PREVENTION IN CORONARY HEART DISEASE

By J. Stamler

The aim of this presentation is to review briefly recent key findings concerning the prevention of coronary heart disease. The focus is on findings that serve as portents of future success for medical practice and public health, particularly in the decisive area of the primary prevention of the contemporary international epidemic of heart attacks among young adult and middle-aged persons.

Scope and Nature of the Contemporary Epidemic of Coronary Heart Disease

The Executive Board of the World Health Organization recently emphasized, "Coronary Heart Disease has reached enormous proportions, striking more and more at younger subjects. It will result in coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend by concentrated research into its cause and prevention." The Board also emphasized the need for increased efforts, "... to set up efficient services for control and to carry out more extensive research programs."

Finland and the United States rank one and two among the economically developed countries (where the epidemic is raging most violently) in coronary mortality rates for young adult and middle-aged men—with consequent high rates for mortality from all causes Fig.1)[1] Data from other large scale studies—both autopsy and prospective living population investigations—confirm that these differences in rates of occurrence of CHD are indeed valid and not artifactual[2-6]. For several European countries recent data indicate that the epidemic is still waxing, not waning. For the economically developing countries, evidence is available indicating that rates are on the rise among them as well.

These elementary epidemiologic data not only indicate the scope of the problem. They permit an immediate basic generalization concerning the etiology of the epidemic—and approaches to its control. The forbears of the great majority of Americans emigrated to the United States from the countries of Europe represented in Fig. 1, i.e., from countries with much lower present-day mortality rates from premature CHD than the U.S.A. The gene pool of the American population must be simliar to the gene pools of these European populations—a fact indeed established in many studies. Therefore, the observed differences in mortality rates for CHD cannot be a result of interpopulation differences in genetic susceptibility. Rather, they must be enviromental in origin, i.e., reflecting interpopulation differences in mode of life.

Similarly, the rising rates in several European countries in the 1950's and 1960's—and the probable recent increases in incidence in the developing countries—have occurred over so short a period of time as to exclude any role for altered population gene pools in their etiology. Rather these increases must be environmental in origin, i.e., due to changes over time in mode of life. The logical inference follows that through improvement in mode of life, the epidemic can be controlled.

A serious effort is just now beginning to be mounted for this purpose. The strategy and methodology of this complex long-term undertaking rests in a major way on epidemiologic evidence, buttressed by data from clinical, pathologic and animal-experimental research. This knowledge demonstrates first and foremost the essentiality of a strategy emphasizing primary prevention, through control of the major coronary risk factors.

The critical importance of a strategy of primary prevention is amply demonstrated by the data in Fig. 2, from the national cooperative Pooling Project in the United States,—i.e., pooled data from the Albany civil servant, Chicago Peoples Gas Company, Chicago Western Electric Company, Framingham community, and Minneapolis—St. Paul business and professional men studies[7]. About 25 per cent of previously healthy young adult and middle-aged men experiencing a first heart attack die within three hours of onset of symptoms. In the majority of cases death occurred prior to hospitalization and before medical care could be summoned to the scene. Another ten per cent died within the first weeks after their attack.

J. STAMLER, M.D.

Professor and Chairman, Department of Community Health and Preventive Medicine, and Harry Dingman Professor of Cardiology, Northwestern University Medical School, Chicago, Illinois; Secretary, Council on Epidemiology and Prevention, International Society of Cardiology.

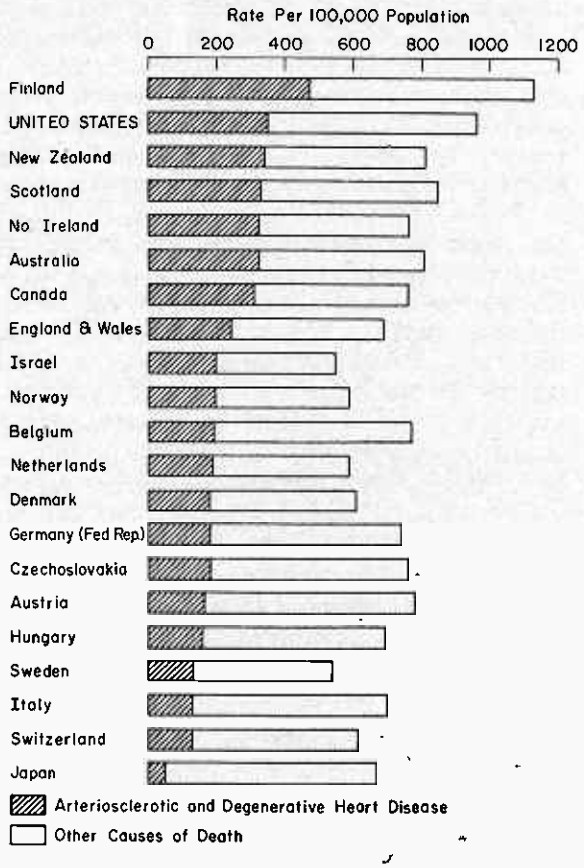


Fig. 1. Death rates from arteriosclerotic and degenerative heart disease and from all causes; selected countries, 1967, men age 45-54 years (1).

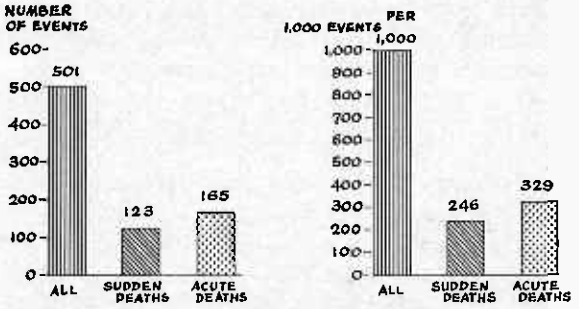


Fig. 2. National cooperative Pooling Project; sudden death and acute mortality with first major coronary episodes; U.S. white males age 30-59 at entry; 10-year findings (7).

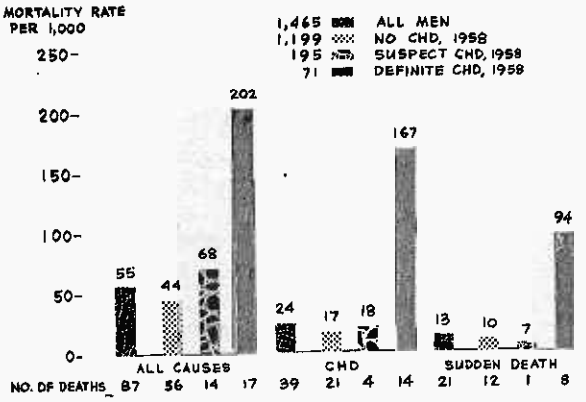


Fig. 3. Peoples Gas Co. Study; coronary heart disease status and five-year mortality, 1958-63, 1,465 men age 40-59 at entry; all rates age-adjusted by 5-year age groups to U.S. male population, 1960 (6).

As our group's study in the Chicago Peoples Gas Company population further showed, for middle-aged persons fortunate enough to recover from an acute episode, prognosis for longevity was on the average markedly impaired. They were approximately five times as likely to die within the next five years as those without a history of previous coronary disease (Fig. 3)[6]. The great majority—about 70 per cent—of deaths, both with first and recurrent attacks, occurred outside the hospital (Fig. 4)[6]. This salient fact accounts for the failure of the age-specific death rate to decline for males in countries like the United States, despite the achievement of the coronary care units. These units can save lives (within the limits of their abilities, i.e., particularly the minimization of arrhythmic deaths) only of those patients surviving long enough to be transported and admitted to their facilities. The overall net effect on mortality is too small percentage-wise to be detected in the mortality statistics.

These facts strongly indicate that major progress in controlling the coronary epidemic is possible only by *primary prevention*—reducing the rate of first clinical episodes by preventing severe atheros-

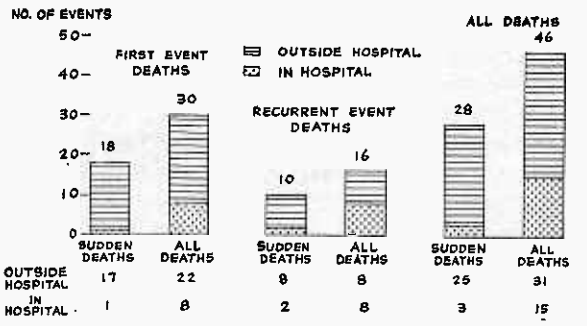


Fig. 4. Peoples Gas Co. Study; hospitalization and mortality with major acute coronary episodes, first and recurrent events; cohort of 1,329 men age 40-59 at entry, free of definite CHD, and followed long-term without systematic intervention, 1958-68 (6).

clerosis and its complications. This must be the main strategic thrust of efforts to control coronary heart disease during the years ahead.

Concept of the Major Risk Factors—its Key Role for Implementing a Strategy of Primary Prevention

The extensive knowledge now available on the major coronary risk factors—i.e., habitual diet, high in saturated fats-cholesterol—calories, hypercholesterolemia, hypertension and cigarette smoking—constitutes a firm scientific basis for the implementation of a strategy of primary prevention. Thus, these major risk factors can be avoided, controlled, or corrected—principally by safe practical approaches related to mode of life. This fact—buttressed by extensive supportive data from all the major research methodologies—strongly indicates, as the Intersociety Commission for Heart Disease Resources recently emphasized, " . . . the possibility of effective primary prevention of atherosclerotic diseases, particularly premature coronary heart disease"[7].

A vast literature is available, including recent review articles, presenting the evidence on the impact of the major risk factors[1-7]. The detailed data powerfully support the conclusion that they are properly designated *major etiologically significant* risk factors for premature atherosclerotic disease, especially coronary heart disease. This designation is appropriate, first because of the impact of these findings on risk, second because of the extent and consistency of the findings now available in multiple studies, third, because of the independent and additive contribution of these factors to risk (at least under the nutritional-metabolic conditions in industrialized countries), fourth because of the frequency of occurrence of these factors (at least in relatively affluent social strata), and fifth because all are potentially amenable to prevention and control.

Habitual diet high in saturated fat and cholesterol: For those still unclear or sceptical about the key role of diet composition, it is worth-while, before dealing with epidemiologic data, to summarize the very recent contributions of animal experimentation especially on nonhuman primates. First, there is the key work of Dr. Bruce Taylor at the Evanston Hospital showing that advanced atherosclerotic lesions—and their clinical sequelae (including fatal myocardial infarction)—can be produced in monkeys by putting them for a long period of time on a diet high in fat and cholesterol[8]. The change in diet to a "rich" one—like those habitually consumed by most of the population in most highly industrialized countries, and by many affluent "westernized" persons of the middle and upper classes in the developing countries—induced a sustained hypercholesterolemic hyperlipidemia with resultant extensive severe atherosclerosis, not only in the coronary but also in the lower extremity circulation. At least one of Dr. Taylor's monkeys developed extensive gangrene of the lower extremities prior to a final coronary event. This finding is food for thought for any one who is sceptical about the fundamental role of diet—particularly dietary cholesterol and saturated fat—in the etiology of hypercholesterolemic hyperlipidemia and severe atherosclerosis. Such diets are the prerequisite for the experimental production of this disease, not only in rabbits and chickens, dogs, rats, pigs, guinea pigs, etc., but also in nonhuman primates, as extensive work in recent years has demonstrated.

Among these studies in monkeys, one of the most relevant from our anthropomorphic standpoint has been done at the University of Chicago by Dr. Robert Wissler, involving the feeding of ordinary human diets from the hospital kitchen to monkeys[9]. Two types of diet were fed, a usual American one and a second one significantly reduced in saturated fat and cholesterol. Marked differences were noted, with the former—the usual American—producing much more severe hypercholesterolemia and atherosclerosis. In this brief review of animal work, it is important to call attention also to the magnificent regression experiments done at the University of Iowa by Doctors Armstrong and Connor and their associates[10]. They conclusively demonstrated that atherosclerotic lesions in primates are capable of regression when the high saturated fat, high cholesterol diets inducing them are withdrawn and replaced either by a diet low in all fats or low in saturated fats and cholesterol but containing unsaturated vegetable oil. These studies confirm in nonhuman primates the fact of reversibility as demonstrated years ago in rabbits and chickens[11]. This is most encouraging in terms of the problem of prevention for man. It is especially encouraging when we keep in mind that for most of us—thus far without clinical evidence of severe atherosclerotic disease—the need is not so much for regression or reversal of lesions, but rather the cessation of progression or at least its slowing.

The animal experimental findings also clarify other key aspects of the etiopathogenesis of this disease, of fundamental importance for achieving its prevention: Thus, they indicate that a diet high in saturated fat and cholesterol is a prerequisite—a *primary, essential, necessary cause*—for the frequent occurrence of hypercholesterolemic hyperlipidemia, and this is in turn a prerequisite for the frequent occurrence of premature severe atherosclerosis. They also show that in the absence of such a diet high in cholesterol and saturated fat, other factors

potentially capable of intensifying atherogenesis have no effect. Hypertension is an excellent example. By itself it does not lead to significant atherosclerosis in any species. It is non-atherogenic. But when the habitual diet is high in cholesterol and saturated fat, leading to frequently occurring hypercholesterolemic hyperlipidemia—i.e., when the nutritive metabolic conditions are present for atherogenesis—then such other factors as hypertension markedly intensify and aggravate the disease process in major arteries. Evidence is also available indicating that repeated "bursts" of catechole release into the blood stream, and significant levels of carboxyhemoglobin, also aggravate atherogenesis in animals fed on a high-cholesterol high-fat diet. These two are of course consequences when human beings smoke cigarettes in quantity daily.

Thus, the animal-experimental findings strongly indicate that such other factors are *contributory* causes of the disease, complementing the effects of an atherogenic diet. They also lend weight to the generally held concept that the disease is multifactorial in its causation.

Extensive evidence is also available from epidemiologic research on the significance of habitual diet in the etiology of the twentieth century epidemic of coronary disease in the economically advanced countries. Studies of three types have been done on human populations: (*1*) analyses of data on nutrition and mortality patterns among the nations, as published in reports of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO); (*2*) analyses of autopsy findings from different countries; (*3*) field investigations of representative population samples. With regard to studies of the first type, six analyses of FAO-WHO data—published over the last 25 years—all demonstrate significant associations between components of national diets (especially saturated fats, cholesterol, calories) and CHD mortality rates for middle-aged men[5,6,12]. In agreement with the concept of the multifactorial nature of the etiology of atherosclerotic disease, and the key role of mode of life (life style), data from these studies also implicate cigarette smoking and sedentary habit.

Illuminating data are also available from the two other types of international studies, one utilizing autopsy material, and the other involving follow-up of representative samples of the living population. The International Atherosclerosis Project is the most comprehensive and systematic study of postmortem findings on aorta and coronary atherosclerosis in different populations[2]. This project quantitated the degree of atherosclerosis of the aorta and coronary arteries at autopsy in over 31,000 persons age 10 to 69 who died during 1960 to 1965 in 15 cities throughout the world. Marked geographic differences were recorded in the occurrence of severe atherosclerosis. Significant correlations were found among intake of fat, serum cholesterol level, and severity of coronary atherosclerosis at autopsy for the populations from the 15 cities. In addition—and again in support of multifactorial etio-pathogenesis—hypertension and diabetes were shown to intensify and aggravate atherogenesis, conspicuously in the economically more affluent populations with the nutritional-metabolic prerequisites for the severe, clinically significant stages of the disease.

The International Cooperative Study on Epidemiology of Cardiovascular Disease has yielded key data on the role of diet-cholesterolemia, along with evidence on the contributory influence of hypertension and cigarette smoking, in accounting for international differences in rates of occurrence of premature CHD[3]. This prospective international study of 18 population samples in seven countries—Finland, Greece, Italy, Japan, Netherlands, United States, and Yugoslavia—deals with observations on approximately 12,000 men, originally aged 40 to 59, who have been studied for about a decade. Marked differences in the prevalence and incidence of coronary heart disease were recorded among the population samples from the seven countries. For samples with high prevalence of coronary heart disease at initial examination, including middle-aged American men, the mean rate was over four times greater than that for countries with low prevalence.

The highest 5 years incidence rates were recorded for men from Eastern Finland and the United States—over 120 and 80 per 1000 population respectively[3]. In contrast, 5 year incidence rates were about 20 or less per 1000 for men in Corfu, Crete, Dalmatia, and Japan. Differences in coronary heart disease mortality rates were frequently paralleled by differences in total mortality rates. This finding supports the conclusion that the differences in coronary heart disease rates were not due to diagnostic variability.

Amount and type of lipid habitually eaten—especially saturated fat, and inevitably cholesterol—varied markedly among the population samples studied[3]. Thus, in Kyushu, Japan, total fat constituted 9 per cent of calories, saturated fat 3 per cent, and polyunsaturated fat 3 per cent. In several of the European communities—e.g., the Greek islands of Corfue and Crete; Velika Krsna and Dalmatia, Yugoslavia; Montegiorgio and Crevalcore, Italy—saturated fat intake was also low (7 to 10 per cent of calories); polyunsaturated fat intake was never high (3 to 7 per cent). (For some of these southern Europe populations consuming considerable olive oil, total fat made up as much as 40 per cent of calories,

but saturated fat intake was still low, as was poly-unsaturated fat intake, since olive oil is composed largely of mono-unsaturated oleic acid.) In contrast, analyses of the diets ingested by the men under study in Finland, the Netherlands, and the United States revealed high saturated fat intakes, in the range of 17 to 22 per cent of calories (total fat 35 to 40 per cent, polyunsaturated fat 3 to 5 per cent). Men from East Finland exhibited the highest levels of saturated fat ingestion—22 per cent of total calories.

Saturated fat intakes and 5 years incidence rates, of coronary heart disease for these population samples showed a high order positive correlation that was statistically significant (Fig. 5)[3]. Saturated fat intake and serum cholesterol level of the populations were highly and significantly correlated (Fig. 5). In turn, serum cholesterol and incidence rates were highly and significantly correlated (Fig. 5).

Most of the other components of the analyzed diets—total calories, total fat mono-unsaturated fat, polyunsaturated fat, total protein—were not significantly related to serum cholesterol levels or coronary heart disease incidence rates of the cohorts[3]. Dietary cholesterol was not systematically evaluated. Sucrose intake—significantly correlated with saturated fat intake ($r = 0{\cdot}84$)—was significantly correlated with CHD incidence in a sample correlation analysis, but the partial correlation coefficient was without statistical significance when controlled for saturated fat intake[13, 14].

Recently, one investigator in particular has emphasized the positive correlation between sucrose intake and incidence rates for coronary heart disease[15]. He has invoked for sucrose a major, primary, and specific role in atherogenesis. This issue has been reviewed at length elsewhere, and its detailed examination is beyond the scope of this presentation[4-6, 13, 14, 16]. Suffice it to note here that several major sets of evidence—animal-experimental clinical and epidemiologic-render untenable the hypothesis that sucrose is a prime and decisive factor influencing atherogenesis.

One of the most important research advances since World War II is the delineation of the chief probable mechanism of the etiologic effect of dietary lipid on atherogenesis in man. This has been the demonstration that populations differing in habitual intake of saturated fat and cholesterol also differ markedly in serum cholesterol-lipid-lipoprotein levels, i.e., interpopulation levels of these two sets of variables are highly correlated, as are dietary saturated fat-cholesterol and coronary heart disease rates, and serum cholesterol and coronary heart disease rates (Fig. 5)[3].

To appreciate the significance of this contribution, it is worthwhile noting that as recently as the middle 1940's it was still unclear that diet composition influences the serum cholesterol of man. The marked rise in serum cholesterol recorded with age in populations of the developed countries was then regarded as an inevitable and invariate physiologic response, completely endogenous in origin and not amenable to environmental influence. As everyone now knows, this is not the case. The slope of serum cholesterol with age varies markedly among different populations, depending upon habitual diet, particularly saturated fat and cholesterol intake. Differences among populations in this regard are not related to their different ethnic and racial backgrounds, but rather to their different habitual diets. This is clear from such comparisons as those of Neapolitan working men and bankers in Italy and Neapolitans in Boston, Irish in Ireland and Boston, or Japanese in Japan, Hawaii, and the United States, and so forth.

Conclusions from the epidemiologic data are in full accord with those from the animal experimental evidence. And, by way of negative collaborative evidence, research on both animals and man indicates that other components of diet—e.g., protein, carbohydrate, sugar—are not capable of markedly influencing serum lipid levels.

In summary, the two-way interpopulation correlation indicated by early research work, prior to World War II, has been broadened and extended to a three-way correlation—among habitual diet (particularly habitual saturated fat and cholesterol intake), levels of serum cholesterol-lipid-lipoprotein, and occurrence rates of premature severe atherosclerotic coronary disease. The principal pathogenetic mechanism of the biologic action of the key environmental etiologic agent—nutrition—has been delineated.

This does not mean that nutrition is involved in the etiology of the atherosclerotic disease solely via saturated fat-cholesterol intake and the influence of these on serum cholesterol. Thus, in terms of composition (quality) of the diet, other nutrients —e.g., complex carbohydrates, polyunsaturated fatty acids—play a modest role in lowering serum cholesterol. In terms of quantity (i.e., total caloric intake, imbalance between consumption and expenditure) the resulting obesity—a common phenomenon among adults in developed countries, even among children and teenagers in the United States —contributes to risk. Its main pathways of pathogenetic operation are probably via the increased proneness of obese persons to hypertension, hyperlipidemia, hyperglycemia, and hyperuricemia.

Hypercholesterolemia:

As indicated above, studies comparing different populations have demonstrated etiologically signi-

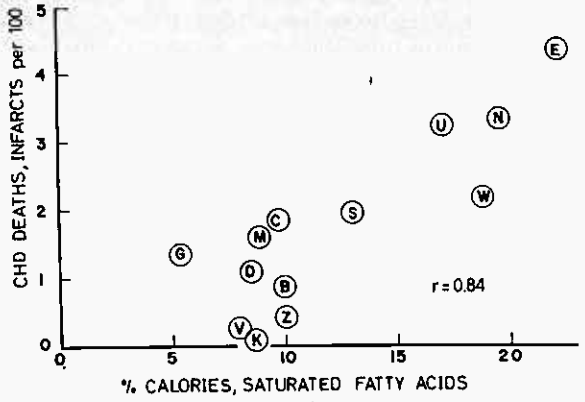


Fig. 5(a).

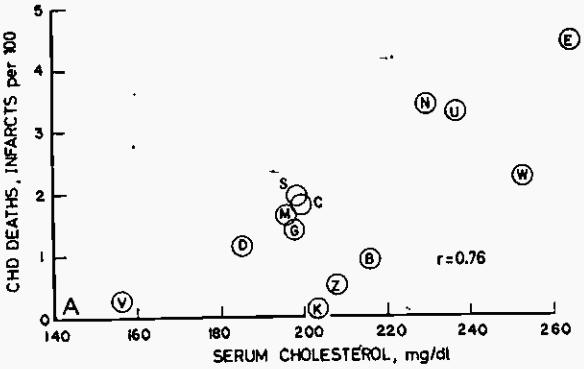


Fig. 5(c).

Figs. 5(a), (b), (c). International Cooperative Study on Epidemiology of Cardiovascular Disease; men originally age 40-59 in seven countries. The upper graph shows the relationship between percentage of total calories provided by saturated fatty acids in the diet of the cohorts and age-standardized 5 year incidence rate for fatal coronary heart disease plus non-fatal myocardial infarction. The middle graph shows the relationship between average percent of total calories from saturated fatty acids in the diet of the cohorts and median serum cholesterol value, as determined at initial examination. The lower graph shows the relationship between median serum cholesterol concentration for the cohorts at initial examination and age-standardized 5-year incidence rate for fatal coronary heart disease plus non-fatal myocardial infarction. The cohorts are: E = East Finland; U = U.S. railroad; W = West Finland; N = Zutphen, The Netherlands; C = Crevalcore, Italy; M = Montegiorgio, Italy; S = Slavonia, Yugoslavia; B = Belgrade, Yugoslavia; Z = Zrenjanin, Yugoslavia; D = Dalmatia, Yugoslavia; V = Velika Krsna, Yugoslavia; G = Corfu, Greece; K = Crete, Greece (3).

ficant independent associations between dietary saturated fat-cholesterol and serum cholesterol, and between serum cholesterol and coronary heart disease rates for middle-aged men. As is evident from Figure 5, the variables used to characterize the populations with respect to nutrients and cholesterolemia are means or medians. For these interpopulation comparions, the range of values within each population—i.e., the interindividual variation—is ignored.

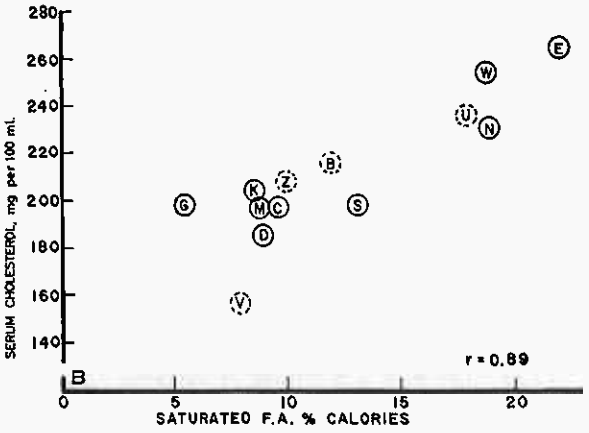


Fig. 5(b).

For any single population interindividual variation in nutrient ingestion (e.g., saturated fat) is generally small. Nevertheless, a large interindividual variation exists in serum cholesterol levels. This is well represented by the finding in our group's study of the middle-aged men employed by the Peoples Gas Company in Chicago[4]. Mean serum cholesterol on initial examination of this cohort of 1465 middle-aged men was 238 mg. per dl., with a standard deviation of 44 mg. per dl., and another 8 per cent of this population had levels under 175 mg. per dl., and another 8 per cent levels of 300 or greater—although differences in nutrient intake were modest.

Even when individuals are placed on a single uniform diet in a metabolic ward, the range of serum cholesterol remains wide, e.g., a standard deviation for a group mean on the order of 30 mg. per dl.

Obviously, to put the matter in its most general form, this is a typical example of biological variability, i.e., the wide range of response of protoplasm to a given environmental stimulus. The specific mechanisms of the large inter-individual differences in serum cholesterol response to diet of a population remain a mystery. Undoubtedly they have a genetic basis, as evidenced by the fact that they are already present in umbilical cord blood. The detailed biochemical-physiologic control systems have yet to be elucidated.

Be this as it may, this wide interindividual variation in serum cholesterol levels within a population permits a further evaluation—in addition to the earlier cited interpopulation evaluation —of the relationship between serum cholesterol and risk of atherosclerotic disease. Extensive data on this matter are available, particularly in relation to premature coronary heart disease in the United States. They are summarized in Fig. 6, from the national cooperative Pooling Project, data from several long-term prospective studies of United

States males[7]. In the analysis of these data use was made of only the first serum cholesterol determination, done at the time of initial examination. Thus, this analysis suffered from all the difficulties of a single measurement, particularly intra-individual fluctuation and laboratory analytical error. Nevertheless, highly significant relationships are clearly evident between serum cholesterol level and each of the four end points.

More detailed analyses of these data indicate that for United States white males aged 40-44, 45-49, 50-54, 55-59, and 60-64, relative risk—i.e., the ratio of risk for a man in a higher compared to one in the lowest quintile (20 per cent) of serum cholesterol level—remains substantial even for the oldest age group, though it tends to decrease with age. *Absolute* excess risk remains the same or even increases with age—i.e., the absolute excess in probability of experiencing a heart attack in any given year for a man in a higher quintile compared to one in the lowest quintile (risk of the former minus risk of the latter). From the point of view of the individual patient, and his physician, *absolute risk* and *absolute excess risk* are the decisive matters. From the data in Figure 6, *relative risk* of a first coronary event for men with serum cholesterol in the range 250 to 274mg. per dl. was 2.5 times as high as risk for men with values less than 170 (112/45). The *absolute risk* over 10 years for these men in the 250 to 274 range was 112 per 1,000, and the *absolute excess* in risk was 67 per 1,000 (112 minus 45). Clearly, these data indicate the potential value of identifying and correcting hypercholesterolemia by safe means, beginning as early in life as possible for purposes of primary prevention.

Recent data from the Coronary Drug Project indicate that serum cholesterol level remains predictive of risk of dying for men who have recovered from one or more myocardial infarctions in middle age. This new finding indicates that there is also a substantial rationale for treatment of hypercholesterolemia in patients with frank clinical coronary heart disease for purposes of secondary prevention.

Finally, data from the Framingham study indicate that for male decedents at autopsy, serum cholesterol measurements made 5 and 9 year prior to death were significantly correlated with severity of coronary atherosclerosis, as measured by both per cent intimal involvement and per cent luminal insufficiency.

Clearly, the evidence on the association between serum cholesterol level and atherosclerosis is extensive and unequivocal.

The amassed data—as illustrated in Fig. 6—further demonstrate that there is a steady increment in premature atherosclerotic disease as level of serum cholesterol rises. As cholesterol concentration increases, risk increases. The relationship is continuous. This is true at all ages, at least from young adulthood through middle age. There is no evidence of a critical level which divides "normal" subgroups (i.e., subgroups "immune" to premature coronary disease) from coronary heart disease-prone "abnormal" subgroups. Nor is there any justification for using the Gaussian distribution to define "normal" levels. It is unfortunate that this distribution was named the "normal curve" by statisticians. They had no intent to imply anything about biologic or medical normalcy. Yet right up to the present this distribution—and particularly the level two standard deviations above the mean in our population—is being used to define upper limit of normal for specific age-sex groups. This is an unjustifiable definition of normal based on what exists—what is prevalent—in our population, without regard to the continuous relationship between serum cholesterol and risk, and without

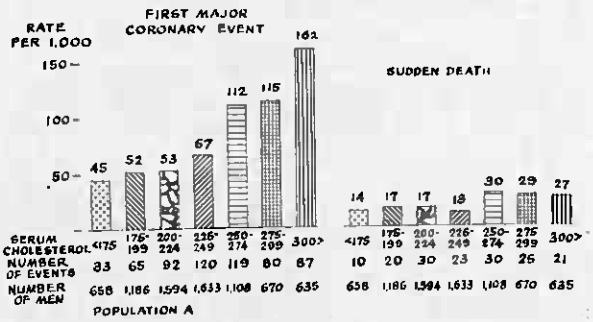


Fig. 6(a).

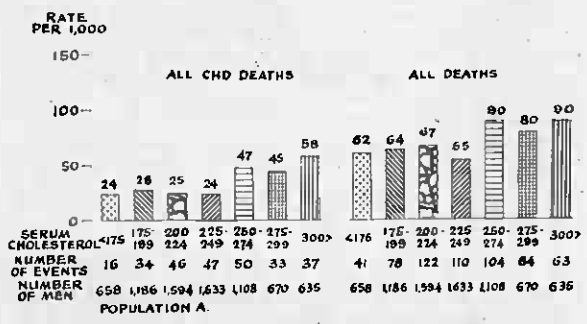


Fig. 6(b).

Figs. 6(a), (b). National cooperative Pooling Project; serum cholesterol level at entry and 10-year age-adjusted rates per 1,000 men for: first major coronary event and sudden death (upper graph), any coronary death and death from all causes (lower graph); first major coronary event includes non-fatal myocardial infarction, fatal myocardial infarction and sudden death due to CHD; U.S. white males age 30-59 at entry; all rates age-adjusted by 10-year age groups to the U.S. white male population, 1960 (7).

regard to the lessons from comparative studies of other human populations (cf. Fig. 5) and other species.

For the physician responsible for patients, the basic facts about the continuous relationship between serum cholesterol level and risk are of the utmost practical importance with regard to prescribing measures for prevention. The greater the probability, the greater the need for prophylaxis—but there is no single "screening level" separating those in need of prophylaxis from those who are not.

The basic set of conclusions does not negate—but rather places in proper context—the clinical use of practical cutting points, e.g., serum cholesterol of less than 200 mg. per dl. as normal, 200 to 249 as borderline, 250 or greater as abnormal for adults age 30 and over. As American Heart Association statements on risk factors have emphasized this 250 mg. per dl. level for defining hypercholesterolemia is approximately the 2 to 1 cutting point, i.e., persons positive for this risk factor are approximately twice as susceptible to premature coronary heart disease as those with lower levels (everything else being equal). The impact of these factors is no small 10 per cent, but rather 100 per cent—a doubling of risk. But as useful as this practical approach of cutting points is, it remains a distortion of reality. After all, a person with a serum cholesterol of 240 is at greater risk than one at 210, and this person in turn is at greater risk than one at 160. Morever, a serum cholesterol level of 240 has an entirely different meaning risk-wise for a pack-a-day cigarette smoker with a diastolic blood pressure of 96, than for a nonsmoker with a pressure of 74 mm. Hg. At present, modern biomathematical techniques for multivariate risk function analysis are becoming available to physicians, to permit them to evaluate risk factors simultaneously, as continuous quantitative variables[17]. This will mean further improvement over present approaches —already useful—for assessing the significance of serum cholesterol level and quantitating susceptibility to premature atherosclerotic disease.

As to other serum lipid and lipoprotein measurements and their relationship to risk of atherosclerotic disease, until recently only three sets of definitive data—i.e., from long-term prospective studies—were available for a scientific assessment[18-20]. A fourth has just been published, with data from Sweden on serum cholesterol and fasting triglycerides as predictors[21]. These data show that serum cholesterol and low density lipoprotein (LDL, betalipoprotein, S_f, 0-12 and 12-20 lipoprotein) are highly correlated—inevitably, since LDL is the main bearer of serum cholesterol. Correspondingly, serum cholesterol and LDL are about equal as predictors of risk of premature coronary heart disease. Further the first three of these studies indicate that once determination of serum cholesterol has been made, little or nothing is apparently added to predictive power by measurement of very low density lipoprotein (VLDL, prebetalipoprotein, S_f, 20-400 lipoprotein)— and therefore of serum triglycerides (VLDL being the main carrier of serum triglycerides). On the other hand, the report from Sweden concludes that fasting serum triglycerides are independent and additively predictive, although—in the judgment of this writer—the published data do not necessarily warrant this inference.

It is very possible that hyperprebetalipoproteinemia has significance for atherogenesis chiefly—perhaps solely—because of the associated hypercholesterolemia. No evidence is available indicating that—in the absence of hypercholesterolemia —hypertriglyceridemia (whether from endogenously synthesized VLDL molecules or from absorbed chylomicrons) is associated with intensified atherogenesis. Evidence is available—although it is not conclusive—indicating that both LDL and VLDL molecules are atherogenic, the former more so. This is not surprising, in view of recent data confirming that the smaller LDL molecules infiltrate across the arterial intima more readily than the larger VLDL particles, are subject to entrapment in the subintimal tissue (owing in part, at least to their electrical charge), and bring into this tissue a much greater amount of cholesterol (especially cholesterol ester) than VLDL per molecule. And it is this cholesterol from the plasma, especially cholesterol ester, that accumulates in excess—10-fold, 40-fold above normal levels—as an integral part of atherogenesis, in smooth muscle cells, then (as these disintegrate due to lipid overloading) in extracellular pools, acting as tissue irritants to stimulate scarification (i.e., the sclerotic components of the pathologic process).

On the basis of currently available data, therefore, serum cholesterol is the best single measurement for assessing risk of premature atherosclerotic disease, particularly coronary heart disease. Fasting serum triglycerides or lipoprotein (e.g., as determined qualitatively by paper electrophoresis) are not superior predictors of risk. Earlier claims of this kind, based on preliminary or unsatisfactory data, have not withstood the test of time.

In the management of hypercholesterolemic patients, on the other hand, fasting serum triglyceride determination is a useful adjunct to cholesterol measurement. It is also worthwhile, when the fasting serum is lactescent, to re-examine it after 24 hours in the refrigerator, to determine if a supranatant chylomicron layer is present. In this way,

the rare chylomicronemias (hyperlipoproteinemia Types I and V) can readily be ruled out. Of course, the patient must indeed have fasted for 15 hours, after a meal moderate in fat and free of (or low in) alcohol. Otherwise, abnormal chylomicronemia may be erroneously diagnosed. Whether in addition to these procedures, serum lipoprotein typing (e.g., by electrophoresis) is also worthwhile for clinical management is at present unclear—claims to the contrary notwithstanding.

In the general population, the common phenomenon is "moderate" hypercholesterolemia, either without hypertriglyceridemia, or with slight, moderate, or marked hypertriglyceridemia but without chylomicronemia. (A reasonable cutting point for fasting serum triglyceride abnormality is 150 mg. per dl.). Once conditions known to induce hyperlipidemia (e.g., uncontrolled diabetes, hyperthyroidism, nephrosis, biliary obstruction, pancreatic disease, alcoholism, myeloma, contraceptive steroids) have been ruled out, it may be concluded that the abnormality is fundamentally diet-induced, i.e., acquired, and it can almost always be alleviated by change in diet habits, i.e., to a calorie-controlled diet low in saturated fat and cholesterol, moderate (not low) in total fat and carbohydrate, moderate (not high) in polyunsaturated fat.

To designate the hyperlipidemic common in a country like the United States as acquired is not to say that genetic factors are not operating. Since some (a small minority) of Americans maintain very low levels of all serum lipids on usual United States diets, there must be an element of host response in all cases of acquired hyperlipidemia, and almost certainly this often reflects inborn (genetic) differences in metabolism. Correspondingly, since almost all persons with familial severe hyperlipidemia respond (at least in part) to diet, their condition is to a degree environmental in origin and related to the usual U.S. diet. Therefore, the distinction between acquired and familial primary hyperlipidemia is relative, not absolute. This conclusion in no way contradicts the fact that among persons with severe hyperlipidemias in particular, disease usually is due predominantly to genetic metabolic abnormalities.

A practical consequence for both diagnosis and treatment—of this and other risk factors—is the importance of evaluating the entire immediate family. For example, children inherit both their parents' genes and living habits. The latter are amenable to environmental influence. Identification of susceptibility in a parent must, therefore, immediately call attention to his or her children and to parental siblings; the converse is equally true. Hence, prevention, especially early prevention, is an intrinsic part of family medicine. The basic aim is, by changing living habits (the environment) on a family basis, to control hereditable risk factors and thereby mute or negate genetic predisposition to premature coronary heart disease. This is a key aspect of the strategy of focusing on risk factors, to curb the epidemic occurrence of this disease.

Hypertension:

Especially for populations from countries with the nutritional prerequisites for premature severe atherosclerosis, elevated blood pressure—in addition to serum cholesterol—is a powerful risk factor for atherosclerotic diseases, in this instance for both premature coronary and cerebrovascular disease. The autopsy data of the International Atherosclerosis Project demonstrated a significant relationship between hypertension and the severity of atherosclerosis[2].

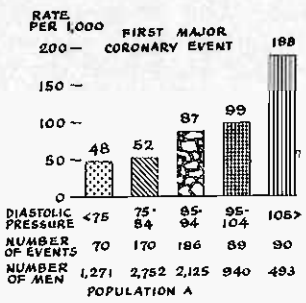
Data from the International Cooperative Study on the Epidemiology of Cardiovascular Disease indicate that interpopulation differences in 5 year incidence rates for coronary heart disease were attributable in part to differences in prevalence of hypertension among the 18 samples of middle-aged men[3].

Data from Americans, from the national cooperative Pooling Project—on interindividual differences in diastolic blood pressure and their relationship to risk or morbidity and mortality over the next 10 years—are presented in Fig. 7[7]. Corresponding data for systolic pressure show a similar relationship to risk.

Cigarette smoking:

International data demonstrate a high-order and significant correlation between average per capita consumption of cigarettes and coronary heart disease mortality rates for both middle-aged male and female populations of the developed countries[5]. These data are particulary intriguing in that the correlation coefficients between cigarette smoking and coronary heart disease mortality are higher for the female than for the male populations.

In regard to interindividual differences in cigarette smoking habit and their relationship to risk of atherosclerotic disease, extensive data from several prospective studies in the United States and Great Britain demonstrate a clear-cut, significant relationship. The data of the national cooperative Pooling Project are typical (Fig, 8)[7]. For men smoking cigarettes at initial examination, the risk of experiencing a first major coronary event, sudden death, coronary heart disease death of any type, and death from all causes, was consistently higher in comparison to men who have never smoked or who had quit smoking. Risk generally increased step-wise with the number of cigarettes used daily.



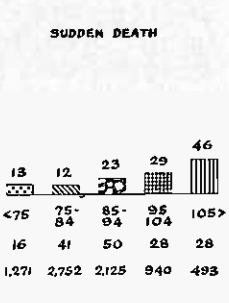


Fig. 7(a).

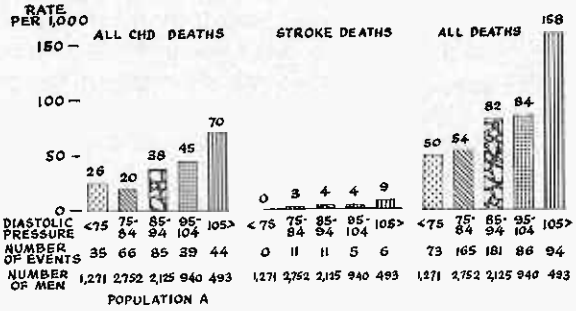
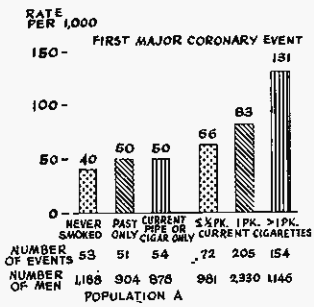


Fig. 7(b).

Figs. 7(a), (b). National cooperative Pooling Project; diastolic blood pressure level at entry and 10-year age-adjusted rates per 1,000 men for: first major coronary event and sudden death (upper graph), any coronary death, stroke death, death from all causes (lower graph); first major coronary event includes non-fatal myocardial infarction, fatal myocardial infarction, sudden death due to CHD; U.S. white males age 30-59 at entry; all rates age-adjusted by 10-year age groups to the U.S. white male population, 1960 (7).



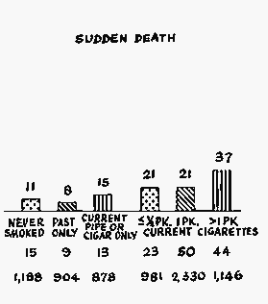


Fig. 8(a).

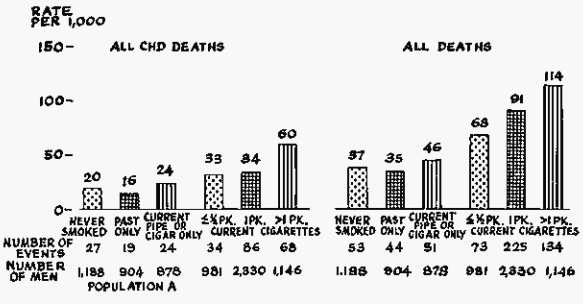
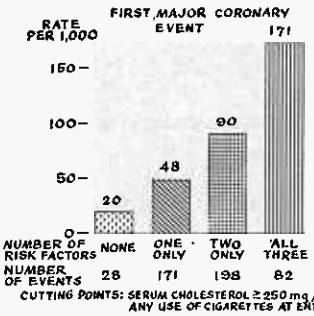
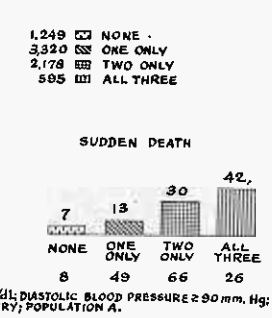


Fig. 8(b).

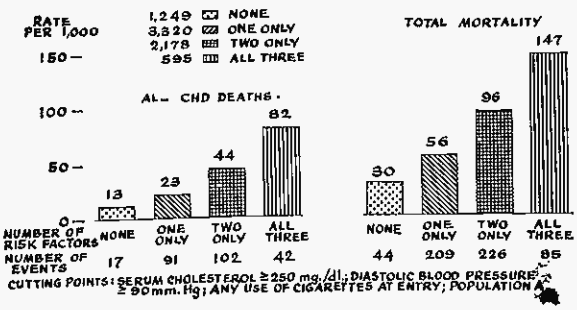
Figs. 8(a), (b). National cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for: first major coronary event and sudden death (upper graph), any coronary death and death from all causes (lower graph); first major coronary event includes non-fatal myocardial infarction, fatal myocardial infarction and sudden death due to CHD; U.S. white males age 30-59 at entry; all rates age-adjusted by 10-year age groups to the U.S. white male population. (7).





CUTTING POINTS: SERUM CHOLESTEROL ≥ 250 mg./dl.; DIASTOLIC BLOOD PRESSURE ≥ 90 mm. Hg; ANY USE OF CIGARETTES AT ENTRY; POPULATION A.

Fig. 9(a).



CUTTING POINTS: SERUM CHOLESTEROL ≥ 250 mg./dl.; DIASTOLIC BLOOD PRESSURE ≥ 90 mm. Hg; ANY USE OF CIGARETTES AT ENTRY; POPULATION A.

Fig. 9(b).

Figs. 9(a), (b). National cooperative Pooling Project; hypercholesterolemia, hypertension, cigarette smoking and 10-year age-adjusted rates per 1,000 men for: first major coronary event, sudden death (upper graph), any coronary death, death from all causes (lower graph); first major coronary event includes non-fatal myocardial infarction, fatal myocardial infarction and sudden death due to CHD; U.S. white males age 30-59 at entry; all rates age-adjusted by 10-year age groups to the U.S. white male population, 1960 (7).

For users of pipe or cigar tobacco, 10 years rates were only slightly and insignificantly higher than those for men who had never smoked.

The data of the Pooling Project studies demonstrate that at least for Americans, cigarette smoking is related to risk of premature atherosclerotic disease independent of and additive to such other major risk factors as hypercholesterolemia and hypertension.

The largest prospective study of cigarette smoking, involving one million men and women originally age 40 to 84, has furnished follow-up data showing that for each sex and age group coronary heart disease mortality increased with intensity of cigarette smoking [22, 23] the younger the age group, the higher the relative risk associated with cigarette smoking. The youngest men smoking two or more packs of cigarettes a day were at highest relative risk. Absolute excess risk remained high for cigarette smokers throughout middle age.

In addition, three autopsy studies have recently shown that atherosclerosis of the aorta and/or the coronary arteries is more severe at autopsy in persons who had been habitual cigarette smokers prior to death, compared to those who had never smoked.

Impact of the major risk factors in combination:

Of decisive importance is the fact that the recent reports from prospective epidemiologic studies now permit clear definition of the quantitative impact on coronary incidence and mortality—and on mortality from all causes—of the major treatable risk factors, not only singly, but most importantly also in combination. Fig. 9—again data from the Pooling Project—presents an analysis of the simplest type illustrating this key point[7]. This analysis is a simple and crude one in that only a single measurement at entry examination is utilized to characterize each man, and his status, with respect to the specified risk factors, was based on dichomotization of the data, utilizing the specified cutting points. Obviously, as already emphasized, a serum cholesterol level of 240 mg. per dl. is by no means an optimal level in terms of risk, and similarly with respect to diastolic blood pressure of 88 mm. Hg. Nevertheless, for purposes of this analysis, such values were designated not high.

Presence of only one risk factor—as compared to none—was associated with a substantial increase in probability of a major coronary event over the next decade, i.e., an increase in risk of almost 100 per cent for the fatal end points, including total mortality (Fig. 9)[7]. When combinations of these major risk factors—any two or all three—were present, susceptibility to overt CHD and fatal disease was substantially higher, attaining levels four or five times as great as for the group with none of the three risk factors. Detailed age-specific analyses demonstrate that these high levels of excess risk—both relative and absolute—are present for men with these combinations of factors at all ages at least through the 60-64 age.

This last point needs emphasis because an impression has been created by epidemiologists—particularly in discussion of relative risk—that these factors tend to attenuate in their impact with age. As already noted, it is true that *relative* risk decreases with age, e.g., the *ratio* of risk for men with any two or all three risk factors compared to men with none. But again *absolute* excess risk—the numerical *difference* in risk for a group with certain risk factors compared to a group without them—does not decrease with age. And for the individual person, and the clinician responsible for him—as well as for the public health physician concerned with population groups and control of an epidemic—the key thing is not so much relative risk as absolute risk and absolute excess risk. For example, in Fig. 9 the men with any two factors have an absolute risk of death from all causes equal to 96 per 1,000 per 10 years, and an absolute excess risk of 60 per 1,000 per 10 years (96 minus 30). The data on U.S. males indicate that in fact, absolute excess risk either remains about the same or actually increases with age. Therefore, to use an American slang expression, one is never "home free" or safe in terms of the impact of the major risk factors.

As indicated above, the data of Fig. 9—as impressive as they are—nevertheless are products of a crude analysis crude in terms of the methodology used, not only because single (rather than multiple) measurements were used, but also because a single cut point was used arbitrarily to designate individuals as high or not high with respect to each of the three risk factors. At present, modern biomathematical techniques for multivariate risk function analysis permit physicians to evaluate risk factors simultaneously as continuous quantitative variables through use—for example—of the American Heart Association *Handbook of Risk Probability* (based on the experience gathered in the Framingham heart study)[17]. This Handbook presents statistical estimates of 6-year risk of developing coronary heart disease for American men from age 35 through 60, and 45 through 60 for women, based on their status with respect to serum cholesterol, systolic blood pressure, cigarette smoking, glucose tolerance, and the resting electrocardiogram.*

*Discussion of the impact of other risk factors—e.g., glucose intolerance-diabetes mellitus, hyperuricemia-gout, obesity, physical inactivity—poor cardiopulmonary fitness, personality-behavior patterns and psycho-social stresses—incongruities, abnormalities in the resting or exercise ECG, positive family history—is beyond the scope of this presentation. cf. references 1-7, 12, 24.

Fig. 10 presents sample sets of data from this *Handbook*.

The Potential for Prevention—and Progress towards its Realization

A decisive implication of all these data is the potential for prevention by shifting people from higher to lower risk status with treatment. Some insight into the scope of this possibility is indicated —at least for U.S. males—by the data of Fig. 9. Despite the rather high cut points used to label a man positive for one or more of the three major risk factors, only 1,249 of these 7,342 U.S. white men aged 30-59 at entry—i.e., only 17 per cent—were classified as exhibiting none of the three risk factors. All the rest exhibited one or more; 3,320 (45·2%) exhibited one abnormality only; 2,178 (29·7%) manifested two only; 595 (8·1%) had all three; 2,773 (37·8%) had at least two or all three.

Actually, clear cut data are also available indicating that high risk status is identifiable at least as early as the teens (Fig. 11)[25]. These are data from a study of nearly 45,00 college students at the University of Pennsylvania examined from 1931 through 1940, and at Harvard University from 1921 through 1950. Information on mortality was subsequently obtained from college alumni office records and official vital statistics sources. Fig. 11 demonstrates that for young men smoking ten or more cigarettes per day in college, CHD mortality in subsequent decades was 1·6 times as high as for men without this habit. Similarly, men with a systolic blood pressure of 130 or greater in college had a subsequent CHD mortality experience 1·6 times as high as men with SBP less than 130 mmHg. For men with both these risk factors at college examination, mortality rate was 2·1 times as high as for men with neither of these risk factors.

Unfortunately, a sizeable proportion of these teen age American college entrants of yesteryear harbored these and/or other risk factors. And this situation is all the more true today, and not just for college entrants, but for our entire U.S. population—and more-or-less similar conditions prevail in the other economically advanced nations nowadays, as well as the more affluent strata in the developing countries.

As soon as one appreciates this fact—intimately related to contemporary life styles in economically developed and affluent society—the reasons for the coronary epidemic are clear, and the key elements of a strategy for controlling the epidemic are equally clear. First of all, from overall public health point of view, is *it not* entirely reasonable to infer that by improvement in life styles, beginning in infancy and childhood when primary habits are formed, the upcoming generations can be influenced so that a much lower per cent of adults are in the very high risk group. Second of all, is it not equally reasonable to proceed to identify high risk persons as early as possible, in the teens, twenties, thirties and forties, by a variety of means—including the work of primary physicians with the family. And, having identified cases, to give attention to studying all members of the family and encouraging family life styles of eliminate or blunt the impact of risk factors—through improvements of diet to lower lipids, encouragement of cessation of cigarette smoking, encouragement of reduction of weight to lower elevated blood pressure, and introduction early of pharmacologic therapy for hypertension when appropriate.

For example: Fig. 12—from the Chicago Heart Association Detection Project in Industry—clearly demonstrates that not only a sizeable proportion of the general population of adults, including young adults (in this case, persons age 25-44) are hypertensive, but that a majority of these people with elevated blood pressure are unaware of their condition, and that further for those giving a history of hypertension, only about half are being treated, and for those being treated, only about half are being treated vigorously enough and are adhering well enough to prescription to have their blood pressure normalized [26,27]. Thus, for all four major sex-race groups, a small minority of the hypertensives are detected, on treatment, and normalized in terms of blood pressure. These phenomena have been repeatedly recorded by population surveys in the U.S.A., North, East, South and West, in whites and blacks, more affluent and less affluent, more educated and less educated—of the estimated twenty-three million hypertensives in the country, at the most three million are receiving treatment adequate enough to normalize blood pressure. Undoubtedly the situation is similar in all countries. Here indeed is a key challenge for the medical and health professions in terms of the effort to control the coronary epidemic.

Whatever the uncertaintics of yesteryear, since the publication of the reports from the Veterans Administration cooperative study on antihypertensive treatment, there is little or no doubt regarding efficacy when sustained effective treatment with combined medication is properly accomplished.[28-30] This is not only true for persons with severe hypertension (diastolic pressures averaging 115 and greater) as originally reported by the V.A. in 1967, but also true for persons with so-called "moderate" hypertension (diastolic pressures averaging less than 115 mm. Hg). Fig. 13 illustrates efficacy of therapy for this latter group. Over the five years of this magnificently designed double

PROBABILITY* OF DEVELOPING CORONARY HEART DISEASE IN SIX YEARS BY SYSTOLIC BLOOD PRESSURE, CHOLESTEROL, LEFT VENTRICULAR HYPERTROPHY BY ECG, CIGARETTE SMOKING AND GLUCOSE INTOLERANCE: FROM THE FRAMINGHAM STUDY[17]

45 Year Old Man**

	Does Not Smoke Cigarettes							Smokes Cigarettes						
LVH-ECG Negative														
	SBP	105	120	135	150	165	180	SBP	105	120	135	150	165	180
	Chol							*Chol*						
	185	1·5	1·8	2·1	2·5	3·1	3·7	185	2·3	2·7	3·3	3·9	4·7	5·6
Glucose	210	1·9	2·2	2·7	3·2	3·9	4·6	210	2·9	3·5	4·2	5·0	5·9	7·1
Intolerance	235	2·4	2·9	3·4	4·1	4·9	5·9	235	3·7	4·4	5·3	6·3	7·5	8·9
Absent	260	3·0	3·6	4·3	5·2	6·2	7·4	260	4·7	5·6	6·6	7·9	9·4	11·1
	285	3·8	4·6	5·5	6·5	7·8	9·2	285	5·9	7·0	8·3	9·9	11·7	13·7
	310	4·9	5·8	6·9	8·2	9·8	11·5	310	7·4	8·8	10·4	12·3	14·5	16·9
	Chol							*Chol*						
	185	1·9	2·3	2·7	3·3	3·9	4·7	185	3·0	3·5	4·2	5·1	6·0	7·2
Glucose	210	2·4	2·9	3·5	4·2	5·0	6·0	210	3·7	4·5	5·4	6·4	7·6	9·0
Intolerance	235	3·1	3·7	4·4	5·3	6·3	7·5	235	4·7	5·7	6·8	8·0	9·5	11·2
Present	260	3·9	4·7	5·6	6·7	7·9	9·4	260	6·0	7·1	8·5	10·0	11·9	14·0
	285	5·0	5·9	7·0	8·4	9·9	11·7	285	7·5	9·0	10·6	12·5	14·7	17·2
	310	6·3	7·4	8·8	10·5	12·3	14·5	310	9·5	11·2	13·2	15·5	18·1	21·0
LVH-ECG Positive														
	SBP	105	120	135	150	165	180	SBP	105	120	135	150	165	180
	Chol							*Chol*						
	185	3·0	3·6	4·4	5·2	6·2	7·4	185	4·7	5·6	6·7	7·9	9·4	11·1
Glucose	210	3·9	4·6	5·5	6·6	7·8	9·3	210	5·9	7·0	8·4	9·9	11·7	13·8
Intolerance	235	4·9	5·8	6·9	8·3	9·8	11·6	235	7·4	8·8	10·5	12·3	14·5	17·0
Absent	260	6·2	7·3	8·7	10·3	12·2	14·3	260	9·3	11·0	13·0	15·3	17·8	20·7
	285	7·8	9·2	10·9	12·8	15·1	17·6	285	11·6	13·7	16·1	18·7	21·7	25·1
	310	9·7	11·5	13·5	15·9	18·5	21·5	310	14·4	16·9	19·7	22·8	26·2	30·0
	Chol							*Chol*						
	185	3·9	4·7	5·6	6·7	7·9	9·4	185	6·0	7·2	8·5	10·1	11·9	14·0
Glucose	210	5·0	5·9	7·1	8·4	9·9	11·7	210	7·6	9·0	10·6	12·5	14·7	17·2
Intolerance	235	6·3	7·5	8·9	10·5	12·4	14·6	235	9·5	11·2	13·2	15·5	18·1	21·0
Present	260	7·9	9·4	11·1	13·0	15·3	17·9	260	11·8	13·9	16·3	19·0	22·1	25·4
	285	9·9	11·7	13·7	16·1	18·8	21·8	285	14·7	17·1	20·0	23·1	26·6	30·4
	310	12·3	14·5	16·9	19·7	22·9	26·3	310	18·0	20·9	24·2	27·8	31·7	35·8

*Per Hundred.

**Framingham men aged 45 yrs. have an average SBP of 131 MM. HG. and an average serum Chol of 235 MG %. 67 percent smoke cigarettes, 1·3 percent have definite LVH by ECG and 3·8 percent have Glucose Intolerance. At these average values the probability of developing coronary heart disease in six years is 4·4/100 or 4·4 percent.

Fig. 10(a).

PROBABILITY* OF DEVELOPING CORONARY HEART DISEASE IN SIX YEARS BY SYSTOLIC BLOOD PRESSURE. CHOLESTEROL, LEFT VENTRICULAR HYPERTROPHY BY ECG, CIGARETTE SMOKING AND GLUCOSE INTOLERANCE: FROM THE FRAMINGHAM STUDY[17]

45 Year Old Woman**

Does Not Smoke Cigarettes

LVH-ECG Negative

	SBP	105	120	135	150	165	180
	Chol						
Glucose Intolerance Absent	185	0·4	0·6	0·7	0·9	1·1	1·4
	210	0·5	0·7	0·9	1·1	1·4	1·7
	235	0·7	0·8	1·1	1·3	1·7	2·1
	260	0·8	1·0	1·3	1·6	2·0	2·6
	285	1·0	1·3	1·6	2·0	2·5	3·1
	310	1·2	1·6	2·0	2·4	3·1	3·8
	Chol						
Glucose Intolerance Present	185	0·7	0·8	1·1	1·3	1·7	2·1
	210	0·9	1·0	1·3	1·6	2·0	2·6
	235	1·0	1·3	1·6	2·0	2·5	3·1
	260	1·2	1·6	2·0	2·5	3·1	3·8
	285	1·5	1·9	2·4	3·0	3·7	4·7
	310	1·9	2·3	2·9	3·7	4·6	5·7

Smokes Cigarettes

LVH-ECG Negative

	SBP	105	120	135	150	165	180
	Chol						
Glucose Intolerance Absent	185	0·5	0·6	0·7	0·9	1·2	1·5
	210	0·6	0·7	0·9	1·1	1·4	1·8
	235	0·7	0·9	1·1	1·4	1·8	2·2
	260	0·9	1·1	1·4	1·7	2·1	2·7
	285	1·1	1·3	1·7	2·1	2·6	3·3
	310	1·3	1·6	2·0	2·6	3·2	4·0
	Chol						
Glucose Intolerance Present	185	0·7	0·9	1·1	1·4	1·8	2·2
	210	0·9	1·1	1·4	1·7	2·2	2·7
	235	1·1	1·3	1·7	2·1	2·6	3·3
	260	1·3	1·6	2·1	2·6	3·2	4·0
	285	1·6	2·0	2·5	3·1	3·9	4·9
	310	2·0	2·5	3·1	3·8	4·8	5.9

LVH-ECG Positive

	SBP	105	120	135	150	165	180
	Chol						
Glucose Intolerance Absent	185	0·7	0·9	1·1	1·4	1·7	2·1
	210	0·9	1·1	1·3	1·7	2·1	2·6
	235	1·0	1·3	1·6	2·1	2·6	3·2
	260	1·3	1·6	2·0	2·5	3·1	3·9
	285	1·6	2·0	2·5	3·1	3·8	4·8
	310	1·9	2·4	3·0	3·7	4·7	5·8
	Chol						
Glucose Intolerance Present	185	1·0	1·3	1·6	2·1	2·6	3·2
	210	1·3	1·6	2·0	2·5	3·2	3·9
	235	1·6	2·0	2·5	3·1	3·8	4·8
	260	1·9	2·4	3·0	3·8	4·7	5·8
	285	2·4	2·9	3·7	4·6	5·7	7·1
	310	2·9	3·6	4·5	5·6	6·9	8·5

Smokes Cigarettes

LVH-ECG Positive

	SBP	105	120	135	150	165	180
	Chol						
Glucose Intolerance Absent	185	0·7	0·9	1·1	1·4	1·8	2·3
	210	0·9	1·1	1·4	1·8	2·2	2·8
	235	1·1	1·4	1·7	2·2	2·7	3·4
	260	1·3	1·7	2·1	2·6	3·3	4·1
	285	1·6	2·1	2·6	3·2	4·0	5·0
	310	2·0	2·5	3·2	2·9	4·9	6·7
	Chol						
Glucose Intolerance Present	185	1·1	1·4	1·7	2·2	2·7	3·4
	210	1·3	1·7	2·1	2·1	3·3	4·1
	235	1·7	2·1	2·6	3·2	4·0	5·0
	260	2·0	2·5	3·2	3·9	4·9	6·1
	285	2·5	3·1	3·9	4·8	6·0	7·4
	310	3·0	3·8	4·7	5·8	7·2	8·9

* Per Hundred.

**Framingham women aged 45 yrs. have an average SBP of 128 MM.HG. and an average serum Chol of 228 MG%. 50 percent smoke cigarettes, 0·6 percent have definite LVH by ECG and 2·5 percent have Glucose intolerance. At these average values the probability of developing coronary heart disease in six years is 0·9/100 or 0·9 percent.

Fig. 10(b).

MORTALITY RATIOS / PREVALENCE % IN CONTROLS	None	Smoking 10+ cigarettes/day	Systolic BP 130+ mm Hg	Height/$\sqrt[3]{\text{weight}}$ = 12.8 or less	Body height <68 inches	A parent dead	Without siblings	No varsity athletics	Emotional index	Scarlet fever
None		1.6	1.6	1.4	1.3	1.3	1.2	1.5	1.6	1.3
Smoking 10+ cigarettes/day	15		2.1	1.9	1.8	1.9	2.5	1.8	3.8	1.8
Systolic BP 130+ mm Hg	27	4		2.3	1.7	1.8	1.4	1.5	1.9	2.1
Height/$\sqrt[3]{\text{weight}}$ = 12.8 or less	25	4	7		1.6	1.6	2.0	1.5	2.0	2.0
Body height <68 inches	24	3	6	10		2.1	1.9	1.4	1.5	1.4
A parent dead	16	3	4	4	4		2.0	1.5	2.6	1.4
Without siblings	14	2	4	3	3	2		1.3	1.5	1.4
No varsity athletics	84	13	24	20	22	13	12		1.9	1.4
Emotional index	21	5	7	6	5	3	4	17		1.4
Scarlet fever	16	2	4	3	4	3	3	13	5	

Fig. 11. Estimated mortality ratios (coronary heart disease) and prevalence ratios for specified factors assessed during college years (25).

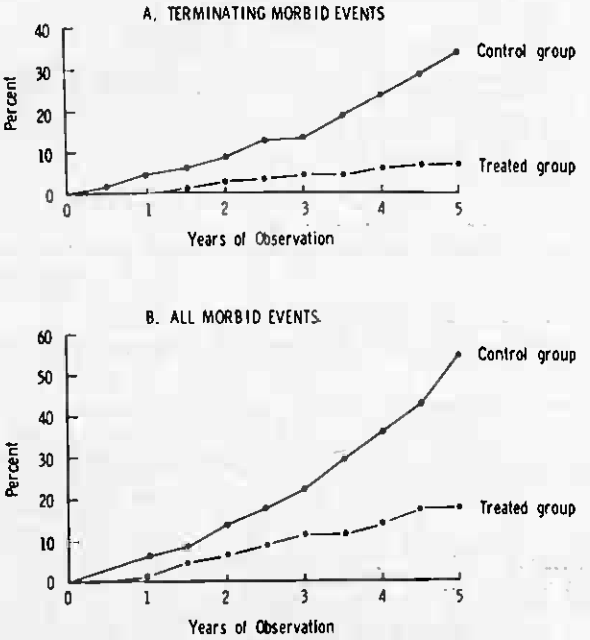


Fig. 13. Veterans Administration Cooperative Study on Antihypertensive Agents; estimated cumulative incidence of morbidity over a 5-year period as calculated by life table method; terminating morbid events (upper graph) and all morbid events (lower graph); men with average diastolic blood pressures 90-114 mm Hg at entry (29).

HYPERTENSION—UNDIAGNOSED, DIAGNOSED BUT UNTREATED, DIAGNOSED AND TREATED BUT NOT NORMALIZED—34,538 EMPLOYED CHICAGOANS NOVEMBER, 1967-MAY, 1972 CHICAGO HEART ASSOCIATION DETECTION PROJECT IN INDUSTRY[26, 27]

Group	White Male		White Female		Black Male		Black Female	
	No.	Rate per 1,000	No.	Rate per 1,000	No.	Rate per 1,000	No.	Rate per 1,000
All	18,142	1,000·0	12,985	1,000·0	1,333	1,000·0	2,078	1,000·0
No Previous History of Hypertension, Blood Pressure Elevated	2,422	133·5	1,093	84·2	202	151·5	99	47·6
History of Hypertension, Not on Treatment, Blood Pressure Elevated	697	38·4	397	30·6	58	43·5	47	22·6
History of Hypertension Not on Treatment, Blood Pressure Not Elevated	891	49·1	604	46·5	61	45·8	150	72·2

Fig. 12.

blind field trial, the placebo group had a rate of morbid events of all types (the lower graph) of almost sixty per cent, whereas the treated group—with blood pressure markedly lower with a combination of thiazide, reserpine and hydralazine—had a rate of only twenty per cent. Therapy was about seventy per cent effective. Even for the group with the most modest elevations of blood pressure (in the 90 to 104 range), effectiveness was at the level of 35 per cent—i.e., a 35 per cent reduction in rate of morbid events. And in all groups, side and toxic effects were of limited frequency and severity, so that the benefit to risk ratio with this judicious treatment was indeed excellent.

Of course, ability of physicians to influence risk is not confined to such pharmacologic modalities of treatment as drugs for hypertension. One of the key areas is cigarette smoking. This undoubtedly has been a decisive aspect—in terms of insult added to injury—of the coronary epidemic at mid-century and since. The Fig. 14 illustrates a key aspect of the matter not appreciated fully by many of us, namely that cigarette smoking does not date as a mass phenomenon to Sir Walter Raleigh, but rather only since World War I [31]. Its prerequisite was the invention of machines for the manufacture of a cheap package of cigarettes, and these were first developed late in the 19th century. Then cigarettes were distributed in this package form free to soldiers in World War I, and then the new modern advertising industry pushed hard for the sustained use of cigarettes not only by men, but also by women. This is the history of the mass use of the cigarette. Once that is understood, it becomes clear why the cigarette smoking and the lung cancer link emerged forcefully only a couple of decades later, after World War II, and why many of the economically developed countries —with the nutritional-metabolic prerequisites for severe atherosclerosis in the form of a high saturated fat, high cholesterol diet and consequent high rates of hyperlipidemia—went on to experience progressively rising rates for premature coronary disease in the post War II period.

Just as this problem of mass cigarette smoking is not a centuries-old phenomenon, so it is not an immutable one incapable of being influenced. Fig. 15 presents the experience of our Coronary Prevention Evaluation Program, in Chicago with a combined initial vigorous approach to encouraging coronary-prone men to quit cigarettes, followed by "firm steady pressure" over the years [32, 33]. Undoubtedly a high per cent of cigarette smokers can be prevailed upon to quit. This is further illustrated by the findings of the Chicago Heart Association large-scale surveys in industry (Fig. 16) [27]. Even for the younger age group, age 25 to 44, 35 per cent of the men who had ever smoked listed themselves as ex-users of cigarettes, and 27 per cent of women. The quit rate is even higher for the older age group. It can indeed be done, not only among adults, but among children and teenagers as well—and of course it is possible to achieve success in encouraging the youngsters never to take up cigarettes. This is especially so if effective ways are used to reach them repeatedly with graphic messages—for example, through the key television medium.

And, as Fig. 17 illustrates, it pays to quit—anywhere along the way, short of massive fatal disease or massive disease bringing the person to death's door[34]. These data are from the Veterans Administration study of hundreds of thousands of veterans, classically illustrating—and there are several sets of such data—that it pays to quit, even in late middle-age, after decades of heavy cigarette smoking (cf. Fig. 8).

Physicians can play a key role in work with individual patients and families in transmitting knowledge about the key importance of avoiding cigarettes or—where necessary—quitting them. The medical profession in the U.S.A., as in Britain, has got the message and the estimate is that one hundred thousand of us have quit cigarettes. There is reason to believe that we have not transmitted this message vigorously enough. We need to reverse the old adage, the cynical one of the obese cigarette smoking doctor who sits and advises his patient, "don't do as I do, do as I say". Nowadays our physicians indeed are generally neither obese nor cigarette smoking—but we don't seem to be telling our patients vigorously and consistently and repeatedly enough to "do as we do"! We have substantial data—as do others—that doctors are not saying enough in this area. We certainly should be vigorous about cigarette smoking, and have confidence that our patients will take us seriously and act on our advice. The evidence—not only from Chicago but throughout the U.S.A.— is that habits are changing. Of course, we also have a responsibility as citizens to work for effective public communication on this matter, for example—to reiterate—for lively antismoking messages regularly and frequently on TV and radio, in the newspapers and magazines[7].

It is also possible to encourage our individual patients and whole families to improve their diet habits. Fig. 18 illustrates the key food groups in "western" diets, in terms of dietary saturated fat and cholesterol—and calories as well, since after all, fats are nine calories per gram, whereas proteins and carbohydrates are only four calories per gram[4, 33]. The key foods high in saturated

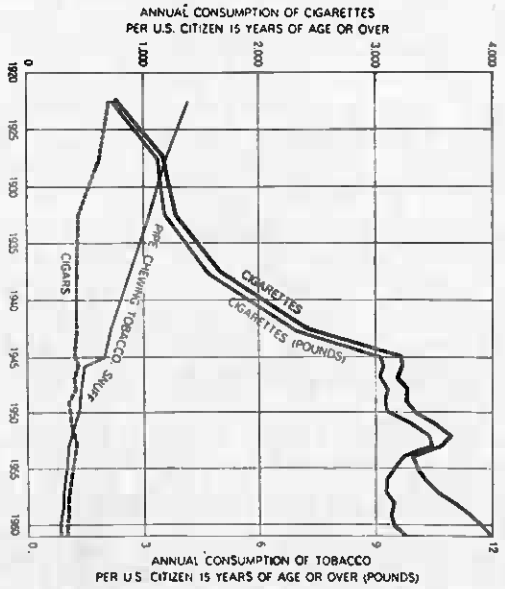


Fig. 14. Changes in tobacco use produced a five-fold rise in cigarette consumption between the early 1920's and 1961, and a drop of nearly 70 per cent in consumption of all other tobacco products. Cigarettes are plotted both in units and in pounds of unstemmed-tobacco equivalent. Other tobacco products are shown only in pounds. Filter cigarettes, which use less tobacco than nonfilter types, have been growing in popularity since 1954 (31).

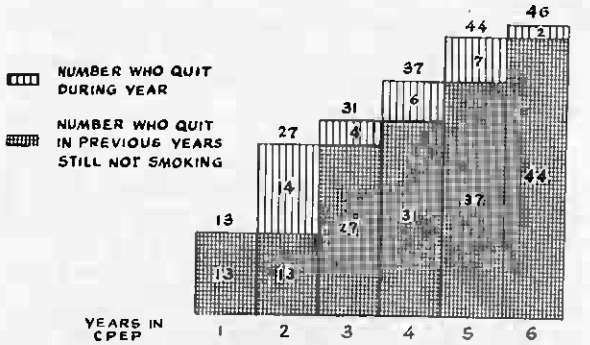


Fig. 15. Coronary Prevention Evaluation Program (CPEP) cumulative record of success in control of cigarette smoking (32, 33).

CIGARETTE SMOKING STATUS, BY AGE AND SEX, WHITES CHICAGO HEART ASSOCIATION DETECTION PROJECT 1967 - 1969[27]

Cigarette Smoking Status	Age-Adjusted Rate per 1,000*			
	3,262 Men Age 25-44	958 Women Age 25-44	2,137 Men Age 45-64	1,249 Women Age 45-64
Never Smoked	261·5	369·6	245·0	511·3
Ex-Smokers	261·2	171·9	340·7	147·2
<10 Per Day	71·8	109·6	63·8	119·6
⩾10 Per Day	405·5	348·9	350·5	221·9
$\frac{\text{Ex-Smokers}}{\text{Ever Smoked}}$ X 1,000	353·7	272·7	451·3	301·2

*All rates age-adjusted by five year age groups to U.S. white population 1960.

Fig. 16.

fats and/or cholesterol can be taught using the fingers of one hand—the fat from dairy products, from meats, from the yolk of the egg, from commercial baked goods, from fats as such. These need to be de-emphasized, while we emphasize the positive nutritional value of low-fat dairy products, lean meats-fish-poultry, egg whites without yolks, home-made baked goods made with unsaturated oils rather than "hard" shortenings, and the use of unsaturated oils and soft margarines at table, in salads and in cooking. Here there is a great deal for all of us to learn—on ways to good eating, even gourmet eating if one wishes—from the life styles of people in places like Singapore. Lest any one fear that the pleasures of eating must be abandoned or curtailed, let us remind ourselves that some of the finest cooking of the world—e.g., from the Mediterranean basin and from the Far East—is considerably lower in saturated fat, cholesterol and calories than ours, and the populations from these areas of the globe have much lower average serum cholesterol levels and lower coronary death rates.

With such changes in eating habit, it is entirely possible to accomplish and sustain a reduction in serum cholesterol (Fig. 19), and for persons with hypertriglycermic hypercholesterolemia, such diets reduce not only serum cholesterol, but serum triglycerides as well, particularly when obesity is concomitantly corrected by moderate restriction of calories for weeks or months, and when high alcohol intake is corrected[32, 33, 35].

Fig. 20 illustrates—from the twelve-year study in two Finnish mental hospitals by Professors Turpeinen, Karvonen and colleagues—that such diet changes are capable not only of lowering serum cholesterol, but of reducing coronary rates [36, 37]. These are data for the first six years in this study. (More recently data from the second six years have been published.) This was a so-called cross over study, with one hospital having the diet of its patients modified for the first six years (essentially replacement of dairy fat with unsaturated oil fat), and then that hospital going back to a usual Finnish diet and the other hospital having the cholesterol reducing diet for the second six years. In both periods, the hospital on the fat-modified diet, producing a reduction in serum cholesterol, had lower coronary rates.

Similar findings are available from the study in a Los Angeles Veterans Administration facility and from the New York Anti-Coronary Club[7, 33].

Our own group since 1958 has been involved in a parallel coronary prevention effort, involving 519 coronary-prone men originally age 40 to 59, assessed to be high risk because of combinations of the major risk factors[4, 32, 33] Our intervention has involved diet, but not diet alone, since it focussed not only on diet correction of hyperlipidemia and obesity, but also on control of hypertension, of cigarette smoking, and encouragement to take up moderate regular exercise for men habitually sedentary. Fig. 21 presents mortality findings of this Coronary Prevention Evaluation Program over seven years, compared to men from the national cooperative Pooling Project of the same age, initial medical status and initial risk factor status. Again, in terms of the three key end points—sudden coronary death, all coronary death, and deaths from all causes—the results are very encouraging.

All of these "first generation" trials, begun in the late 1950s, sent a little boy to do a giant's work. They all were huge undertakings considering the resources available, since each involved working with several hundred men for years. However, it is now clear that to do an effective and definitive field trial on the primary prevention of coronary disease, sample sizes of 10,000 or more are needed. Only now are such second generation trials being undertaken. The results of the earlier ones are encouraging but not definitive.

What then is the course for practitioners of medicine and public health? Clearly, the evidence is overwhelming that this contemporary epidemic of coronary heart disease obeys the fundamental scientific laws about epidemics in general that were first set down in modern post-Hippocratic times by Rudolf Virchow: Don't crowd diseases point everywhere to deficiences of society? One may adduce atmospheric or cosmic conditions or similar factors. But never do they alone make epidemics. They produce them only there where due to bad social conditions people have lived for some time in abnormal situations[38]. The history of artificial epidemics is therefore the history of disturbances of human culture. Their changes announce to us in gigantic signs the turning points of culture into new directions[38].

Epidemics resemble great warning signs on which the true statesman is able to read that the evolution of his nation has been disturbed to a point which even a careless policy is no longer allowed to overlook[38].

The current coronary epidemic is a magnificent illustration of this law—as was the TB epidemic a century ago. That is, epidemic disease occurs only in populations whose socioeconomic and sociocultural evolution has produced life styles en masse replete simultaneously with the multiple causes essential for the massive onslaught of sickness. A century ago in "western" countries

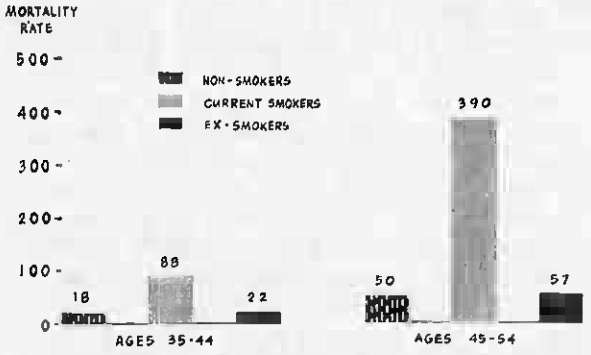


Fig. 17(a).

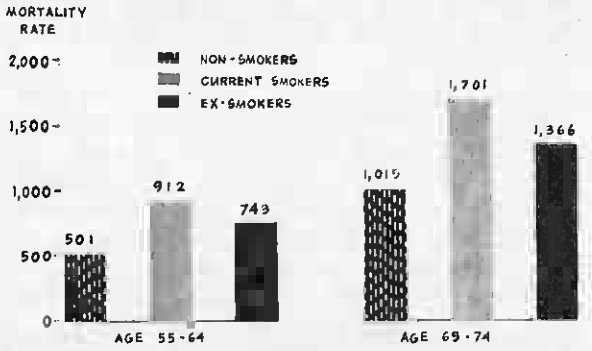


Fig. 17(b).

Figs. 17(a), (b). U.S. Veterans Study; coronary heart disease mortality rates of non-smokers, current smokers of 20-39 cigarettes per day, and ex-smokers of 20-39 cigarettes per day, age 35-54 (upper graph) and age 55-74 (lower graph); ex-smokers stopped for reasons other than doctors' orders; rates are per 100,000 per year (34).

FOOD GROUP	CALORIES	TOTAL FAT	CHOLESTEROL
1. MEAT, FISH, POULTRY	22	38	35
2. FATS AND OILS	12	29	6
3. DAIRY PRODUCTS	13	15	16
4. COMMERCIAL BAKED GOODS	6	4	8
5. EGGS	2	4	35
6. ALL OTHER FOOD GROUPS	45	11	--

Fig. 18. Major food groups in the U.S. diet and per cent of calories, total fat and cholesterol derived from each (4, 32, 33).

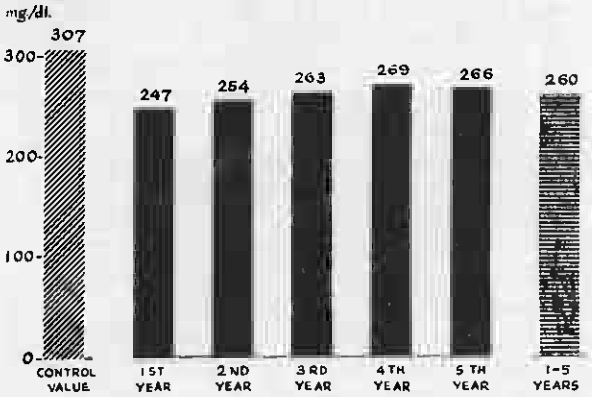


Fig. 19. Coronary Prevention Evaluation Program (CPEP); effect of program on mean serum cholesterol, 63 men with control values of 260 mg./dl. or greater, in CPEP for at least 5 years, as of March 31, 1968 (32, 33).

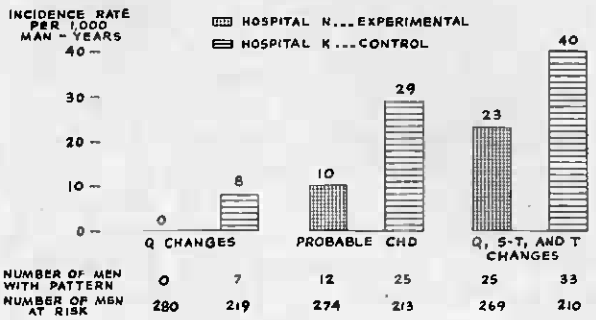


Fig. 20. Finnish mental hospital study; incidence of ECG patterns attributable to CHD, men age 34-64 at entry, 1959-65 (36).

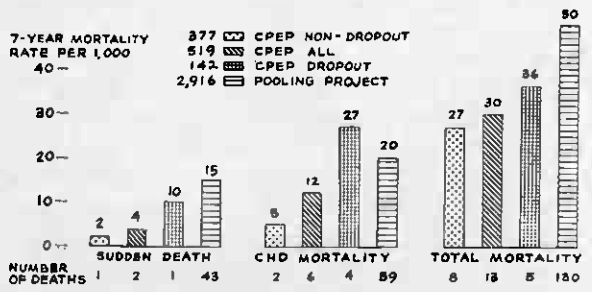


Fig. 21. Coronary Prevention Evaluation Program (CPEP); 7-year cumulative age-adjusted mortality rates of high-risk disease-free men age 40-59 at entry; Pooling Project and CPEP cohorts; all CPEP data as of March 31, 1970; of the total cohort of 519 men in the CPEP study, 377 were continuing active participants (non-dropouts), 142 were dropouts as of March 31, 1970; of the men in the Pooling Project, 2,916 met CPEP age, medical and risk factor criteria; all rates age-adjusted by 5-year age groups to U.S male population, 1960 (7).

it was epidemic TB, in the infancy and childhood of modern urban society, a resultant of the multiple new social circumstances generated by the industrial revolution—rapid chaotic expansion of towns into cities, with inadequate housing, slums, mass overcrowding, poor sanitation, long hours of grueling dusty and dirty work, child labor, inadequate public health and medical care, etc. Now, in the maturity of industrial society in these countries, in the era of their relative affluence, TB is mastered, and the coronary epidemic emerges, perhaps the first epidemic of mass human excess—too "rich" a diet, too much smoking, too much sedentary living, etc.

Based on this understanding, it is clear that pharmacologic treatments can at most play a secondary and adjuvent role in controlling the coronary epidemic. Of key importance for medicine and public health is encouraging better approaches to good life style—from childhood on, for whole families, children and pa·ents both, and for whole communities and nations especially, with regard to eating, smoking and exercise habits. Along with this broad overall approach, concentrated attention is also needed for identifying very high risk persons and controlling their risk factors through safe and enjoyable nutritional approaches, the encouragement of cessation of cigarette smoking, the encouragement of moderate regular frequent exercise. All these offer great possibilities for prevention, and little or no risk. The only possible exception is in regard to exercise, and if this is approached soundly, the risks are avoidable. Finally, the data also indicate the potential from effective long-term treatment of hypertension.

Given the scope of the continuing epidemic, and the possibility of prevention, every effort should be made to attempt to realize this possibility by the effective application of currently available knowledge, precisely as the WHO Board urged two years ago.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the cooperation of the author's senior colleagues in the long-term investigations presented here: especially David M. Berkson, M.D., Yolanda Hall, M.S., Howard A. Lindberg, M.D., Louise Mojonnier, Ph.D., James A. Schoenberger, M.D., Richard Shekelle, Ph. D. and Rose Stamler, M.A. It is also a pleasure to express appreciation to the many Chicago Organizations giving invaluable cooperation in the cited research efforts, particularly the Peoples Gas Light and Coke Company, its Chairman, Remick McDowell and its Medical Director, Howard A. Lindberg, M.D., the Newspaper Division of the Field Enterprises, particularly Wilbur Munnecke, formerly Vice-President and General Manager, John G. Trezevant, Vice-President and General Manager, and Jacques Smith, M.D., Medical Director; the Medical Department of the American oil Company, particularly Gilbert Collings, M.D., and Peter M. Wolkonsky, M.D.; Armour and Company, particularly William Wood Prince, former Chairman of the Board, Illinois Bell Telephone Company and its Medical Director, Robert R.J. Hilker, M.D.; the Internal Revenue Service and its former Medical Director, Michael W. Langello, M.D., Donald J. Erickson and Jack Cull of Arthur Anderson and Company; and to the staff of the Chicago Heart Association and its Detection Project in Industry, particularly Louis deBoer, Executive Director, Susan Shekelle, Project Coordinator and Kay Westfal, Program Director. It is a pleasure also to acknowledge the cooperation and support of Eric Oldberg, M.D., President, Chicago Board of Health, and Chairman, Board of Directors, Chicago Health Research Foundation, and to express gratitude to the entire staff of the Heart Disease Control Program, Division of Adult Health and Aging, Chicago Health Department, and of the Chicago Health Research Foundation, aiding in this research.

The author is most grateful to his colleagues in the national cooperative Pooling Project, the Principal Investigators of the studies of Albany civil servants, Chicago Western Electric Company employees, Framingham community residents, Los Angeles civil servants, and Minneapolis-St. Paul business and professional men, and to the coordinators of this Project for making data available from these major U.S. prospective studies. It is a pleasure to acknowledge the cooperation and aid of our colleagues in this endeavour, Drs. Henry Blackburn, John M. Chapman, Thomas R. Dawber, Joseph T. Doyle, Frederick H. Epstein, William B. Kannel, Ancel Keys, Felix J. Moore, Oglesby Paul and Henry L. Taylor.

Appreciation is also expressed to other colleagues and to publishers for permission to cite from published works: Drs. Edward D. Freis, Cuyler Hammond, H. Kahn, Ancel Keys, Ralph S. Paffenbarger and O. Turpeinen; the American Heart Association, *American Journal of Clinical Nutrition*, *American Journal of Public Health*, *Journal of the American Medical Association*, and *Sceintific American*.

The author's program of research has been supported by the American Heart Association; Chicago Heart Association: Best Foods Research Center, A Division of C.P.C. International, Inc.; and the National Heart and Lung Institute, Na-

tional Institutes of Health, United States Public Health Service.

REFERENCES

1. Task Force on Arteriosclerosis of the National Heart and Lung Institute: Arteriosclerosis, Vol. I, U.S. Department of Health, Education and Welfare Public Health Service, DHEW Publication Number (NIH) 72-137, Washington, D.C., June 1971.
2. McGill, H.D., Jr., Ed.: Geographic Pathology of Atherosclerosis, Williams and Wilkins, Baltimore, Md., 1968.
3. Keys, A., Ed.: "Coronary Heart Disease in Seven Countries." Circulation, 41, Suppl. 1, 1970.
4. Stamler, J.: "Lectures on Preventive Cardiology, Grune and Stratton, New York, N.Y., 1967.
5. Stamler, J., Stamler, R. and Shekelle, R.B.: "Regional Differences in Prevalence, Incidence and Mortality from Atherosclerotic Coronary Heart Disease." deHaas, J.H., Hemker, H.C. and Snellen, H.A., Eds., Ischaemic Heart Disease, Leiden University Press, Leiden, The Netherlands, p. 84, 1970.
6. Stamler, J., Berkson, D.M. and Lindberg, H.A.: "Risk Factors: Their Role in the Etiology and Pathogenesis of the Atherosclerotic Diseases." Wissler, R.W. and Geer, J.C., Eds., Pathogenesis of Atherosclerosis, Williams and Wilkins, Baltimore, Md., p. 41, 1972.
7. Inter-Society Commission for Heart Disease Resources: "Atherosclerosis Study Group and Epidemiology Study Group." Primary Prevention of the Atherosclerotic Diseases. Circulation 42, A55, 1970.
8. Taylor, C.B., Patton, D.E. and Cox, G.E.: "Atherosclerosis in Rhesus Monkeys". VI. Fatal Myocardial Infarction in a Monkey Fed Fat and Cholesterol. Arch. Path., 76 404, 1963.
9. Wissler, R.W.: "Recent Progress in Studies of Experimental Primate Atherosclerosis." Progr. Biochem. Pharmacol., 4, 378, 1968.
10. Armstrong, M.L. Warner, E.D. and Connor, W.E.: "Regression of Coronary Atheromatosis in Rhesus Monkeys." Circ. Res., 27, 59, 1970.
11. Katz, L.N. and Stamler, J.: Experimental Atherosclerosis, Charles C. Thomas, Springfield, Ill, 1953.
12. Katz, L.N., Stamler, J. and Pick, R.: Nutrition and Atherosclerosis. Lea and Febiger, Philadelphia, Pa., 1958.
13. Keys, A.: "Sucrose in the Diet and Coronary Heart Disease." Atherosclerosis, 14, 193, 1971.
14. Keys, A.: "Letter to the Editors. Atherosclerosis". 18, 1973, in press.
15. Yudkin, J. and Morland, J.: "Sugar Intake and Myocardial Infarction." Amer. J. Clin. Nutr., 20, 503, 1967.
16. Walker, A.R.P.: "Sugar Intake and Coronary Heart Disease." Atherosclerosis, 14, 137, 1971.
17. Committee on Reduction of Risk of Heart Attack and Stroke, American Heart Association, Handbook of Coronary Risk Probability, American Heart Association, New York, N.Y., EM590B, 1972.
18. Gofman, J.W. *et al.*, and Andrus, E.C. *et a.l*: "Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis." Report of a Cooperative Study of Lipoproteins and Atherosclerosis. Circulation 14, 691, 1956.
19. Gofman, J.W., Young, W. and Tandy, R.: "Ischemic Heart Disease, Atherosclerosis and Longevity." Circulation, 34, 679, 1966.
20. Kannel, W.B., Castelli, W.P., Gordon, T. and McNamara, P.M.: "Serum Cholesterol, Lipoproteins, and the Risk of Coronary Heart Disease." The Framingham Study. Ann. Intern. Med., 74, 1, 1971.
21. Carlson, L.A. and Böttiger, L.E.: "Ischaemic Heart-Disease in Relation to Fasting Values of Plasma Triglycerides and Cholesterol." Lancet, 1, 865, 1972.
22. Hammond, E.C.: "Smoking in Relation to the Death Rates of One Million Men and Women." Haenszel, W., Ed., Epidemiological Approaches to the Study of Cancer and Other Diseases, National Cancer Institute Monograph No. 19, US. Public Health Service, Bethesda Md., p. 127, Jan., 1966.
23. Hammond, E.C. and Garfinkel, L.: "Coronary Heart Disease, Stroke and Aortic Aneurysm—Factors in the Etiology." Arch. Environ. Health, 19, 167, 1969.
24. Stamler, J.: "Epidemiology of Coronary Heart Disease." Med. Clin. No. Amer., 57, 5, 1973.
25. Paffenbarger, R.S. Notkin, J., Krueger, D.E., Wolf, P.A., Thorne, M.C. LeBeauer, E.J. and Williams, J.L.: "Chronic Disease in Former College Students". II. Methods of Study and Observations on Mortality from Coronary Heart Disease. Amer. J. Public Health, 56, 962, 1966.
26. Schoenberger, J.A., Stamler, J., Shekelle, R.B. and Shekelle, S.: "Current Status of Hypertension Control in an Industrial Population." J.A.M.A., 222, 559, 1972.
27. Stamler, J.: "Prevention in Atherosclerosis and Hypertension, ALC Medical Proceedings, 1972, Proceedings of the 60th Annual Meeting of the Medical Section of the American Life Convention, May 29-31, 1972, American Life Convention, Chicago, Ill., p. 69, 1973.
28. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of Treatment on Morbidity in Hypertension—Results in Patients with Diastolic Blood Pressures Averaging 115 through 129 mm Hg. J.A.M.A., 202, 1028, 1967.
29. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of Treatment on Morbidity in Hypertension. II. Results in Patients with Diastolic Blood Pressure Averaging 90 through 114 mm Hg. J.A.M.A., 213, 1143, 1970.
30. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of Treatment on Morbidity in Hypertension. III. Influence of Age, Diastolic Pressure, and Prior Cardiovascular Disease; Further Analysis of Side Effects. Circulation, 45, 901, 1972.
31. Hammond, E.C.: "The Effects of Smoking". Sci. Amer., 207, 3, 1962.
32. Stamler, J.: "Prevention of Atherosclerotic Coronary Heart Disease by Change of Diet and Mode of Life". deHaas, J.H., Hemker, H.C. and Snellen, H.A., Eds., Ischaemic Heart Disease, Leiden University Press, Leiden, The Netherlands, p. 311, 1970.
33. Stamler, J.: "Acute Myocardial Infarction—Progress in Primary Prevention". Brit. Heart J., 33 (Suppl.), 145, 1971.
34. Kahn, H.A.: "The Dorn Study of Smoking and Mortality among U.S. Veterans: Report on 8 1/2 Years of Observation". Haenszel W., ED., Epidemiological Approaches to the Study of Cancer and Other Diseases, National Cancer Institute Monograph No. 19, U.S. Public Health Service, Bethesda, Md., p. 1, Jan. 1966.
35. Hall, Y., Stamler, J., Cohen, D.B., Mojonnier, L., Epstein, M.B., Berkson, D.M., Whipple, I.T. and Catchings, S.: "Effectiveness of a Low Saturated Fat, Low Cholesterol, Weight-Reducing Diet for the Control of Hypertriglyceridemia". Atherosclerosis, 16, 389, 1972.
36. Turpeinen, O., Miettinen, M., Karvonen, M.J., Roine, P., Pekkarinen, M., Lehtosuo, E.J. and Alivirta, P.: "Dietary Prevention of Coronary Heart Disease: Long Term Experiment". I. Observations on Male Subjects. Amer. J. Clin. Nutr., 21. 255, 1968.
37. Miettinen, M., Turpeinen, O., Karvonen, M.J. Elosuo, R. and Paavilainen, E.: "Effect of Cholesterol-Lowering Diet on Mortality from Coronary Heart-Disease and Other Causes—A Twelve-Year Clinical Trial in Men and Women." Lancet, 2, 835, 1972.
38. Ackerknecht, E.H.: Rudolf Virchow—Doctor, Statesman, Anthropologist, University of Wisconsin Press Madison, Wisc., 1953.