be sure that the opinions expressed diverged from common ground. In order of decreasing enthusiasm, the evaluations stated that the experiments had shown "lower IHD incidence in previously healthy men" [Lewis (57)]; "an amelioration of CHD . . . advice to middle-aged men is not without benefit" [Hegsted (37)]; "suggestive but not unequivocal, reduction in hard and soft endpoints for CHD" [Glueck et al, (30)]; "suggestive but not conclusive evidence that the incidence of new events was reduced" [Ahrens (2)]; "at best suggestive evidence for . . . efficacy" [Hulley (41)]; and "no diet therapy has been shown effective for the prevention of coronary heart disease" [Mann (59)].

One may, perhaps should, disagree with George Mann's conclusion, but as an exercise in declarative English expression his statement is far superior to "suggestive, but not unequivocal, reduction." The latter, employing the forms so fondly embraced by attending physicians on ward rounds, is a syntactical swinging door, so that one may slip in or out depending on how matters shape up. Perhaps the judgments of some would be more enthusiastically expressed had they had Oslo II data in hand; but perhaps some would be less enthusiastic after reviewing MRFIT. Since the data, the research findings, are a constant, the differences in the opinions expressed about them must be due to one or more of the following: (*a*) different weighing of evidence other than the three studies cited affected the evaluations of these studies; (*b*) different criteria were used in assessing the research; or (*c*) the authors had different antecedent biases.

CONCLUSIONS

Epidemiological research has produced consistently strong associations between serum cholesterol and ischemic heart disease, but contradictory findings for the relations between diet and serum cholesterol and between diet and ischemic heart disease. For the latter two, the dietary hypothesis is generally not supported in comparisons of individuals. The discrepancy can be resolved totally if the argument is accepted that the problem arises because of the variability in measurement of diet, serum cholesterol, and disease. Although a case has been made, some observations support the view that measurement error is not a fully adequate explanation. Debate on this issue could be brought to abrupt closure by establishing the efficacy of dietary modification in controlled experiments. Unfortunately, the various essays in this arena have led to additional ambiguity rather than clarification.

In the best of all possible worlds, we could now look back over this trail of research findings and assessments, make due allowance for the biases that may

have crept into this presentation, and pluck the flower of truth from the nettle of confusion. However, in this instance truth is not readily apparent, and we must instead accept a better appreciation of the reasons for widely divergent perceptions of whatever truth may lie beneath the welter of data. Judgments on matters such as this are made in three spheres—personal, scientific, and public—and they need not agree.

Personal position. In a society such as ours, each individual is generally free to exercise dietary choice, constrained by manufacturing and merchandising patterns and economic resources, and within the tight confines of cultural imperatives. These choices may be influenced by scientific findings and by actions resulting from public policy decisions, but a person may assign the weights to be placed on these advices. One of the problems at present is that a person may not be able to make well-informed choices when the messages from scientists and policy-makers are conflicting and uncertain.

Scientific posture. A scientist knowledgeable in the field has a right and a responsibility to pick a position. This scientific position may range from total conviction to firm disbelief, and may include the category "don't know/can't decide." This is unfortunate. For issues with a scientific basis, public policy should be determined, or at least informed, by scientific judgment; and policy-makers are not well served by conflicting expert opinions, or shrugged shoulders. Questions of scientific fact are not resolvable by majority vote, as Galileo would attest; either high-fat diets are responsible for ischemic heart disease or they are not. Consensus among scientists is uncommon, but that we are now far from consensus is testimony to the ambiguity in the information base.

Public policy. In this situation, the public policy issue is whether or not to promote large-scale changes in the diet of the population of the United States. To fail to promote dietary change is as firmly a public policy decision as to promote a change, for a primary characteristic of public policy is that a neutral position, such as deciding to wait for scientific clarification, is not truly neutral. Since the evidence leaves a significant number of experts unconvinced, public policy arguments tend to revolve around other issues, such as whether a dietary change is likely to be harmful. Although the prudent diet that is widely recommended is probably innocuous, concerns are expressed with respect to a possibly deleterious effect of low serum cholesterol, and about the wisdom of imposing a restrictive diet in infancy. Furthermore, a massive change in the national diet calls for aggressive promotion and large economic dislocations. Whether this is an important issue depends, of course, on the side of the economic fence one occupies. As long as the scientific questions are unresolved, the public policy debate must continue. The truly bright spot in all of

this is that while the debate goes on, the mortality rates for ischemic heart disease continue to decline as a log-linear function. This trend, which dates back to the mid-1960s, gives us assurance that while we may not be right, we cannot be distressingly wrong if we hesitate before taking aggressive action to alter the dietary customs of the nation.

Literature Cited

1. Ad Hoc Committee on Dietary Fat and Atherosclerosis. 1961. *Dietary Fat and Its Relation to Heart Attacks and Stroke*. Dallas: Am. Heart Assoc.
2. Ahrens, E. H. 1979. Dietary fats and coronary heart disease: unfinished business. *Lancet* 2:1345–48
3. American Heart Association. 1980. *Risk Factors and Coronary Disease*. Dallas: Am. Heart Assoc.
4. Armstrong, A., Wilson, R. B. 1964. Coronary heart disease in elderly men in a rural area of Southwest Scotland. *Scot. Med. J.* 9:438–44
5. *Arteriosclerosis: A Report by the NHLBI Task Force on Arteriosclerosis*. 1971. DHEW Publ. 72–219. Washington DC: USGPO
6. Barrow, J. G., Quinlan, C. B., Cooper, G. R., Whitner, V.S., Goodloe, M. H. R. 1960. Studies in atherosclerosis. III. An epidemiological study in Trappist and Benedictine monks: a preliminary report. *Ann. Intern. Med.* 52:368–77
7. Bierenbaum, M. L., Fleischman, A. I., Raichelson, R. I., Hayton, T., Watson, P. B. 1973. Ten-year experience of modified-fat diets on younger men with coronary heart disease. *Lancet* 1:1404–6
8. Blackburn, H. 1979. Diet and mass hyperlipidemia: a public health view. In *Nutrition, Lipids, and Coronary Heart Disease,* ed. R. Levy, B. Rifkind, B. Dennis. NY: Raven Press
9. Bronte-Stewart, B., Keys, A., Brock, J. F. 1955. Serum-cholesterol, diet, and coronary heart disease. An inter-racial survey in the Cape Peninsula. *Lancet* 2:1103–7
10. Carlson, L. A., Bottiger, L. E. 1972. Ischemic heart disease in relation to fasting values of plasma triglycerides and cholesterol. *Lancet* 1:865–68
11. Christakis, G., Rinzler, S. H., Archer, M., Winslow, G., Jampel, S., Stephenson, J., Friedman, G., Fein, H., Kraus, A., James, G. 1966. The Anti-Coronary Club. A dietary approach to the prevention of coronary heart disease—a seven year report. *Am. J. Publ. Health* 56:299–314
12. *Community Control of Cardiovascular Diseases. The North Karelia Project*. 1981. Copenhagen: WHO Reg. Off.
13. Connor, W. E., Cerqueria, M. T., Connor, R. W., Wallace, R. B., Malinow, M. R., Casdorph, H. R. 1978. The plasma lipids, lipoproteins, and the diet of Tarahumara Indians of Mexico. *Am. J. Clin. Nutr.* 31:1131–42
14. Cooperative Study of Lipoproteins and Atherosclerosis. 1956. Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. *Circulation* 14(Pt. 2):691–741
15. Cornfield, J. 1962. Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure: a discriminant function analysis. *Fed. Proc.* 21(Pt. II):58–61
16. Cornfield, J., Mitchell, S. 1969. Selected risk factors in coronary disease. Possible intervention effects. *Arch. Envir. Health* 19:382–94
17. Darby, W. J. 1962. Diet and coronary atheroma. *J. Am. Med. Assoc.* 182: 1328–29
18. Dayton, S., Pearce, M. L., Hashimoto, S., Dixon, W. J., Tomiyasu, U. 1969. A controlled trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 40:(Suppl. II):1–63
19. Epstein, F. H. 1967. Predicting coronary heart disease. *J. Am. Med. Assoc.* 201: 795–800
20. Epstein, F. H., Simpson, R., Boas, E. P. 1957. The epidemiology of atherosclerosis among a random sample of clothing workers of different ethnic origins in New York City. II. Associations between manifest atherosclerosis, serum lipid levels, blood pressure, overweight, and some other variables. *J. Chron. Dis.* 5: 329–41
21. Food and Nutrition Board. 1980. *Toward Healthful Diets*. Washington DC: Nat. Acad. Sci.
22. Frantz, I., Dawson, E. A., Kuba, K., Brewer, E. R., Gatewood, L. C., Bartsch, G. E. 1975. The Minnesota

coronary survey: effect of diet on cardiovascular events and deaths. *Circulation* 51, 52(Suppl. II):4
23. Fraser, G. E., Swannel, R. J. 1981. Diet and serum cholesterol in Seventh Day Adventists: a cross-sectional study showing significant relationships. *J. Chron. Dis.* 34:487–501
24. Frederickson, D. S. 1968. The field trial: some thoughts on the indispensable ordeal. *Bull. NY Acad. Med.* 44:985–93
25. From Hansen, P. 1962. Dietary fats and thrombosis. *Lancet* 2:1193–94
26. Garcia-Palmieri, M. R., Costas, R., Cruz-Vidal, M., Cortez-Alicea, M., Colon, A. A., Feliberti, M., Ayala, A. M., Patterne, D., Sobrino, R., Torres, R., Nazario, E. 1970. Risk factors and prevalence of coronary heart disease in Puerto Rico. *Circulation* 42:541–49
27. Garcia-Palmieri, M. R., Sorlie, P., Tillotson, J., Costas, R., Cordero, E., Rodriguez, M. 1980. Relationship of dietary intake to subsequent coronary heart disease incidence: the Puerto Rico Heart Health Program. *Am. J. Clin. Nutr.* 33: 1818–27
28. Gertler, M. M., Garn, S. M., White, P. D. 1951. Young candidates for coronary heart disease. *J. Am. Med. Assoc.* 147:621–25
29. Gertler, M. M., Woodbury, M. A., Gottsch, L. G., White, P. D., Rusk, H. A. 1959. The candidate for coronary heart disease. *J. Am. Med. Assoc.* 170: 149–52
30. Glueck, C. J., Mattson, F., Bierman, E. L. 1978. Diet and coronary heart disease: another view. *N. Engl. J. Med.* 298: 1471–74
31. Gordon, T. 1970. *The Framingham Study. An Epidemiological Investigation of Cardiovascular Diseases. Sect. 24. The Framingham Diet Study: Diet and the Regulation of Serum Cholesterol.* Washington DC: Nat. Heart, Lung and Blood Inst.
32. Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B., Dawber, T. R. 1977. Predicting coronary heart disease in middle-aged and older persons. *J. Am. Med. Assoc.* 238:497–99
33. Gordon, T., Kagan, A., Garcia-Palmieri, M., Kannel, W. B., Zukel, W. J., Tillotson, J., Sorlie, P., Hjortland, M. 1981. Diet and its relation to coronary heart disease and death in three populations. *Circulation* 63:500–15
34. Gordon, T., Kannel, W. B., Halperin, M. 1979. Predictability of coronary heart disease. *J. Chron. Dis.* 32:427–40
35. Groen, J. J., Tijong, K. B., Koster, M., Willebrands, A. F., Verdonck, G., Pierloot, M. 1962. The influence of nutrition and ways of life on blood cholesterol and the prevalence of hypertension and coronary heart disease among Trappist and Benedictine monks. *Am. J. Clin. Nutr.* 10:456–70
36. *Healthy People. The Surgeon General's Report on Health Promotion and Disease Prevention.* 1979. DHEW Publ. No. 79–55071. Washington DC: USGPO
37. Hegsted, D. M. 1978. Dietary goals—a progressive view. *Am. J. Clin. Nutr.* 31:1504–9
38. Hjermann, I., Velve-Byre, K., Holme, I., Leren, P. 1981. The effect of diet and smoking intervention on the incidence of coronary heart disease. *Lancet* 2: 1303–10
39. Hopkins, P. N., Williams, R. R. 1981. A survey of 246 suggested coronary risk factors. *Atherosclerosis* 40:1–52
40. Hulley, S. B., Rosenman, R. H., Bawol, R. D., Brand, R. J. 1980. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. *N. Eng. J. Med.* 302: 1383–89
41. Hulley, S. B., Sherwin, R., Nestle, M., Lee, P. R. 1981. Epidemiology as a guide to clinical decisions—II. Diet and coronary heart disease. *West J. Med.* 135:25–33
42. Hunter, J. D. 1962. Diet, body build, blood pressure, and serum cholesterol in coconut-eating Polynesians. *Fed. Proc.* 21:36–43
43. Intersociety Commission for Heart Disease Resources. 1970. Primary prevention of the atherosclerotic diseases. *Circulation* 42:A55–95
44. Jacobs, D. R., Anderson, J. T., Blackburn, H. 1979. Diet and serum cholesterol. Do zero correlations negate the relationship? *Am. J. Epidemiol.* 110:77–87
45. Jervell, A., Meyer, K., Westlund, K. 1965. Coronary heart disease and serum cholesterol in males in different parts of Norway. *Acta Med. Scand.* 177(Fasc. 1):13–23
46. Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society on Prevention of Coronary Heart Disease. 1976. Prevention of coronary heart disease. *Brit. Med. J.* 1:881
47. Kagan, A., Harris, B. R., Winkelstein, W., Johnson, K. G., Kato, H., Syme, S. L., Rhoads, G. G., Gay, M. L., Nichaman, M., Hamilton, H. B., Tillotson, J. 1974. Epidemiologic studies of coronary

heart disease and stroke in Japanese men living in Japan, Hawaii, and California: demographic, physical, dietary and biochemical characteristics. *J. Chron. Dis.* 27:345–64
48. Kahn, H. A., Medalie, J. H., Neufeld, H. N., Riss, E., Balogh, M., Groen, J. J. 1969. Serum cholesterol: its distribution and association with dietary and other variables in a survey of 10,000 men. *Israel J. Med. Sci.* 5:1117–27
49. Kato, H., Tillotson, J., Nichaman, M. Z., Rhoads, G. G., Hamilton, H. B. 1973. Epidemiological studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California. Serum lipids and diet. *Am. J. Epidemiol.* 97:372–85
50. Keys, A. 1980. *Seven Countries. A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, MA: Harvard Univ. Press
51. Keys, A., Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N., Keys, M. H. 1958. Lessons from serum cholesterol studies in Japan, Hawaii, and Los Angeles. *Ann. Intern. Med.* 48: 83–94
52. Keys, A., Vivanco, F., Rodriguez Minon, J. L., Keys, M. H., Castro Mendoza, H. 1954. Studies on the diet, body fatness and serum cholesterol in Madrid, Spain. *Metabolism* 3:195–212
53. Labarthe, D., Reed, D., Brody, J., Stallones, R. 1973. Health effects of modernization in Palau. *Am. J. Epidemiol.* 98:161–74
54. Lee, K. T., Kim, D. N., Han, Y. S., Goodale, F. 1962. Geographic studies of arteriosclerosis. The effect of a strict vegetarian diet on serum lipid and electrocardiographic patterns. *Arch. Envir. Health* 4:10–16
55. Lee, K. T., Nam, S. C., Kwon, O. H., Kim, S. B., Goodale, F. 1963. Geographic pathology of arterioslcerosis: a study of the "critical level" of dietary fat as related to myocardial infarction in Koreans. *Exp. Molec. Pathol.* 2:1–13
56. Leren, P. 1966. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. *Acta Med. Scand.* 466:1–92 (Suppl.)
57. Lewis, B. 1978. Hypothesis into theory—the development of aetiological concepts of ischaemic heart disease—a review. *J. R. Soc. Med.* 71:809–18
58. Liu, K., Stamler, J., Dyer, A., McKeever, J., McKeever, P. 1978. Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. *J. Chron. Dis.* 31:399–418
59. Mann, G. V. 1977. Diet—heart: end of an era. *N. Engl. Med. J.* 297:644–50
60. Mann, G. V., Munoz, J. A., Scrimshaw, N. S. 1955. The serum lipoprotein and cholesterol concentrations of Central and North Americans with different dietary habits. *Am. J. Med.* 19:25–32
61. Mann, G. V., Shaffer, R. D., Anderson, R. S., Sandstead, H. H. 1964. Cardiovascular disease in the Masai. *J. Atheroscl. Res.* 4:289–312
62. Deleted in proof
63. Marmot, M. G., Syme, S. L., Kagan, A., Kato, H., Cohen, J. B., Belsky, J. 1975. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: prevalence of coronary and hypertensive heart disease and associated risk factors. *Am. J. Epidemiol.* 102:514–25
64. Marr, J. W., Morris, J. N. 1981. Letter to the editor: dietary intake and the risk of coronary heart disease in Japanese men living in Hawaii. *Am. J. Clin. Nutr.* 34:1156–57
65. Masironi, R. 1970. Dietary factors and coronary heart disease. *Bull. WHO* 42: 103–14
66. McCullagh, E. P., Lewis, L. A. 1960. A study of diet, blood lipids and vascular disease in Trappist monks. *N. Engl. J. Med.* 263:569–74
67. McGill, H. C. 1979. The relationship of dietary cholesterol to serum cholesterol concentration and to atherosclerosis in man. *Am. J. Clin. Nutr.* 32:2664–702
68. Medical Research Council Committee. 1968. Controlled trial of soya-bean oil in myocardial infarction. *Lancet* 2:693–99
69. Mendez, J., Tejada, C., Flores, M. 1962. Serum lipid levels among rural Guatemalan Indians. *Am. J. Clin. Nutr.* 10:403–9
70. Miller, D. C., Trulson, M. F., McCann, M. B., White, P. D., Stare, F. J. 1958. Diet, blood lipids and health of Italian men in Boston. *Ann. Intern. Med.* 49: 1178–1200
71. Morris, J. N., Marr, J. W., Heady, J. A., Mills, G. L., Pilkington, T. R. E. 1963. Diet and plasma cholesterol in 99 bank men. *Br. Med. J.* 1:571–76
72. Morrison, L. M. 1960. Diet in coronary atherosclerosis. *J. Am. Med. Assoc.* 73: 884–88
73. Multiple Risk Factor Intervention Trial Research Group. 1982. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. *J. Am. Med. Assoc.* 248:1465–77

74. National Diet-Heart Study Research Group. 1968. *The National Diet-Heart Study Final Report*. Monogr. No. 18. NY: Am. Heart Assoc.
75. Nichols, A. B., Ravenscroft, C., Lamphieau, D. E., Ostrander, L. D. 1976. Daily nutritional intake and serum lipid levels. The Tecumseh Study. *Am. J. Clin. Nutr.* 29:1384–92
75a. Nichols, A. B., Ravenscroft, C., Lamphieau, D. E., Ostrander, L. D. 1976. Independence of serum lipid levels and dietary habits. The Tecumseh Study. *J. Am. Med. Assoc.* 236:1948–53
76. Nutrition Committee of the American Heart Association. 1982. Rationale of the diet-heart statement of the American Heart Association. *Arteriosclerosis* 4: 177–91
77. Nutrition Committee of the American Heart Association. 1978. *Diet and Coronary Heart Disease*. Dallas: Am. Heart. Assoc.
78. Padmavati, S., Gupta, S., Pantula, G. V. A. 1959. Dietary fat, serum cholesterol levels, and incidence of atherosclerosis in Delhi. *Circulation* 19:849–55
79. Page, I. H. 1959. In: A decade of progress against cardiovascular disease. *Congress. Rec.* A1803–4
80. Paul, O., Lepper, M. H., Phelan, W. H., Dupertuis, G. W., McMillan, A., McKean, H., Park, H. 1963. A longitudinal study of coronary heart disease. *Circulation* 28:20–31
81. Pooling Project Research Group. 1978. *Relationship of Blood Pressure, Serum Cholesterol, Smoking Habit, Relative Weight, and ECG Abnormalities to Incidence of Major Coronary Events: Final Report of the Pooling Project*. Monogr. No. 60. Dallas: Am. Heart Assoc.
82. Reed, D., Labarthe, D., Stallones, R. 1970. Health effects of westernization and migration among Chamorros. *Am. J. Epidemiol.* 92:94–112
83. Research Committee. 1965. Low-fat diet in myocardial infarction. *Lancet* 2:501–4
84. Ringrose, H., Zemmet, P. 1979. Nutrient intakes in an urbanized Micronesian population with a high diabetes prevalence. *Am. J. Clin. Nutr.* 32:1334–41
85. Rose, G. A., Thomson, W. B., Williams, R. T. 1965. Corn oil in the treatment of ischemic heart disease. *Br. Med. J.* 1: 1531–33
86. Rosenman, R. H., Brand, R. J., Jenkins, C. D., Friedman, M., Strauss, R., Wurm, M. 1975. Coronary heart disease in the Western Collaborative Group Study. Final follow-up experience of 8½ years. *J. Am. Med. Assoc.* 233:872–77
87. Rosenman, R. H., Friedman, M., Strauss, R., Wurm, M., Jenkins, C. D., Messinger, H. B. 1966. Coronary heart disease in the Western Collaborative Group Study. *J. Am. Med. Assoc.* 195:130–36
88. Russek, H. I., Zohman, B. L. 1958. Relative significance of heredity, diet and occupational stress in coronary heart disease of young adults. *Am. J. Med. Sci.* 235:266–75
89. Scrimshaw, N. S., Trulson, M., Tejada, C., Hegsted, D. M., Stare, F. J. 1957. Serum lipoprotein and cholesterol concentrations. Comparison of rural Costa Rican, Guatemalan, and United States populations. *Circulation* 15:805–13
90. Shaper, A. G. 1962. Cardiovascular studies in the Samburu tribe of Northern Kenya. *Am. Heart J.* 63:437–42
91. Shaper, A. G., Jones, K. W. 1959. Serum cholesterol, diet and coronary heart disease in Africans and Asians in Uganda. *Lancet* 2:534–37
92. Shekelle, R. B., Shryock, A. M., Paul, O., Lepper, M., Stamler, J., Liu, S., Raynor, W. J. 1981. Diet, serum cholesterol and death from coronary heart disease. *N. Eng. J. Med.* 304:65–70
93. Sherwin, R. 1978. Controlled trials of the diet-heart hypothesis: some comments on the experimental unit. *Am. J. Epidemiol.* 108:92–99
94. Sinnett, P. F., Whyte, H. M. 1973. Epidemiological studies in a total Highland population, Tukisenta, New Guinea. *J. Chron. Dis.* 26:265–90
95. Stallones, R. 1980. To advance epidemiology. *Ann. Rev. Publ. Health* 1:69–82
96. Stuart, K. L., Schneckloth, R. E., Lewis, L. A., Moore, F. E., Corcoran, A. C. 1962. Diet, serum cholesterol, protein, blood haemoglobin, and glycosuria in a West Indian community (St. Kitts, W.I.). *Br. Med. J.* 2:1283–88
97. Stulb, S. C., McDonough, J. R., Greenberg, B. G., Hames, C. G. 1965. The relationship of nutrient intake and exercise to serum cholesterol levels in white males in Evans County, Georgia. *Am. J. Clin. Nutr.* 16:238–42
98. Toor, M., Katchalsky, A., Agmon, J., Allalouf, D. 1957. Serum lipids and atherosclerosis among Yemenite immigrants in Israel. *Lancet* 1:1270–73
99. Turpeinen, O., Karvonen, M. J., Pekkarinen, M., Miettinin, M., Elosuo, R., Paavilainen, E. 1979. Dietary prevention of coronary heart disease: the Finnish mental hospital study. *Int. J. Epidemiol.* 8:99–118

100. US Department of Agriculture and Department of Health, Education and Welfare. 1980. *Nutrition and Your Health—Dietary Guidelines for Americans*. Washington DC: USGPO
101. US Senate Select Committee on Nutrition and Human Needs. 1977. *Dietary Goals for the United States*. Washington DC: USGPO. 2nd ed.
102. Walker, A. R. P., Arvidsson, U. B. 1954. Fat intake, cholesterol concentration, and atherosclerosis in the South African Bantu. *J. Clin. Invest.* 33: 1358–65
103. Werner, G. T., Sareen, D. K. 1978. Serum cholesterol levels in the population of Punjab in Northwest India. *Am. J. Clin. Nutr.* 31:1479–83
104. Yano, K., Rhoads, G. G., Kagan, A., Tillotson, J. 1978. Dietary intake and the risk of coronary heart disease in Japanese men living in Hawaii. *Am. J. Clin. Nutr.* 31:1270–79
105. Yerushalmy, J., Hilleboe, H. E. 1957. Fat in the diet and mortality from heart disease. *NY J. Med.* 57:2343–54
106. Zukel, W. J., Lewis, R. H., Enterline, P. E., Painter, R. C., Ralston, L. S., Fawcett, R. M., Meredith, A. P., Peterson, B. 1959. A short-term community study of the epidemiology of coronary heart disease. *Am. J. Publ. Health* 49:1630–39