

Cardiovascular Conferences of Howard University and Freedmen's Hospital, VII**Epidemiology as an Investigative Method for the Study of Human Atherosclerosis**

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IN MEDICAL research, there are three fundamental methods for attacking a disease of unknown or obscure etiology. The first is the *Clinical-Pathologic Method*. It is the oldest. It involves the study of sick people while living (clinical investigation), and after death (pathologic investigation).

The second method is *Animal Experimentation*. Its prerequisite is the successful reproduction of the particular disease in experimental animals.

Both these methods have been and are making highly important contributions to the solution of the atherosclerosis problem^{1-4,33,*}

The third method, under discussion in this paper, is the *Epidemiologic Method*. This has come to the fore recently as a fruitful approach to perplexing questions concerning the so-called chronic degenerative diseases, the major public health problems in our country today.

Everyone in medicine is familiar with epidemiology in connection with infectious diseases. Everyone, for example, knows the exciting story of the conquest of yellow fever in the Panama Canal Zone, as a classic achievement of epidemiology. But the role of epidemiology in research on non-infectious diseases has not been widely understood and appreciated. The facts of medical history reveal, however, that the epidemiologic method has also contributed fruitfully to the solution of problems of non-contagious disease.

PELLAGRA

The etiology of pellagra, for example, was worked out by epidemiologic methods. It is well-known today, of course, that pellagra is a nutri-

tional disease. However, in the early 1900's it was believed to be an infectious process. Consequently the Public Health Service sent a bacteriologist, Joseph Goldberger, to the South to study pellagra. From detailed observation of the disease in the field, Goldberger very soon concluded that this could not be an infectious disease. He proceeded to prove this unequivocally, by very courageous experiments in which he was one of the guinea pigs.

Goldberger was convinced that pellagra was a "hidden hunger", a nutritional disease due to an habitual diet adequate in total calories (energy), but lacking in certain essential nutrients. He proceeded over a number of years to prove this by epidemiologic methods. First by descriptive and analytic epidemiology, i.e. a precise characterization of the demographic, ecologic, socioeconomic and nutritional circumstances of the occurrence of pellagra. Then by experimental and applied epidemiology, i.e. the production of the disease by dietary means in a small group of volunteer prisoners, and the prevention and cure of the disease in sizeable population groups by corrective nutritional measures.

This is an outstanding example of the solution of a problem of non-infectious disease through proper utilization of the epidemiologic method. Another and more recent graphic example is the epidemiologic research on the relationship between smoking and lung cancer and other diseases (Fig. 38)^{42, 43}.

SCOPE OF EPIDEMIOLOGY

What precisely is epidemiology? If clinical medicine is the study of disease in individuals, epidemiology is the study of disease in populations. The clinical investigator generally is not con-

* Since extensive bibliographies are included in other recent reports (1-4, 33) this paper makes reference only to these other review articles, except where specific data or direct quotations are cited.

FIG. 1.
FAT INTAKE, SERUM CHOLESTEROL AND FATAL
CORONARY HEART DISEASE-
AMERICANS VS. BANTUS

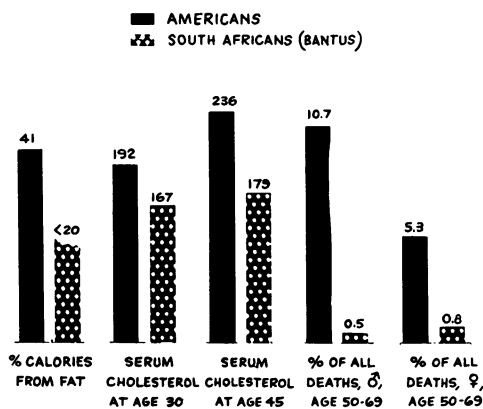


Fig. 1. Walker, A. R. P. and Arvidsson, U. B.⁸; Higginson, J. and Pepler, W. J.⁹ Here and in most subsequent figures, the numbers at the top of the column are the actual values. Note the differences in fat intake, serum cholesterol level and per cent of all analyzed deaths attributed to coronary heart disease. Note also the marked tendency for the serum cholesterol of Americans to rise from age 30 to age 45—a tendency virtually absent in the South African Bantu. Note also the sex differential in the occurrence of coronary disease in the Americans and its absence in the Bantus. In this and subsequent figures graphing several variables separate scales were frequently used for each set of variables, in order to facilitate charting.

cerned with the population of origin of his patients. In studying myocardial infarction, for example, he does not systematically analyze whether his cases come from Atlanta or Chicago, rural Illinois or Georgia, whether they are white or Negro, of Irish or Italian descent, Catholic, Protestant, or Jew, millionaire or pauper, carpenter or clerk, banker or ditchdigger. At most, these are matters of incidental interest to the clinical investigator. He focuses on the problem of achieving a more detailed and profound description and analysis of the disease by studying its clinical-pathologic characteristics in a series of patients.

The epidemiologist's framework of reference is quite different. His concern is not with sick individuals, but with populations, patterns of disease in populations, and the factors responsible for those patterns. His approach, therefore, is complementary to that of the clinical investigator.

FIG. 2
Age trend of Serum Cholesterol—Minnesotans
and Italians of different social classes
and different dietary patterns

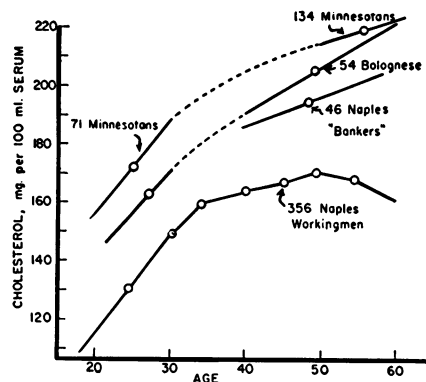
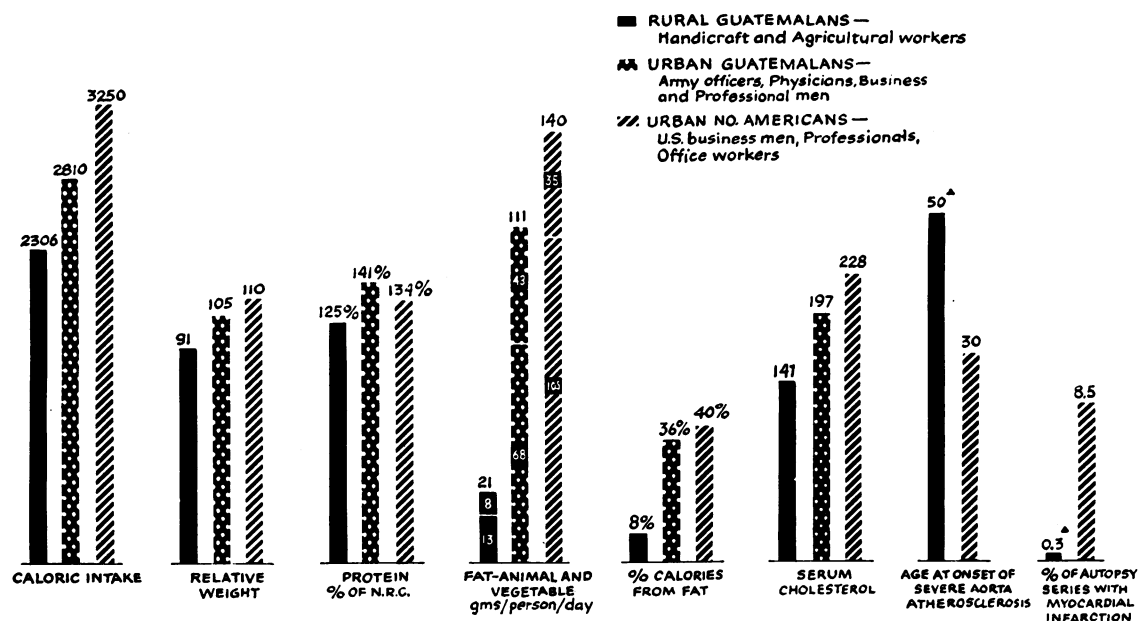


Fig. 2. Keys, A.¹⁰ The Naples working men consumed 20% of total calories in the form of fat; the Naples "bankers" are described as having diets much fatter than the usual for Naples. The Bolognese ate 30% of calories from fat; the Minnesotans, 42%. Note the difference in levels of cholesterolemia in Naples working men and "bankers." Note that this difference is accentuated with age. Note that the serum cholesterol level of the Naples working men does not rise significantly after age 35, in contrast to the Naples bankers" and the middle class Minnesota men.

It is based on the premise that important leads to the etiology of disease may be obtained by getting answers to such questions as: Is there more of a given disease today than 50 years ago (disease in time) and if so, why? Is there more of a given disease among Americans than among British, or Italians, or Guatemalans, or Japanese, or Nigerians (disease in space) and if so, why? Are there varying patterns of a given disease among different population strata of a given country, e.g. by age, sex, place-of-residence (North vs. South, urban vs. rural), racial and ethnic origin, income, occupation, smoking and dietary habits, etc., and if there are differences, or similarities, why?

In attempting to obtain answers to these questions on patterns of disease occurrence, epidemiology collects data from a variety of sources and in a variety of ways. These include mortality statistics, medical examiners' and coroners' reports, life insurance findings, hospital and clinic records, autopsy analyses, data from general and special surveys of disease in various strata of the population (e.g. Selective Service System

FIG. 3 Diet, Serum Cholesterol and Atherosclerosis in Middle Aged Guatemalans and North American Males



▲ Data on 300 Guatemalans autopsies on lower-income workers, not classified by place of residence

Fig. 3. Data from Scrimshaw, N. S., Trulson, M., Tejada, C., Hegsted, D. M. and Stare, F. J.,¹⁰ Mann, J. V., Munoz, J. A. and Scrimshaw, N. S.,¹¹ Tejada, C. and Gore, I.¹² Caloric intake is calories per person per day. Relative weight is an index; it is the ratio ($\times 100$) of an individual's observed weight to the median weight for his sex-height group. Protein intake is expressed in relation to the level of daily intake recommended by the National Research Council. In the fat intake columns, the upper values are for vegetable fat, the lower for animal fat.

findings, National Health Survey reports, industrial medical department observations, special research studies on prevalence and incidence of disease). As in all other research areas, each of these types of epidemiologic data presents its special problems, with which the investigator must be thoroughly familiar if he is to proceed effectively. The idea that epidemiology is confined to working with vital statistics data on mortality is a gross misconception.

In posing the foregoing problems concerning patterns of disease in populations, epidemiology is particularly concerned with the *why* in these questions. For the answers to these inquiries concerning patterns of disease occurrence are not ends in themselves. They are not decisive objects of epidemiologic research. Rather, they are only means to an end. If the concern is with etiology of disease, it is quite appropriate to ask: Suppose there is a higher incidence of myocardial infarc-

tion in men than in women, or in North Americans than in Guatemalans? What is the value of these data in relation to the problem of disease causation?

Obviously, once a clear pattern of disease has been delineated, this becomes a key to fit into a lock to open a door. It becomes a clue to help solve the mystery, the "whatdunit". Thus, once epidemiology knows that coronary disease occurs much more frequently in middle-aged American males than females, as is the case, then the decisive question arises: *Why?* Similarly, if it is established, as seems to be the case, that coronary disease is relatively rare in middle-aged Guatemalans, or South African Bantus, or Japanese, and is relatively common in middle-aged North Americans, then the problem clearly and critically presents itself: *Why?* What are the causative factors responsible for this? The delineation of patterns of disease in populations serves, there-

FIG. 4

Diet, Serum Cholesterol and Coronary Heart Disease in different social strata in India

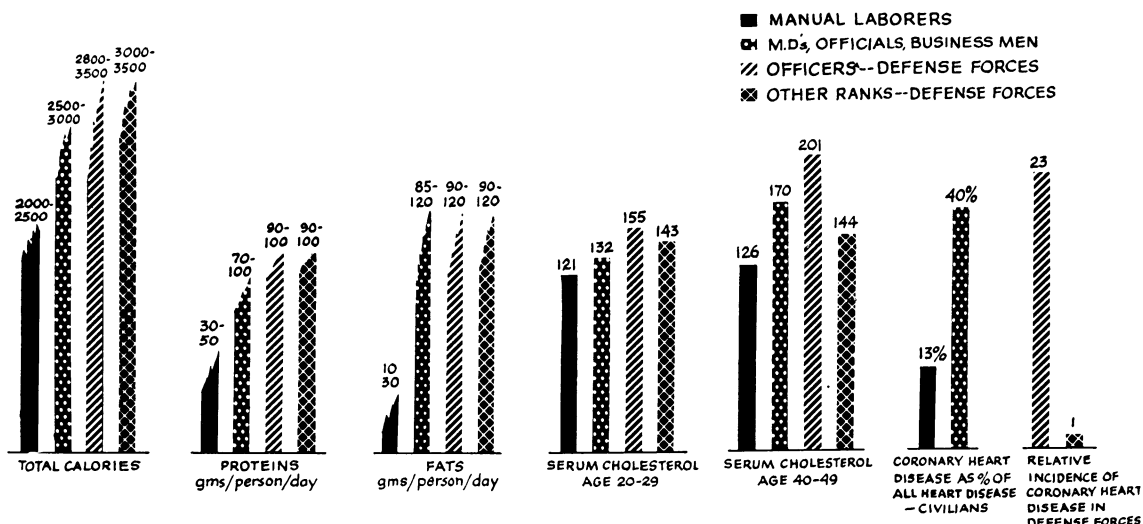


Fig. 4. Gopalen, C. and Ramanathan, K. S.¹³ (cf. also ref. 14). The fat intake of the lower-income manual laborers was chiefly sesame oil (containing 40% essential fatty acid, i.e. linoleic acid). The fat intake of the other three groups was chiefly hydrogenated vegetable oil and animal fat, in a ratio of approximately 2 to 1. Note the correlation among diet, serum cholesterol at age 40-49 and disease for manual laborers, physicians—officials—business men and defense officers. Note also the apparent discrepancy for the fourth group, the other ranks of the defense forces; this group apparently has a high calorie, high-fat intake, a low serum cholesterol level and a low relative incidence of coronary heart disease. It is not clear from the source if these relative morbidity data are for age-matched groups. Additional data on the soldiers, including relative weights, life-span dietary histories (including intakes of saturated and unsaturated fats) and levels of energy expenditure (habitual physical activity), would seem to be particularly relevant. The authors attributed the low serum cholesterol levels of the fourth group—despite high intake of calories and saturated fats—to a high energy expenditure.

fore, to pose a series of crucial questions for further research.

This further research is pursued by epidemiologic, clinical-pathologic and animal-experimental means, i.e. by all three methodologies. For its part, epidemiology seeks to account for observed patterns of disease occurrence by studying the role of multiple factors that may possibly be operative, e.g. income, occupation, place-of-residence, housing conditions, diet, physical activity, smoking, climate, mores, tensions, stresses, antecedent diseases, race, ethnic origin, heredity, genetics, etc. In assessing these variables, several of which may play a significant etiologic role, epidemiology seeks to determine which one (if any) is the decisive one in the process of causation. It also concerns itself with how these factors which may operate to

produce their morbid effects. Income, for example, may be meaningful as a factor in disease causation by virtue of its relationship to occupation, or habitual physical activity of work, or nutritional status. Thus Goldberger showed that pellagra “. . . attaches itself to poverty as the shadow to the body”; because the poor people of the South could not afford red meat, milk, eggs, they lived year-in-and-year out on the “. . . famous Three M’s white meat, hog fat, meal and molasses”⁵. Similarly, race may be significant, not because of inherited genetic factors, but because of associated socioeconomic conditions. Obviously, these complex questions posed by epidemiology can be successfully clarified only by extensive cross-fertilization among many disciplines (sociology, economics, anthropology, psychology, genetics, etc.)

FIG. 5

DIET IN MORE DEVELOPED AND LESS DEVELOPED COUNTRIES-1950

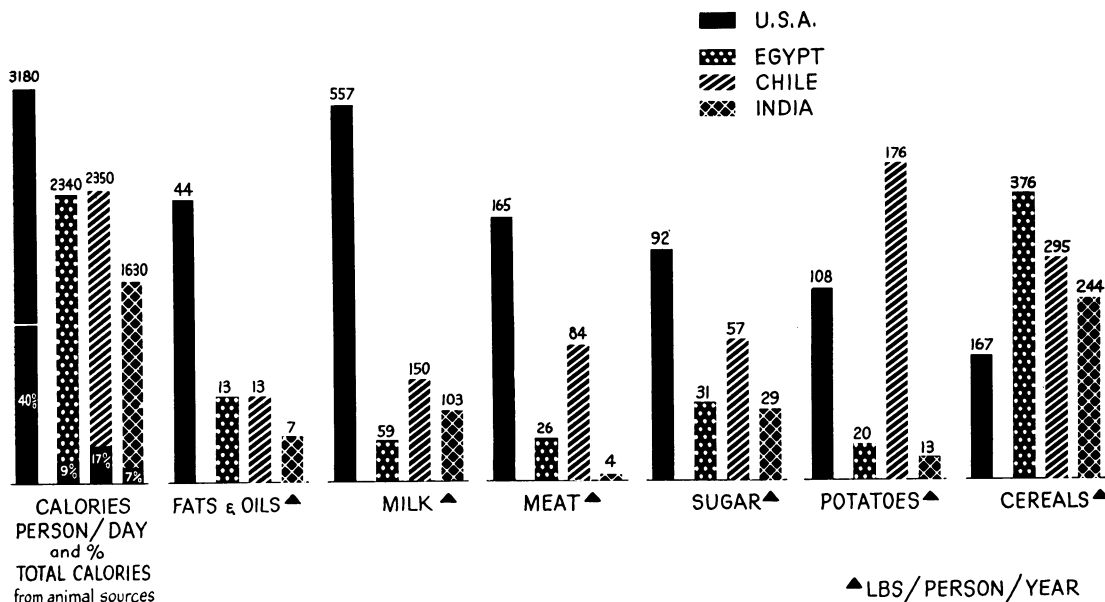


Fig. 5. Stamler, J.³ For source of data, cf. ref. 15. All data represent foods available to the population for consumption, not foods actually consumed. Here fats and oils are the amounts of these foodstuffs as such, not the total amounts of fats derived from all dietary sources (as in Figs. 1-3).

and by close coordination among medical investigators utilizing the clinical-pathologic, animal-experimental and epidemiologic approaches.

In studying the relationships between possible causative factors and the occurrence of disease, analytic epidemiology seeks to delineate positive and negative correlations. Thus, Finlay and Reed noted that yellow fever disappeared in the United States with onset of cold weather, and that cases skipped houses or blocks in the city of Havana. These observations suggested an insect vector. Goldberger and his colleagues noted that in institutions where pellagra was rife among inmates, staff members remained free of the disease. This observation suggested not an infectious, but a nutritional cause of pellagra.

Thus, specific hypotheses are both formulated and put to an initial test, e.g. concerning the role of insect-born infection or hidden hunger in the causation of given diseases.

It is essential to emphasize that the delineation of such correlations, positive and negative, be-

tween possible etiologic agents and occurrence of disease cannot constitute demonstration of cause-and-effect relationships. Such correlations obtained by descriptive-analytic epidemiology can by their cumulative impact become indicative of cause-and-effect relationships, but they cannot prove them. Further work is necessary. Among other things, the epidemiologic data must be evaluated in relation to clinical-pathologic and animal-experimental findings concerning the given disease. Thus, Goldberger returned to the animal laboratory and tested his concepts concerning the nutritional etiology of pellagra. He reproduced the disease in dogs and rats by feeding a diet essentially similar to that being eaten by the poverty-stricken pellagrins in the South. Moreover, he made a fresh discovery by animal-experimentation, viz. that yeast also prevented and cured the disease. He then returned to the field and demonstrated in further clinical-epidemiologic studies that this held for man as well.

The indispensability of this interdigitation, this

FIG. 6

DIET IN THE UNITED STATES COMPARED WITH ITALY AND JAPAN—1950

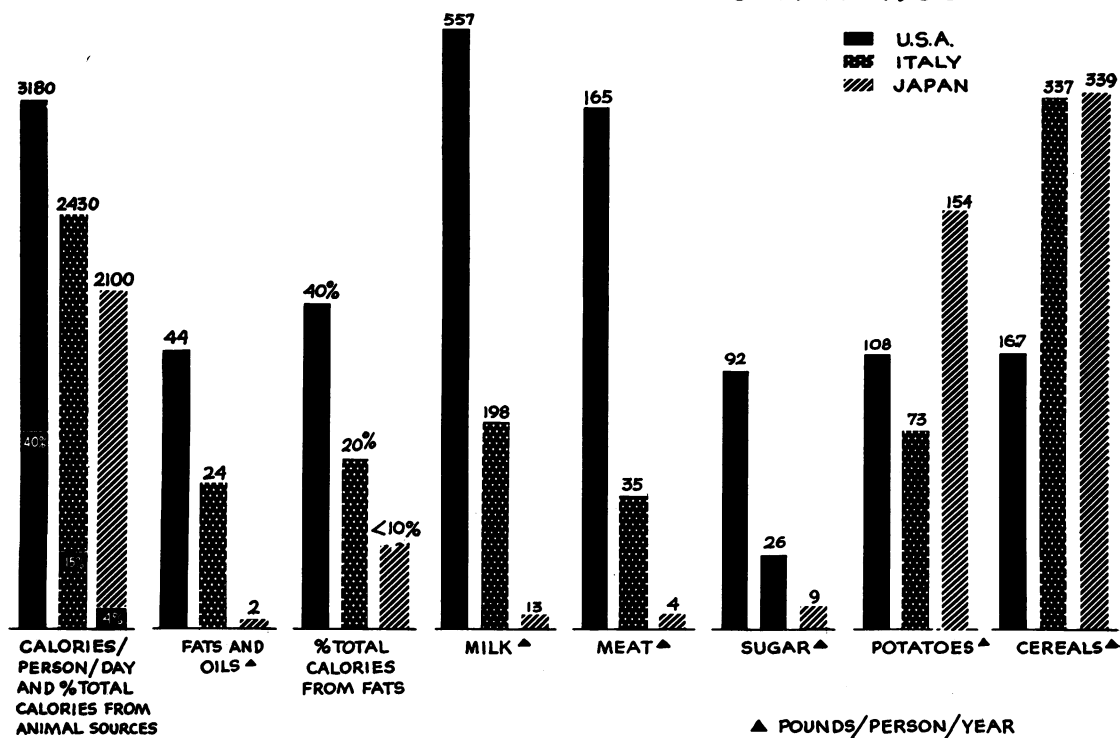


Fig. 6. Stabler, J.³ For source of data, cf. ref. 15.

shuttling back and forth among the three basic methodologies is one of the crucial lessons to be learned from the history of medical advance. It is a basic research principle.

It is an equally valid principle that theories of causation—derived from descriptive-analytic epidemiology, clinical-pathology, animal experimentation—must be critically tested by deliberate, planned intervention in the mode of life of human population groups. This involves controlled alteration of a specific variable or set of variables, with evaluation of the resultant effects upon occurrence of disease.

The success of experimental epidemiology then creates the basis for applied epidemiology—that is, the application of new knowledge throughout the population, in order to control and eliminate disease. As the experiences of Walter Reed and Joseph Goldberger amply testify, this constitutes the acid test of the validity of theories concern-

ing causation.

With these general remarks about the epidemiologic method as background, consideration can now be given to the epidemiology of atherosclerosis and atherosclerotic disease.

ATHEROSCLEROSIS

First a few words to assure clarity concerning the entity under discussion, i.e. atherosclerosis, and the distinction between arteriosclerosis and atherosclerosis: As pathology long ago noted (cf. any textbook of pathology), arteriosclerosis is a generic term inclusive of several different diseases, e.g. Mönckeberg's sclerosis, or medial calcinosis; hyperplastic intimal sclerosis; the inflammatory arteritides; arteriolar sclerosis; atherosclerosis. Since the generic term arteriosclerosis embraces several pathologic processes, almost certainly of different etiologies, it might be wiser to use the plural, i.e. the arterioscleroses, and thereby obviate confusion.

FIG. 7

Diet † Cholesterolemia in 284 Clinically Healthy Japanese Men Age 40-49 in seven groups

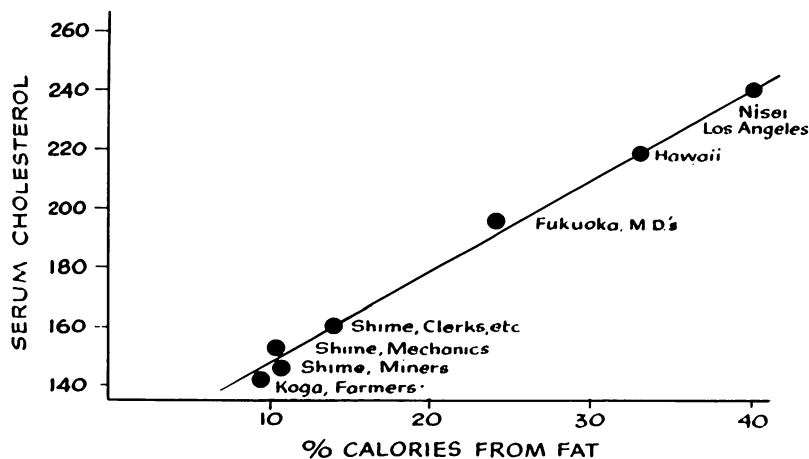


Fig. 7. Keys, A.¹⁷ Note the similar low levels of serum cholesterol in Japanese farmers, miners, mechanics, clerks—values correlating with habitual diets low in fats, and not with occupation and physical activity of work. Note the higher serum cholesterol concentrations in Japanese physicians and in Japanese-Hawaiians and Japanese-Americans—again correlating with dietary patterns.

Atherosclerosis is a specific entity. It is one among the arterioscleroses, but by far the most important in respect to morbidity and mortality. This is due not only to its frequency of occurrence (at least among the populations of certain countries), but also to certain of its morphologic peculiarities which lead frequently to the production of serious illness: It is primarily an intimal lesion which impinges on and narrows the arterial lumen with resultant tissue ischemia; it tends to slough, ulcerate and become a nidus for thrombus formation with closure of the vessel and tissue infarction; the atherosclerotic plaque also tends to become vascularized by capillaries which may hemorrhage with resultant intimal swelling, closure of the vessel, and tissue infarction. All these pathologic features, together with the frequency of occurrence of this process among middle-aged and elderly people in a country like the United States, account for the fact that atherosclerosis is the most important of the arterioscleroses and the major producer of mortality in the United States today.

A few other aspects of the pathology of atherosclerosis merit attention prior to a discussion of its epidemiology. Among populations frequently victimized by atherosclerotic disease, the process

tends to begin in childhood, decades before it becomes manifest as clinical disease. This cardinal fact concerning the natural history of atherosclerosis has been extensively documented in studies on American autopsy material, white and Negro. Its recognition serves to emphasize the important principle, particularly valid for the so-called chronic degenerative diseases, that departure from health is a continuing process. With the years, the process of lesion formation tends to proceed inexorably, so that by age 25 many Americans, especially males, have grossly detectable coronary atherosclerosis. And by age 45 or 55 this sclerosis is severe in degree in a high per cent of the population (Fig. 10)^{6, 7}.

PRECLINICAL AND CLINICAL ATHEROSCLEROSIS

Fortunately, extensive morphologic lesions frequently exist without the development of frank clinical manifestations. Hence it is necessary to speak of atherosclerosis and atherosclerotic disease. The well-known iceberg analogy serves to point up the distinction between the two: clinical atherosclerotic disease is the visible one-tenth of the total iceberg; nine-tenths of the whole never reveals itself during life.

FIG. 8

Death rates...United States, Italy, Japan...Age 45-54, 1950

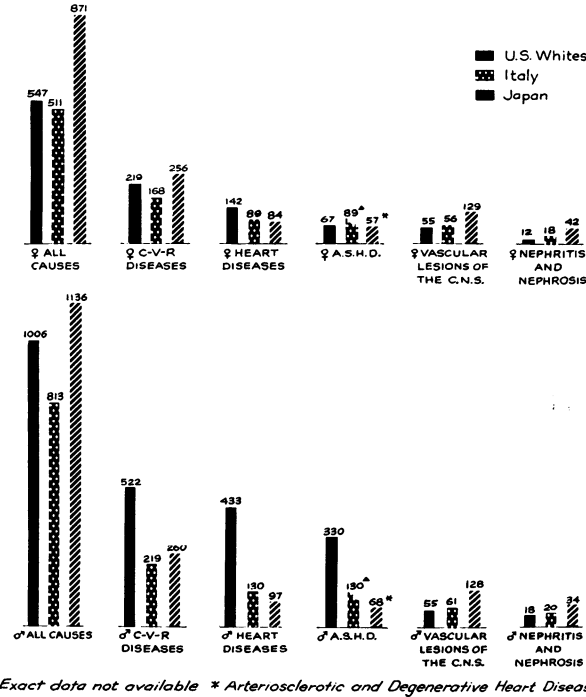


Fig. 8. Stamler, J., Kjelsberg, M., Hall, Y. and Scotch, N.²⁴ For source of data, cf. ref. 18. Note the markedly lower death rates for Cardiovascular-Renal (C-V-R) Diseases, Heart Diseases, Arteriosclerotic Heart Disease (A.S.H.D.) in the Italian and Japanese men, compared with U. S. males. Note also that the sex differential for all these causes, particularly for A.S.H.D., is considerably lower for Italians and Japanese than for Americans, due principally to the lower rates in the Italian and Japanese males (cf. Fig. 1). Note further that there is no national or sex difference with respect to mortality rates for Vascular Lesions of the Central Nervous System, in contrast to A.S.H.D. This markedly different epidemiologic pattern is in all likelihood reflective of the fact that Cerebrovascular Disease death rates in middle-age are chiefly a by-product of hypertensive disease, not atherosclerotic disease (cf. text and ref. 2).

What factors are responsible for the qualitative change from the occult, submerged, pre-clinical process to frank clinical disease? This is an important problem for atherosclerosis research. Unquestionably part of the answer is quantity, the extent and degree of atherosclerosis. For it has been conclusively demonstrated that any group of persons with clinical atherosclerotic disease (e.g. coronary heart disease*) has more severe atherosclerosis than a group without clinical manifestations. But it is moot whether quantity is the whole answer. Thus, the transition from pre-clinical to clinical disease is frequently a resultant of the so-called "complications" of atherosclerosis, e.g. thrombosis on plaques and/or hemorrhage into plaques, producing vessel closure and tissue infarction. The etiology of these complica-

* Throughout this paper, particular attention is given to the epidemiology of atherosclerosis and atherosclerotic disease in the coronary arteries. This focus has a twofold basis: First the bulk of the available epidemiologic data deals with coronary atherosclerosis. Information is very limited on the epidemiology of atherosclerosis in other arterial beds. Second, the correlation between clinical coronary heart disease and morphologic coronary atherosclerosis is of a very high order. At least 90% of all cases of coronary disease have atherosclerosis as the underlying pathologic process. Therefore, data on the occurrence of clinical coronary disease are a close reflection of the occurrence of morphologic atherosclerosis of severe degree in a population. This correlation does not necessarily hold to a high degree for disease at other sites. With clinical cerebrovascular disease ("strokes"), for example, it is difficult to differentiate among cerebral embolism, hemorrhage and thrombosis. These are processes having different etiopathologic bases. Thus recent pathologic studies indicate that cerebral hemorrhage in hypertensives may be a complication, not chiefly of atherosclerosis (as has been widely believed), but of a hypertensive miliary aneurysmal lesion in the smaller cerebral vessels. Unlike with coronary disease, therefore, it is probably not correct to assume that prevalence and incidence rates for cerebrovascular disease reflect the occurrence of severe cerebral atherosclerosis in a given population. This invalid assumption has tended to obscure understanding concerning epidemiologic trends. For valid comparisons, cerebral thrombosis (usually atherosclerotic in its pathologic basis) would have to be separated out from the heterogeneous cerebrovascular disease group-

FIG. 9

Death rates in Italian and Japanese migrants to U.S. compared with Italians in Italy and Japanese in Japan
Males, age 45-54, 1950

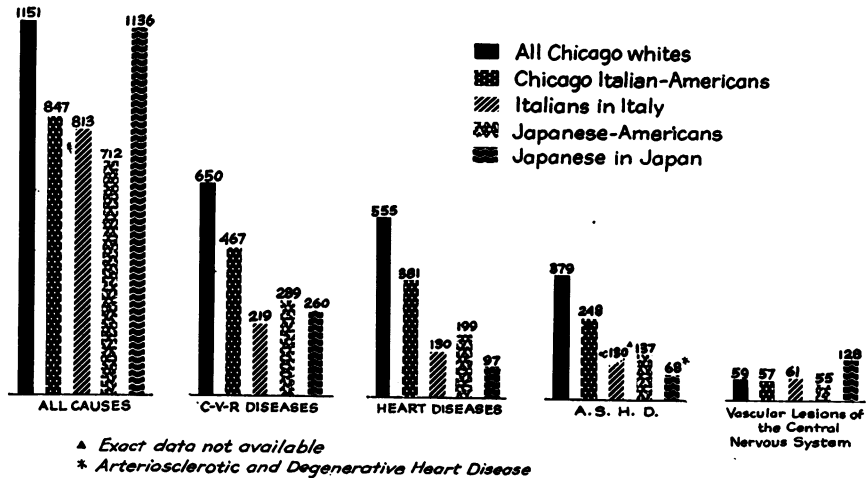


Fig. 9. Stamler, J., Kjelsberg, M., Hall, Y. and Scotch, N.²⁴ Note that the Italian-Americans have higher death rates than the Italians in Italy. The difference is conspicuous for Cardiovascular-Renal Disease, Heart Diseases, Arteriosclerotic Heart Disease. The same phenomenon obtains for the Japanese-Americans compared with the Japanese in Japan. Note also that for these three cause-of-death categories the Italian-Americans and the Japanese-Americans have lower mortality rates than all Americans. Finally, note the different epidemiologic patterns for mortality due to Vascular Lesions of the Central Nervous System—patterns probably reflecting chiefly hypertensive (not atherosclerotic) vascular disease in this age group.²

FIG. 10

Incidence of high grade Coronary Sclerosis in consecutive autopsies U.S. vs. Japan

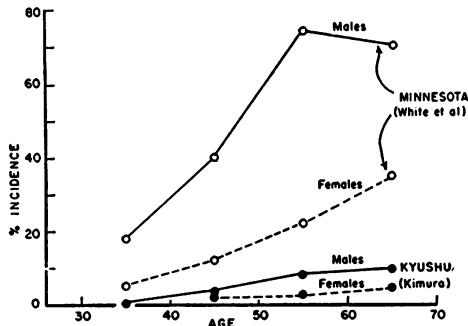


Fig. 10. Kimura, N.,⁶ White, N. K., Edwards, J. E. and Dry, T. J.⁷ Note the markedly higher incidence of severe coronary sclerosis at autopsy in American males at all ages. Note also the presence of a gross sex difference for Americans, and its virtual absence for the Japanese (cf. Figs. 1-7 and 8).

tions may be different from that of the atherosclerotic plaques *per se*. The study of this problem is therefore an important aspect of atherosclerosis research. It should be kept in mind, however, that these processes are complications of atherosclerosis. Were there no atherosclerosis, there could be no complications. It is essential, therefore, to keep the research focus on the central and primary problem, the etiology of atherosclerosis.

EPIDEMIOLOGY OF ATHEROSCLEROSIS

What, then, are the facts concerning the epidemiology of atherosclerosis, and what light do these facts shed on the problem of the causation of this disease? It is best to begin with the data on patterns of atherosclerosis in different countries, particularly countries with marked contrasts in the modes of life of their populations, e.g. the U.S.A. vs. the economically less developed nations of Africa, Asia and Latin America. Differences between the economically underdeveloped countries and the United States are multiple and complex—

FIG. 11

Findings in old and recent Yemenite Jewish Migrants to Israel--Men age 45-54

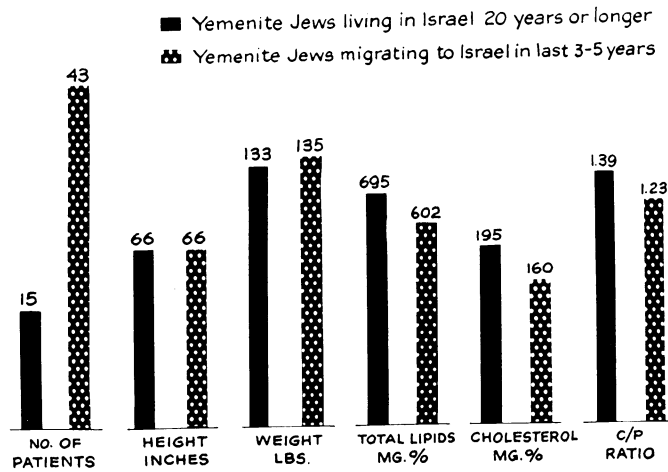


Fig. 11. Data from Brunner, D. and Lobl, K.²¹; Toor, M., Agmon, J. and Allalouf, D.²²; Epstein, F. H., et. al.²⁰⁻²² and Keys, A.¹⁷ Note the higher serum cholesterol and lipid levels in Yemenite Jews residing in Israel for 20 years or longer, compared with recent migrants from Arabia. Yemenite Jews in Israel generally manifest a low coronary heart disease incidence rate, correlating with their generally low intakes of total fat and saturated fat, and their low serum cholesterol levels. Note the correlation throughout between fat intake and serum cholesterol levels. Note that these values are higher in Jewish-Americans and Italian-Americans, compared with Jews in Israel and Italians in Italy. cf. the death rates—Figs. 9, 13 and 23.

racial, ethnic, climatic, socioeconomic, nutritional, cultural, public health, medical, etc. It is essential for epidemiologic research to concern itself with all these variables and to focus upon those seeming from initial observation to be more closely correlated with recorded patterns of disease occurrence.

What then are the observed patterns of disease? Extensive data are available concerning them, data collected a generation or two ago, as well as quite recently. Incidentally, it is to be regretted that contemporary research papers in this field tend to ignore the older work. Here, as elsewhere in science, an historic approach is an indispensable part of the effort to achieve mastery of the subject.

The accumulated data are remarkably consistent in their findings. Marked variations exist in the frequency of occurrence of atherosclerotic coronary heart disease in different countries. In the economically less developed countries, clinical coronary disease and severe morphologic atherosclerosis with myocardial infarction at postmortem are rarities at all ages (Figs. 1, 3, 4)^{8, 14}. Data leading to this conclusion are available from China, Ceylon, Costa Rica, East Africa, Egypt, Guatemala,

India, Indonesia, Iraq, Israel, Malaya, Mexico, Nigeria, Okinawa, South Africa and Uganda.

THE ROLE OF DIET

What is responsible for this phenomenon? More than 20 years ago it was suggested that life-span pattern of diet is the decisive causative factor. Recent work amply supports this concept. In these economically less developed countries, habitual diets are much different than ours. The overwhelming mass of the population subsists on cheap, high energy cereal and root foods. The diet is low in total calories, empty calories,* foods of animal origin, total fats and saturated fats, cholesterol, refined carbohydrates, total proteins and animal proteins (Fig. 5).

In recent years, this two-fold correlation between diet and disease has been extended to a three-fold correlation, among habitual diet, plasma cholesterol-lipid-lipoprotein levels and occurrence of coronary disease (Figs. 1, 3, 4). These peoples,

* Empty calories are calories derived from processed, refined foods high in energy value and low in essential nutrients (minerals, vitamins, essential amino and fatty acids)—foods such as sugar, white flour breads and pastries, processed fats, etc.²³

FIG. 12

Diet and Incidence of severe Coronary Atherosclerosis in Japanese--in Japan and in Hawaii

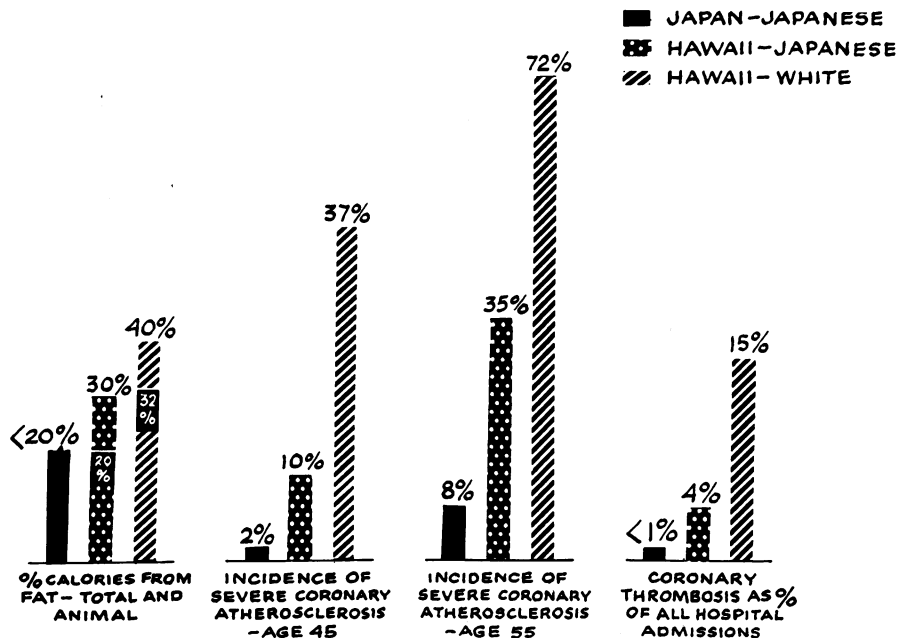


Fig. 12. Larsen, N. P.²⁸; cf. also Keys, A.¹⁷ Note the correlation among habitual fat intake (total and animal, the latter largely saturated), per cent of individuals with severe morphologic coronary atherosclerosis in middle-age, and per cent of hospital admissions for coronary thrombosis—cf. Figs. 2, 6, 7, 10.

subsisting chiefly on cereal-root diets, have low levels of serum cholesterol and little atherosclerotic coronary disease (clinical or morphological). This correlation has been consistently observed in every economically less developed country studied to date. It has also been found to hold for Spain, Italy and Japan—countries somewhat higher in the scale of economic development, whose populations *en masse* nevertheless subsist on cereal-root diets (Figs. 6-8, 10)^{6, 7, 16, 17}.

In addition to the foregoing findings, other data are available indicating that such variables as race, geography and climate cannot account for the international epidemiologic patterns. Thus, in several countries different social classes have been studied, including the more prosperous urban upper strata whose patterns of diet and physical activity differ from those of the population *en masse* of their own countries, and resemble those prevailing in the United States (Figs. 2, 3, 6, 7). Data from Guatemala, South Africa, Egypt, India,

Japan, Italy, Spain indicate that the higher income groups exhibit levels of serum cholesterol and occurrence rates of coronary disease considerably higher than the bulk of the population.

Data are also available concerning the effects of migration, e.g. on Yemenite Jews migrating from Arabia to Israel, Italians from Italy to the U.S.A., Japanese from Japan to Hawaii or the U.S.A. In all cases, the attendant socioeconomic changes, including the change in habitual nutrition toward a diet higher in total calories, total fats, saturated fats, cholesterol, were associated with a rise in serum cholesterol levels and atherosclerotic disease incidence rates (Figs. 9, 11, 12)^{17, 19-24}.

All these data are of great importance because they suggest that racial and ethnic origin, geography, climate are not significantly responsible for patterns of coronary disease occurrence in large population groups. They suggest that socioeconomic factors are critically important. They lend further support to the concept that habitual diet

FIG. 13 Mortality from Arteriosclerotic and Degenerative Heart Disease and percent of total calories from fat--Males age 55-59, 1950

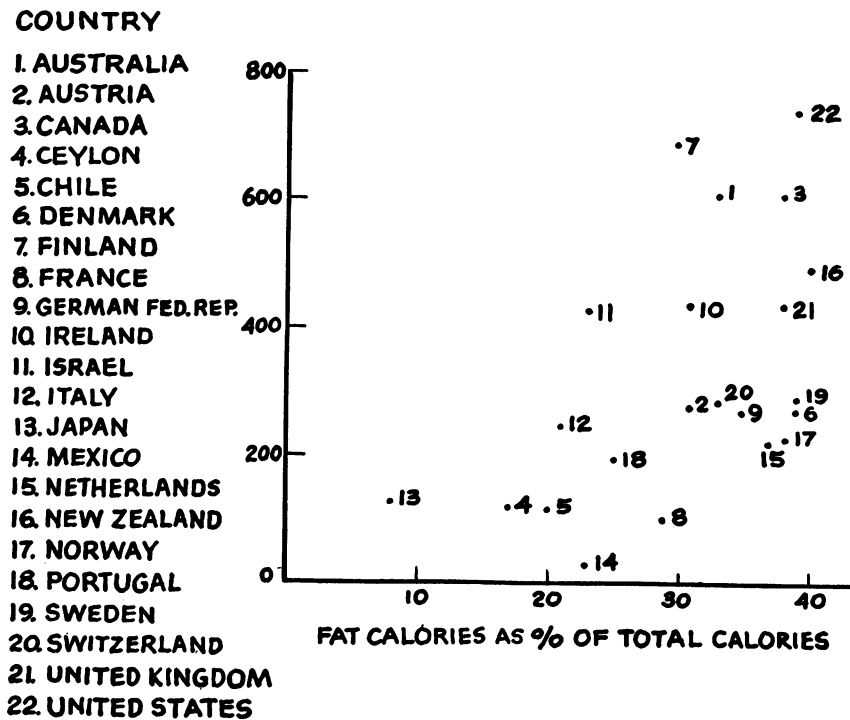


Fig. 13. Yerushalmy, J. and Hilleboe, H. E.²⁵

is a decisive influence.

SERUM CHOLESTEROL

These international epidemiologic findings are of great importance for another reason. They cast serious doubt upon the validity of the standards commonly accepted in the United States for normal serum cholesterol concentration. They pose the questions: Is the life-span pattern of diet inducing a chronic low grade hypercholesterolemia in millions of Americans and thereby creating the metabolic preconditions for widespread atherogenesis? What is an optimal serum cholesterol level, affording maximum freedom from atherosclerotic disease over a maximum life span?

In this connection it is essential to appreciate that two approaches are identifiable to standards of normalcy for a biological variable like serum cholesterol. The first, and hitherto predominant approach in dealing with serum cholesterol con-

centration, involves measurement of the variable in a sample of individuals who at that moment are clinically well. The values obtained are then accepted as the mean and range of normal.

A second, and it would seem more valid, approach to establishment of norms involves consideration of the long-term medical significance of a given value. In arriving at estimates for normal serum cholesterol, this approach requires the posing of the question: What values (mean and range) are associated with maximum freedom from atherosclerotic disease over a maximum life span? The recent research data, epidemiologic, clinical-pathologic and animal-experimental, would seem to indicate the need for redefining standards of normalcy for serum cholesterol, based on this latter approach.

In addition to the foregoing international epidemiologic findings, an overall analysis of 1950 data for 22 countries demonstrated statistically sig-

FIG. 14 Trend of Cardiovascular-Renal Mortality in middle aged Americans by sex and race—1920-1955

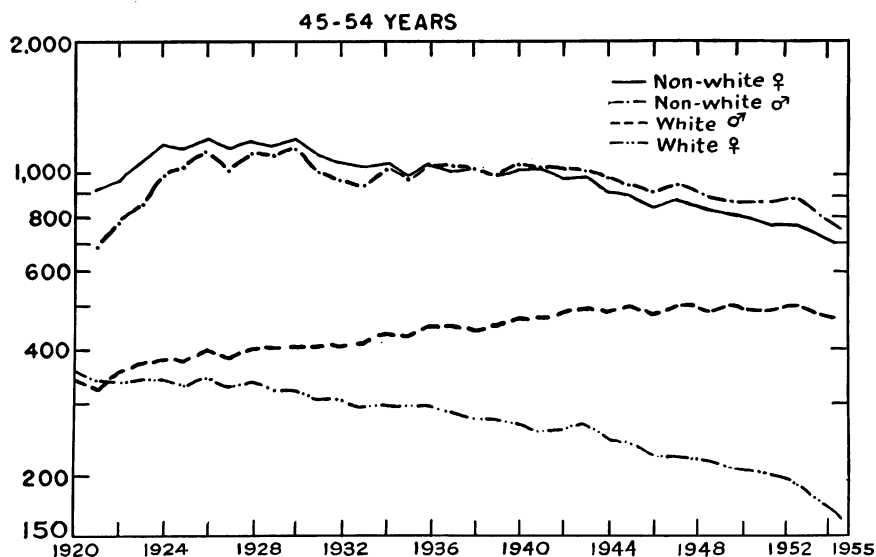


Fig. 14. Moriyama, I., Woolsey, T. and Stamler, J.²⁷

nificant correlations between death rates and intakes of total calories, total fats, animal fats.* However, a considerable spread was noted in the data (Figs. 13, 15)²⁵. For several economically developed countries with total fat intakes in the range

* A negative correlation was noted between intake of vegetable lipid and death rates attributed to arteriosclerotic plus degenerative heart disease. This finding is particularly intriguing in view of recent data demonstrating low serum cholesterol levels in American vegetarians and in Yugoslavs subsisting on diets high in vegetable oils. It is also of interest in connection with observations on the reduction of cholesterolemia by incorporation of unsaturated vegetable oils in American-type diets.

All these findings emphasize the need for further work on the relationship of high intakes of unsaturated vegetable and marine oils in some countries to the observed patterns of serum cholesterol and coronary disease occurrence.

The cited study also noted a positive correlation between protein intake and arteriosclerotic heart disease death rates²⁶. This finding offers a concrete example of the aforementioned principle concerning evaluation of the cause and effect significance concerning statistical correlations, and the need to go beyond the given data in making such an assessment. This particular positive correlation was to be expected once positive correlations were recorded between death rates and total calorie, total fat, animal fat ingestion. For these intercorrelations among a number of nutritional factors reflect shifts with improved socioeconomic conditions from grain-root to meat-dairy product dietetics. From the nature of the ingested foodstuffs, levels of intake of total calories, total fat, cholesterol, animal fat, total protein, animal protein would almost inevitably be inter-correlated.

The question therefore becomes: Does the statistical correlation between death rates and levels of total protein, animal protein consumption reflect a *cause and effect* relationship between protein intake and arteriosclerotic disease? These data pose this question, but cannot answer it. The answer must be sought from other available evidence.

Extensive experimental data indicate that this is not the case. On the contrary, they suggest that high protein intake may afford a partial protection against the hypercholesterolemic and atherogenic effects of high-fat, high-cholesterol diets. On the other hand, extensive clinico-pathologic and animal-experimental data indicate that the correlation between death rates and intakes of total calories, total fats, animal fats is significant cause-and-effect-wise.

30-40 per cent of total calories, age-specific death rates varied from 300-600 or more per 100,000 population (e.g. Austria, West Germany, Sweden, Norway, Denmark, the Netherlands, Australia, Canada, Finland [U.S.: 739 per 100,000]). The populations of some of these countries, e.g. Sweden and Finland, exhibited levels of fat intake and coronary disease occurrence rates approximating those observed in the United States. On the other hand, a few of these countries manifested middle-aged death rates considerably lower than those for the United States.

Based on such findings, several reports recently challenged the validity of the correlation between intake of lipids (total and saturated) and occurrence of atherosclerotic coronary disease. In evaluating these critiques, it is appropriate to note that the broad statistical data, despite their recognized limitations, *verified* significant overall correlations between death rates and intakes of total calories, total fats, saturated fats. These findings, therefore, do not refute the validity of the correlation indicated by a vast array of international epidemiological data. They merely suggest that the correlation among diet, serum cholesterol and coronary disease is not a simple one-to-one correlation. (See p. 174).

Further, a number of the countries, particularly

FIG. 15

Rank correlation coefficients (r) between various dietary components and death rates for 22 countries -- Males, age 55-59

| Dietary Component | Arteriosclerotic and Degenerative Heart Disease | Arteriosclerotic and Degenerative Heart Disease and other Diseases of the Heart |
|--|---|---|
| total calories | 0.723 | 0.593 |
| calories from fat | 0.659 | 0.470 |
| calories from animal fat [▲] | 0.684 | 0.562 |
| calories from vegetable fat [▲] | -0.236 | -0.282 |
| calories from protein | 0.709 | 0.694 |
| calories from animal protein | 0.756 | 0.695 |
| calories from vegetable protein | -0.430 | -0.153 |
| calories from carbohydrate | 0.305 | 0.423 |
| % calories from fat | 0.587 | 0.390 |
| % calories from animal fat [▲] | 0.677 | 0.557 |
| % calories from vegetable fat [▲] | -0.468 | -0.509 |
| % calories from protein | 0.172 | 0.465 |
| % calories from animal protein | 0.643 | 0.608 |
| % calories from vegetable protein | -0.651 | -0.483 |
| % calories from carbohydrate | -0.562 | -0.386 |

▲ Number of countries (N) = 21 (data not available for France); otherwise N = 22

| Critical Values of r | | |
|------------------------|-----------------|-----------------|
| N | $\alpha = 0.05$ | $\alpha = 0.02$ |
| 21 | ± 0.438 | ± 0.521 |
| 22 | ± 0.428 | ± 0.508 |

Fig. 15. Yerushalmy, J. and Hilleboe, H. E.²⁵

the Scandinavian and Low Countries, were in 1950 only a few years away from the privations of World War II, with its significant restrictions in diet and concomitant declines in arteriosclerotic heart disease death rates (Fig. 16)²⁶. It is highly possible, aside from other considerations, that these effects of World War II still found expression in 1950, particularly since atherosclerosis is a disease developing over many years.

Moreover, the observed patterns of mortality for these European countries and the United States all range on the *high* side of a distribution curve for middle-aged population groups, particularly in comparison with the economically underdeveloped countries. Irrespective of the observed differences in rates, therefore, coronary heart disease is unquestionably a major public health problem in these European countries, in contrast to the underdeveloped nations.

Finally, these differences indicate the need for further detailed field studies, going beyond the overall national vital statistics and dietary data, studies of the hospital-clinical-pathological survey type on diet, serum cholesterol and coronary dis-

ease. The several such investigations accomplished in recent years have in fact yielded impressive data supporting the theory of the key role of diet.

As already suggested this conclusion is amply supported by the findings on time-trends of diet and disease in the Scandinavian and Low Countries during World War II. The marked reduction in intake of total calories, total fats, saturated fats, cholesterol imposed by the German occupation was associated with a gross decline in arteriosclerotic heart disease mortality rates (Fig. 16)[†]. Similar findings were reported from Leningrad during the World War II siege, and from Central Europe during the famine years following World War I.

This whole problem of the trend of atherosclerotic disease over the years and its relationship, if any, to evolving dietary patterns has recently received the attention of several investigators. American and British data suggest a marked increase in middle-age mortality rates in these two countries

[†] In view of recent clinical research findings indicating that dietary fats increase blood coagulability and decrease fibrinolysis, it is noteworthy that the occurrence of thromboembolic episodes also declined during the war years. Hence it has been suggested that the decrease in coronary heart disease occurrence rates reflected a diet-induced decline in atherogenesis and/or thrombogenesis.

FIG. 16

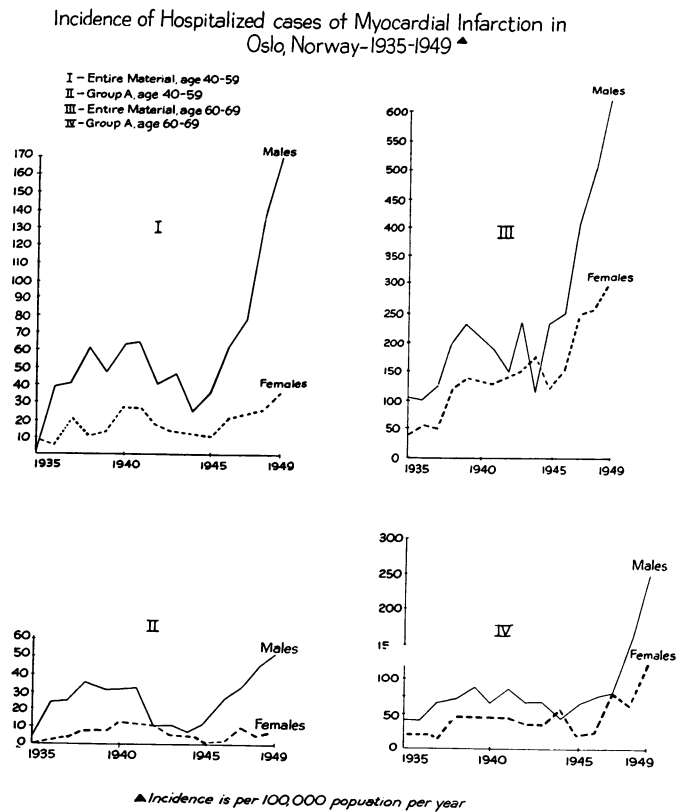


Fig. 16. Muller, C., Ustvedt, H. J., et al.²⁶ The study included patients with myocardial infarction who during the years 1935-1949 were discharged from or died in five departments of three hospitals in Oslo. These patients apparently embraced the greater part of all diagnosed myocardial infarction in Oslo during those years. The total material, 1654 patients, was drawn from the diagnostic files of the five medical departments and included all cases with the diagnosis of myocardial infarction. Group A is a sub-group of the total, characterized by no previous infarction, admission to the hospital not more than 14 days after onset of pain, and typical infarction pattern in the first electrocardiogram. It was estimated that the diagnosis was much more likely to be correct in this sub-group than in the material as a whole.

Note the sex differential. Note the decline during World War II.

in recent decades. Here it is necessary to emphasize that the evaluation of these trends is complicated by a host of statistical and methodological problems, some of them permanently beyond precise quantitation, because of the nature of the data. Hence, it is not surprising that disagreements arise concerning the actual degree and extent of the apparent increases in coronary disease mortality.

POPULATION EFFECTS

In any attempt to arrive at a tentative judgment in this matter, the following fact stands out. Cardiovascular-renal death rates[‡] for middle-aged white males have been high throughout the last

30-40 years. During these decades, middle-aged white male rates rose to even higher levels. In contrast, middle-aged white female rates declined markedly (Fig. 14)²⁷. The question therefore arises, if the increase in white male rates is chiefly an apparent one, due merely to changes over the years in diagnostic acumen and death certification procedures (as some investigators have suggested), why have these changes produced a rising trend for males only? Is there a differential in diagnostic acumen and certification procedures for males

[‡] Problems inherent in the available statistics render difficult any evaluation of the trend of death rates over the last 30-40 years for arteriosclerotic heart disease *per se*. Hence, an interpretation must be made of the data for a broad grouping of several diseases, the cardiovascular-renal diseases.

FIG. 17

CONSUMPTION OF FOOD IN THE UNITED STATES -1909 & 1952

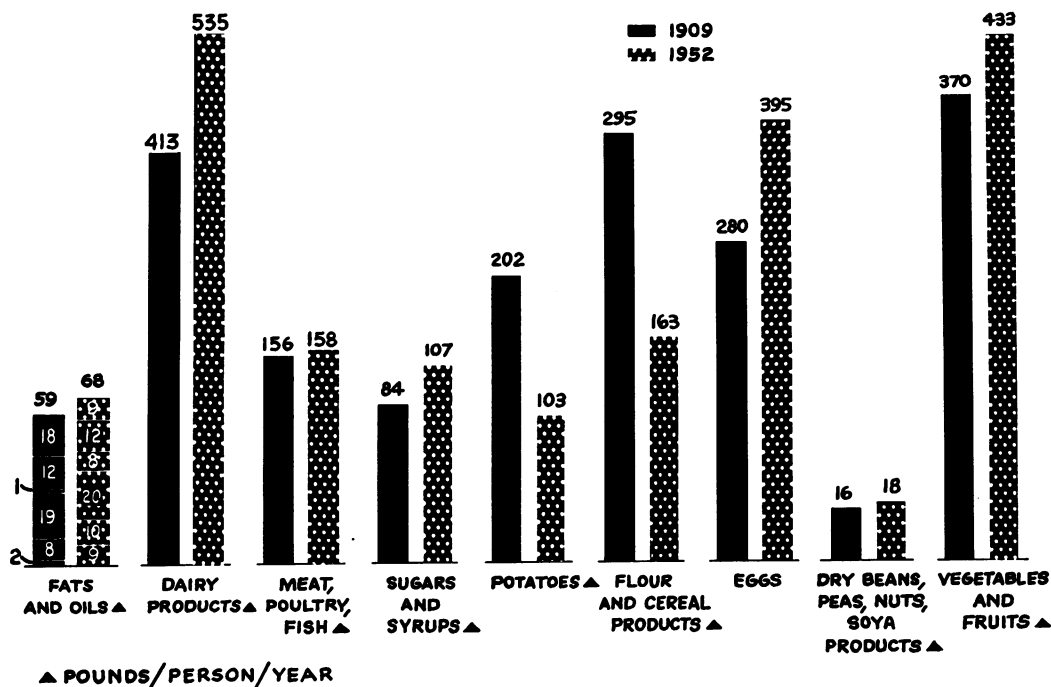


Fig. 17. Stamler, J.³; for source of the data, cf. ref. 28. Date indicate food available for consumption, not food actually consumed. Unlike Figs. 5 and 6, based on United Nations sources, the data on fats and oils from the U. S. Dept. of Agriculture include bacon and salt pork, hence the higher values. The data on fats and oils are subdivided into specific components; from above, down, they are: butter, lard, margarine, bacon and salt side, shortening, other edible oils. Values for eggs are number of eggs per person per year. The following estimates have recently been made of total fat content of all foodstuffs brought into the American kitchen daily; Total fats—146-164 gms/person/day (the range is reflective of variations in different sections of the country); saturated fats—63-69 gms/person/day; oleic acid (mono-unsaturated essential fatty acid)—16-18; percent of total calories from total fat—42-45%; percent of total calories from saturated fats—17-19%.³⁹

vs. females, leading to a rise in rates for the former and a decline for the latter? This hardly seems tenable.

As is well known, atherosclerotic coronary heart disease is common in middle-aged American males, whereas it is remarkably rare in premenopausal females. This sex differential in susceptibility is in the order of 5-25 to 1 for middle-aged whites.

Given this well known fact, it is not difficult to deduce that the 1920-1955 trend of middle-aged white male vs. middle-aged white female cardiovascular-renal deaths in the United States reflects the following: for males, a sizeable rise in coronary disease, leading to a net increase in cardiovascular-renal disease mortality, despite declining death rates for infectious diseases involv-

ing the cardiovascular-renal system; for females, continued low coronary disease rates, with little or no rise, and a marked decline in death rates due to the puerperal and infectious diseases of the cardiovascular-renal system, resulting in a gross fall in overall cardiovascular-renal death rates.

This tentative conclusion that coronary disease death rates for middle-aged white males increased sizably is borne out by other data. Thus, while life expectancy at birth for Americans has risen by about 20 years since 1900, life expectancy of white males at age 50 has increased only 2.2 years. In view of the great advances during these decades in the prevention of death in middle-age due to pneumonia, tuberculosis, leucic and rheumatic heart diseases, subacute bacterial endocarditis, dis-

FIG. 18

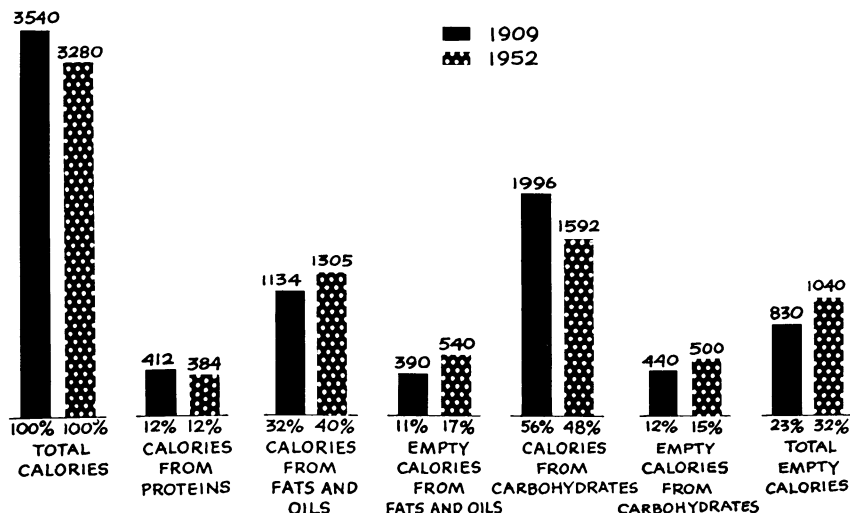
COMPOSITION OF DIET IN THE UNITED STATES
— 1909 AND 1952

Fig. 18. Jolliffe, N.²⁰ These calculations are again based on foods available for consumption, not foods actually consumed. The % values below the bars represent per cent of total calories, derived from each of the cited principal dietary components. For definition of the concept, empty calories, see text. The apparent decline in total calorie intake should be evaluated in relation to declining levels of physical activity (energy expenditure) over these decades.

increase in life expectancy at age 50 might have been anticipated. Almost certainly, this absence of a marked improvement is attributable chiefly to an increasing mortality from coronary heart disease in middle-aged white males.⁵²

If this foregoing analysis is sound, the qualitative judgment must be accepted that a true increase has actually occurred in mortality among middle-aged white American males due to atherosclerotic coronary heart disease.

What are the factors possibly responsible for this trend? Certainly many changes have occurred in the United States during this period.* There has been steadily increasing urbanization, mechanization, sedentary living, use of tobacco, etc. Less and less human energy is expended in work. Muscle power is more and more replaced by non-human energy, from coal, oil, water or atomic power sources. This, of course, is very different

from the economically and underdeveloped countries, which as yet have relatively little non-human energy and must rely on producing the necessities of life in the old way, by the sweat of the brow. Undoubtedly some people still do very heavy work in the United States, but smaller and smaller percentages, compared with previous decades. Many employees, e.g. factory operatives, may have work patterns that are exacting, intense, concentrated, fatiguing. But the fact remains that diversified large-muscle activity is no longer widespread in our country.

Those are some of the changes. Many observers also believe that life has become more hectic, complex, competitive, insecure, stressful in the twentieth century, particularly since World War I. If this is true, what relationship does this have, if any, to the apparent increase in coronary disease in middle-aged white American males during this 40 year period?

What about evolving dietary patterns? Here again, serious methodological limitations exist, due not only to a relative paucity of data, but the particular scarcity of information concerning diets

* Here it is important to note that people aged 50 dying of coronary disease in 1955 lived their life span over the years 1905-1955. Those aged 50 dying in 1920 lived from 1870-1920. If aspects of the habitual mode of life exert a key influence in the etiology of atherosclerosis, then it is essential to seek out data on conditions prevailing in the third and fourth quarters of the nineteenth century, as well as in the twentieth century.

FIG. 19

**SEX-RACE AND DEATH RATES
CHICAGO, 1951--
AGE 45-54**

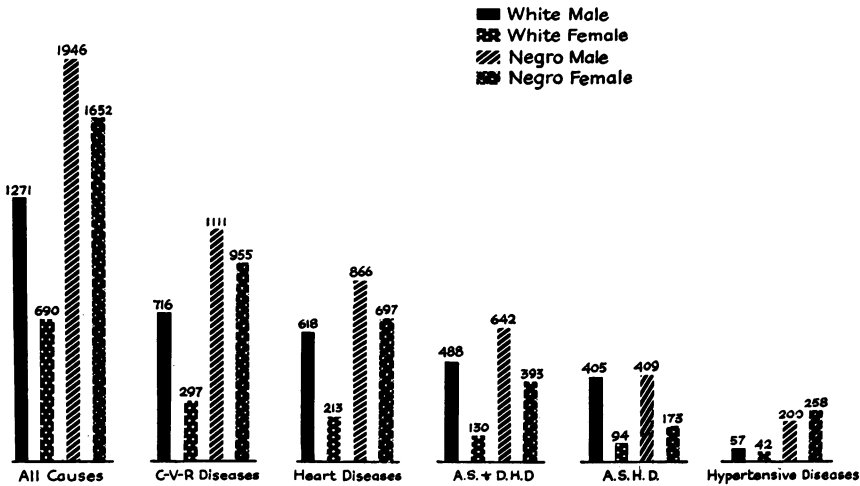


Fig. 19. Stamler, J., Kjelsberg, M., and Hall, Y.³⁰ All death rates in Figs. 19-23 are per 100,000 population, based on the 1950 census data. A. S. and D. H. D. is the sum of death rates due to Arteriosclerotic Heart Disease and Degenerative Heart Disease, categories 420 and 422 in the International Statistical Classification of Diseases and Causes of Death.

FIG. 20

**URBAN-RURAL DEATH RATES
ILLINOIS, 1951--
MALES AGE 45-54**

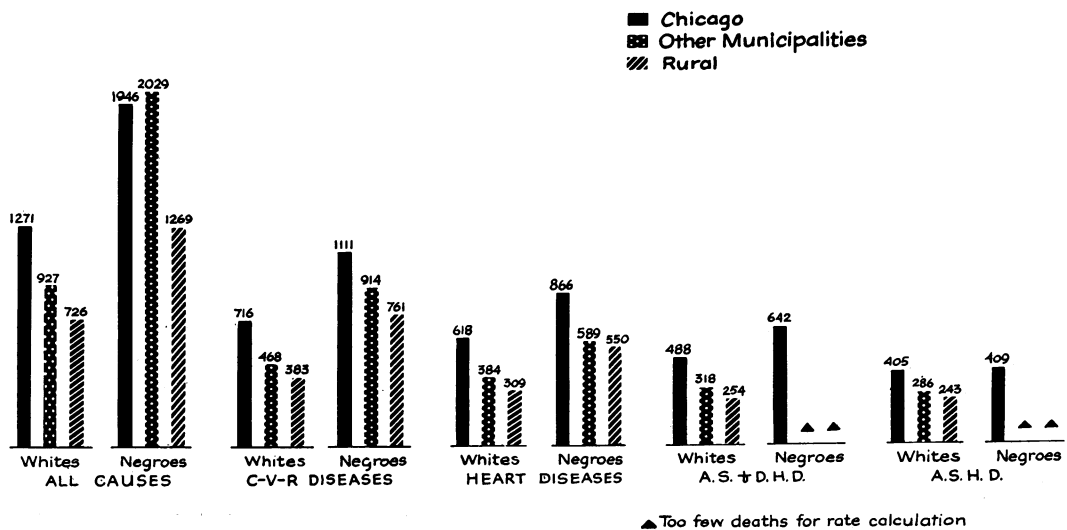


Fig. 20. Kjelsberg, M. and Stamler, J.³¹ The Other Municipalities are all Illinois municipalities exclusive of Chicago.

FIG. 21 OCCUPATION, RACE, AND DEATH RATES DUE TO ARTERIOSCLEROTIC AND DEGENERATIVE HEART DISEASE

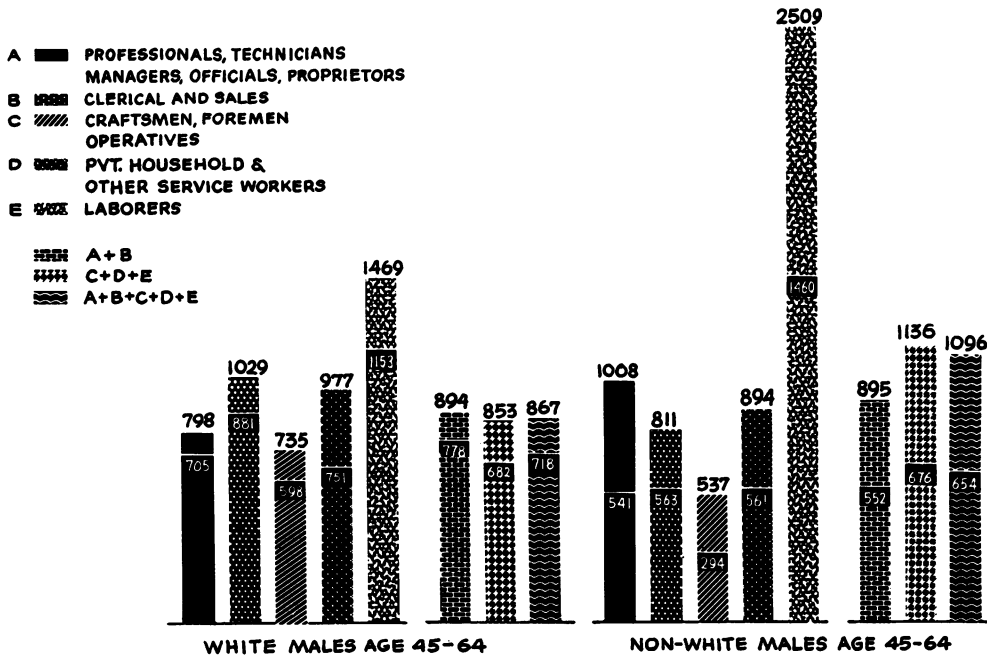


Fig. 21. Stamler, J., Kjelsberg, M. and Hall, Y.³⁰ The value at the top of each bar is the mortality rate attributed to arteriosclerotic and degenerative heart disease; the value within each bar is for arteriosclerotic heart disease only. It is likely that the death rates for the laborers, white and Negro, are falsely high, probably due to inaccurate listings of occupation on death certificates. The data were therefore pooled into two broad groups—white collar workers (A and B) and blue collar (manual) workers (C+D+E).

in different regions of the country and among different racial, ethnic and socioeconomic strata at different times (e.g. during peace and war, prosperity and depression).[†] With these shortcomings in mind, it is possible to delineate the following broad trends: Meat consumption has generally tended to be relatively high in the United States, and has remained so, much higher even than in most other economically developed countries (Figs. 5, 17, 18)²⁹. Another longstanding unique American dietary characteristic has been the large intake of butter, lard and other predominantly saturated fats. This has apparently been further accentuated.[§]

Intakes of milk, dairy products, eggs have also exhibited significant increases. A marked rise in ingestion of refined sugars (100% empty calories)

[†] A further difficulty stems from the fact that much of the data on dietary patterns in Americans deals with foods available for consumption, rather than foods actually consumed.

is another important long-term development in the American diet—from 8 pounds/person/year in 1820, to 30 in 1860, 66 in 1900 and 95 today. All these upward trends have been associated with a steady decline in grain consumption, of such marked proportions that for tens of millions of Americans today bread can hardly be designated the "staff of life."[§]

[§] In recent decades, the composition of ingested saturated fat has tended to change, as a result of the introduction in 1910 of the catalytic hydrogenation process for converting vegetable oils into plastic shortenings and margarines. As a consequence of this process, which saturates double bonds, these fats have a high percentage of *trans* fatty acid isomers (23-42%) and a low content of essential fatty acids (2-8%). Unless enriched, they are practically devoid of other essential nutrients, e.g., fat soluble vitamins, hence they are an "excellent" source of empty calories.

A qualitative metamorphosis in flour has also occurred over the decades, i.e. a decline in percentage utilization of whole meal. The resultant nutritional losses have been only partially compensated by the limited bread enrichment measures of recent years.

The increased consumption of highly processed, refined foods has also involved a decline in intake of bulk—a decline only partially compensated for by the increased ingestion of fruits and vegetables. Little work has been done on the possible implications of this trend for health and disease.

FIG. 22

SOCIOECONOMIC CHARACTERISTICS OF
PLACE OF RESIDENCE AND ARTERIOSCLEROTIC
HEART DISEASE DEATH RATES—CHICAGO, 1953
MALES, AGE 45-54

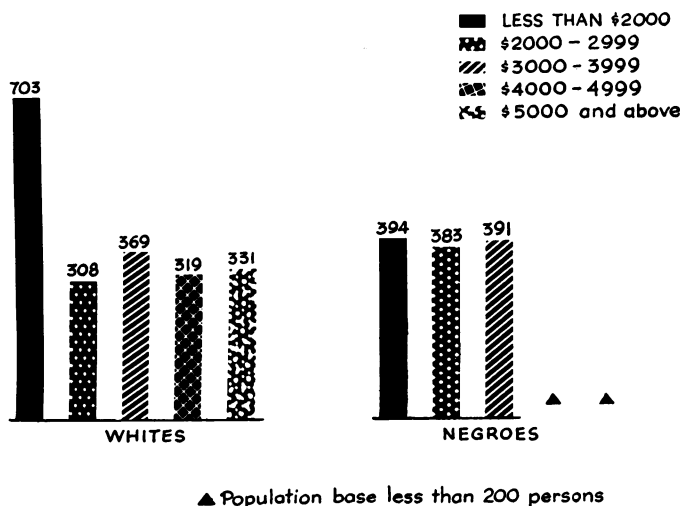


Fig. 22. Stamler, J., Kjelsberg, M. and Hall, Y.,³⁰ and Kjelsberg, M. and Stamler, J.³¹ Income data are median family incomes per annum; they represent median incomes of the census tracts of origin of the population groups. They were obtained from 1950 census reports.

Viewed overall, these trends are, within the limitations noted above, highly suggestive of a definite increase (relative and absolute) in consumption of total fats, saturated fats, cholesterol and empty calories. §§

This is the path our country has apparently taken nutritionally in evolving its unique pattern of dietary imbalance.

This conclusion, it should be noted, is not shared by all investigators. They emphasize that little information is available on food actually consumed, as distinct from data on food available for consumption. They further stress the difficulty of estimating waste of fats in cooking. Based on these and other considerations, they suggest that there has been little or no increase in fat consumption in twentieth century America. These writers are also skeptical about the data indicating an increase in coronary disease incidence in middle-aged males over these years. Thus, these authors imply that both fat intake and coronary disease incidence have been high since the turn of the century. If

§§The slight decline in total calorie ingestion must be assessed in terms of another related phenomenon, the decline in physical activity. The problem of the possible effects of sedentary life on lipid metabolism and atherogenesis is discussed below.

these are actually the facts, and the two phenomena are so correlated, this certainly is not inconsistent with the nutritional-metabolic theory.

In this connection, one other problem merits attention. Even if fat intake has increased since the turn of the century, it was, as already noted, high even then. If coronary disease incidence in middle-aged males was much lower then, as some data suggest, why *this* lack of correlation? This question highlights the need, in evaluating the trends over the last 40-60 years, to focus attention not only on evolving dietary patterns, but also on the interplay between diet and psychological stress, and between diet and large-muscle activity.

Thus, the apparent changes with time in patterns of diet and disease may or may not be significantly interrelated cause and effectwise. As already suggested, these decades witnessed manifold other changes in American life, e.g. increase in urbanization, automobile transportation, cigarette consumption, sedentary work, etc., phenomena emphasizing the need for multifactorial analysis of arteriosclerotic disease causation. Because of these complexities and the limitations of both the mortality and the nutritional data, plus the insurmountable

FIG. 23

NATIONALITY and DEATH RATES
CHICAGO MALES 45-54, 1951

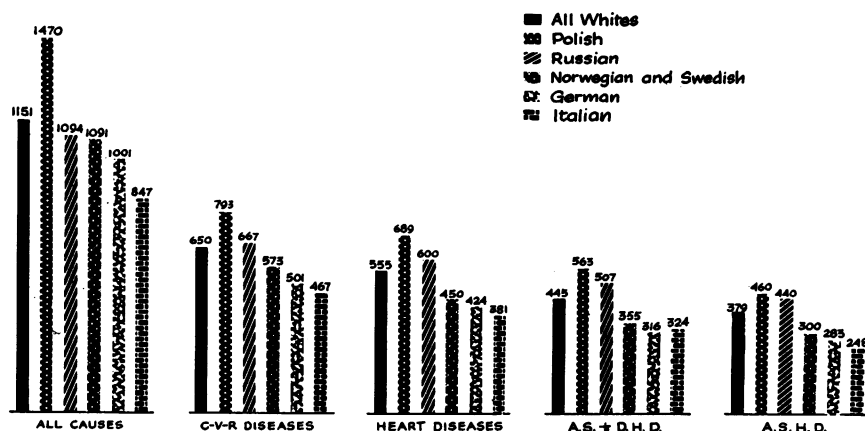


Fig. 23. Stamler, J., Kjelsberg, M., Hall, Y. and Scotch, N.²⁴ These rates are for the Chicago Metropolitan Area (exclusive of Lake County, Indiana), rather than the city of Chicago. All data on nationality groups refer to the foreign-born only. A high percent of the foreign-born Russian-Americans in Chicago are Jewish. Cf. Figs. 8, 9, 11, 13, 14.

obstacles to their further delineation, extreme caution is essential in interpreting them. Here the danger of "reading" cause and effect into statistical correlation is particularly acute. With these reservations it is not inappropriate to note the suggestive positive correlations and their consistency with extensive findings from other sources. Again it is valid to conclude that the concepts of the nutritional-metabolic theory are certainly not contradicted by these data.

THE U.S. AN EPIDEMIOLOGICAL "LABORATORY"

Recent years have also witnessed a definite quickening of epidemiologic research of a different type in the United States. It has come to be widely recognized that this country, with its large population stratified by region, occupation, income, ethnic and racial background, etc., constitutes an excellent epidemiologic "laboratory." Based on this approach, our group late in 1954 initiated a long-term investigation on the epidemiology of the major cardiovascular-renal diseases in the city of Chicago and the state of Illinois.

The first phase of this study involved analysis of 1951 and 1953 mortality data for specific groups in the population stratified by age, sex, race, nationality, occupation, place of residence (including urban-rural)—with a particular focus on the middle decades of life (Figs. 8, 9, 14, 19-24)^{24, 27, 30, 31}. For present purposes, the following findings

assumes particular significance: the death rates for arteriosclerotic heart disease were several-fold higher in middle-aged men than women (Figs. 19, 24), an observation fully in accord with extensive data from multiple sources. This is the most striking, unquestionably valid epidemiologic fact about coronary disease in the United States. The question forcefully presents: Why? What is responsible for this gross sex differential?

SEX DIFFERENTIAL

Before proceeding to touch briefly upon this problem, two further facts, rarely alluded to, are worthy of note. This sex differential, so clearly apparent in the middle-aged white population of the United States and other economically developed countries, is either absent or much less marked in economically less developed countries. This reduction in the ratio of male to female coronary disease comes about chiefly because of the lower male rates (Figs. 1, 8, 10).

Compare the findings in the middle-aged American Negro population. Note that for the cardiovascular-renal diseases as a whole, virtually no sex differential is demonstrable for Negroes at any time from 1920 to 1955 (Fig. 14). Note also that cardiovascular-renal death rates for Negroes are much higher than those for whites. Note further that arteriosclerotic heart disease death rates for

FIG. 24

Death rates for specific components of the Cardiovascular-renal group by sex and race-- Age 45-54--United States, 1955

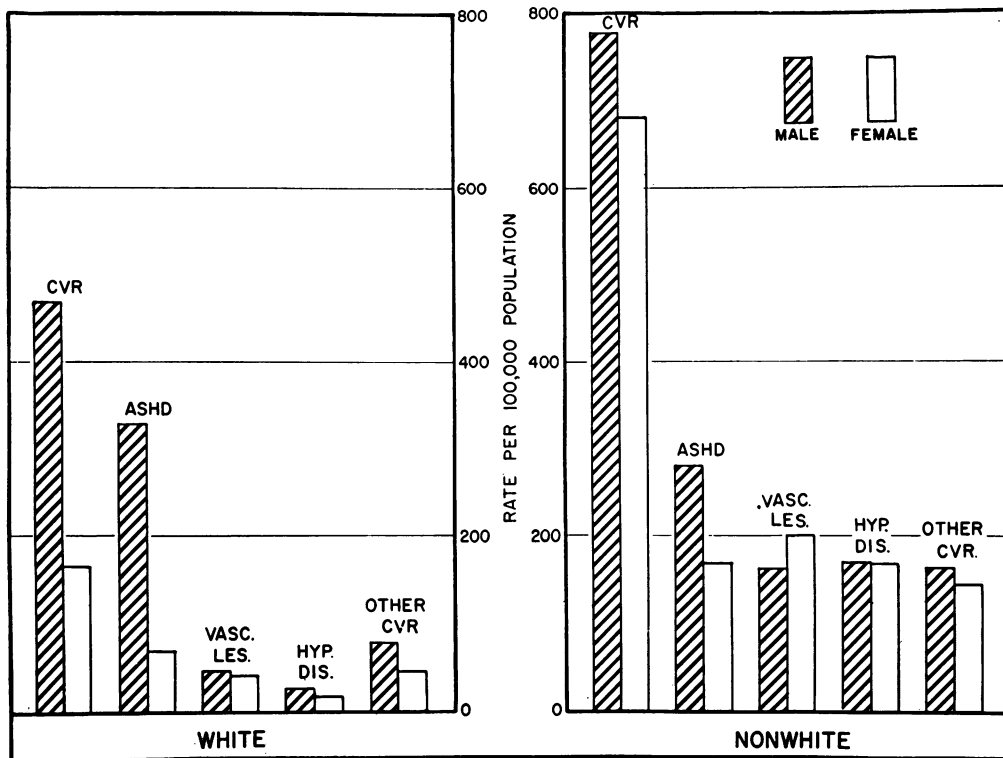


Fig. 24. Moriyama, I., Woolsey, T. and Stamler, J.²⁷ The population estimates of the Bureau of the Census for 1955 were utilized to calculate the death rates. Cf. Fig. 19. Vasc. Les. is Vascular Lesions of the Central Nervous System (I.S.C. group 330-334); Hyp. Dis. is Hypertensive Disease (I.S.C. group 440-447).

middle-aged Negro males are about the same as or moderately lower than those for white males (Figs. 19, 20, 21, 24). Note finally that A.S.H.D. death rates for middle-aged Negro females are considerably higher than those for white females (Figs. 19, 24). Consequently the sex differential in A.S.H.D. mortality rates for Negroes is less marked than for whites. This lower sex ratio, it may be emphasized, is not the same qualitatively as that recorded for the economically less developed countries. In American Negroes it is reflective chiefly of higher rates in the denominator, i.e. higher Negro female rates. In the economically less developed countries it is reflective mainly of lower rates in the numerator, i.e. lower male rates.

The end result in both cases is a similar ratio, but on a different basis.

CORONARY DISEASE

What is the meaning of all these diverse findings, in terms of the problem of causation of coronary disease? Based on present knowledge, the following approaches and interpretations may be suggested: It is not likely that nutrition is a decisive factor responsible for the marked sex differential in coronary disease in middle-aged Americans, particularly whites, since from the limited data available there do not appear to be marked differences in the dietary habits of American men and women. Obesity is, however, less

FIG. 25 Prevalence of Overweight in U.S. Population, age 15-59, by age and sex-1950

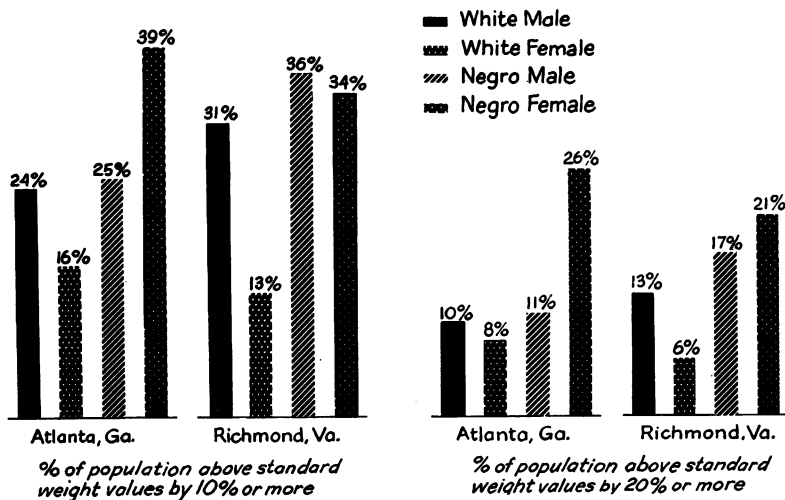


Fig. 25. Anonymous.³² Note the considerably greater prevalence of overweight in Negro women, especially compared with white women. Cf. data on obesity and on disease-death rates, Figs. 19, 24, 40 and 41.

prevalent in white females than males (Fig. 25)³². Therefore, the matter of dietary patterns in men and women merits further investigation, particularly in view of the paucity of reliable data.

Considerable evidence has accumulated indicating that gonadal function, specifically estrogenic secretion, is a key factor responsible for the high

resistance of premenopausal women to atherosclerotic coronary heart disease. (A detailed discussion of this aspect of the problem is beyond the scope of this paper^{1-4, 33}.)

Does diet enter at all? The data from the economically less developed countries indicate that diet is definitely involved. These data suggest that

FIG. 26

Food Consumption of Farm Families North & South, White & Negro-Summer, 1945

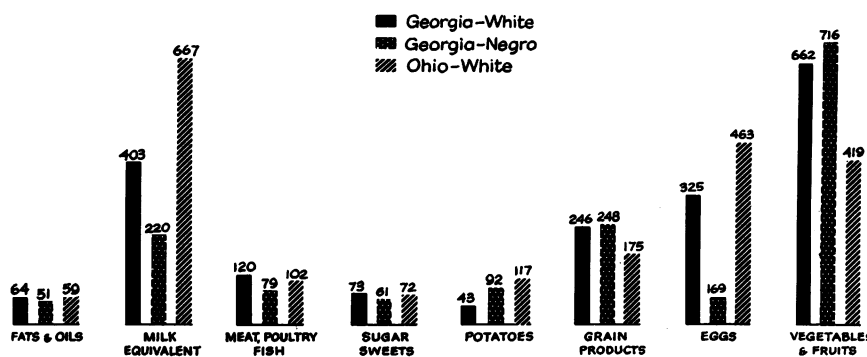


Fig. 26. Adelson, S. F. and Blake, E. C.³⁴ All values, except eggs, are pounds per person per year; eggs are number of eggs per person per year. All data are foodstuffs available for consumption, not foods actually consumed. As in other Dept. of Agriculture reports (cf. Fig. 17), fats and oils include bacon and salt pork. Note the considerably lower values for milk, meat-poultry - fish, eggs for Georgia Negroes, compared with whites, North and South. The values for Negroes for fats and oils, and for sugar and sweets, are also moderately lower than for whites, whereas values for potatoes, grain products, vegetables and fruits are relatively high. Note the differences between Southern whites and Northern whites. Cf. ref. 39 for more recent data comparing dietary patterns, North and South. Cf. Figs. 5, 6, 17, 18, 25, 30, 32.

FIG. 27

Age adjusted annual incidence rates of initial Myocardial Infarction in middle aged males of different occupation groups

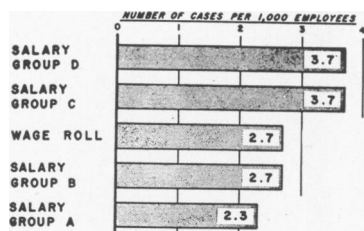


Fig. 27. Pell, S. and D'Alonzo, C. A.⁴⁰ This study was on 90,000 employees of E. I. DuPont De Nemours and Company, throughout the United States, chiefly in Delaware, New Jersey, New York and Virginia. The data of this graph are for 1956, on males age 25-64. The employees are divided into 2 main groups, wage and salaried. The salaried employees are subdivided into 4 groups, A, B, C, D, based on degree of job responsibility. Group A included the top-level managers and executives; Group 4, clerical workers "—with a minimum of responsibility"; groups B and C, employees "—whose job responsibility lies between the two extremes." Note that the lowest rates of myocardial infarction were in the managers and executives (Group A); the highest rates were in the wage and clerical workers; all-in-all the groups had similar rates—a finding in accord with those previously cited. Other data from this study revealed a sex differential of 10 to 1 (2.9/1000/year vs. 0.2/1000/year), with the female cases only in the age group 60-64. The following data were reported on the effects of hypertension and obesity on rate of myocardial infarction in males aged 25-54; group free of hypertension and obesity—2.3/1000/year; group with hypertension only—3.4/1000/year (increase in risk: 1.5X); group with hypertension only—3.8/1000/year (increase in risk: 1.7X); group with hypertension and obesity—8.1/1000/year (increase in risk: 3.5X). The rate in males age 45-64 was 8.5/1000/year. (cf. Fig. 41). The overall fatality rate was 33.8% of cases of infarction. Data on the increased risk of myocardial infarction in the obese and hypertensive were qualitatively similar to those in Framingham (Fig. 41). No data on racial and geographic sub-groups were presented.

a certain nutritional pattern, an habitual diet high in total calories, total fats, saturated fats, cholesterol, is essential to effectuate the metabolic prerequisites for atherogenesis in sizable sectors of a population. Without that dietary prerequisite, atherosclerotic disease rarely develops in middle-aged persons of either sex and the sex differential is absent or slight. With the dietary prerequisite operating, the susceptible male sex is frequently

victimized. The female sex by virtue of the protection afforded through estrogenic secretion tend to be particularly resistant in the premenopausal years. Thus the American female, particularly the white female, exhibits a relatively low coronary disease rate in middle-age, although this rate is somewhat higher than that of her counterparts in the economically less developed countries, where the potential for atherogenesis based on diet is generally low (Figs. 1, 8, 10).

This interpretation of the data on the sex differential emphasizes the concept of an interplay between diet (exogenous) and endocrines (endogenous) in the etiology and pathogenesis of atherosclerotic disease. It views diet as a key, but not exclusive causative factor. It is in contradistinction to trends of thinking which demand an either-or, yes-no answer to the problem of the relationship between diet and atherosclerosis.

RACIAL DIFFERENCES

It is essential to add that the foregoing interpretation of the sex differential is in itself not adequate to account for the apparent findings on American Negroes. In this connection, it must first be emphasized that the data on coronary disease in American Negroes, particularly the findings indicating a relatively high A.S.H.D. rate in middle-aged Negro women, are as yet limited. Further studies on groups of varying geographic and socioeconomic backgrounds are needed to check on the validity of the extant data.

Suppose the validity of this observation, that coronary disease rates are higher in middle-aged Negro than white women, is tentatively accepted for the moment: What can be said about possible causes of this phenomenon? Is it related to differences between the races in estrogenic secretion? This should be investigated, but it would appear to be an unlikely possibility. Is it related to other endocrine functions—thyroidal, pancreatic? Is it related to differences in diet, and different prevalences of obesity (cf. Fig. 25). Is it related to the greater prevalence of hypertension in Negro women? Is it related to a higher incidence in Negro women of genitourinary tract infections and complications of pregnancy (pre-eclampsia, eclampsia, etc.) with consequent renal damage and hypertension? Is it related to socioeconomic and socio-cultural differences between the races, in

FIG. 28
 Four year incidence rates of Atherosclerotic
 Heart Disease in males age 45-62 of
 different educational status--Framingham study

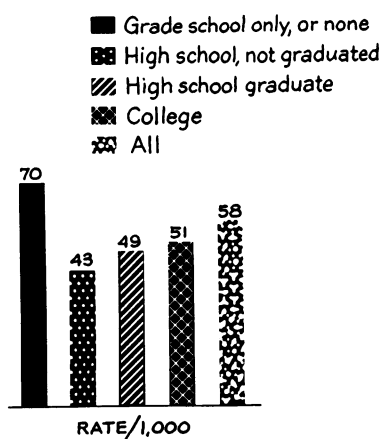


Fig. 28. Dawber, T. R. Moore, F. E. and Mann, G. V.³⁰ Note that the highest incidence of clinical coronary heart disease (70 per 1000 population in 4 years) is in the group with the least education. Note that the overall range of rates is not great; no gross differences were observed among the several groups.

income, employment status, psychological stresses, strains, and frustrations (e.g. those relating to discrimination and segregation of Negroes)? All these questions can and should be explored by epidemiologic research in the years ahead.

Further studies along these lines are particularly essential in view of the confused, contradictory picture emerging from many papers in the literature on coronary disease in Negro compared with white American males. Some reports present data indicating that coronary disease has been occurring much less frequently in Negro than white men, an impression receiving some support from recent overall national mortality data, particularly for males in age groups 55 and over (Fig. 24). Other publications contain findings indicating no substantial difference between Negro and white males in age specific coronary disease rates, particularly in middle-age, an impression supported by recent mortality data from large Northern cities (Figs. 19, 20, 21, 22). These findings are not necessarily mutually exclusive. Rather they may reflect real differences in disease patterns within the Negro population based on socioeconomic differences prevailing during particular decades, in Northern vs. Southern and urban vs. rural areas, in different income-occupation groups (Fig. 25)³⁴. Additional

research, especially in representative samples of the living population, is needed to clarify this important set of problems.

While these unclaritys exist concerning coronary disease in U. S. Negroes compared with whites, it is an unquestioned fact that a gross differential exists between the two racial groups in morbidity and mortality due to hypertensive disease and its sequela, cerebral hemorrhage (Figs. 19, 24). The rate of occurrence of hypertensive disease is several-fold greater in Negroes than whites.* This is the unassailable, outstanding, solid fact of our present knowledge concerning the epidemiology of hypertensive disease in the United States.

HYPERTENSION IN THE NEGRO

It is this high rate of hypertensive disease and its complications (particularly cerebral hemorrhage) in Negroes that largely accounts for the fact that overall cardiovascular-renal death rates

* Note that the highest death rates for hypertensive and cerebrovascular diseases are in Negro women (Figs. 19, 24). Note also, in contrast to arteriosclerotic heart disease findings, the absence of any tendency in either whites or Negroes for women to exhibit lower mortality rates from these causes. That is, for hypertensive disease, there is no sex differential in favor of females. Thus the data on the epidemiology of hypertensive and atherosclerotic diseases present markedly different patterns. This fact emphasizes the validity of the conclusion that these are two different disease processes etiologically.

FIG. 29 Arteriosclerotic Heart Disease Death Rates
among ordinary and industrial policy holders
--White males, 1953

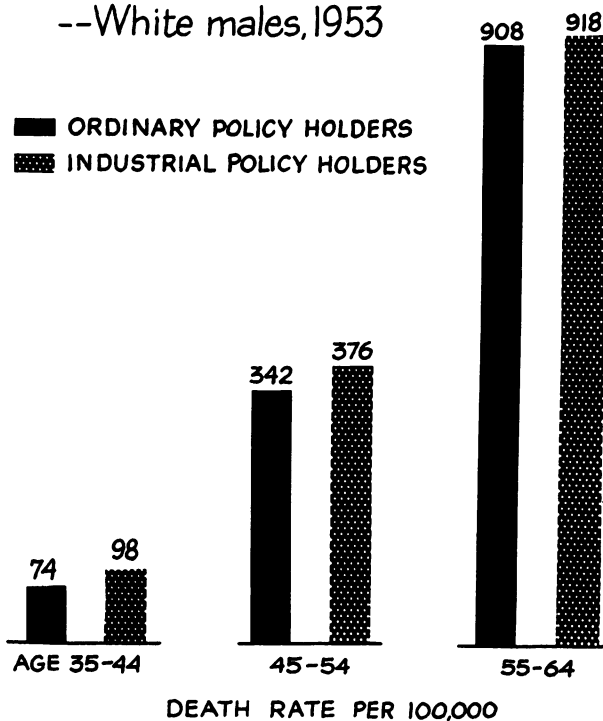


Fig. 29. Lew, E. A.³⁵ The ordinary policy holders are drawn chiefly from the urban middle and well-to-do classes of the population engaged in non-hazardous occupations, e.g. professions, business, trade and clerical occupations. The industrial policy holders are largely members of urban wage-earning families in the lower income brackets. They include a high proportion of men engaged in manufacturing and mechanical industries, mining, transportation and personal services. Note the higher death rates in the industrial policy holders at all ages from 35 to 64, particularly in the younger age groups.

have consistently been higher in Negroes than in whites during the period 1920-1955 (Fig. 14).

The factors etiologically responsible for this phenomenon remain largely unknown, although it is not difficult to formulate meaningful hypotheses concerning possible variables, nutritional, infectious, psychological, etc., to be investigated epidemiologically.

In evaluating the foregoing data on the epidemiology of the cardiovascular-renal diseases in the United States, it is important to ponder the apparently paradoxical nature of some of the findings. On the one hand, hypertensive disease has a several-fold greater prevalence in Negro than white males; on the other hand, the occurrence of atherosclerotic coronary disease is no greater, and may even be less, in Negro than white men. But

it has been repeatedly shown experimentally and clinically that hypertension increases the risk of coronary disease. Why, then, don't Negro men, with so much more hypertension, have more coronary disease? This fascinating and important problem of the coexistence and interdigitation of these two diseases in various age-sex-race-socio-economic groups certainly merits further investigation in various parts of the country.

URBAN-RURAL COMPARISONS

Several other intriguing sets of data emerged from the analyses of Chicago and Illinois cardiovascular-renal disease mortality. Thus, urban-rural comparisons revealed high arteriosclerotic heart disease death rates for the city of Chicago, for other Illinois municipalities and for rural Illinois.

FIG. 30

FOOD CONSUMPTION OF LOW AND
HIGH INCOME URBAN FAMILIES
U.S.A.-1948

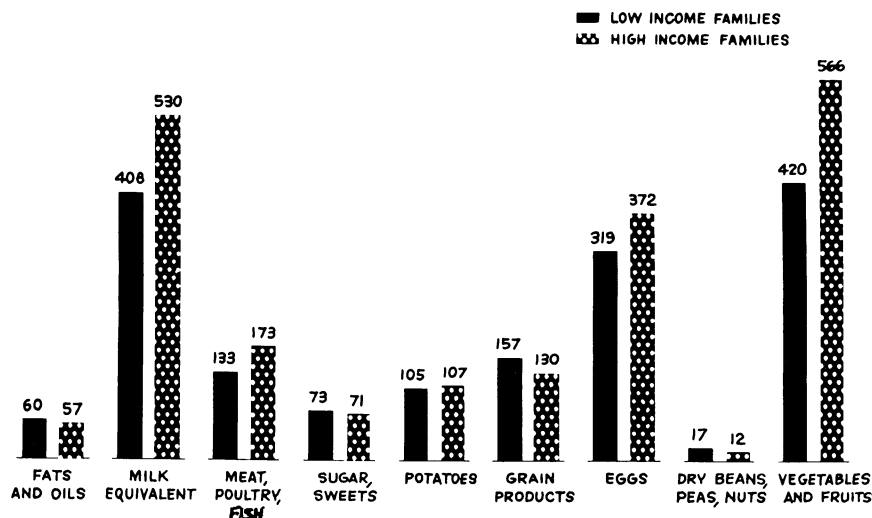


Fig. 30. Stamler, J.;³ for source of data, cf. ref. 38; cf. also ref. 39; cf. legends of Figs. 17-32.

However, a considerable differential was noted, viz., relatively higher rates for Chicago, lower rates for the other municipalities and rural areas. (Fig. 20). These observations are in accord with data from other states. Here again, further work, particularly in the living population, is necessary to verify these findings. If their validity is tentatively accepted for the present, the question may be posed of their possible bearing upon problems of etiology. Available data indicate that dietary patterns are not very different in urban and rural areas of the northern United States. In both areas the habitual diet apparently tends to be high in total calories, empty calories, total fats, saturated fats, refined carbohydrates, cholesterol. If this is the case, it again becomes essential to delineate the interplay between diet and other factors, habitual large muscle activity, fatigue, psychological stress, strain, tension, frustration, etc., in the etiology of atherosclerotic disease.

In calling attention to this consideration, however, it is also essential to observe that both rural and urban rates are high, particularly when the distribution curve includes the countries of Europe, Asia, Africa, Latin America (cf. Figs. 8, 13, 20). This fact suggests that the high caloric-

lipid-cholesterol diet of most Americans, urban and rural, does in fact result in extensive atherosclerotic disease, irrespective of other factors possibly operating to produce differential effects in urban vs. rural areas.

Analysis of the foreign born by nationality leads to a similar conclusion. Thus, death rates were high for all nationality groups, considerably higher than those for the given nationalities in their countries of origin* (Fig. 23, cf. Figs. 8, 9, 13). However, a moderate range in rates was recorded, with the distribution tending to parallel that for the countries of origin. The foreign born nationalities, therefore, seem to bear the stamp of their tenure in both their countries of birth and in the United States. This is in all likelihood true not only for the death rates, but also for the dietary patterns of these first generation Americans. Almost certainly their nutritional habits represent an amalgam of old country and American dietetics. Therefore, without discounting the possible influence of other factors which need investigation, it

* One subgroup of the American Indian ethnic grouping, the Navaho, has recently been the subject of several reports, differing in their conclusions. The much discussed, but inadequately studied, Eskimo was analyzed in detail previously.³

FIG. 31 Relative Incidence of Coronary Disease in 30 month follow-up of males aged 40-70, stratified by level of physical exertion of habitual work—Los Angeles study

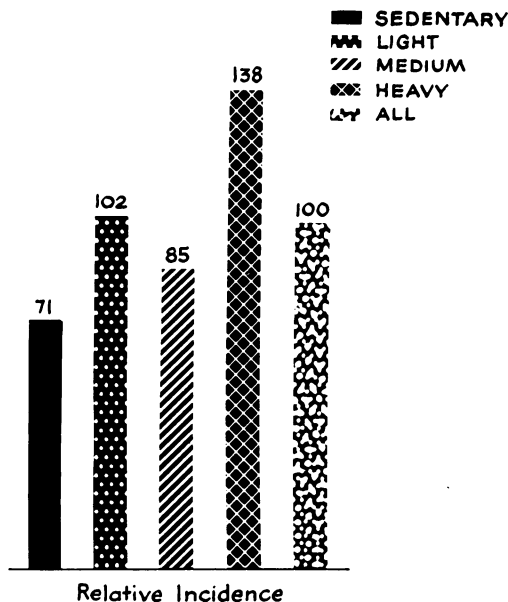


Fig. 31. Chapman, J. M., Goerke, L. S., Dixon, W., Loveland, D. B. and Phillips, E.³⁷ Unlike the data of Figs. 28 and 29, these are relative incidence rates for the subgroups stratified by level of physical activity. The entire group is set arbitrarily at 100. Note the highest relative rate, 138, in the heavy workers, the lowest, 71, in the sedentary workers. Here again it is evident that among middle-aged American Males lower-income, blue-collar, more active workers do not have lower coronary heart disease incidence rates, compared with higher-income, white-collar less active workers.

may be suggested that these findings are consistent with the concept that diet plays a key (although not exclusive) role in the causation of atherosclerotic disease.

The epidemiologic analysis of Chicago mortality data also revealed that coronary heart disease death rates were high for middle-aged males of both Negro and white races of all occupation-income groups (Figs. 21, 22). The toll from atherosclerotic disease was at least as great in the poorer strata as in the more well-to-do. Other data, particularly from northern cities, corroborate the basic finding that coronary heart disease is widely prevalent in middle-aged American males of most population subgroups (Figs. 27-31)^{35-37, 49*}.

* Data from Norway indicate that a similar situation prevails for that country. The data concerning Great Britain are more complex. There, a social class difference in arteriosclerotic heart disease mortality has been observed for several decades, a finding complicated by the fact that an opposite social class distribution has been recorded for so-called degenerative heart disease. Conspicuous in these data is the trend for coronary disease death rate to rise

ECONOMIC INFLUENCES

These findings forcefully pose one question in particular: Why is it that the poor in countries like Egypt, Guatemala, Japan, India, Italy, Spain have low coronary disease death rates, whereas Americans on the lower rungs of the U. S. economic ladder have rates at least as high as more well-to-do groups? Are these apparently contradictory trends inconsistent with the basic thesis of a key relationship between diet and atherosclerosis? By no means, since important differences exist in the dietary patterns of lower income Americans and the poorer classes of all the

over the recent decades, while the social class differential narrowed. It would seem that Great Britain may be experiencing an increase in the incidence of this disease, embracing all sectors of its population. Despite this increase, death rates in Great Britain were in 1950-1954 still considerably below those for age-sex-race-matched groups in the United States. Nonetheless, in Great Britain, as in Norway and the United States, this disease has apparently become widespread in the middle-aged male population of all social classes.

FIG. 32

Inadequacies in American Diets

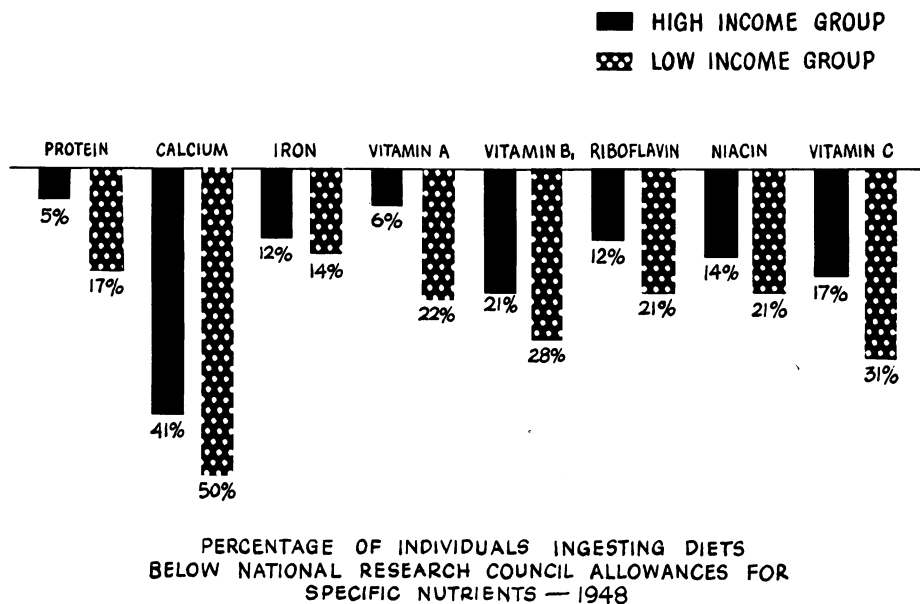


Fig. 32. Coons, C. M.⁴⁰; cf. also ref. 38; cf. legends of Figs. 27, 26, 30. The high and low income groups had 1947 annual family incomes in the range \$1,000-1,999 and \$4,000-4,999 respectively. Note that a higher per cent of the low income than the high income group had diets which failed to meet National Research Council recommendations with respect to specific essential nutrients. More recent data are contained in refs. 39 and 50. Among the many facts emerging from the latest 1955 comprehensive household surveys of the U. S. Department of Agriculture, the following may be briefly cited: For the urban families in the income range \$2,000-\$2,999 and \$6,000-\$7,999, only 18% and 14% respectively had food available for consumption totaling less than 3000 calories/person/day. Only 8% and 3% respectively had less than 36% of total calories from fats; 72% and 80% respectively had more than 40% of calories from fats. For these two income levels, the percent of families consuming inadequate amounts (by National Research Council Standards) of essential nutrients in 1955 were: Protein (less than 75gms/person/day)—13% and 4% respectively; calcium (0.8 gm/person/day)—42% and 22%; iron (12 mg/person/day)—14% and 9%; Vitamin A (5,000 I.U./person/day)—18% and 11%; thiamine (1.5 mg/person/day)—22% and 19%; riboflavin (1.9mg/person/day)—30% and 14%; niacin (15 mg/person/day)—11% and 5%; ascorbic acid (75mg/person/day)—30% and 16%. Generally similar data were obtained for urban, rural nonfarm and rural families in different sections of the country. No analysis by race, color or sex was presented.⁵⁰

It is apparent that the pattern of dietary imbalance described in the text continued to prevail in wide strata of the U. S. population throughout the country during the years of economic prosperity in the 1950's.

aforementioned countries.

In contrast to the populations *en masse* of these other countries, the economically less privileged in the United States have for the most part been consuming large amounts of meat, milk, eggs, fats and oils, white flour products, refined sugar, salt (Figs. 26, 32)^{38-40, 50}. This seems to be generally

true with limited exceptions (cf. rural southern Negroes, [Fig. 26]) at least since the end of the depression in about 1940. The intakes of total calories and empty calories, saturated fats (animal and vegetable), cholesterol among most lower income Americans are not very different from those of their upper income compatriots. More-

FIG. 33
Distribution of Cholesterol levels in clinically healthy American Males, age 40-59

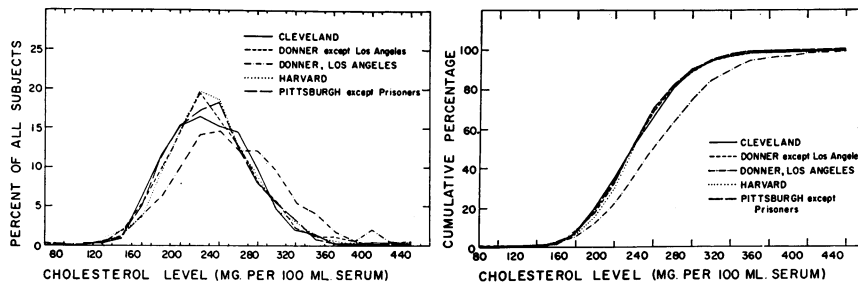


Fig. 33. Lewis, L. A., et. al.⁴¹. Note the tendency for serum cholesterol levels to rise with age; cf. Figs. 1, 3, 6. The subjects were almost exclusively white Americans. Note also the sex difference in serum cholesterol levels, with females exhibiting lower values than males in the age range—25-45 years. The possible role of dietary and hormonal factors in effecting this sex difference is discussed in the text and in refs. 1, 3, 4, 33 also cf. these sources for a discussion of the problem. of the possible relationship of this sex differential in cholesterolemia to the sex differential in occurrence rates of atherosclerotic coronary disease (cf. Figs. 1, 8, 10, 14, 19, 24, 25). Note that only a minority of Americans, males or females only about 20% have serum cholesterol levels below 200 mg. %; about 40% have values above 240 mgr. %; cf. data on groups from the populations of other countries, particularly the economically less developed nations—Figs. 1-4, 7, 11, 36, 39.

over, while lower income Americans consume diets virtually as "rich" in the foregoing constituents as those of their upper income fellow citizens, a larger per cent of them tend to ingest sub-optimal

amounts of certain essential nutrients (vitamins, minerals, proteins, essential amino acids) (Fig. 32)^{38, 40, 50}. Rather than eating "too well" (as has been alleged), they tend to consume diets that are

FIG. 34 Serum Cholesterol levels of clinically healthy American males, age 40-59, of different social classes in different sections of the country

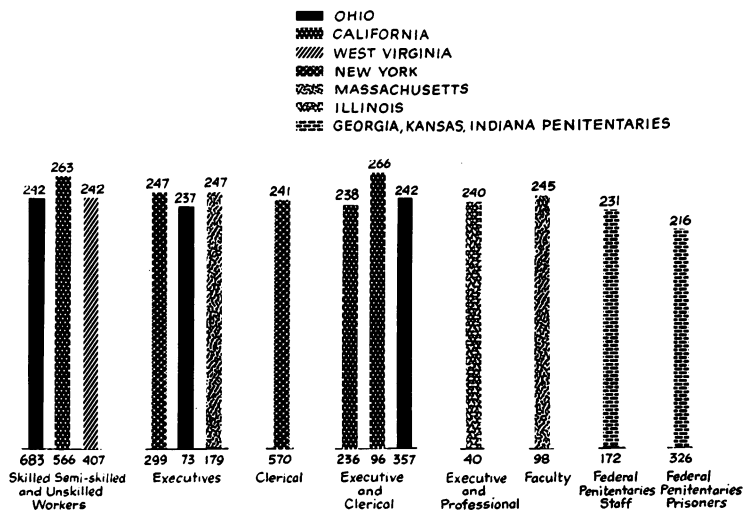


Fig. 34 Lewis, L. A., et. al.⁴¹ The subjects are almost exclusively white. Note the similar high mean serum cholesterol levels in different groups of middle-aged American males, irrespective of occupation and geographic region. The single exception is the group of Federal penitentiary prisoners with a somewhat lower mean value. Dietary data on this group would be of considerable interest. The particularly high values for Californians also remain to be accounted for.

FIG. 35 Relative mortality among insured persons reporting two or more cases of early Cardiovascular-Renal diseases in their families

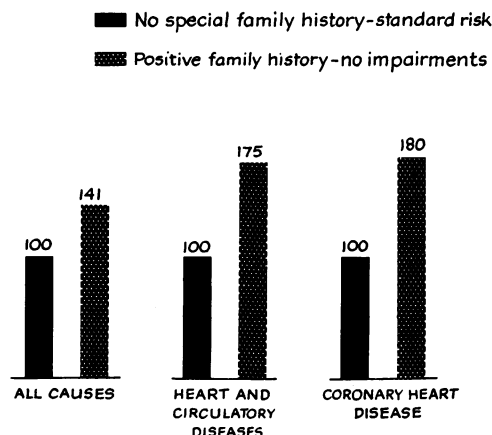


Fig. 35. Lew, E. A.³⁵ Positive family history represents two or more occurrences of cardiovascular-renal disease in the middle-aged members of the persons immediate family. These data indicate that familial factors, possibly hereditary and genetic, influence the occurrence of atherosclerotic disease in individuals from population groups ingesting an habitual diet high in calories-lipids-cholesterol.

markedly unbalanced, unique combinations of over-nutrition and undernutrition (malnutrition, in the literal meaning of the word).

This unique dietary aberration may be particularly pernicious in its potential for provoking the so-called degenerative cardiovascular-renal diseases, particularly atherosclerotic coronary heart disease. The widespread prevalence of this nutritional derangement among lower income Americans may be a key factor making for extensive coronary heart disease morbidity and mortality among them.

The validity of this imbalance hypothesis needs to be tested in future investigations. Irrespective of the outcome of such studies, however, the evidence is substantial that most social strata in our country, irrespective of socioeconomic rank, ingest an habitual diet that is potentially atherogenic. Therefore, the finding that coronary heart disease is prevalent among most sections of the American middle-aged population does not contradict, but rather lends additional strong support to the theory of a decisive interrelationship between life span pattern of diet and atherogenesis.

SERUM CHOLESTEROL LEVELS

This concept is further reinforced by abundant data indicating that serum cholesterol levels tend to be high compared with values observed in the peo-

ple of many other countries in virtually all strata of the middle-aged United States population (Figs. 33, 34, cf. Figs. 1-4, 7, 11, 36, 39, 41, 42).⁴¹ Based on the extensive international epidemiologic data indicating a threefold correlation among habitual dietary patterns, serum cholesterol levels, and occurrence rates of coronary heart disease, these findings in representative strata of the United States population are certainly the expected ones. It was to be anticipated that most groups of middle-aged American males, since they ingest life-span diets high in total calories, total fats, saturated fats, cholesterol, would exhibit high mean values for serum cholesterol concentration and high coronary heart disease incidence rates.

It is essential that research in this field clearly confront the theoretical problem posed by these data. What is responsible for the distribution of serum cholesterol levels in the middle-aged American male population, and particularly the high mean values, compared with those of other peoples? Extensive data support the concept that this phenomenon is critically a byproduct of habitual, life span dietary patterns. Virtually no evidence to the contrary, convincing or otherwise, has been presented. Nor have any significant data been advanced to support other hypotheses accounting for these patterns of cholesterolemia and the asso-

FIG. 36

Serum Cholesterol in Light and Heavy Workers--Malmö, Sweden and Naples, Italy

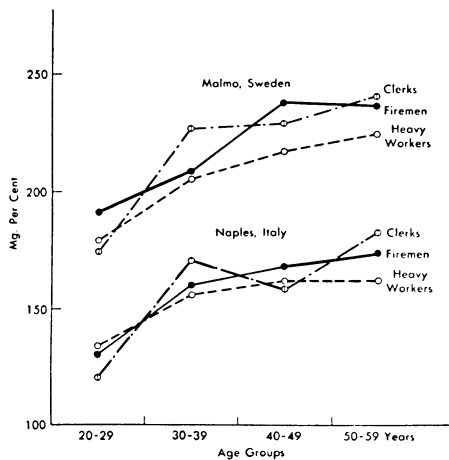


Fig. 36. Björck, G.⁴⁰ Note the similar serum cholesterol concentrations in the nationals of a given country, irrespective of occupation and physical activity of a habitual work. Contrast the levels of cholesterolemia in like occupation groups from Malmö, Sweden and Naples, Italy. Cf. Fig. 34.

FIG. 38

Distribution of excess deaths, by disease among men with a history of regular cigarette smoking

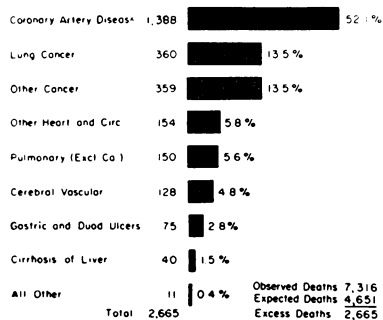


Fig. 38. Hammond, E. C. and Horn, D.⁴²⁻⁴³ A total of 187,783 men aged 50-69 in 1952 were followed, with almost 12,000 deaths occurring in 5 years. The age-adjusted death rate for all causes for the regular cigarette smoker was 68% higher than that for the group who never smoked, with a total of 2,665 excess deaths in the smokers. Of these 2,665 excess deaths, 1,388—52.1%—were due to coronary artery disease. The coronary disease mortality rate of these regular cigarette smokers was 70% higher than that of those who never smoked. These epidemiologic data suggest that smoking increases the risk of coronary disease in middle-aged males habitually ingesting a diet high in total calories, total fats, saturated fats, cholesterol.

FIG. 37

Incidence of Coronary disease in active vs. inactive workers, Great Britain

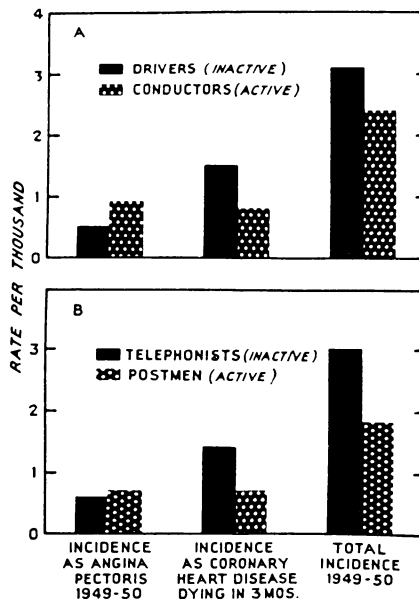


Fig. 37. Morris, J. N., Heady, J. H., Raffle, P. H. B., Roberts, C. G. and Parks, J. W.⁴¹ These data suggest that the incidence of coronary disease (nonfatal and fatal) is higher in inactive than active workers in Great Britain, i.e., physical activity of habitual work may tend to lower coronary disease incidence in a population ingesting an habitual diet moderately high in total calories, total fats, saturated fats, cholesterol. Cf. Figs. 21, 27, 29, 31.

ciated patterns of coronary disease incidence.

In making these observations, it is essential to reemphasize that this concept attributes a *key*, but not exclusive, role to diet. It in no way implies that atherosclerosis is purely and simply a dietary disease. Such a viewpoint is definitely at variance with well established facts, and therefore quite untenable. Thus, the fact that many individuals, eating a typical American diet for decades, reach old age without clinical evidence of atherosclerotic disease, this fact alone refutes any attempt to imply a one-to-one cause and effect relationship between diet and disease. Further, the marked sex differential, the high incidence of coronary disease in middle-aged American males in contrast to females, almost certainly contravenes any pure and simple dietary concept. Similarly, the greater in-

FIG. 39

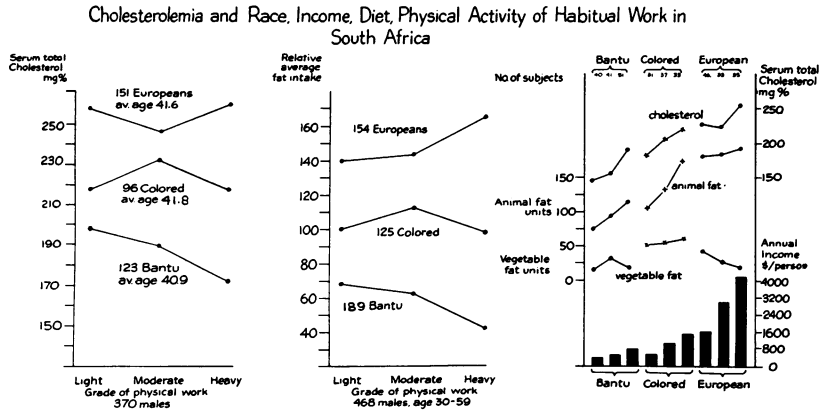


Fig. 39. Brock, J. F. and Bronte-Stewart, B.⁴⁵; Keys, A., et al.⁴⁶. Relative average fat intake (2nd graph) is the ratio x 100) of the fat intake of the given group to the mean fat intake for all 9 groups. Data on fat intake were obtained by semiquantitative weekly dietary surveys, which assumed that each individual consumed an "average" helping. But this method, fat intakes were apparently estimated in grams per person per day and apparently converted into fat units (3rd graph) by dividing by 3.15. It was estimated that the Bantu consumed 17% of total calories in the form of fats; the coloured, 25% and the Europeans, 35%. The greater total fat with greater incomes were due to greater intakes of animal (chiefly saturated) fat, not vegetable fat. Note the correlation between cholesterolemia and race, income, total fat intake, animal fat intake. Note that for any given ethnic group, cholesterolemia correlates with income, total fat intake, animal fat intake—i.e. race per se is apparently not a decisive influence. Note the lack of correlation between cholesterolemia and grade of physical work.

The Bantu group is a predominantly Negro group modified historically by Hamitic (Southern Arabian) influence. The Bantu migrated south from central equatorial Africa. The term Bantu is mainly linguistic in significance. The Cape Colored group is a mixture of the original Hottentot inhabitants of southern Africa, Indonesians, Malayans and whites. The European group is made up of white of European stock, born and reared in the Union of South Africa⁴⁵.

FIG. 40 Life Insurance Co data on effects of Overweight and of weight reduction on Mortality experience

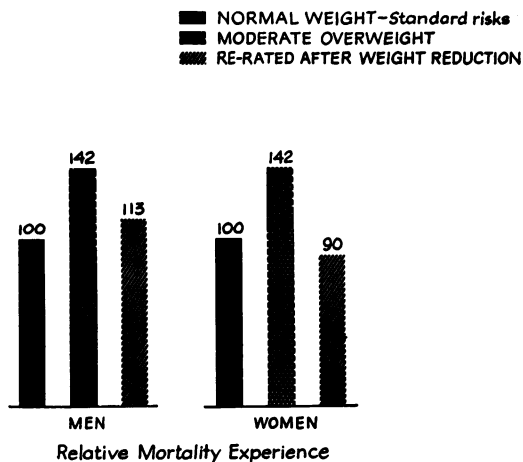


Fig. 40. Shepard, W. P. and Marks, H. H.⁴⁷ Note that relative mortality is not grossly excessive in persons who were originally overweight, were reduced and then re-rated for life insurance after weight loss. In contrast, note the 42% increase in mortality rate in the uncorrected overweight group. Apparently successful treatment of obesity effectively lowers the mortality rate to or toward normal levels.

FIG. 41 EFFECTS OF OBESITY, HYPERCHOLESTEROLEMIA AND HYPERTENSION ON FOUR-YEAR INCIDENCE OF ARTERIOSCLEROTIC HEART DISEASE IN MEN AGED 45-62

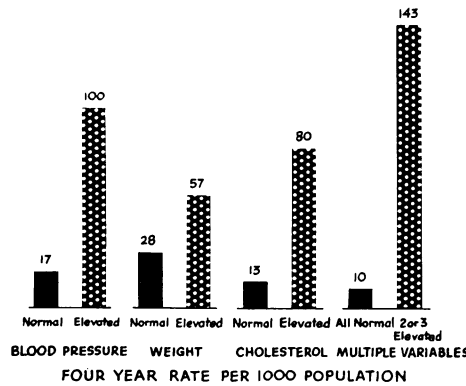


Fig. 41. Dawber, T. R., Moore, F. E. and Mann, G. V.³⁶ Normal blood pressure—consistently below 140/90; elevated blood pressure—consistently 160 systolic or over, or 100 diastolic or over. Normal weight—relative weight under 100; elevated weight—relative weight 113 or over. Normal cholesterol—under 225 mg %; high cholesterol—260 mg % or above.

idence of atherosclerotic disease in persons with diabetes, nephrosis, xanthomatosis, hypothyroidism and hypertension contradicts any exclusive dietary concept. Actually, no serious scientist is making any such futile attempt to “fit” all the phenomena of atherosclerotic disease into the confines of a pure and simple dietary “explanation.”

Obviously, as extensive clinical and experimental data demonstrate, the nature of the organism plays an important role in determining the effects of life-span ingestion of a potentially atherogenic diet. Hence, different individuals ingesting similar habitual diets exhibit different

levels of cholesterolemia and different patterns of atherogenesis. In these individuals, many factors may interact significantly with diet—genetics and heredity, metabolism and endocrinology, clotting mechanisms, previous medical history, psychological make-up and physical condition (fatigue, stress, tension, frustration, etc.), environmental factors, (smoking, habitual physical activity of work, urbanization, etc.) (Figs. 35, 38)^{35, 42, 43}. Antecedent allergic or infectious disease, for example—possibly by damaging vessels and setting up sites of predilection for atherogenesis—may be of great importance in some cases. Hypertension, hypo-

FIG. 42 PERCENT OF MALES AGE 45-62 WITH HYPERCHOLESTEROLEMIA, OBESITY, HYPERTENSION -- FRAMINGHAM STUDY

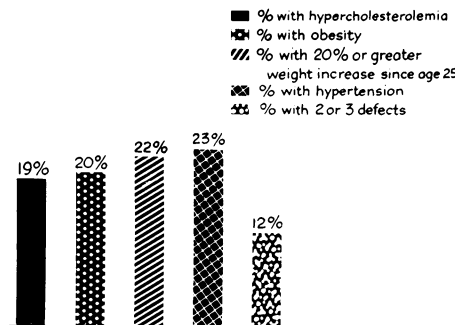


Fig. 42. Dawber, T. R., Moore, F. E. and Mann, G. V.³⁶ Cf. legend of Fig. 41. It is clear that a sizable per cent of middle-aged males have one or more of the cited defects.

thyroidism, renal dysfunction, diabetes, xanthomatosis certainly tend to potentiate atherogenesis. The evidence is considerable that estrogenic secretion in women has an opposite effect.

PSYCHOLOGICAL INFLUENCES

In recent years, great interest has been aroused concerning the possible influences of psychological stress and physical activity on the development of atherosclerotic disease, particularly coronary heart disease. Until recently, virtually no reliable evidence was available concerning the first of these, an understandable fact in view of the complex and difficult problems of objective mensuration. Within the last year, a few reports were presented on the effects of various types of stress on cholesterolemia, but not on coronary disease occurrence rates, in subjects ingesting usual American diets. Further information on this important problem area may be anticipated in the years immediately ahead.

PHYSICAL ACTIVITY

Epidemiologic data have been reported from Great Britain concerning the influence of physical activity. Comparisons were made of subgroups within relatively homogeneous socioeconomic strata of the British population. These indicated that the incidence of coronary heart disease tended to be lower in the subgroups habitually engaged in greater physical activity of work. Data along these lines were obtained in comparisons of sedentary bus drivers vs. active postmen, etc. (Fig. 37)⁴⁴. However, further studies by the same British group tended to cast doubt upon the significance of some of these observations. Moreover, all strata of the population in Britain, as in the United States and Norway, irrespective of socioeconomic status and habitual physical activity of work, apparently manifest high coronary heart disease incidence rates.

Correspondingly, most recent observations indicate that epidemiologic patterns of cholesterolemia and atherosclerotic disease were more decisively influenced by diet than by level of physical activity at work.* Thus, in South African Bantu with an habitual diet low in total fats, saturated fats, cholesterol, the level of cholesterolemia and the incidence of coronary disease were found to be

low in both sedentary and active workers (Fig. 39)^{45,48}. Similar observations were also reported from Japan and Italy. Contrariwise, in Sweden and Finland, with habitual diets high in total calories, total fats, saturated fats, cholesterol, level of cholesterolemia and incidence of coronary disease were observed to be high in both sedentary and active workers (Fig. 7, 39)⁴⁶. Similarly, recent studies in the United States consistently revealed high levels of cholesterolemia, and a high prevalence and incidence of coronary disease in virtually all sectors of the middle-aged male labor force, irrespective of nationality, socioeconomic status, income, occupation, physical activity of work, urban or rural residency (Figs. 19-23, 27-29, 31, 33, 34).

DIET DECISIVE FACTOR

These data impressively support the concept that diet is the decisive variable determining the pattern of atherosclerotic disease in a *population*. Nonetheless, research on the interrelationships among nutrition, physical activity, atherosclerosis and atherosclerotic disease, particularly in countries where large segments of the population ingest high-calorie, high-fat high-cholesterol diets and lead a relatively sedentary life, is still limited. Recent reports indicate that physical activity may prevent an increase in serum cholesterol, under circumstances when increased fat is ingested to meet greater caloric need. It has also been suggested that continued physical activity through middle-age may be a possible factor in the prevention of atherosclerotic disease. Further work is therefore certainly indicated on the effects of energy expenditure and large muscle activity in persons and groups ingesting potentially atherogenic diets.

With respect to the individual, therefore, the relationship between diet and other factors may be formulated as follows, based on our present knowledge: In the individual member of a population group habitually ingesting a potentially atherogenic diet, the development of morphologic atherosclerosis and atherosclerotic disease is influenced by multiple factors. There is a complex interplay between diet and other factors which operate to accelerate or to retard atherogenesis. Thus, it is not a matter of one factor to the exclusion of others; it is not a matter of either-or. But, among these multiple factors interacting to influ-

* The data available from India seem to be exceptional in this regard cf. Fig. 4.

ence atherogenesis, *diet is a decisive factor*[†]. For, without the habitual ingestion of a potentially atherogenic diet, clinical atherosclerotic disease would be rare among the middle-aged members of any population, irrespective of the operation of their potentially offensive factors.

These basic conclusions have been designated the nutritional-metabolic cholesterol-lipid-lipoprotein theory of atherogenesis⁴. They have received a significant further verification in the recently published findings of the Framingham, Albany and Los Angeles epidemiologic studies. In general, the results of all these investigations point in the same direction. When sizable groups of middle-aged American males, originally free of clinical coronary heart disease, were followed prospectively, the risk of developing this disease was definitely found to be proportional to levels of body weight, blood pressure* and cholesterolemia (Fig. 4)³⁶. Thus, from the Framingham report, in the population-at-risk normal with respect to all three of these variables (originally free of clinical coronary heart

disease), the four year incidence rate was only 10 per thousand. This is one-fourth the rate for American middle-aged males in general (40/1,000/4 years). In contrast, in the population-at-risk with two or three of these variables abnormally elevated, the four year incidence rate was 143 per thousand, a more than ten-fold increase in risk, compared with the Framingham normals.

PRACTICAL APPLICATIONS

These data are not only of great theoretical and research significance. They also have profound implications for the practice of medicine.

Thus, they pose critical questions concerning the approach of medicine to the prophylaxis of coronary disease. In particular, they pose the question: What can and should the medical profession do for the many middle-aged males who, while not yet victimized by clinical coronary heart disease, run an inordinately high risk of developing it? These are the individuals with two or more derangements, obesity, hypercholesterolemia, hypertension, renal damage, diabetes and/or a poor family history.

Before proceeding to discuss this problem, it is advisable to clarify a possible misconception. It has been stated that such predictions concerning the development of clinical coronary heart disease in individuals cannot be made based on determinations of their serum cholesterol, weight, blood pressure, etc. It is essential that this matter be understood with utmost clarity and precision.

It is perfectly correct that no one can definitively predict whether a given person will or will not develop clinical coronary heart disease in the next year or two. However, long-term prognostic predictions of the actuarial type, predictions of risk, can be made. Inevitably, a small per cent of these actuarial predictions of risk will be false positives and false negatives, respectively. However, these "errors" are of minor importance, reckoned against the achievement, i.e. the ability to identify high-risk individuals with the consequent possibility of successful prophylactic intervention.

Based on recent investigations, it is becoming quite possible to estimate the scope of this problem of high-risk individuals in specific quantitative terms. Based on the data of the Framingham Heart Study (Fig. 4)³⁶, for example, it can be roughly

† Thus, it would seem valid to designate a certain type of habitual diet as virtually a *sine qua non* for atherosclerosis and atherosclerotic disease, even as the tubercle bacillus is a *sine qua non* for tuberculosis although patently a multiplicity of host and environmental factors enter into complex interrelationship with the decisive causative factor to influence the developmental patterns of the disease.

* These data re-emphasize the important role of hypertensive disease as a factor in the development of clinical coronary disease during middle-age, particularly in populations with the prerequisite cholesterol-lipid-lipoprotein metabolic derangements. Once again, therefore, the conclusion must be reached that a multiplicity of factors (exogenous and endogenous) operate to produce coronary disease, and that the critically important nutritional factor has no simple one-to-one interrelationship with atherosclerosis and atherosclerotic disease.

At the same time, it is also essential to recognize that the incidence of coronary disease was by no means insignificant in the nonhypertensive middle-aged American males followed in these prospective studies. The etiology of coronary disease in normotensive persons therefore remains a key problem.

Similarly with respect to obesity: Thus, while the overweight group in Framingham had a coronary disease rate approximately twice that of the normal weight group, the rate in the latter (28/1,000/4 years) was itself a high one. In this regard, available data on obesity and cholesterolemia are worthy of attention. In at least two studies, a positive correlation has been demonstrated between serum cholesterol levels and body weight, but this is a *low order* correlation. Put somewhat differently, the middle-aged American population ingesting its habitual diet tends generally to be at least slightly obese and to have high values for serum cholesterol, with or without concomitant gross obesity.

When this high-fat, high-cholesterol diet is ingested in excess, with resultant development of gross obesity, serum cholesterol levels tend to be slightly but markedly higher. Given this nutritional-metabolic situation, it is to be expected that incidence of coronary disease would be substantial in non-grossly-overweight middle-aged American males, and even greater (but not several-fold greater) in the obese.

Life insurance data indicate that healthy thin persons have a significantly lower risk of coronary disease. No systematic serum lipid data are available on such persons.

In brief, the non-hypertensive, non-overweight middle-aged American males, better-off though they may be, nonetheless still have an insignificant incidence of elevated serum cholesterol levels and coronary disease. The relationship of life-span diet to these phenomena cannot be gainsaid.

estimated that a low risk middle-aged male, normal in weight, blood pressure and serum cholesterol, has one chance in 20 of developing clinical coronary heart disease during the 45-64 age period. In contrast, a middle-aged male with two or three abnormalities (obesity, hypercholesterolemia, hypertension) stands almost one chance in two. These are markedly different risks.

About one of every eight middle-aged American males falls into this high-risk category (Fig. 42)³⁶. When it is further recognized that 20-30 per cent of first attacks of myocardial infarction are acutely fatal, the serious nature of the high-risk situation is even more starkly apparent. Is it not extremely valuable for both patients and physicians to be able to identify these high-risk individuals, in order to attempt to do something for them prophylactically?

From the foregoing, the critical question emerges with utmost clarity: In bad risk subjects, can risk be prophylactically reduced several-fold by correcting defects? This is perhaps the most compelling practical problem posed as a result of the research achievements of the last ten years.

It is known that these defects are amenable to correction, in whole or part, by relatively simple medical—hygienic means, the decisive one among them being dietotherapy. It is *not yet known* definitively whether coronary heart disease can be significantly lowered thereby, although the findings of the life insurance companies on the positive results of correcting obesity are highly suggestive in this regard (Fig. 40)⁴⁷. Five or ten years of additional work still lie ahead before an unequivocal answer will be definitively in hand.

Actually, the element of controversy in this discussion has on occasion been artificially inflated, particularly in the lay press. There is widespread agreement among investigators on the individualized prescription of reasonable, moderate, safe, palatable dietary correction in high-risk patients, particularly those with obesity, hypercholesterolemia, hypertension, renal damage, diabetes, poor family history, etc.

It is of course obvious that particularly during this transition phase of our knowledge, recommendations for prophylaxis should be virtually without danger of any type—biological, sociological or psychological. For this reason and

because the accumulated evidence strongly suggests that the best results are likely to be achieved with *dietary* prophylaxis (coupled with a good general hygienic regimen, including regular physical exercise), our general recommendations focus on this approach.

Finally, it is worth emphasizing that this review on epidemiology as an investigative method for the study of human atherosclerosis has concluded with a discussion of the status of *applied* epidemiology in this field. For that is precisely what the foregoing discussion of prophylaxis is, a discussion of the implications of recent investigative findings for the day-to-day practice of modern medicine. This is as it should be, particularly since the last decade has witnessed highly significant research advances, epidemiologic, clinical-pathologic and animal-experimental, toward a practical solution, based on scientific knowledge, of the atherosclerosis problem.

QUESTIONS AND ANSWERS

Question: In view of the significant epidemiological data indicating a relation between dietary fat and atherosclerosis, what is known about atherosclerosis and coronary disease in vegetarians?

Answer: In regard to vegetarians there is at least one published study, dealing only with lipid levels, not with patterns of coronary disease (Hardinge, M.G. and Stare, F.J., *J. Clin. Nutr.*, 2: 83, 1954). A comparison was made of a group of males eating usual American diets; a group of "lacto-ovo-vegetarians," i.e. vegetarians consuming eggs and dairy products; and a group of true vegetarians, eating no foods of animal origin. Although the intake of total calories and total fats of the true vegetarians was almost as high as that of the omnivores (130 vs. 176 gms./person/day), the plasma cholesterol levels were 80 mgms. per cent lower (206 vs. 288 mg. per cent). As to coronary disease in these vegetarians, information is not available. However, another study is in progress on a religious order, Trappist Monks, who adhere to a vegetarian diet. Long term follow-up will eventually yield a reliable estimate concerning coronary disease among them. Finally, extensive clinical data are now available indicating that elevated plasma cholesterol levels fall when subjects transfer from omnivorous to herbivorous diets.

Question: Experimental atherosclerosis has been produced, but these animals don't get spontaneous myocardial infarctions—Why?

Answer: This is a very critical question. The equivalent situation in man is being widely discussed now. Attention is being called to the unequivocal fact that millions of people have atherosclerosis, even extensive athero-

sclerosis, without ever developing clinical manifestations. It is essential to distinguish between the basic pathological process and its so-called complications, i.e. the development of hemorrhage into plaques, ulceration, thrombosis, occlusion with resultant infarction and development of clinical signs and symptoms of disease. Time does not permit a discussion of this complex problem of inter-related processes—cf. Figs. 2-4.

With respect to the particular problem of spontaneous myocardial infarction in experimental animals, the apparent inability to produce infarction in animals with atherosclerosis, it is in order to state forthrightly that a full answer to this "Why" is not yet available. However, a very important development has taken place recently. For the first time in the history of experimental atherosclerosis research, myocardial infarction has been consistently produced in a high per cent of animals, primarily by dietary means. Dr. W. S. Hartroft and his colleagues in St. Louis fed rats a diet high in saturated fat, cholesterol and cholate, together with thiouracil to depress thyroid function. A significant per cent of their animals succumbed to coronary thrombosis and myocardial infarction. Our group has recently induced aortic atherosclerotic plaques complicated by intimal hemorrhage, ulceration and dissection—again chiefly by dietary means. This basic problem, therefore, seems on the way to solution.

Question: What is meant by empty calories?

Answer: Empty calories are calories from highly processed, refined foods which have a high energy content but a low content of essential nutrients, i.e. a low content of essential amino acids, vitamins, minerals, essential fatty acids. Empty calorie foods include refined sugar in all forms, cooking and table fats, unenriched white flour products, spirits.

Question: What could be wrong with a large intake of empty calories?

Answer: For one thing, a diet high in empty calories is a low bulk diet. Twenty or thirty years ago medicine talked a good deal about bulk; it is not stylish now-a-days to give attention to bulk in the diet, but there is reason to believe that bulk may be nutritionally important.

Second of all, there is sound experimental evidence to support the concept that need for essential nutrients is a function among other things of total caloric intake. Thus, a level of intake of methionine or vitamins B₁₂ or B₆ metabolically adequate for a person consuming 2400 calories may become inadequate if caloric intake is raised to 3400. In other words, the body's needs for essential nutrients are not arbitrary and fixed. Rather they are related to many things—heredity, work, infections, diet. The more empty calories consumed, the greater the need for essential nutrients to "cover" metabolically.

Finally, a high intake of empty calorie foods tends to occur at the expense of or as a substitute for, foods high in essential nutrients. It is noteworthy that no "primitive" diet, no diet of natural foods (i.e. unprocessed foods) can contain a lot of empty calories. It must give a high

ratio of nutrients to calories. Just consider whole grain vs. white flour, meat vs. lard, fruit vs. candy; compare calories and nutrients in each. Natural foods invariably yield less calories and more nutrients than the refined foods. And the more refined foods eaten, the less natural foods consumed.

That is why millions of Americans have a high caloric intake, and yet an inadequate intake of essential nutrients. That is why, although Americans generally eat more meat than most other peoples in the world, the ratio of calories from protein to total calories is not high. Rather it is lower than in a number of poorer countries, being 12 to 14 per cent of total calories.

Those are some of the reasons to be concerned with the high intake of empty calorie foods in the United States today.

Question: How does one account for the different degrees of atherosclerosis in different arteries in the same patient?

Answer: This question poses the problem of localization of lesions, and the different factors influencing atherogenesis in different vascular beds. Earlier workers were much preoccupied with these matters, but they have received scant attention in the last decade or two. A few recent reports support the concept that there generally is a close parallelism but not identity in the severity of atherosclerosis in different vessels.

There is apparently no parallelism between severity of atherosclerosis and other forms of arteriosclerosis, e.g. medial calcinosis, which is the common lesion palpated in a sclerotic radial artery, for example. That type of arteriosclerosis apparently has no correlation with atherosclerosis. But atherosclerosis—the usual lesion at the aortic bifurcation, in the coronary, renal and cerebral arteries—apparently exhibits a tendency to parallel degrees of severity in different vessels of the same person. At least, this is what some of the newer data suggest. Yet there are other data indicating a lack of parallelism between aorta and coronary atherosclerosis, particularly in the female. This particular problem, therefore, needs to be pursued further.

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CHOLESTEROL AND DIET

The cholesterol level in the blood can be kept down within reasonable limits by diets which still contain lean meat, dairy products, eggs and fats if adequate amounts of certain vegetable oils are also included.

A moderate fat intake is desirable and that there are significant differences between the effects of various types of fat on the serum cholesterol levels. In fact, by proper choice of the dietary fat, lower cholesterol levels may be achieved on fat-containing diets than on fat-free diets, even when as much as 70 per cent of the total calories is derived from fat. Certain unsaturated vegetable oils actually tend to lower the blood cholesterol level. Because corn oil seems to be more effective than all other vegetable oils in lowering the cholesterol level, it has become the standard of comparison in most research that is still being exhaustively pursued. Excess calories, regardless of the type of food, seem to increase the cholesterol levels.

DR. DOROTHY RATHMAN, at the 22nd Annual Meeting of the Industrial Hygiene Foundation, October 1957.