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86th Congress
1st Session

COMMITTEE PRINT

PATTERNS OF INCIDENCE OF CERTAIN DISEASES THROUGHOUT THE WORLD

OPPORTUNITIES FOR RESEARCH THROUGH EPIDEMIOLOGY

PREPARED FOR THE

COMMITTEE ON GOVERNMENT OPERATIONS
UNITED STATES SENATE

AND ITS

SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL ORGANIZATIONS

(PURSUANT TO S. RES. 347, 85TH CONGRESS, AND S. RES. 42, 86TH CONGRESS)

NOVEMBER 9, 1959

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LETTER OF TRANSMITTAL

U.S. SENATE,
November 9, 1959.

Hon. JOHN L. MCCLELLAN,
Chairman, Committee on Government Operations,
U.S. Senate, Washington, D.C.

MY DEAR MR. CHAIRMAN: For your information, there is submitted a publication entitled "Patterns of Incidence of Certain Diseases Throughout the World—Opportunities for Research Through Epidemiology."

The purpose of this publication is to provide helpful background information to the subcommittee in its international health study. This study was originally authorized under Senate Resolution 347, 85th Congress, as supplemented by Senate Resolution 42, 86th Congress, and Senate Resolution 176, 86th Congress.

The original resolution provided for a complete study—

** * * of any and all matters pertaining to international health research, rehabilitation and assistance programs * * * and * * * the coordination of programs related to international health.*

This is the sixth publication in this series. The five previous prints are listed in the page which follows.

Additional publications are in process in our review.

With all good wishes, I am,

Sincerely,

HUBERT H. HUMPHREY,
Chairman, Subcommittee on Reorganization and International Organizations.

PREVIOUS PUBLICATIONS IN THIS SERIES

Committee Print No. 1 (S. Rept. 160, 86th Cong.) was entitled "International Medical Research—A Compilation of Background Materials" (117 pages). It set forth highlights of international research contributions in most of the major fields of disease, in addition to fulfilling other background purposes.

Committee Print No. 2 was entitled "Statutory Authority for Medical and Other Health-Related Research in the U.S. Government—The Basis for International Cooperation" (66 pages). It contained the texts of the legal authority for medical research efforts by diverse agencies of the U.S. Government.

Committee Print No. 3 (S. Rept. 161, 86th Cong.) was entitled "The Status of World Health—In Outline Text and Chart" (81 pages.). Within it were presented charts on the incidence of certain major diseases throughout the world.

Committee Print No. 4 was entitled "The United States and the World Health Organization—Teamwork for Mankind's Well-Being" (145 pages). It represented a personal report of the chairman of the subcommittee on the subject of WHO, based upon his conferences with its officials and other authorities in Europe and on subsequent review.

Committee Print No. 5 (S. Rept. 1009, 86th Cong.) was entitled "Cancer—A Worldwide Menace; Some Facts and Figures on Its Incidence in the United States and Abroad" (40 pages). It presented text and charts on the patterns of occurrence of malignant neoplasms in different countries of the world.

FOREWORD

(By Hon. Hubert H. Humphrey, chairman, Subcommittee on Reorganization and International Organizations)

This publication concerns one of the most useful keys for the unlocking of riddles of disease. The key is the science of epidemiology.

The meaning of epidemiology is presented in part I of this committee print. Unfortunately, it is a term not generally familiar to laymen. Researchers all over the world, however, recognize this science as indispensable to the advancement of biomedical knowledge.

They know that its record of accomplishment confirms that this science of "mass phenomena of diseases and human defects" is one of the most important weapons of discovery in the worldwide fight against disease and disability.

SOLVING DISEASE—AN ANALOGY TO A DETECTIVE MYSTERY

For understanding by the layman of the role of this science, an analogy may be invoked. The process of solving the mysteries of a disease may be likened somewhat to the solution of a detective mystery.

A killer or a crippler exists (in this instance, a baffling disease).

The specific disease may be any one of the many maladies which are mentioned in these pages—cancer, heart disease, diabetes, arthritis, peptic ulcer, mental illness, neurological disorders, etc.

Each of these diseases takes its toll not simply here in the United States but throughout the world. Clues as to why the disease occurs and how it develops may, therefore, be found not simply in the 50 States of our own Federal Union, but throughout the entire globe.

Indeed, the important fact for the layman to remember is that sometimes the clues may exist more plentifully or more discernibly outside the borders of the United States than within its perimeter. There are many reasons which may account for this circumstance. One of the reasons, which is frequently mentioned in this report, is the genetic factor. In some areas of the globe, the forces of heredity may be observed far more clearly than here in the United States. A reason, in turn, is that certain remote areas outside our borders are often so comparatively isolated that there has been more inbreeding among families, clans, tribes, and other groupings. Thus, inherited defects—for example, possible predisposition to a disease—may be more readily observed.

In addition, there are many other factors which may account for the fact that it may be easier to discover certain clues abroad than within our own borders. One such factor is the important but subtle influence of climatological differences in various parts of the world.

All in all, clues vary from place to place, both quantitatively and in character.

But the clues may fit together, may supplement and complement one another in unforeseeable ways.

Wherever he works, the epidemiologist will ask certain key questions: "Why does this killing or crippling disease strike a particular population, or a particular age group, or sex, or vocational group, or urban or rural group—with particular severity or comparatively mildly or not at all? Or why does it strike regularly or infrequently? Why does it tend to strike one particular organ or organ-system in one country and another organ or system in still another land?"

If the answers can be found to these and similar questions, science may be on its way toward unlocking the mysteries of unsolved diseases.

The "disease detective," the epidemiologist, patiently compiles his data. A police force, in seeking a criminal, fills countless notebooks on the basis of interviews. So, too, an epidemiological team accumulates a vast amount of scientific information. Much of the information may eventually lead up blind alleys. A so-called significant clue may turn out to be false, misleading, or irrelevant.

Unforeseen deficiencies in the fact-finding technique itself may impair effectiveness of any overall international search: perhaps an inadequate scientific sample in one or more countries, or an unintentional bias, or disuniform definitions.

Often, too, data which was compiled with one disease in mind may turn out to be more applicable to a different disease.

In effect, the trail of one criminal may intertwine with the trails of others.

At any phase of the search no one can state with certainty whether some fragment of information on a virus or on some other suspected agent may prove useful to science 1 month, 1 year, 20 years from the date or ever.

But each searcher or search team contributes what he can to the world pool of knowledge. Gradually, perhaps, a pattern may emerge or seem to emerge; a theory may be hypothesized on the cause, process, or cure of a disease. The hypothesis will be subjected to experimental proof or disproof. Ultimately perhaps, a vaccine may be developed.

Science may thus come to round a significant turn in the struggle toward partial or complete, temporary or "permanent" victory over a heretofore mysterious killer or crippler.

This, then, is the general background of the subject of this publication.

ORGANIZATION OF THIS PUBLICATION

It is organized specifically, as follows:

In part I are presented the general reasons for this science. Herein also is found an indication as to the many national, international, and intergovernmental organizations using this discipline.

In part II are found some of the worldwide clues on specific killers or cripplers which are now being studied.

SHORTAGE OF EPIDEMIOLOGISTS

It would be gratifying to be able to report that the detective work against these and other diseases is proceeding at full speed. The unfortunate fact is, however, to the contrary. Despite the fine progress reflected in these pages, the total of international detective work, is, in my personal judgment, lagging in relation to (*a*) need and

(*b*) opportunity. This is by no means due to any lack of dedication on the part of scientists in the United States or abroad. Fortunately, here and elsewhere in the world, epidemiologists, notwithstanding what are often seriously insufficient resources, are working as hard as humanly possible to compile clues.

But the regrettable fact is that the disease detectives are only able to follow up on a comparatively small proportion of known clues and in far less depth than they would otherwise hope.

Why? In part because the nations do not have enough trained epidemiologists. Most who are trained tend to be clustered in the industrialized western nations. Epidemiologists are few and far between in the less developed countries. Yet there health needs are most acute, and leads may often be equally or more plentiful and promising, particularly on certain infectious maladies.

The distressing shortage of epidemiologists has been reported to this subcommittee virtually since the inception of our study. Evidence has come in the form of scores of letters from scientists in many nations, as well as in direct testimony in hearings. Over and over again the subcommittee has heard that, for a comparatively modest investment in training of personnel and in their subsequent field studies, immense dividends might ultimately accrue to research.

But the investment will not necessarily pay off quickly. While a single brilliant investigator may develop a major epidemiological report, quick shortcuts cannot be anticipated. The training of the individual epidemiologist and of a team is a time-consuming process. Data must be patiently accumulated, analyzed, correlated, invariably over protracted periods of time. The necessity is constant for refining the search by eliminating undesired variables.

But the bonuses from the search may prove very considerable and often may be unforeseen.

IMPORTANT NATIONAL INSTITUTES OF HEALTH CONTRIBUTIONS TO EPIDEMIOLOGY

Indeed, the potential values of international epidemiological cooperation represent one of the underlying reasons, cited by scientists, for strengthening present overseas programs of the National Institutes of Health. Fortunately, this great research agency has long since been keenly aware of these values, as well as of epidemiological needs and opportunities. That fact is confirmed by parts of the first publication in the subcommittee's series, Senate Report 160, 86th Congress, "International Medical Research." It shows NIH's 1959 fiscal year overseas grants for epidemiological (and other) purposes.

NIH's interest is further confirmed by the technical judgments expressed within this very publication itself, for herein basically are the judgments of NIH scientists.

DIFFERENT CONTENTS IN "THE STATUS OF WORLD HEALTH"

Still another print in this series which will come readily to the reader's mind is Committee Print No. 3, Senate Report 161, 86th Congress, 1st session, "The Status of World Health." It, however, should be carefully distinguished from the present print. "The Status of World Health" singled out certain major diseases which, in terms

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of the hundreds of millions of people involved, represent the principal problems of public health throughout the world. These are diseases basically of an infectious character.

By contrast, the present print is devoted almost exclusively to non-infectious diseases. The fact that infectious diseases are omitted herein does not in any way indicate a diminished stress on the importance of combating such ailments.

The omission simply indicates that, having devoted attention to the infectious maladies in the earlier print, the subcommittee turns now to other diseases—chronic, degenerative and others—in the present publication.

For purposes of readability, the subcommittee sought to maintain the present print in a relatively condensed form. Had it sought to enlarge the contents, it would certainly have included the fungus diseases and viruses, the latter illustrated, for example, by different types of encephalitis.

The subcommittee has earlier made reference to virus-born diseases, particularly in Committee Print No. 4, which was devoted to the World Health Organization and its important Epidemic Intelligence Service.

RECURRENT THEME OF IMPORTANCE OF GENETICS

In this, as in future publications, a theme which the reader will note as recurring again and again concerns the importance of genetic research. In all the vast gamut of current scientific endeavors which have been presented to the subcommittee, few, if any, appear more promising, more challenging, more dynamic than that of genetic research of all types. Of this, the subcommittee will comment at further length not only throughout this report, but in several of the publications which follow.

LIMITED NATURE OF THIS PUBLICATION

Against this general background, the following facts should be noted specifically concerning the contents of this publication:

1. It is hardly intended as a definitive work on epidemiology; it is simply a brief sampling of pertinent information.
2. The handful of diseases selected for purposes of illustration are but a few out of a great many examples which might have been selected as being of interest, especially to the layman.

ACKNOWLEDGMENT OF WORK OF NATIONAL INSTITUTES OF HEALTH

As in the case of several other past and future committee prints in this series, the subcommittee relied principally in this task upon the invaluable cooperation of the National Institutes of Health. Appreciation is expressed herewith to the information specialists in the various institutes who cooperated in the compilation, as well as the scientists who contributed ideas and suggestions. Special thanks are due to Mr. Clifford F. Johnson of the Office of Research Information, who collated the material.

In the process, Dr. James Hundley, Special Assistant on International Affairs to the Director of the National Institutes of Health, worked closely with the project director of the International Health

Study, Mr. Julius N. Cahn. The latter is responsible for the series of publications mentioned on page V and for over a dozen publications which will follow.

CONCLUSION

The search for the mysterious killers and cripplers continues throughout the world. A basic question presents itself for decision by the legislative and executive branches of the U.S. Government. It is a decision as to the extent and the timetable by which the United States may propose to strengthen resources for the science of epidemiology. That is, by how much and how soon will we enable the disease detectives to find the clues which may ultimately lead so significantly toward reducing pain, suffering, and premature death throughout the world.

CONTENTS

LIST OF CHARTS

Part 1

BACKGROUND ON EPIDEMIOLOGY

Each civilization, it has been said, makes its own diseases.

The first half of the 20th century, with its many social, industrial, and economic changes, confirms that present civilization follows the time-tried pattern. A list of significant changes in the 20th century might include:

Newly discovered and improved types of transportation;
Increasing use of radioactive sources of energy;
Development of new knowledge for infectious disease control;
Steadily increasing world population;
Increasing numbers of older people; and
Emerging importance of chronic disease as a health factor.

These changing patterns of living are universal. They contribute to the worldwide problem of disease in a wide variety of ways. The network of sources, causes, and carriers of disease is so intricate that it suggests the need for a special effort (*a*) aimed at defining the questions and (*b*) pinpointing the answers to diseases and disabling conditions that occur on a worldwide basis.

One of the most interesting and hopeful avenues of approach to the control and eradication of today's major diseases is through world epidemiology.

A. EPIDEMIOLOGY DEFINED [1]

Epidemiology has been defined as a science of mass phenomena of diseases and human defects. It describes significant varieties of these phenomena in time and place. It draws upon statistical methods and theory, all phases of medicine, and the natural sciences to give a true picture of the occurrence, distribution, and types of diseases or defects.

As an illustration, the epidemiological study of hypertension (high blood pressure) seeks—as in similar studies—to evaluate the influence of diverse genetic and environmental factors upon the occurrence and severity of the disease. No one has succeeded in demonstrating specifically what causes high blood pressure. Yet marked differences in the incidence and severity of the disease in different population groups support the hope that epidemiological studies may succeed in defining the causative factors.

By contrast with clinical medicine, the unit of study in epidemiology is the population or group, not the individual. Deaths, or any other event, are studied only if information can be obtained or inferred about the population in which the events occurred. The population may be a small and well-defined group in a municipality, may include a whole country or even an entire continent. The epidemiologist, therefore, as opposed to the clinician who deals in cases, is concerned with cases as they occur in their population. He may start with a

[1] Other terms frequently used to denote this general discipline, but implying somewhat differing meanings are *medical geography* and *ecology*. The more accepted term, epidemiology, is, however, used throughout this publication. *Ecology* is referred to on p. 11.

population and find the cases in it, or he may start with a number of cases and refer them to a population or group that can be taken to represent a population. In addition to observing the occurrence of cases, the epidemiologist must be keenly aware of the importance of variations in human traits and must understand what effect environmental factors might have on individuals under his observation.

B. USES OF EPIDEMIOLOGY

Epidemiology was originally the study of epidemics—usually of one particular disease. From those early studies it is possible to establish a framework of questions to seek out the characteristics of the disease: where and when it occurs, the frequency and intensity of the occurrences, the persons most likely to be affected, and whether such conditions as climate or weather are a factor. Armed with the answers to these and other questions, which together describe the pattern of the disease, it is then possible to advance theories about the source and mode of spread of the disease and to put these theories to the test by clinical, field, or laboratory study. Finally, it may be possible to establish a logical plan for the control of the disease under study.

One of the principal uses of epidemiology is to discover populations or groups with high and low rates of disease, in the hope that causes of disease and of freedom from disease can be found. The epidemiological approach to a search for the cause of a disease may often suggest steps that may be taken for prevention and control. Thus, it is possible to reduce the impact of a major disease before the exact nature of the disease is understood.

C. EXAMPLES OF HISTORICAL CONTRIBUTIONS

John Snow established an important landmark in epidemiological research with his conclusions about the source of cholera. Long before bacteria were discovered, the features of cholera epidemics had been explored thoroughly, and the existence of minute living causative organisms had been theorized. In 1854, Snow through masterly detective work in the Broad Street pump epidemic in London, held that a contaminated water source was responsible for the outbreak. Later, the well-known Hamburg-Altona epidemic of 1892 indisputably established the theory of waterborne disease.

Smallpox

Edward Jenner, an English physician, observed that milkmaids throughout the countryside who contracted cowpox while milking were subsequently immune to smallpox. In 1796, he vaccinated against smallpox by transferring material from a cowpox pustule on the hand of a milkmaid to the arm of a small boy. Six weeks later the boy was inoculated with smallpox and failed to develop the disease. Although it was to be many years until the virus of smallpox was discovered and the exact nature of this highly infectious disease understood, the epidemiological method pointed to an effective means for curbing the spread of smallpox. By 1800 the scientific basis of this method, still in use today, was firmly established.

Childbirth fever

Ignaz Semmelweis, a Hungarian obstetrician, noted that the death rate of women at childbirth was higher in certain clinics where the

medical students and physicians came directly to the wards from the morgue or gross dissection room. After making other observations, he concluded rightly that puerperal fever was an infectious disease. He required physicians on his own wards to clean their hands scrupulously before examining patients, and the mortality dropped immediately. Unfortunately, his views met with strong opposition and were not accepted for 20 years after his death.

Typhus

Charles Nicolle, French physician and director of the Pasteur Institute, observed that even though typhus patients were lodged in a common ward, no other patients caught the disease. He also noted that their families and the hospital admitting personnel who relieved them of their clothing caught the disease. He reasoned that the disease agent was something attached to the skin or to the patient's linen—something which yielded to soap and water. He concluded that the carrier could only be the body louse, which he verified by reproducing the malady in animals in 1902.

D. HISTORICAL SUMMARY OF USES OF EPIDEMIOLOGY

A British scientist[2] has summarized some of the classic illustrations of epidemiological research as follows:

> The main use of epidemiology is to discover populations or groups with high rates of disease, and with low, in the hope that causes of disease and of freedom from disease can be postulated.
>
> Examples can readily be drawn from the riches of classical epidemiology. The observations on nutritional deficiencies (scurvy, goiter, beri-beri, pellagra). The experience of peoples in relation to climate and season, "the epidemic constitutions of the atmosphere" (malaria; or pellagra), and to geographic and geological features (iodine deficiency). "Dangerous trades," and the industrial pulmonary diseases or the occupational cancers (epithelioma of the skin from cutting oils, and lung cancer associated with asbestosis are among the recent ones identified). The "unhealthiness of towns" (malaria, dysentery; pellagra; respiratory disease).

The writer, director of the social medicine research unit of the Medical Research Council, London Hospital, adds:

> When affected groups are thus characterized by their environment, their living conditions and special ways of life, the epidemiological method is in fact beginning to unravel "causes" of disease, causes about which it may be possible to suggest and do something by way of control and prevention. This may happen before the intimate nature of the disease is understood, as in the achievements of Snow and the cholera, Takaki and beri-beri, Goldberger and pellagra.
>
> "Ways of life" can often be described only in simple terms, and the causes of health and disease postulated in them may therefore be in simple terms of the satisfaction of elementary human needs, of gross hazards and trauma. "Ways of life" as they are presently known, are thus often "general" factors, causes of *disease* or of *diseases*, rather than of any specific disease. Such are the relations of purity (and abundance) of water supply to bowel infections of many kinds—and not merely the cholera. Or of living space with respiratory infections—as a class. And the manifold connections of income levels with nutrition, and with child growth, development and health. These "general" principles include much of what we know of healthy living. Likewise, it may be possible to define the groups being studied only in broad biological and social categories. But simple studies should not on that account be dismissed. The history of the search for means to prevent disease shows how the reconnaissance and the large scale map, and courageous generalisations from these (the "filth" theory for instance), can be of value. Many of the illustrations in the paragraph above are of this nature.

[2] Morris, J. N., "Uses of Epidemiology," E. S. Livingstone, Ltd., Edinburgh and London, 1957, pp. 61-63.

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With the development of clinical and laboratory diagnosis, of statistics and survey methods, epidemiological inquiry into the causes of disease is increasingly being refined.

E. CHANGING WORLD PATTERNS OF DISEASE

The conquest of many of the infectious diseases in the We tern World, thanks to epidemiological and many other scientific economic and social advances, has resulted in a dramatic change in the patterns of disease. This change was alluded to in Committee Print No. 4 entitled "The United States and the World Health Organization" (p. 24ff.).

The change can be clearly noted in facts such as the following:

In 1900, the 10 leading causes of death in the United States included five infectious diseases; the current list has only one. First place in 1900 was occupied by influenza and pneumonia, and second place by tuberculosis; by 1956, influenza and pneumonia had dropped to sixth place and tuberculosis no longer appeared among the 10 leading causes of death in the United States. (Source: National Office of Vital Statistics, Public Health Service: Summary of Health and Vital Statistics, June 1958, pp. 11, 12.) The community problems of the present, as measured in terms of death, are resident in diseases not communicable nor caused by a specific infectious agent. They include heart disease, the cancers, diabetes, and others.

The main direction of effort in epidemiology is still toward communicable diseases. But it becomes increasingly evident, as the following pages of this print will show—that a limitation of activities to the infections or to a closely circumscribed area is no longer warranted. That conviction is supported to such an extent that it may now be accepted as a principle, applying with little reservation to the countries of North America and Western Europe.

This line of thought reflects the altered conditions of the new world. There should, however, be no misunderstanding that this view implies any slackening of effort against the communicable diseases, which are still the major problem in many areas of the world.

F. LIFE EXPECTANCY CLIMBS

Along with the changing pattern of disease in the United States, from emphasis on infectious or communicable disease to the so-called chronic diseases, there has been an accompanying increase in the proportion of older people. This pattern is reflected in many other countries of the world in varying degree (fig. 1).

	Millions	*Percent*
Total world population, 1957 (estimated)	2,790.0	-----
Life expectancy 65 years and over	713.9	25.6
Life expectancy 50 to 64 years	278.5	10.0
Life expectancy less than 50 years	801.3	28.7
Life expectancy data not available	996.3	35.7

In Puerto Rico, for example, life expectancy at birth has increased from 46 years in 1940 to 68.3 years in 1955. In Ceylon, the increase has been from 42.8 years, as late as 1946, to 59.9 years just 8 years later in 1954. Even in India, life expectancy has gone from 26.7

years in the 1920's to 32.1 years in the 1940's. (Source: Statistical Bulletin, Metropolitan Life Insurance Co., April 1958.) The pattern is repeated around the world, and understandably more clearly defined in the better developed nations of Scandinavia, Europe, and the Western Hemisphere. A great part of the earth's population now lives more than 50 years, including that in Central America; the southern half of South America; Ecuador; British Guiana; Spain; Portugal; Eastern Europe; Turkey; the Sudan; South Rhodesia; Ceylon; Thailand; Malaya; and the Philippines. Those areas where persons live to be 65 and over include Russia, Sweden, the Netherlands, the United Kingdom, Denmark, the United States, New Zealand, Israel, Australia, and Norway, which tops the list with a life expectancy of 73. (Source: U.N. Statistical Office.) Concurrently there have been sharp increases in the total numbers of older people in proportion to total populations.

These conditions, if ignored, have the potential for posing serious international economic, social, and even political problems; for unless the aging populations are kept productive, through better health, as well as through vocational and avocational opportunities, they can become a weight on their homes and families, communities, and central governments.

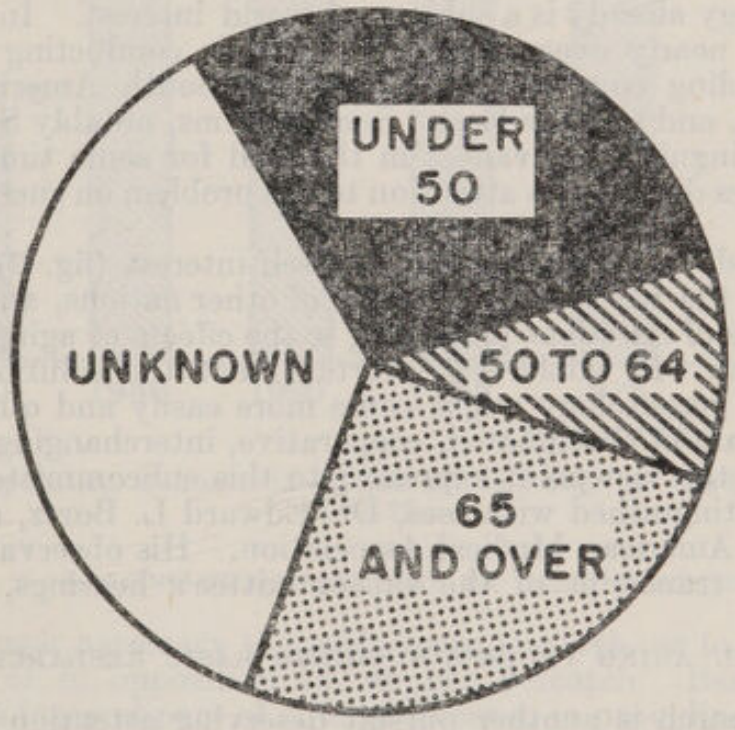

FIGURE 1.—Life expectancy of world population.

G. WORLD AGING STUDIES NEEDED

The genetic factor, climate, occupation, radiation, food and the sanitary standards, general health of the community, social mores, and religion, all are considerations in the worldwide study of aging. At present it is not certain what part these considerations play in the process of aging, but we do know that these conditions vary widely in different parts of the world, and that there are variations in the longevity of different peoples.

It is clear that a sound approach to the study of aging must include work in a broad number of fields. These include:

The biological sciences, wherein biochemists, biophysicists, and investigators in numerous other basic sciences must study age changes in matter and energy at the most basic levels, where the origins of the process of aging most likely rest.

The clinical sciences, where we must seek means to prevent the development of chronic disease as a part of aging. There is need also to develop methods for assessing the benefit an ill or disabled person may receive from available rehabilitation procedures.

The behavioral and social sciences. Here we would assess the older worker's response to increasingly complex technology, his place in a changing social structure and his mental health.

All this work, however, can have its greatest meaning only when it is projected onto an international level. Theories and findings about the genetic, biological, physiological, mental, and social aspects of aging, and about the methods for giving the aged persons more dignified and healthier lives, will have firm bases only when they have been evaluated and tested under the many variables in different cultures.

Gerontology already is a subject of world interest. In one degree or another, nearly every civilized nation is conducting research in aging, including countries in Central and South America, Europe, Scandinavia, and the Far East. Some nations, notably Sweden, were making distinguished advances in the field for some time before the United States directed its attention to the problem on such a relatively broad scale.

It obviously would be in our own self-interest (fig. 2) to learn in more detail the work in gerontology of other nations, and to answer the hundreds of questions pertaining to the effects of aging of different environments. It would seem certain that the solutions to many problems in gerontology might come more easily and quicker with a broad program of coordinated, cooperative, interchanging effort.

This was the viewpoint expressed to this subcommittee by one of its most distinguished witnesses, Dr. Edward L. Bortz, a past president of the American Medical Association. His observations will be found in a transcript of the subcommittee's hearings, soon to be published.

H. AGING PROCESS SUGGESTS BASIC RESEARCH

Basic research is another pursuit deserving attention on a worldwide basis. Its potential value is enormous in providing new knowledge about the aging process itself, as well as new insight into other major diseases. This importance of basic research in biology and medicine is manifested in two ways:

The first is in the interchange of newly developed fundamental knowledge among scientists around the world in a mutual, cooperative system of assisting each other.

The second is the need for medical science to understand better the incidence and variable characteristics of specific diseases in different parts of the world and to relate them to variations in climate, altitude, food, culture, and other factors—often referred to as the geographic pathology of disease.

This need is a part of the growing importance of basic research in its own right. When note is taken as well of the greatly expanding requirements for fundamental knowledge (brought about by advances in many areas of clinical research), it becomes clear that if basic research is to fulfill its mission in the most desirable manner, it must be international in character.

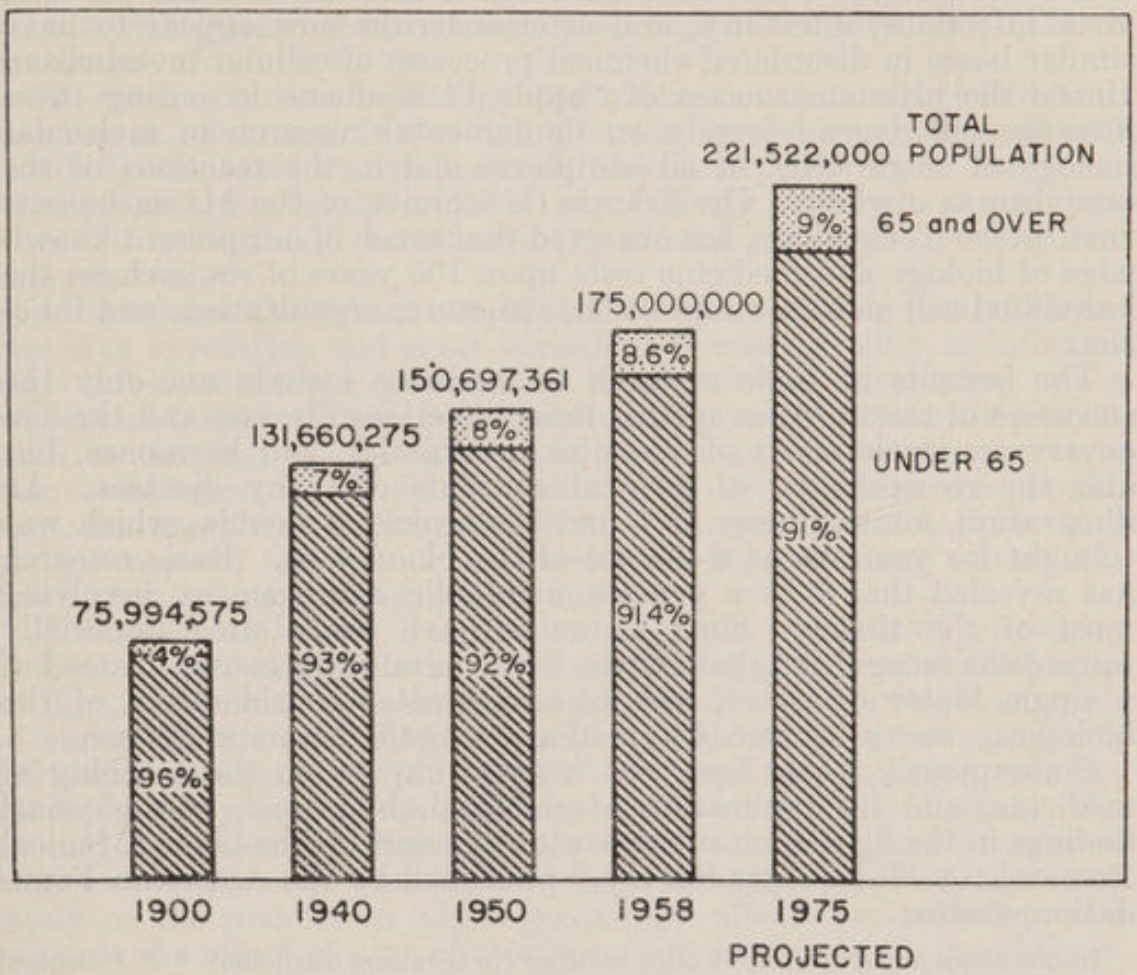

FIGURE 2.—Population increase in people 65 and over in the United States, 1900–75.

I. LONG-TERM BENEFITS OF BASIC RESEARCH

It is no longer necessary to justify basic research, or to justify it in relation to, or in opposition to, applied research. Basic research is, in fact, an integral part of clinical research in providing the fundamental building blocks and tools of applied knowledge.[3]

The relationship can be somewhat indirect and extend over long periods of time. Basic observations by Pasteur in 1877, for example, were used in the development of penicillin in the 1940's. Or the relationship—indeed, interrelationship—can be very direct. Daily there are instances in which the clinician uncovers problems or ideas which he must take back to the laboratory where only fundamental investigations can give him the knowledge he needs to proceed.

[3] In this connection, it should be noted that another in the series of committee prints to be issued shortly by the subcommittee sets forth the vital work of the National Science Foundation. The observations presented above will be elaborated in that print which is entitled, "The National Science Foundation and the Life Sciences."

In many ways there is an even tighter relationship in the very nature of many of the diseases the clinician is attempting to cure. Diseases—and the process of aging—are changes in the normal function of tissues and cells; hence the need to uncover new knowledge on the normal conditions of, and the normal variations in, cellular biology—clearly the domain of the basic research scientist.

Such seemingly different and unrelated diseases as schizophrenia, virus infections, infertility, and arteriosclerosis now appear to have similar bases in disordered chemical processes of cellular metabolism. Hence the ultimate success of "applied" medicine in curing these diseases will depend largely on fundamental research in molecular biology of single cells, of all complexes and in the reactions of the organism as a whole. Dr. Francis O. Schmitt, of the Massachusetts Institute of Technology, has observed that much of our present knowledge of biology and medicine rests upon 100 years of research on the individual cell and its composition, structure, organization, and function.

The benefits of basic research to medicine include not only the successes of recent years against most infectious diseases and the discovery or development of vitamins, antibiotics, and hormones, but also the reorientation of medical concepts of many diseases. An illustration, among many, is found in pernicious anemia, which was thought for years to be a disease of the blood cells. Basic research has revealed that it is a genetic, metabolic derangement, involving most of the tissues. Such instances have contributed materially toward the recognition that disease involves multiple causes, instead of a single factor or agent, and toward greater consideration of the biological concept of constitutional and genetic factors in disease.

Consequently, there has been a great impact on the teaching of medicine, and its application of chemical, biological, and physical findings in the fight against the world's illnesses. The book "Medical Research: A Midcentury Survey," published by the American Foundation, states:

> In one academic department after another (in teaching medicine) * * * central problems (of disease) are reduced to chemical and physical phenomena produced in the living organism in relation to its environment and its inherited factors.

As a part of the great progress in medical research in recent years, we have come to define more clearly the things we do not know, the processes we do not understand. Many areas of knowledge about metabolism, hormones, and mitosis, as examples, have hardly been opened. Dr. Paul A. Weiss, of the Rockefeller Institute for Medical Research, has said:

> We do not know the physical basis of intracellular organization, the principles that sort biochemical processes and diverse molecular realms in space without the aid of rigid mechanical frameworks. We do not know * * * what causes orderly substance transport within cells, nor do we know the motive mechanism of cell locomotion. We do not know how cells recognize each other, their foods, their enemies, and how they can react selectively to this environment. We still have no more than shrewd guesses about the mechanism of protoplasmic reproduction that we call growth * * * nor do we know what activates and checks and reawakens the powers for such growth in development, disease and aging. (We do not know) the supracellular principles of field character which order the cellular community both in development and in the coordination of our nervous functions, and whose disburbances may yield freaks in the former case, mental disorders in the latter.

J. UNIVERSAL NEED FOR BASIC RESEARCH

All the aforesaid considerations leave no question as to the importance of international cooperation and coordination in the effort toward more healthful, longer, and more productive lives. Disease is not national or political; and critical to its defeat is the requirement that the United States and other nations widen the scope of their efforts with expanded interchange programs in research and research training.

Research scientists in biology and medicine around the world have a common advantage in the fact that the human organism is fundamentally the same everywhere. A biological discovery in India, for example, is immediately useful in, say, Canada, adding to the obvious value of a close and constant international exchange of effort and information.

At the same time there can be differences in disease patterns from one area to another and great variations in susceptibility to infection and infestation from population to population, depending on a variety of factors. These factors include the more obvious conditions, such as the degree of sanitation in the living and working circumstances of a people. They also include the eating habits of a population, the organic and mineral content of the soil in which their crops are grown; and the manner in which their religions may control the foods they eat, as, for example, in India.

Consideration is also due the geographical location of a country and its climate and altitude. The great lung and chest development of the people living high in the Andes Mountains is a ready example of biological interest. Tropical peoples suffer from a great number of parasitic diseases. Populations in cold regions eat heat-producing foods, possibly increasing their susceptibility to heart disease. For some years there has been greater interest in the possible relation between weather and suicides, and more recently there has been more study of the manner in which geography affects air pollution and, in turn, the effect of air pollutants on human biology. In addition, there are the obvious differences in occupations and cultural habits.

K. WORLDWIDE OPPORTUNITIES FOR GENETIC AND OTHER BASIC RESEARCH

Far greater knowledge is required as to the manner and extent that all these conditions affect the incidence and patterns of disease.

One field in which this is true is genetics, an area that has undergone an almost explosive development in recent years. Relatively recent findings in genetics have redirected attention to the importance of inborn constitutional and genetic factors in the manifestations and patterns of disease, emphasizing the tremendous importance of concurrent basic research efforts to understand just what a gene is and how it operates. Thus will we learn how diseases are produced genetically; and conversely, it is important that we study the genetic diseases for the insight they can give us into the nature and function of genes. The significance of this work is seen in research against diseases such as phenylketonuria which can cause brain damage in babies because of a congenital faulty metabolism of the amino acid phenylalanine. Very recently it has been found that this genetic failure, if discovered in time, can be minimized by feeding the child a phenylalanine-free diet.

Foreign areas often offer great advantages for genetic studies in the incidence of certain diseases in geographic areas or among certain races. Congenital spherocytosis—a type of anemia—is found among peoples around the Mediterranean Sea, and sickle-cell anemia is a disease which afflicts almost exclusively members of the Negroid races.

Foreign research offers opportunities for studying almost completely homogeneous populations and for studying the possible effects of factors such as climate and soil on the size of the human body, differences in pigment, and variations in basal metabolism rates as well as disease susceptibility.

Thus, basic research in these foreign fields is critical not only to the solution of local disease problems, but also in the international exchange of greater and more accurate knowledge on man, and on man in relation to his environment.

In effect, the need is also an opportunity for great medical progress which could be realized with an enlargement of American research programs. Such enlargement would afford closer collaborative effort between fundamental medical and biological research and training projects in this country and abroad.

L. BROAD-GAUGED UNDERSTANDING NEEDED

It cannot be too strongly reiterated that the modern epidemiologist mobilizes data on a broad-gauged basis which previous generations of science would not have foreseen. Among the scientists who have presented the case for the most comprehensive understanding of man in relation to his total environment is Dr. Jacques May. He pointed out in a recent book:[4]

> At a meeting in Colorado Springs in 1952, North American epidemiologists agreed to define their field as "the study of all factors and their interrelationships which affect the occurrence and course of health and disease in a population." This definition is all-embracing. It certainly takes into equal consideration both the *inorganic* factors of climate and soil, which play a role in shaping societies of living things, and the *organic* factors, which govern the interrelationship of one living thing with another and of one society of living things with another. It includes the study of the responses offered by the tissue. It also includes the study of the cultural and social factors that bring stress or avoid it.
>
> * * * * * * *
>
> Disease cannot arise without the convergence at a certain point in time and space (in our case a human being) of two orders of factors: factors that take the form of an environmental *stimulus* (a virus in the throat, poison in food or in the air, or an emotional stress), and second, factors that condition the *response* of the tissues. These stimuli, these challenges to adjustment, are not the same in every environment. They vary with the geographical or cultural location. The response is conditioned by the genetic makeup of the recipient.
>
> Environmental factors that may place human tissues in jeopardy can be studied under three headings: inorganic, organic, and sociocultural.

Other scientists have similarly stressed the need for a broad view of man and his environment:

> Epidemiology must be used as a broad term to mean "that field of medical science which is concerned with the relationships of the various factors and conditions which determine the frequencies and distributions of an infectious process, a disease, or a physiologic state in a human community (Maxcy). This broad use of the term is really not altogether a new concept. Hippocrates said that one should treat a person and not a disease, and Galen emphasized the effect on health of quiet habits and a mode of life based upon appropriate diet and behavior.

[4] May, Jacques M., M.D., "The Ecology of Human Disease," M.D. Publications, Inc., New York, pp. 2, 3, 25.

A broader science of which epidemiology is itself a part is called ecology which, according to Gordon, has to do with the mutual relationships of various living organisms in an environment, and their reaction to animate and inanimate surroundings. It is the influence of total environment on the behavior of living things. This broad science can be narrowed by the term "human medical ecology," to signify the interaction of man and his total environment and the ways in which this interaction contributes toward or otherwise affects significantly the development of disease or physiologic conditions. Hence, epidemiology in its modern sense is human medical ecology. Disease is not a struggle between host and agent with the environment a mere battleground. Environment contributes many active factors in the development of disease. The practical tools for control of disease may lie in our ability to modify various sets and combinations of these epidemiologic factors.[5]

Dr. May indicates the need for proceeding to map the world's diseases, as follows:

If the distribution of diseases had been accurately plotted on geographical maps by a team of skillful physicians and cartographers since the beginning of recorded history, the study of the changes that such maps would undoubtedly bring to light would certainly reveal many of the secret workings of nature. Unfortunately, such a census was never made. Our forebears did not realize its possible importance. They lacked a global view of the universe, without which such a study would have lost most of its significance. Having no precise means of diagnosis, nonrelated diseases would have been mapped together.

We are now in a better position to make a study of this problem: the mapping of the diseases of our time, which we shall bequeath to our descendants, will certainly be inaccurate and incomplete, but it can be hoped that when comparing it with their own findings, profitable avenues of research will be opened.

M. THE WORLD HEALTH ORGANIZATION AND EPIDEMIOLOGY

No organization is better qualified to spearhead epidemiological research than the World Health Organization. Stronger cooperation in factfinding on health is available through WHO's unique resources and through its 90 member nations than through any other comparable organization on the world scene.

This fact does not detract from the impressive contributions of a national organization such as our own outstanding National Institutes of Health in Bethesda, Md., nor does it downgrade the work in a specialized field which is possible through an international professional organization such as the International Congress of Cardiology or the International Union Against Cancer or, to cite one of the newer and very promising organizations, the World Federation of Neurology.

But WHO, by its very nature, offers special assets for advancing epidemiological science, particularly as it operates through organizations such as those mentioned above.

It was clear from the fourth committee print in this series that WHO has had to concentrate during its first 11 years on epidemiology in the communicable diseases. WHO summarizes[6] this and related situations as follows:

During the 10 years of its activities, WHO has collected a great deal of information on those diseases on which it concentrated its efforts, such as tuberculosis, yaws, malaria, bilharziasis, etc. * * *.

[5] James, George, M.D., FAPHA, and Greenberg, Morris, M.D., FAPHA. "The Medical Officer's Bookshelf on Epidemiology and Evaluation"; "Part I—Epidemiology," American Journal of Public Health, April 1957.

[6] World Health Organization, "The First Ten Years of the World Health Organization," Geneva, 1958 pp. 282, 283, 287.

International cooperations in the study of the epidemiology of communicable diseases is more advanced than in that of the epidemiology of other conditions. Early measures to prevent the spread of diseases over national boundaries stimulated research into their epidemiology. The discovery of the causative organisms and much of the manner in which they are spread has led to the better control of these diseases and even to the eradication of some of them in certain circumstances. Nevertheless, many problems connected with their international epidemiology still await solution.

* * * * * * *

The modern view that epidemiology is relevant not only to communicable disease but to all factors affecting the health of a community has led, particularly in the last few years, to the Organization's being concerned with studies dealing, *inter alia*, with the epidemiology of mental diseases, nutritional diseases, chronic circulatory conditions, accidents, respiratory conditions, and dental diseases. The recommendations of expert committees and other groups on nomenclature, definitions, classifications, survey and sampling methods, have been put to use in these studies. Attention has also been given to the possibility of extending the epidemiological method by the use of radioisotopes. The Organization has, moreover, attempted to provide material for study by local services and institutions, by publishing the available data in its routine statistical publications, and has encouraged the preparation of studies for publication in the WHO *Bulletin*.

Particularly since 1953, epidemiological research has been made a part of many programs of WHO advisory services to governments. Even when research is not the declared objective of such a program, opportunities for collecting epidemiological data are taken wherever possible. The need for such work to be included in all the programs WHO assists has been evidenced by the number of requests made to the Organization in recent years for information on the international aspects of many diseases and other conditions affecting public health. The tendency to look to the Organization as a source of medical "intelligence" has grown during the last 10 years. The requirements of local institutions and services, universities, and research laboratories for data on which to base programs for national and regional development have increased, particularly since the passing of the "emergency" phase of the first few years. To meet these requests the Organization, since 1953, has strengthened its epidemiological and health statistical services, which are being developed in the expectation that in due course they will be one of the main international channels for the transmission of epidemiological and statistical information.

A later WHO report [7] points up current needs:

It is estimated that only 80 percent of the world's population was enumerated in the last decade, and only 33 percent of the total number of deaths was registered in 1951–55. The proportion of deaths of which the cause is known is far smaller still, and the WHO "Annual Epidemiological and Vital Statistics, 1955," issued in 1957, do not include more than 40 countries for which these data are both available on a nationwide scale and deemed reliable for international comparison.

Both United Nations experts in vital statistics and WHO experts in health statistics have recommended that countries unable to produce statistics covering the whole of their territory initiate pioneer registration areas in their main cities or in selected areas where administrative arrangements can be made.

There are, in fact, many towns throughout the world where vital registration is practiced and where crude vital rates could be computed, distinguishing between residents and nonresidents. There are also many cities in which physicians would be sufficiently numerous to certify the cause of most deaths, and where arrangements could be made to ascertain the cause of death in those patients not attended by doctors. It is hoped that statistics based on such material will be compiled in increasing quantity, and the mistake thus avoided of publishing as national totals data of varying degrees of completeness and reliability obtained from separate cities and other local government units.

Meanwhile, acting on the recommendation of its Expert Committee on Health Statistics, WHO, through regional seminars and field experimentation, is seeking methods which may provide health administrations with information on the health situation of territories in which physicians and trained officials are too few to produce vital and health statistics according to standard methods.

[7] World Health Organization, "First Report on the World Health Situation—1954-56," Geneva, 1959, p. 73.

N. ROLE OF NATIONAL VITAL AND HEALTH STATISTICS SYSTEMS

It is clear that the adequacy in each nation of its vital and health statistics systems may crucially affect its contributions to international epidemiological research.

The Chief of the National Office of Vital Statistics of the U.S. Public Health Service has enumerated six important objectives for the vital and health statistics systems of all countries:

1. To produce satisfactory vital and health records and statistics, as needed by tne country according to the nature and stage of its economic development.
2. To introduce the degree of uniformity in materials, methods, and tabulations necessary for the production of tne minimum core of comparable vital and health statistics needed for international purposes.
3. To insure a free flow of information and exchange of viewpoints, so tnat the needs and preferences of all levels of producers and consumers of vital and health records and statistics receive full expression and due weignt in tne development of recommendations in which they have an interest.
4. To intermesh the activities and functions of the diverse units that make up the system so that they work as a coordinated whole, avoiding both overlapping of effort and important gaps in essential parts of the statistical data.
5. To illuminate and interrelate the routine body of statistics by stimulating and coordinating special statistical activities by all units or groups able to conduct tnem.
6. To produce and maintain an adequate supply of skilled workers in vital and health statistics, by stimulating, promoting, and coordinating all potential means of education, orientation, and training.[8]

The second listed objective is central to the theme of this publication, but the other objectives are inextricably related to it, as well.

O. EPIDEMIOLOGICAL ACTIVITIES THROUGHOUT THE UNITED STATES AND ABROAD

The uses of epidemiology are demonstrable in the day-to-day operations of public health departments in communities throughout the United States as well as by Federal and State officials and departments abroad. Perhaps this discipline finds one of its most dramatic expressions in the crucial work of the Epidemic Intelligence Service of the Communicable Disease Center of the U.S. Public Health Service, whose headquarters are in Atlanta, Ga.

In many other Federal agencies, as well epidemiology proves one of our most invaluable health tools. Future subcommittee publications will refer to the work of several such agencies.

Armed Forces Epidemiological Board

There is cited at this point but a single such activity because the general public may be relatively unfamiliar with it. This is the Armed Forces Epidemiological Board. The board consists of civilian medical scientists of renown who serve as consultants to the three military services on the control or prevention of diseases and injuries. This consultant body serves both in an advisory function and in a participating capacity through research and epidemiological assistance in the field.

[8] Dunn, Halbert L., M.D., Ph. D. "Objectives Underlying Future Patterns of Work of National Committees on Vital and Health Statistics," Bulletin, World Health Organization, 1954.

A number of individual Commissions carry out the basic responsibilities of the Board:

1. Commission on Acute Respiratory Diseases.
2. Commission on Enteric Infections.
3. Commission on Immunization.
4. Commission on Influenza.
5. Commission on Parasitic Diseases.
6. Commission on Rickettsial Diseases.
7. Commission on Streptococcal Diseases.
8. Commission on Viral Infections.

Occasionally the layman may read the press news of an outbreak of a disease like hepatitis involving Armed Forces personnel stationed overseas, a matter of intensive attention by the Board.

Thus, too, during the Mideast crisis which involved the landing of U.S. troops for the peaceful protection of Lebanon, the Board's Commission on Parasitic Diseases found that enteric diseases had emerged once again as a major problem of military health.

This type of work is extremely significant not simply in terms of the well-being of members of our own U.S. Armed Forces, but in terms of the strength of the free world—in enabling it to offer more effective deterrence to aggression.

P. SUMMARY OF USES OF EPIDEMIOLOGY

The uses of epidemiology may be summarized, for our purposes, in a threefold outline, set forth by by one physician [9] as follows:

* * * the epidemiologist is interested in variations in frequency of diseases by such characteristics as age, sex, race, social class, and occupation. This knowledge if useful for the following reasons:

1. It permits the development of hypotheses concerning etiological factors. Thus, if the disease is observed to be more frequent in a particular population segment than in others, hypotheses are developed to explain this increased frequency.

2. It can be used to test hypotheses developed in the laboratory or clinic. It is important to determine if an etiological hypothesis, based on laboratory or clinical observations, is consistent with the known distribution of the disease in human populations; to the extent that it is not consistent, the hypothesis will have to be modified.

3. It provides the scientific basis for public health administrative measures to control the disease. Even if knowledge of etiological factors is inconclusive or erroneous, epidemiological data may still be used for such control measures as case finding and the early detection of affected individuals.

* * * * * * *

An epidemiological study provides data from which may be derived a series of statistical associations between a disease and various characteristics of the population. From this pattern of statistical associations, biological inferences may be drawn. The totality of the associations and the inferences constitutes the epidemiology of a disease.

[9] Lilienfield, Abraham M., M.D., "Epidemiological Methods and Inferences in Studies of Non-Infectious Diseases," Public Health Reports, January 1957.

Part 2

SELECTED WORLDWIDE OPPORTUNITIES FOR EPIDEMIOLOGICAL RESEARCH BY DISEASE CATEGORY

A. CANCER

Cancer is a popular term for malignant neoplasms, a great group of diseases of unknown (and probably multiple) causes, occurring in all human and animal populations and arising in all organs and tissues.

The basic facts and figures regarding cancer were presented separately in a previous print entitled "Cancer: A World-Wide Menace" which contained 40 pages of text and charts. Information contained in this section summarizes data presented in that previous special cancer print.

The toll from cancer

With the control over infectious diseases, the resulting prolongation of man's lifespan, and with ever-increasing industrialization, cancer now stands second only to heart disease as a cause of death among populations of the Western World. Over 2 million people die of cancer each year in the world population of 2.7 billion, and this figure is on the rise as less advanced regions approach the health standards of the Western countries.

In the United States, approximately 450,000 people develop cancer each year, and approximately 260,000 die of cancer each year. At birth, the chances of developing cancer in a lifetime are 1 in 5 for men and 1 in 4 women. It has been estimated that the economic burden of cancer to society amounts to about $12 billion a year in the United States alone.

Cancer incidence rates continue to rise to the end of the lifespan for both men and women. But although cancer is more frequent at older ages, no age is free of the disease. In the United States, more children under 5 now die from leukemia and other types of cancer than from all infectious diseases combined.

The total age-adjusted incidence and mortality from cancer is somewhat higher for men than for women. Between the ages of 20 and 55 the high incidence of cancers of the breast and reproductive organs leads to a higher overall incidence of cancer among women than among men, but at older ages the rates are higher for men than for women.

Geographic differences in cancer

Important differences in the occurrence of cancers by type and by site are observed in different regions of the world. Specific types of cancer are influenced by a variety of factors, including residence, habits, and occupation. The analysis of such differences by epidemiologic methods provides important clues to advance knowledge concerning the causation of cancer.

Epidemiologic research is best conducted on a worldwide basis, because cancer is found everywhere in the world and because the wide

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Since Percival Pott in 1775 observed that English chimney sweeps developed cancer of the scrotum, numerous instances of occupational cancer have been recorded. These include lung cancer among those who work with chromate ore, nickel, coal gas, and isopropyl oil; of bladder cancer among workers handling aromatic amines; of leukemia and bone cancer among workers exposed to X-ray, radium, and other sources of ionizing radiation; of skin cancer, among workers exposed to coal tar, petroleum, shale, creosote and other oils, arsenic, X-ray, and ultraviolet radiation.

Intensive, long-term observations among various industries and occupations, requiring active cooperation of management and labor with epidemiologists, would add much important information to our understanding and prevention of cancer. At the same time, broad-based population studies, in which large groups of people would be followed and the occurrence of disease related to their habits and occupations, also would yield invaluable data.

An international approach to cancer

The benefits of an international approach in cancer research are not limited to epidemiology. In all of the many disciplines of science being trained toward the goal of solving the cancer problem, the combined talents of research workers everywhere should be harnessed. Rapid flow of information would hasten the development of effective chemicals for the treatment of disseminated cancer, and of effective preventive measures against many types of cancerous growth.

The World Health Organization summarizes the cancer situation as follows:[10]

> Cancer research is being conducted on an impressive scale, especially in North America and in parts of Europe. As such local investigation meets most of the immediate needs for laboratory, clinical, and field research, international programs have been restricted to certain specific subjects. International research work on cancer has therefore been mainly concerned in the last 10 years in the coordination of local statistical studies. The Organization has continued the study, initiated by the League of Nations, on cancer of the uterine cervix. It has followed the lead given by the League in assisting research workers in different countries to agree on such matters as definitions, nomenclatures and classifications; such standardization, and common techniques of diagnosis and treatment, are necessary in the study of, for example, the geographical variations in the types and forms of cancer. In 1951 a WHO Subcommittee on the Registration of Cases of Cancer discussed the general principles which should govern the statistical classification of neoplasms, and agreed that such classification should distinguish the anatomical site, the histological type, and the degree of malignancy. A modified classification for malignant neoplasms was prepared, and was ultimately included in the seventh revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death. The help of the National Committees on Vital and Health Statistics and of other agencies has been enlisted in promoting the adoption of the definitions and classifications recommended.
>
> Another development during the 10 years which has received much attention from the WHO subcommittees concerned with cancer statistics has been the introduction of cancer registries in countries where the medical and statistical services are sufficiently developed to make them a practical possibility. The assessment of the results of the different treatments of cancer—surgical, radiological, and other—has also received attention. The lack of adequate epidemiological and statistical knowledge of the course of neoplasms under different conditions has made many earlier deductions from clinical records of little value. As early as 1950 the Subcommittee on the Registration of Cases of Cancer suggested definitions, rules, and procedures for compiling statistics on the results of treatment and for computing survival and recovery rates.

[10] The First Ten Years of the World Health Organization, op. cit., pp. 285–287.

Data from the returns received from countries, supplemented by those obtained from certain investigations undertaken by the Organization, have been classified and made available in tables published in the *Annual Epidemiological and Vital Statistics* and in some issues of the monthly *Epidemiological and Vital Statistics Report*. Studies published have included: cancer mortality in Europe during the 20th century; mortality from malignant neoplasms of the respiratory system; mortality from Hodgkin's disease and leukaemia; and mortality due to cancer of the breast and female genital organs.

In 1955 a group of experts advised the Organization on its work connected with cancer research. The group confirmed the view that it was of prime importance that countries should adopt and apply uniform definitions, nomenclatures and criteria of diagnosis. In this connection the group also made a proposal, on which action is being taken, for the establishment of international pathological reference centers. Difficulties still arise in the pathological diagnosis of neoplasma and in comparing the diagnoses made in different countries. The group therefore considered that it would be useful if the Organization would make standard pathological specimens available to interested local laboratories and specialized workers. There are differences in type and prevalence of neoplasma in different parts of the world which are not yet understood but which may be related to local epidemiological circumstances; if such relations could be determined, they might explain some of the causative and correlative factors of cancer and the group considered that every assistance should be given to workers on such problems.

* * * * * * *

Nongovernmental organizations, in particular the International Union against Cancer, have cooperated in this branch of the Organization's work. The Union has been attempting to extend the studies, referred to earlier, of geographical variations in types of cancer. WHO has also kept in touch with the work of the International Congress of Radiology on the results of treatments of cancer.

Thus, cancer is a world problem, best solved by research on a world basis. The combined efforts of scientists throughout the world should be applied to developing and exploiting leads wherever they occur.

B. HEART DISEASE

There is mounting evidence today that cardiovascular disease, the Nation's leading killer and disabler, is related to the mode of life. There is growing interest, therefore, in the possible contributions international epidemiology might make in unraveling the many problems involved.

The epidemiological approach to the study of the causes of cardiovascular diseases so far has been applied on little more than an exploratory basis, but it has already provided much valuable information. Fine beginnings have been made—as this selection of highlights will show—but they only tend to reinforce the present need for further development in order to meet the challenges and opportunities of the future.

Epidemiology of arteriosclerosis

Much measurable progress has been made during recent years against heart disease resulting from such infections as rheumatic fever and syphilis. However, the self-generating heart diseases continue to dominate the mortality statistics of many countries: arteriosclerosis (an inclusive term for hardening and thickening of the artery walls), atherosclerosis (a thickening of the inner layer of the blood vessels caused by deposits of fatty materials), myocardial degeneration (degeneration of the heart muscle), and myocarditis (inflammation of the heart muscle).

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With this as the general principle, studies in the following problem areas have been suggested as likely to yield useful information.

Dietary factors

Studies conducted in this problem area thus far show that diet is directly or indirectly influential in the cause of atherosclerotic heart disease. Of special importance in this respect is the large body of clinical evidence that atherosclerosis can be induced experimentally in laboratory animals, through dietary manipulation. Dietary manipulation has also been shown to alter the concentration of cholesterol (a fat-like substance) and serum lipoproteins (a complex of fat molecules and protein molecules) in both laboratory animals and humans.

Dietary surveys among selected population groups have also produced a large body of evidence that diet is of special importance in the development of heart disease. Among the factors considered in these surveys are: the effect upon serum cholesterol and serum lipoproteins of total fat intake; the kind of fat consumed (animal versus vegetable, saturated versus unsaturated); long chain versus short and intermediate chain fatty acids; and the protein-fat-energy ratio of the diet.

In 1950 a study of aortas collected at autopsy in New Orleans was begun, using quantitative methods devised to measure the degree and location of atherosclerotic lesions in their successive stages of development. The results of this study were later compared with a similar study begun in Guatemala and later extended to other Central American countries. The rate of development of atherosclerosis was found to be highest in the New Orleans population, intermediate among rural Costa Ricans, and lowest among the Guatemalan Indians. Rapid rates of development were associated with high fat and caloric intake, high serum cholesterol levels, and high serum lipoprotein patterns. Since Costa Ricans are essentially of European extraction, these data suggest that environment, rather than heredity, is the most important factor in the development of atherosclerosis. A similar inference might be drawn from data collected in Chile, where primitive Indian groups have far less cardiovascular disease than does the general population. However, preliminary data from studies presently underway in Puerto Rico and Colombia indicate that heart disease is fairly common in these countries, even though fat and protein consumption is far lower than that in the United States.

A sharp drop in deaths from atherosclerosis was reported from Sweden, Norway, and Finland during World War II, when German occupation or the naval blockade made food rationing necessary with a corresponding drop in fat intake. Denmark experienced no such drop; however, during the "lean years" their decrease in total fat consumption was accompanied by a sharp increase in the consumption of eggs and butter. Since the war, the incidence of heart disease in these countries has climbed to former or even higher levels.

In Croatia the population falls conveniently into "animal fat, low fat, and olive oil areas." Subjects from these respective areas exhibited significant differences in serum cholesterol, indicating that perhaps the kind of fat consumed is more important than the quantity consumed.

In Nigeria, where heart disease is relatively rare, natives subsisting on a diet low in both proteins and fat were compared with a group of

age-and-weight matched Americans. Although their serum cholesterol was lower than that of the Americans, their serum lipoprotein levels showed no significant differences.

Although the incidence of heart disease is low among African blacks, these people suffer from a degenerative disease of the heart muscle fibers of undetermined origin, which may account for from 14 to 20 percent of deaths from heart failure in Uganda, Northern Nigeria, West Africa, and Northern Rhodesia. The fact that Europeans living in the tropics have contracted this disease plus its high incidence in the Negro made it appear that endomyocardial fibrosis was primarily a disease of the tropics. However, there are indications that the disease is by no means rare in northern Europe or even in America. Its presence in populations having a high incidence of degenerative heart disease may make it more difficult to detect than in populations where the incidence of such diseases is low. Although malnutrition, infestation, infections, liver disease, and allergy are suspect, the cause or causes of this disease have not yet been determined. Further study of this problem might contribute greatly to our knowledge of the epidemiology of heart disease.

Other studies indicate that fat consumption tends to rise with increased levels of income and is higher in urban than in rural areas. As an occupational group, farmers seem especially resistant to heart disease, which may bear on the finding that people engaged in heavier work tend to get their extra calories from carbohydrates rather than from fats.

CARDIOVASCULAR DEATH RATES (1955) FOR AGES 45-64, COMPARED WITH FAT CONSUMPTION (1952)

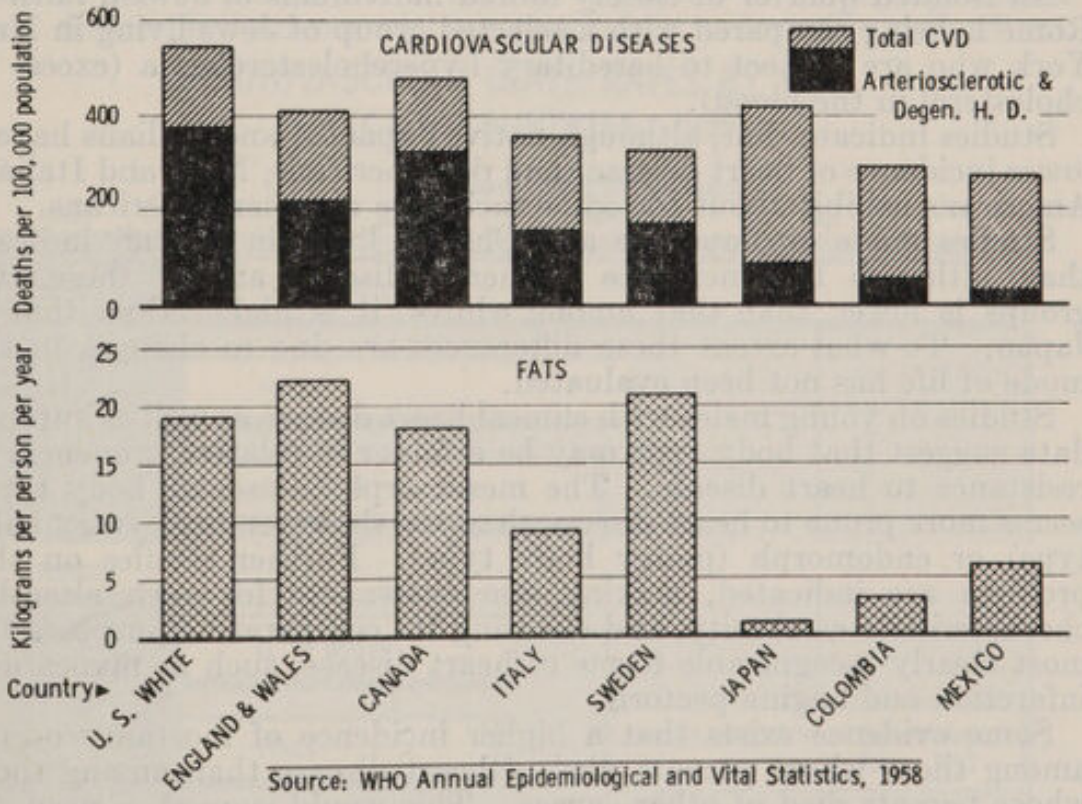

FIGURE 4.—Cardiovascular death rates compared with fat consumption.

A factor that may be of primary importance, but which has thus far received relatively little attention, is the effect of diet upon coagulation and thrombus formation. Studies thus far indicate that major differences in diet seem to be associated with differences in the frequency of strokes in general as well as differences in the incidence of mortality from heart disease. Although clot formation in the body and coagulation in the test tube are not necessarily identical, growing evidence suggests that diet may influence coagulation.

The evidence collected by dietary surveys thus far is highly suggestive; however, further studies of these groups are needed, especially with simultaneous analyses of long-term patterns of diet, body weight and fatness, incidence of all kinds of heart disease, blood lipid patterns, and substances involved in blood clotting. Present data on food intake in different countries is far from adequate, especially with regard to what may constitute the dietary patterns of different segments of the population. Too, to be of maximum value, dietary studies should be conducted in the same populations over a span of years, and in most cases such long-term data are rare.

Genetic factors

Although studies of hereditary factors that may be operative in the development of heart disease have opened a number of avenues that might be profitably explored, there are as yet insufficient data to justify strong statements as to the role of heredity in atherosclerosis. The type of genetic study lending itself most readily to the epidemiological approach is the comparison of ethnic, religious, and racial groups living in their native country with groups from the same stock living in different environments as migrants. A number of such studies have been carried out.

An isolated quarter of closely inbred individuals of Jewish faith in Rome is being compared with a selected group of Jews living in New York who are subject to hereditary hypercholesterolemia (excess of cholesterol in the blood).

Studies indicate that, although native Japanese and Italians have a lower incidence of heart disease than do Americans, Nisei and Italian-Americans exhibit about the same incidence as other Americans.

Studies made on Japanese and Chinese living in Hawaii indicate that, although the incidence of heart disease among these two groups is lower than that among whites, it is higher than that in Japan. To what extent these differences are due to changes in the mode of life has not been evaluated.

Studies on young males with clinical heart disease as well as autopsy data suggest that body type may be a factor in relative proneness or resistance to heart disease. The mesomorph (muscular body type) seems more prone to heart disease than are the ectomorph (wiry body type) or endomorph (pudgy body type). Further studies on this problem are indicated, making due allowances for such alterable characteristics as obesity, and choosing for comparative purposes the most clearly recognizable forms of heart disease, such as myocardial infarction and angina pectoris.

Some evidence exists that a higher incidence of mortality occurs among those whose parents died of heart disease than among those whose parents died of other causes. This would suggest a need for long-term studies to determine the incidence of heart disease in parents and siblings of subjects suffering from heart disease for com-

parison with similar data obtained from a group of healthy controls comparable in age, sex, occupation, and other factors. Another approach deserving further study is the comparison of susceptibility to heart disease in identical and fraternal twins.

In connection with these genetic studies, inborn metabolic disturbances which might predispose to heart disease and which might be inherited should be considered.

A high incidence of heart disease is associated with hypercholesterolemia and hyperlipemia (excess of lipids in the blood).

Uncontrolled diabetes appears to produce high serum cholesterol and other serum lipid values, and atherosclerosis is by far the leading cause of death among diabetics. Also noteworthy is the fact that the sharp decline in mortality from atherosclerosis in Sweden, Finland, and Norway during World War II was virtually paralleled by the decline in mortality from diabetes.

Myxedema, a form of hypothyroidism, is associated with an excess of cholesterol in the blood, and victims seem prone to atherosclerosis. The mechanism of thyroid metabolism, as yet little understood, merits a great deal of further study.

Sex factors

In the United States, where incidence of heart disease is high, tremendous differences in mortality exist between premenopausal women and men of the same ages. This difference tends to disappear in postmenopausal age groups. This relative protection against heart disease in premenopausal women appears due to the estrogens, which have been shown to prevent, and even to reverse, the development of atherosclerosis in laboratory animals. Long-term studies are now underway to evaluate the effects of estrogens in modifying clinical heart disease in humans without producing undesirable side effects.

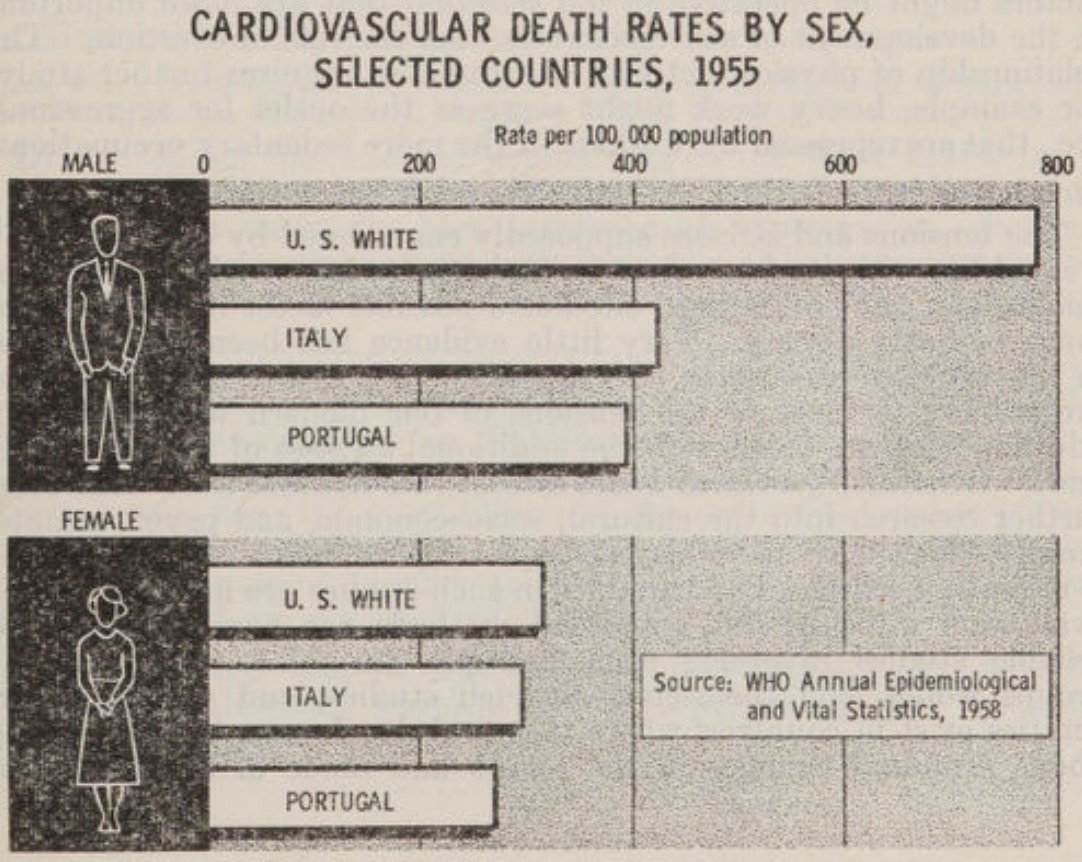

FIGURE 5.—Cardiovascular death rates by sex.

In Portugal and Italy, where the incidence of heart disease is low, however, the differences in incidence between men and women is slight. English studies also indicate that heart disease is more common in married women who have borne no children than it is in those who have borne children.

Studies made on hospital populations in the United States and Sweden also suggest that the differing incidences might be due in part to the male's suffering from types of heart disease characterized by more dramatic and rapidly fatal development, since the numbers of female heart disease patients in hospitals seem higher than might be expected from studies of mortality statistics. Other factors must also be considered: the mode of life of men and women differs in many respects, and these differences should be considered in addition to sex-linked inheritance and endocrine differences.

Occupation and degree of physical activity

Studies in England, Sweden, and Italy indicate that heart disease is relatively rare in persons engaged in heavy work, intermediate in moderately active occupations, and highest in more sedentary occupations. Increasing incidence of heart disease has also been observed in countries where improved technology is bringing about decreased expenditure of energy in various occupations. Since modern technology with its increased automation is oriented toward reducing physical labor generally in most or all jobs and since the amount of leisure is generally increasing, it is important to discover whether the habitual level of physical activity is actually a major factor in the development of atherosclerosis.

But physical activity and expenditure of energy seem related to dietary habits, mode of life, obesity, climate, and other factors. Too, a question not yet answered is whether metabolic and psychological factors might be operative in job selection that are more important in the development of atherosclerosis than the role of exertion. The relationship of physical activity to stress also requires further study: for example, heavy work might serve as the outlet for aggressions, etc., that are repressed by workers in the more sedentary occupations.

Stress

The tensions and stresses supposedly engendered by our "western" way of life with its faster tempo, social insecurity, striving for dominance, etc. have often been cited as a possible factor in the development of heart disease. Very little evidence has been accumulated in this problem area, most of it negative. Even the Bantu, it seems, are subject to most of the tensions of our modern way of life; in addition they are faced with the additional stresses of tribal conflicts and "witchcraft," yet their heart disease rate remains low. However, further research into the cultural, socioeconomic, and psychosomatic factors which may have bearing on the development of heart disease is urgently needed. The variables in such studies are many and their evaluation difficult, but statistical methods are now available for reliable studies involving such multiple variables. Many ethnic groups would lend themselves to such studies, and special opportunities exist in countries where technical developments are bringing about profound changes in the tempo and mode of life of the in-

habitants. (Sources: (1) Sherman, M.: Diet, Hormones, and Atherosclerosis (National Heart Institute) Washington, D.C.: Government Printing Office, 1959. (2) World Health Organization Technical Report Series No. 143. (3) World Health Organization Technical Report Series No. 168. Geneva: WHO, 1959. (4) Cardiovascular Diseases, Section XVIII, Excerpta Medica.)

Epidemiology of hypertension

Hypertension is a disease area in which the epidemiological approach offers some unique advantages. Hypertension is divided roughly into two broad categories. These are primary hypertension (which is what we generally know as high blood pressure and comprises the great majority of hypertensive patients) and secondary hypertension (which is hypertension resulting from certain specific conditions). It is extremely important in the study of hypertension to realize that almost all means of producing experimental elevations of blood pressure produce secondary hypertension and may have little or no bearing on primary hypertension, the big health problem.

Clinical studies have given us great hope for the better management of the hypertensive patient. But for the study of primary hypertension itself, definition of the disease and its causes, epidemiological studies are essential because of the nature of the disease. It has been believed for some time that hypertension is a disease in which both hereditary and stress components are particularly important. The relationship between genetic and environmental factors in hypertension, however, is yet to be defined.

Studies of incidence in different racial and ethnic groups have provided a good beginning in the epidemiological study of hypertension.

High blood pressure is probably more frequent in the Orient than in the United States or Europe—

Dr. Henry Schroeder, of Washington University, reports:

Areas where incidence of hypertension is high, in descending order of frequency, are Beirut, Manila, Hong Kong, Bangkok, Taipei, Bombay, Luchow, and Agra.

Dr. M. Moser has selected populations of the West Indies for a study of the relationship of many environmental factors in a racial group with an unusually high incidence of hypertension. Several studies have been made of the high incidence of hypertension in the American Negro and the low incidence of hypertension in African groups.

It is obvious from the epidemiological studies now going on in hypertension that this field is international by its very nature. In 1956, at the Conference on Epidemiology of Atherosclerosis and Hypertension held by the National Heart Institute and the American Heart Association, the contribution of the epidemiological approach to hypertension was discussed in great detail. Among the factors suggested as having a possible relationship to the cause or course of primary hypertension were the following:

> Host: Age, sex, race, heredity, constitutional type, psychological influences, physical activity, pregnancy, and vascular hyperactivity.

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These are only a few of the studies now being reported. But it is clear that efforts are being made to acquire the preliminary data on hypertension called for in the 1956 Conference, and it is important to see that these efforts are by no means limited to the United States.

(Sources: (1) Report of Conference on Epidemiology of Atherosclerosis and Hypertension. Held at Arden House, Harriman, N.Y., January 29–February 2, 1956. New York: American Heart Association, 1956. (2) Report of Conference on Methodology in Epidemiological Studies of Cardiovascular Diseases. Held at Princeton, N.J., April 24–26, 1959. New York: American Heart Association (yet to be published). (3) World Health Organization Technical Report Series No. 168. Geneva: WHO, 1959. (4) Cardiovascular Diseases, Section XVIII, Excerpta Medica.)

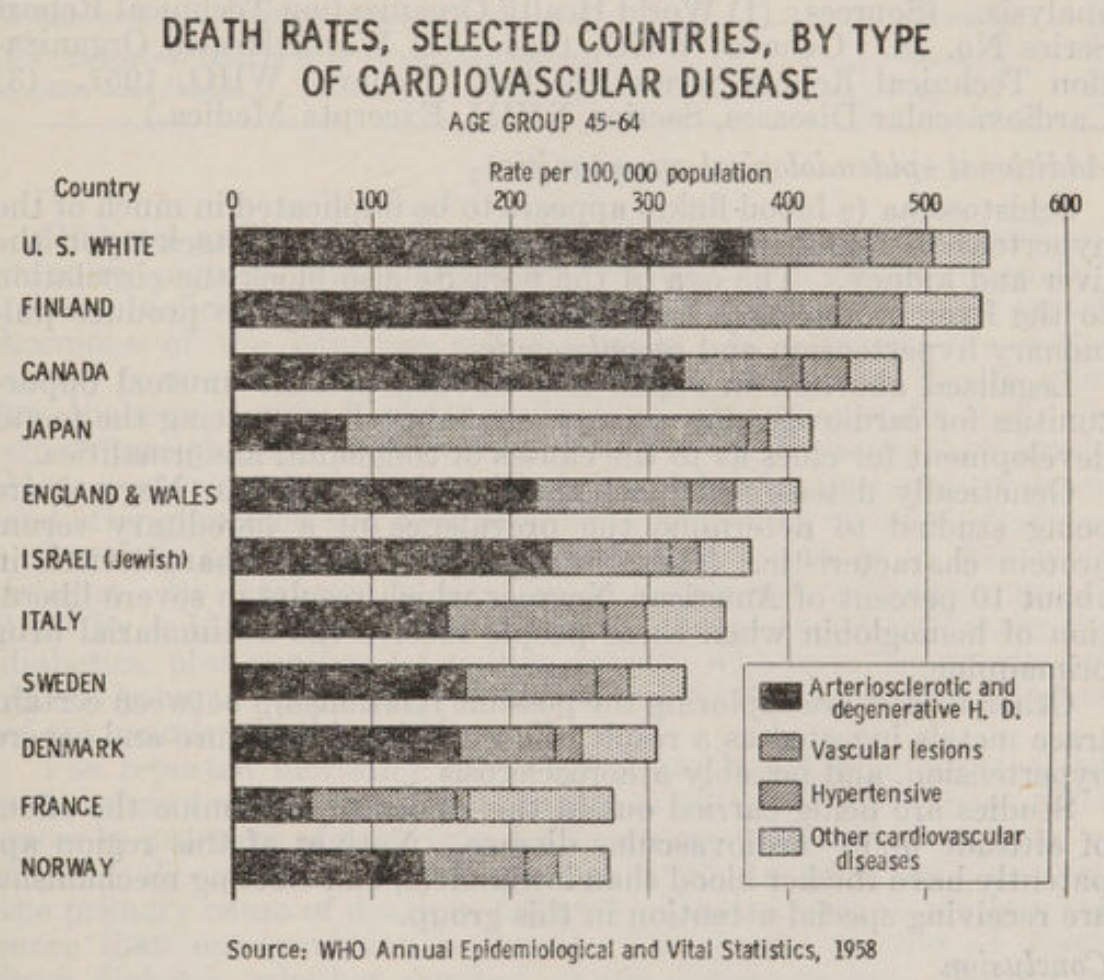

FIGURE 6.—Death rates, selected countries, by type of cardiovascular disease.

Epidemiology of rheumatic fever and rheumatic heart disease

Rheumatic fever and rheumatic heart disease have been studied epidemiologically for years. The relationship of streptococcal infection to the onset of rheumatic fever has been demonstrated epidemiologically and is the basis for programs of prevention and control; this, in spite of the fact that the mechanism by which streptococcal infection causes rheumatic fever is still unknown.

During or since the Second World War numerous statistical studies of the prevalence and incidence of rheumatic fever and rheumatic heart disease have been made in the United States, Israel, England, France, Sweden, Italy, Mexico, and the Netherlands. No definite

conclusions about the cause or development of rheumatic fever and rheumatic heart disease can be drawn from the studies so far, however.

The general features which emerge from these prevalence studies mostly concern age and sex incidence. The prevalence of rheumatic fever would appear to be profoundly affected by the age of the host, environment, and probably hereditary factors. Sex, race, and nutrition have not been shown to be significant in the development of rheumatic fever. The prevalence of rheumatic fever varies greatly, being higher in the temperate zones of the earth than in the regions further north or further south. The influence of geography on the prevalence of the disease is extremely complex and inextricably bound up with climate, housing, occupation, population density, and socio-economic factors—each of which deserves careful epidemiological analysis. (Sources: (1) World Health Organization Technical Report Series No. 78. Geneva: WHO, 1954. (2) World Health Organization Technical Report Series No. 126. Geneva: WHO, 1957. (3) Cardiovascular Diseases, Section XVIII, Excerpta Medica.)

Additional epidemiological opportunities

Schistosoma (a blood fluke) appears to be implicated in much of the hypertension found in Egypt through its parasitic attack upon the liver and kidney. The ova of the parasite also block the circulation to the liver producing a hepatitis and to the lungs to produce pulmonary hypertension and *corpulmonale*.

Legalized abortion in Japan and Sweden present unusual opportunities for cardiovascular research on embryology, tracing the foetal development for clues as to the causes of congenital abnormalities.

Genetically determined biochemical traits in African Negroes are being studied to determine the prevalence of a hereditary serum protein characteristic. There is apparently such a characteristic in about 10 percent of American Negroes which results in severe liberation of hemoglobin when these people receive the antimalarial drug primaquine.

Other studies are exploring the possible relationship between certain trace metals ingested as a result of occupational exposure and severe hypertension, and possibly atherosclerosis.

Studies are being carried out in the Andes to determine the effect of altitude upon cardiovascular disease. Natives of this region apparently have thicker blood than lowlanders, and clotting mechanisms are receiving special attention in this group.

Conclusion

It would be difficult to produce a better closing statement on the need for a concerted international effort against cardiovascular disease than that delivered by Dr. Paul Dudley White [11] in the Biggs Lecture before the New York Academy of Medicine in 1940. It is as true today as it was then.

Statistics from surveys are slowly accumulating in this country and in certain other countries—

said Dr. White—

but by different uncorrelated groups, making them often difficult or even impossible for direct comparison. We need a large, well-organized study that can in a

[11] Dr. White's testimony before this subcommittee will be published shortly in a hearing volume.

several year program collect information, not just from clinics or from private practice, but from entire communities that will really show how common are hypertension and rheumatic valvular disease and syphilitic aortitis and coronary heart disease in relation to climate and mode of life * * * well and similarly trained groups armed with good clinical observers, stethoscopes, sphygmomanometers, electrocardiographs, X-ray apparatus, and autopsy technic could, in a few years, accomplish more than the next century of desultory work, and [would] cost less than a single air raid over a city at war.

TABLE A.—*Diseases included in charts follow international statistical classification codes*

	Detailed numbers	Summary list numbers
1. Arteriosclerotic and degenerative	420–422	B26
2. Vascular lesions CNS	330–334	B22
3. Rheumatic fever and rheumatic heart disease	400–416	B24, B25
4. Hypertensive disease (with or without involvement)	440–447	B27, B28
5. Other heart disease	430–434	B29

C. DIABETES

Diabetes mellitus is a chronic, inheritable metabolic disorder found in every country, and affecting every race. It is characterized by a relative deficiency of, or an inability of the body to use, a protein hormone of the pancreas called insulin. As a result, the body's ability to convert blood sugar into energy is impaired. In this country, diabetes is more likely to strike those who are over 40, those who are overweight, and those with a history of the disease in their family. More women get it than men. It is the eighth leading cause of death, and after glaucoma and cataract, the third leading cause of blindness.

Accurate knowledge on the international incidence of diabetes is meager. Its incidence in the United States was estimated early in 1959 by a U.S. Public Health Service official at 1.5 million known diabetics, plus another 1.4 million persons who have the disease and do not know it. This degree of incidence is believed to be the highest of any country in the world.

The reported mortality rate of diabetes in different parts of the world shows an extremely wide range, in part because of great differences in practices of reporting death causes. For many countries no data at all are available. There are varying methods of classifying the primary cause of death in different offices of vital statistics where more than one condition is stated. The great majority of deaths from diabetes, whether ascribed to the disease or not, actually are due to or associated with various complications of a degenerative nature, so that even mortality figures do not provide a good indication of the known or estimated prevalence of the disease. Even with an allowance for different reporting methods, mortality figures indicate that the United States has the highest death rate from diabetes, with other English-speaking countries including Canada, Australia, and New Zealand closely following. The death rate is lower in eastern and southern Europe, in Central and South America and Asia, and lowest of all in the underdeveloped countries. Of the European countries Denmark and Belgium reported higher rates than Austria

and Germany. The contrast in incidence of the disease between the United States and Japan is striking. (See fig. 7.)

The reasons why diabetes varies so widely in incidence and death rate are not known. There is ample evidence of a direct association of the disease with abundant nutrition and the association of the disease with obesity is well recognized. One study in the United States indicates that about 85 percent of those who have become diabetic at the age of 40 or above are overweight. In some diabetics weight reduction diminishes the diabetic symptoms, and may even obviate the need for medication. Striking decreases in the incidence and severity of diabetes accompanied the loss of body weight in certain European countries during both world wars. When the food supply increased after the war, so did the incidence of diabetes.

The association of diabetes with abundant nutrition does not hold true, however, in the case of several European countries as compared with others which are similar in population structure, standard of living, and medical and public health organizations. There are great reported differences, for example, between the diabetes incidence in 1956 for Denmark and Austria, as compared with France and Belgium. In each of the four countries, nutrition standards were relatively high, yet the incidence of diabetes varied widely. (Source: "Diabetes—Overweight: U.S. Problems." Hundley, J. M., Journal of American Dietetics Association, Vol. 32, pp. 417–422 (1956).)

Coordinated investigation of the reported difference in diabetes incidence throughout the world would prove of great value in the study of this widespread disease. Dependable new data on the actual incidence, provided by surveys or other sources of morbidity statistics, are a vital need.

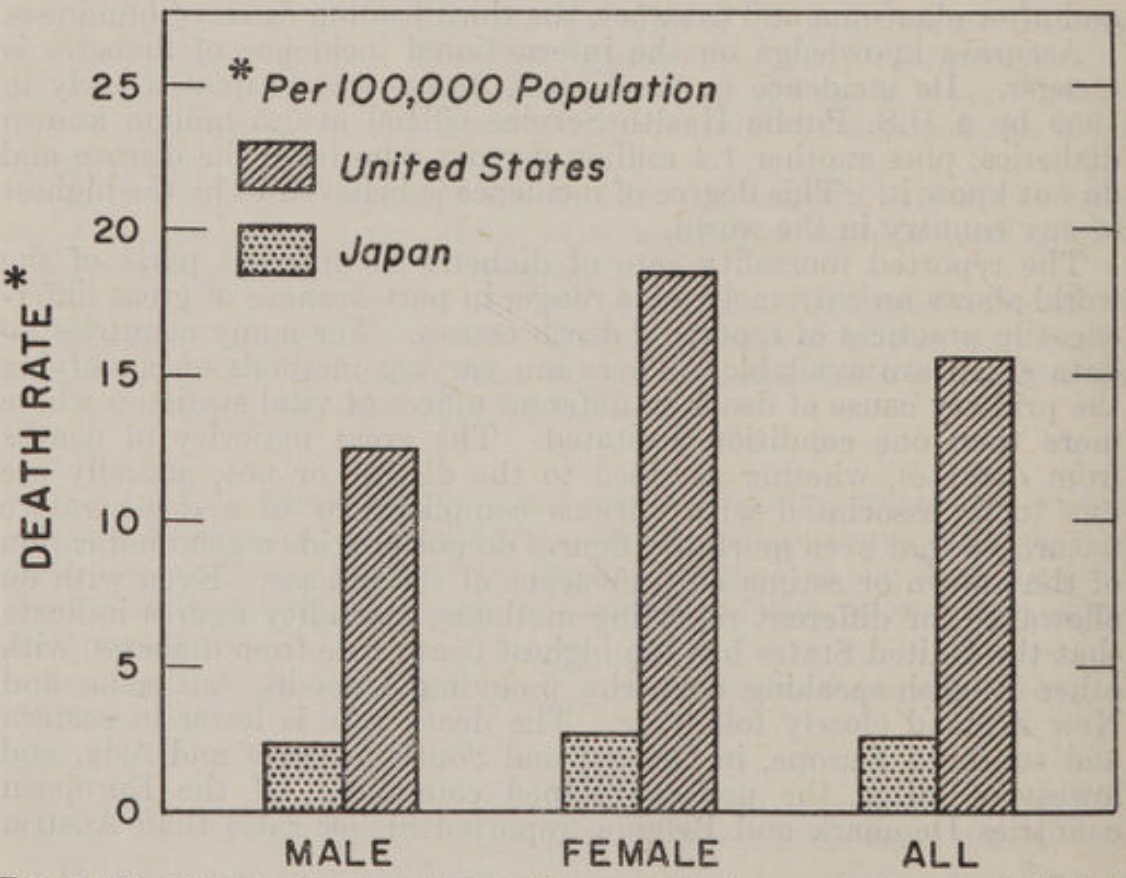

FIGURE 7.—Diabetes death rate for total population by sex for Japan and United States, 1955.

Spot checks in several countries indicate an increase in the diabetes death rate in the past 20 or 30 years. These increases have been usually greatest in countries with the highest rates. In part, this upward trend reflects the increased average age of the populations, the maintenance of higher standards of living, and improvement in medical care, as well as intensive new efforts to detect the disease by means of testing programs such as that conducted in this country by the American Diabetes Association.

Before the discovery of insulin in 1921, the outlook for the person with diabetes was very poor. Today, the disease can be controlled so successfully that most people who have it do not have to make great changes in their usual living habits. The use of insulin and other drugs has lengthened the lives of people with diabetes. The achievements of modern treatment are clearly reflected by the long-term decline in the death rate from diabetes in childhood and among young adults. The drastic reduction in diabetes mortality in this period of life shows effectively the boon which insulin has brought to the young diabetic.

The development of "substitutes" for insulin has been rapid since 1957 and today about half a million diabetics in the United States are using oral antidiabetic compounds. Such widespread use of these drugs offers medical science a useful new means of studying the action and nature of diabetes, and of learning more about how these drugs affect the metabolic functions of the body.

D. ARTHRITIS

Arthritis is a crippling disease that is known to occur in almost all parts of the world. Although great advances have been made in its treatment, the basic cause or causes are still unknown and until they are fully understood, it is doubtful that a cure will be found. By providing important clues to some of these basic causes, international research in arthritis would be most valuable.

International studies would provide us with a better understanding of the predisposing factors in this disease. Apparently, certain groups of people within a population are more susceptible to arthritis than others, and certain populations as a whole have a higher incidence of the disease than others. Careful examination of the differences between these groups on a worldwide scale might provide essential information about why some people get arthritis and some do not.

The many possible predisposing factors include differences in climate and humidity, differences between industrial and nonindustrial populations, and differences between urban and rural ones. A geographical study of rheumatoid arthritis, the most crippling form of the disease, was recently made in Great Britain and points up how the incidence of the disease may vary from one area to another. A comparison was made between the town of Leigh and the Vale of Glamorgan in South Wales, and revealed that the rural population of the Vale had considerably less rheumatoid arthritis. Definite rheumatoid arthritis was found in 2.3 percent of the Leigh females but in only 1 percent of those in South Wales. (Source: Arthritis and Rheumatism Foundation. "Population Studies in Rheumatoid Arthritis: 1957," pp. 13–26.)

Is the difference a question of latitude? It has often been suggested that rheumatoid arthritis is infrequent in tropical countries. Similarly, a relationship to humidity or a racial influence might be argued. But conclusions about these will require further data from the comparison of populations both within a single country and among several countries.

Genetics, as indicated earlier in this publication, is another important research area that could be illuminated more fully by international research. The genetic studies are needed to clearly define the importance of hereditary factors in the development of arthritis. The most reliable way to do this is to study identical twins, especially in comparison to fraternal twins, and see if an individual's genetic makeup makes him more or less susceptible to the disease. Because the numbers of both identical and fraternal twins are limited in any one country, an international research project would provide data on a great number of twins. Also in some countries, particularly the Scandinavian ones, valuable central registries of diseases have been developed, including information on not only the contagious diseases but also on those thought to be hereditary. In Denmark this registry is quite complete since long ancestral lines are on record and all citizens report to the Government whenever they move.

International research would uncover any differences in the forms of arthritis, as they occur in various countries. We know too little about the similarities or differences between the types of arthritis occurring in this country and those which may occur in other geographical areas of the world.

E. SICKLE-CELL ANEMIA

The story of sickle-cell anemia provides a good example of how international medical research could provide information about biochemical variations between human beings throughout the world, and how these variations may make certain people more susceptible to disease than others.

Sickle-cell anemia is an inherited disorder found predominately in the Negro race and distinguished by the presence of an abnormal type of hemoglobin in red blood cells. Hemoglobin is the material in the cells which enables them to carry oxygen throughout the body. Sickle-cell hemoglobin differs in its molecular structure from normal hemoglobin and causes the red cells to twist into a sickle shape after they have released their oxygen in the body. Because of this change in shape, the blood cells are no longer able to pass freely through many of the smaller capillaries of the blood system. The twisted cells often pile up, causing blood clots and blocking off the flow of blood. When the obstruction is extensive it causes death.

This striking finding in biophysical research, which related a change in molecular structure to a disease process, represented the first definition of a "molecular" disease. Since then, the basic biochemical defects in other molecular diseases such as galactosemia and alkaptonuria have been determined.

In certain parts of East Africa, hemoglobin studies done on the natives have shown that a large number of them have the sickle cell hemoglobin. In some cases, all or almost all of the body hemoglobin is of the abnormal type and many of these individuals, known as

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The morbidity of peptic ulcer is of serious concern in every country because the disease so often affects men and women in responsible positions at the peak of their most productive periods, and because it may recur often. Peptic ulcer, taken together with other, less common, diseases of the gastrointestinal tract, ranks second only to heart disease in this country in number of illnesses requiring attendance by a physician. Autopsies and X-ray studies have shown that about 10 percent of all persons in the United States suffer at some time in their lives from a chronic gastric or duodenal ulcer.

Peptic ulcer offers a fertile field of investigation internationally, for a wide variation in incidence has been reported in different countries. A low incidence, for example, has been reported in certain sections of northern India and in Malaya, Java, and Sumatra. Confirmation by careful surveys of these variations in incidence and assessment of the underlying reasons would help to determine the cause and nature of the disease. (Source: "Methods of Geographic Pathology." Report of the study group convened by the Council for International Organizations of Medical Sciences, Chas. C. Thomas, Springfield, Ill., 1959.)

This varying incidence of peptic ulcer in different parts of the world was pointed up in May 1958, when nearly 2,000 clinicians and investigators from 50 countries met in Washington, D.C., to attend the Third World Congress of Gastroenterology.

In a country partially detached from world stresses, Switzerland, a lower incidence of duodenal ulcer than in other countries was reported, and hemorrhage was found to be a rare complication. Among a group of 17,500 miners working at high altitudes in Peru, the stomach was found to be the most frequent ulcer location, hemorrhage was a frequent occurrence, and the age of the patients was much younger than in other countries.

Consistent findings reported by scientists at the Congress from most nations, however, included a higher incidence of duodenal ulcer as compared to gastric, a considerably higher incidence of ulcers in males as compared to females, a maximum age incidence between 40 and 70 years, and a greater number of smokers among ulcer patients than in the general population.

With regard to social status or occupation, an English investigator reported that duodenal ulcers were more likely to occur among people with responsible positions and less likely among agricultural workers. For gastric-ulcer cases, however, a higher rate was found among laborers than in semiprofessional and professional groups.

A scientist working in Syria reported that peptic ulcer was a frequently encountered disease in the Middle East. Although the aspects of life are different in Asia from other continents, he found in a group of 635 ulcer patients that 92 percent of the cases were duodenal and only 7 percent gastric, coinciding with the worldwide preponderant incidence of duodenal ulcer over gastric.

Analysis of the variety of data presented at the International Congress indicated that more peptic-ulcer research is needed throughout the world on the roles of seasons, diet, occupation, emotional stress, and genetic factors; the significance of the latter influence is suggested by higher incidences of ulcer in families and association with particular blood groups.

G. DENTAL DISEASES

Dental disease is a term used to refer to a broad spectrum of disorders of the teeth and their adjacent structures. These disorders are generally noncommunicable and chronic in nature. They include not only tooth decay but also diseases of the gums, the cheeks and lips, the throat, the jaws and their related muscular and skeletal components.

Early dental research activities of the U.S. Public Health Service centered around the study of an endemic dental disease known as mottled enamel. These investigations included epidemiologic, chemical, and experimental studies. The epidemiologic studies yielded a relatively precise quantitative data on the relation of the disease to the fluoride concentration of the domestic water and pointed significantly to the conclusion that fluoride in drinking water is responsible for mottled enamel. In subsequent years, the beneficial effect of certain levels of fluorides on dental caries was demonstrated. We now have water fluoridation as an effective dental public health control measure. Thus, as a result of the epidemiologic approach during the past three decades, dental research in this country has provided methods for preventing one dental disorder and partially controlling another.

Recognizing that a major fraction of the American adult population is afflicted with periodontal disease, research emphasis is currently being focused on this category of oral disease. In recent years the development and testing of field methods for the measurement of this disease of the gums in large population groups in this country has made significant progress. However, periodontal, as well as most oral disease, is international in scope; and the dental-disease profile of the U.S. population reflects only a small fraction of a worldwide pattern of prevalence and severity. In light of a recognized and oftimes wide contrast in world population groups, the dental scientist would be derelict not to examine closely the implications and potentialities in terms of research opportunities for advancing knowledge, particularly through epidemiologic study in foreign lands.

We know, for example, that the principal dental problems both in this country and abroad are related to the great prevalence of at least two disorders—dental caries and periodontal disease—and to the lack of basic knowledge concerning their respective etiologies. Research has already shown that these diseases are most likely not the result of a single agent but rather a plurality of integrated conditions. Because of this aspect of both a multiple and nonspecific etiology conception, it becomes necessary, through meticulous research, to isolate and group each of the various causal elements. Only in this way will it be possible to evaluate their interaction in the etiologic pattern.

Findings in India

In recognition of the need to study oral disease among other population groups, the Public Health Service extended its dental epidemiological program in 1957 to include selected foreign countries. In that year, the National Institute of Dental Research cooperated with the University of Michigan in studies of periodontal disease initiated by the Government of India through its Council for Medical Research

and the World Health Organization. Data gathered from this study program have shown, for example, that (1) a considerably more advanced gingivitis exists at earlier ages in India than is seen in the United States, (2) calculus formation occurs at earlier ages and more rapidly in India than in similar groups in this country; and (3) persons studied in rural areas around Bombay had more severe periodontal disease than did those in the city of Bombay. (Source: Personal communication, chief dental officer, Public Health Service.) The rural persons also had more calculus than did the urban residents. In the study of dental caries in India, other investigators have reported an average of less than one decayed tooth per person 15 years of age. In other words, the rates are far below those recorded in the optimum fluoride areas in the United States. The obvious question that comes to mind is, What factors are responsible for this low rate of decay? Chemical analyses have shown that these people do obtain some fluoride through their water or diet, but this does not fully explain the extremely low incidence of caries.

Also unanswered is the reason for the magnitude of the periodontal disease problem seen in India. Perhaps the prevalence of calculus in the Indian population studied is partly the answer. But, why should they have more calculus than similar groups in this country?

Of even greater interest in the Indian study was a second and highly important objective concerning the encouragement and training of native dental investigators in epidemiological research techniques to assure continuous study of oral diseases in India. That this objective is approaching accomplishment is indicated by the fact that one dental team in the Bombay area has independently completed a survey of some 4,000 children, and that the Indian Council for Medical Research recently made grant-in-aid awards to 2 additional clinical teams. These developments are indicative of significant accomplishments in the vital area of dental research education made possible by the extension of American research activities to this foreign country.

Data on Eskimos

More recently, epidemiological studies of periodontal disease have been extended to other global areas. Coordinated with a study sponsored by the Interdepartmental Committee on Nutrition for National Defense, and in conjunction with the Public Health Service Arctic Health Research Center, a field survey was initiated in 1958 to study a group of Eskimo men of the Alaskan National Guard. In comparing the prevalence of oral disease in individuals living under relatively civilized conditions with that of men from primitive villages, it was found, for example, that many of the latter were essentially free of both dental caries and periodontal disease. Early findings seem to indicate that when Eskimos have lived for some time under relatively civilized conditions, the prevalence of oral disease increases to a point quite comparable to the average adult male population in the United States. (Source: Interdepartmental Committee on Nutrition for National Defense, "Alaska—Appraisal of the Health and Nutrition Status of the Eskimo," August 1959.) Similar studies, also in collaboration with the Interdepartmental Committee on Nutrition for National Defense, have recently been completed in Ethiopia and Peru. Data collected under different environmental conditions from primitive and civilized areas of these countries will afford a check of pre-

viously obtained data. Such data is expected to give greater insight into the influence of nutritional and environmental factors on oral health.

There are opportunities for further epidemiological studies in the United States, but these are overshadowed by still greater opportunities in other lands. By participating in a limited number of studies in several underdeveloped countries of the world, the dental investigator has already had the opportunity to see firsthand the oral status and observe the habits of people in simple primitive villages that in the main have gone unchanged for centuries. Under such conditions the research investigator has observed how the picture can and does change in orderly or perhaps erratic progression from village to village, gradually advancing toward areas with more modern culture.

Benefits for studies abroad

Finally, it must be emphasized that these are fertile fields in foreign lands for conducting a great variety of dental research studies. The subcontinent of India has been cited only as an example, as there are many other countries in which these same opportunities exist. Of no less significance is this point borne out by experience: Where such health research activities are conducted, we not only add substantially to our still incomplete knowledge, but the host country invariably benefits from its cooperation in such activities.

Inasmuch as dental diseases are not among the killers, it is ofttimes difficult to elicit concern and even a token interest in the dental health problems of the people in the underdeveloped parts of the world. Some notion of the level of dental needs may be gained from two examples—that of Burma, where only 19 trained dentists are available to serve the needs of 20 million people; and in Ethiopia where there are only 12 qualified practicing dentists to administer to a population of 19.5 million. (Source: Personal communication, Chief, Epidemiology and Biometry Branch, National Institute of Dental Research.) Further, in these and other countries, there is little or no semblance of proposals or plans for action which will foster the evaluation of a cadre of dental research personnel, so that the future situation will be better than the present. Toward this goal, the further extension of global health activities through medical-dental research cannot help but accrue benefits for people and nations associated with such ventures.

H. MENTAL ILLNESS

There is great need for research on an international level in the field of mental illness and mental health. In a recent WHO report the problems in this field were highlighted by pointing out the "relatively early and unsatisfactory knowledge regarding the etiology (study of causes of a disease) and epidemiology of mental disorders."

There is evidence that mental disorders are found in all parts of the world but that social and cultural differences and attitudes have a bearing on frequency and the nature of clinical manifestations of these diseases.

At the present time the only statistical data on the prevalence and incidence of mental illness are those provided through records of hospitalized mentally ill. Not all countries have such data and even

the available information is not suitable for comparative purposes either from one country to another or regions within the same country. Among the basic issues to be resolved before such comparisons are possible are:

1. Agreement on what constitutes a case of a specified type of mental disorder;

2. Development of standardized case-finding methods for detecting cases in the various population groups and standardized methods of classification;

3. Devising standardized methods for measuring duration of illness and for characterizing the psychologic status, the degree of psychiatric disability, social and familial adjustment, and physical condition at various intervals following onset of disease.

A working paper on the "Epidemiology of Mental Disorders" prepared by the Expert Committee on Mental Health, WHO, points up some of the difficulties in obtaining data on mental disorders but goes on to emphasize the needs for such studies. It points out that in this way the limits of our knowledge can be defined and we can build up a body of fact and theory to be used in the control of mental illness. Four reasons given as contributing factors to the difficulty of epidemiological studies in the field of mental disorders are:

1. Mental disorders are different in many ways from other diseases. Individual factors in the causes and manifestations of many psychiatric diseases cannot be measured. There are, on the other hand, general and quantifiable aspects of mental illness which are important from a public health point of view.

2. Available information suggests there is a multiplicity of causes in all types of mental disorders. In these diseases one must study genetic, physiological, and psychological factors.

3. The lack of uniform nomenclature, and social and cultural differences in what is considered deviant behavior.

4. Very little is known about mental health itself. We are not sure about the factors which make some individuals and groups able to withstand stresses while others succumb. It is important then to remember that the epidemiology of mental disorders must be accompanied by an epidemiology of mental health.

Since knowledge of the extent and various types of mental disorders in the world today is limited, it is important to encourage epidemiological studies and other kinds of research. Epidemiological studies have provided insight into the causes of other diseases and may well do the same for mental disorders. The present thinking that mental disorders undoubtedly result from a combination of factors opens up many channels for research. The WHO has a unique opportunity for fostering investigations in different population groups with varying socioeconomic and cultural characteristics. Recommendations being made for projects in connection with the observance of World Mental Health Year in 1960 include—

(*a*) collaborative studies with geneticists to investigate the relevance of recent developments in population genetics to the understanding of changes in distributions of mental disease in different countries;

(*b*) studies of the influence of prenatal factors in the production of brain damage;

(*c*) pilot projects on the development of case-finding studies in different areas; and

(*d*) studies of the reliability and comparability of psychiatric diagnosis made by psychiatrists in different areas of the same country as well as between countries.

It has also been recommended that one study might be made which would demonstrate the role of epidemiological research in establishing the etiology of mental disorders. The study of relationships of prenatal factors to subsequent development of mental disorders was also suggested. This problem could be approached in a country with a low standard of living by studying the effect of increasing food supplies, prior to conception and during pregnancy, on the incidence of specific mental disorders among infants and children.

World Mental Health Year activities in 1960 are also designed to stimulate mental health education of the public, research, and the dissemination of research findings and program information.

I. NEUROLOGICAL DISORDERS

There is reason to believe that some of the answers to unsolved neurological problems could be found by pooling all detailed scientific information, reviewing it carefully, and moving forward on the basis of this new knowledge. In some instances this would undoubtedly lead to studies in the geographic and population distribution of disease. Studies of this nature have provided answers in the past, and presently, scientists are aware of a number of leads in the field of neurology. Among the neurological disorders in which epidemiology studies encompass research possibilities are cerebrovascular diseases, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, neurological disorders of childhood (cerebral palsy and mental retardation), and disorders of muscle (muscular dystrophy).

Cerebrovascular diseases

Cerebrovascular diseases, which quite frequently result in stroke, are the third ranking killer and the foremost crippler among all diseases in the United States. In primitive areas where people on the average die younger than in the United States, not as many persons live to reach the period when stroke becomes common. In other words, the seriousness of stroke in America may reflect assets in our health picture, rather than some invidious factors causing more stroke here than elsewhere. (Source: "Demographic Yearbook," a United Nations Publication, by Statistical Office of the United Nations, Department of Economic and Social Affairs, New York, 1958.)

Nevertheless, in the United States almost 190,000 persons die every year from cerebrovascular lesions, and of these about 40,000 are in the "working age" group of 25 to 64 years. When cerebrovascular diseases do not kill, they often leave a person disabled. Such disability adds to 1 million Americans presently crippled because of these disorders of the brain. (Source: "Vital Statistics of the United States, 1957," Vol. 2, U.S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics. Published, Government Printing Office, 1959.)

This is an economic toll as well as one of misery; our research investment in prevention and treatment provides economic returns on each step of progress. Already the mortality rate from rupture of ballooned, weakened arteries can be dropped significantly by surgical correction before such aneurysms break.

For an overall attack on stroke and cerebrovascular diseases, epidemiological studies of a variety of nations may reveal factors in modes of living which will help to correct the American problem.

Cerebrovascular diseases appear to be more frequent in American Negroes than in the white population, in spite of an average lower age at death in Negroes. Because cerebrovascular diseases are heavily weighted in the elderly age span, this frequency of cerebrovascular diseases in Negroes may be more significant than statistics indicate. Epidemiological studies are needed to determine whether this is a reflection of differences in diagnosis or differences in range of blood pressure, diet, or other factors.

Recorded rates from around the world require considerable interpretation. (Source: Merritt, H. Houston, M.D., citizens' testimony, House Appropriations Committee, 1959.)

The low rate of cerebrovascular deaths in Norway from brain hemorrhage, embolism, and thrombosis of 56.8 per 100,000 compared to the U.S. rate of 90.7 may be explained because many Norwegian deaths were reported in a different category. An epidemiologist suggests that the real rates are about on a par. A similar explanation may account for the apparent low rate in Ireland of 69.2 per 100,000. However, the high rate in Japan of 198.1 per 100,000 is unexplained.

Cerebrovascular lesions are reported as the leading cause of death in Japan, with almost twice the American mortality. Does this indicate a genetic predisposition, a dietary or other environmental influence, or does it reflect a difference in medical reporting? (Source: Unpublished data, Epidemiology Branch, NINDB, 1959, Kurland, L., Myrianthopolous, N., and Siedler, H.)

International study on blood vessels

Basic research is not confined to test tube or animal investigations. A basic study on the most common cause of stroke, the narrowing of blood vessels serving the brain, focuses on humans.

Scientists, through support of the National Institute of Neurological Diseases and Blindness, made a systematic study of a large series of subjects, carefully evaluating the location and degree of narrowing of the brain arteries of all sizes.

The changes found in these arteries are being correlated with the age of the patient, the sex, the diet, and other factors which might hasten the narrowing of blood vessels.

These changes will be compared with alterations in the blood vessels of subjects of similar ages in different countries around the world. Such an international study may well offer leads in the understanding of the causes of this narrowing of blood vessels serving the brain.

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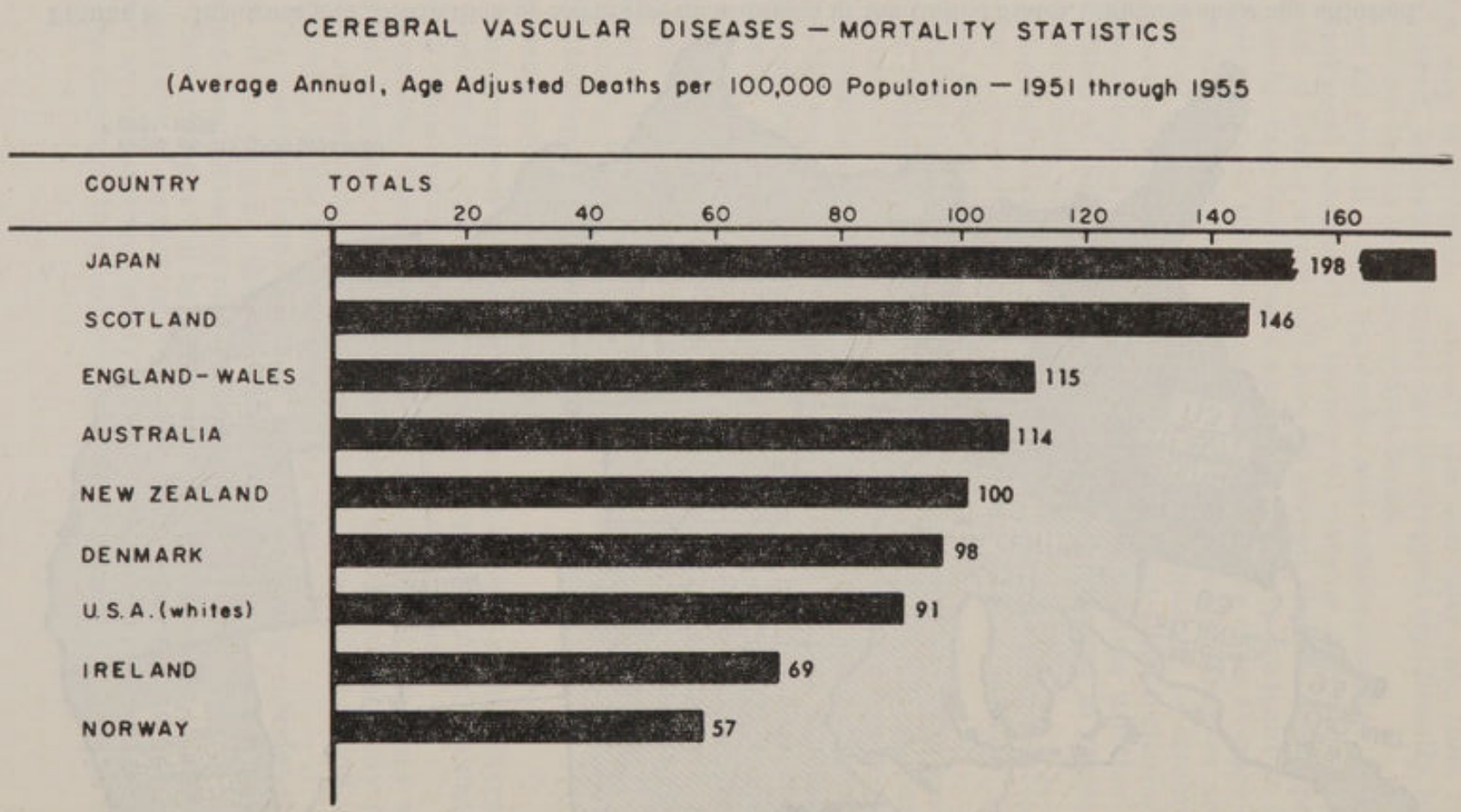


FIGURE 9.—Death rates from cerebral vascular disease, selected countries.

Multiple sclerosis

Multiple sclerosis is one of the neurologic "demyelinating" disorders affecting perhaps half a million Americans, usually in their youthful prime between 20 and 40 years. Multiple sclerosis is termed a "demyelinating disorder."

Myelin is the fatty insulating sheath which covers nerves. When myelin disappears in scattered patches, the patient suffers a variety of symptoms depending upon which nerves are damaged. Weakness and difficulty in walking and talking are common results. Neither cause nor cure has been proven for multiple sclerosis.

Because multiple sclerosis disables individuals for many years, research in demyelinating disorders is a major concern of the National Institute of Neurological Diseases and Blindness.

Multiple sclerosis is strangely and dramatically more prevalent in colder than in warmer climates (fig. 10). In tropical and subtropical climates it is rare—at least, to date, reports of cases of it in the tropics are rare.

MS may occur from 5 to 10 times as often in the northern states as in the Carolinas or New Orleans, for example. The rate among Negroes in Boston is higher than among Negroes in New Orleans and suggests that some feature of geographic exposure and not of race is crucial in MS. Yet there is no indication that incidence varies with the season.

The higher prevalence in Canada and Northern United States is similar to rates for Denmark, northern Scotland, and northern Ireland.

This variation of occurrence of MS with variation in geography is one of the more interesting and intriguing problems of neurology. Many questions have been raised by epidemiologists. Does the cold winter temperature account for more MS in northern United States and Canada than in our Southland? Could a soil difference be the cause? A difference in racial stock? Or some unsuspected factor?

Although MS is more prevalent in colder parts of America and Europe, it is considered to be uncommon in Japan, yet the Japanese climate in most areas is similar to that of northern portions of America. Is this truly a smaller incidence of MS in Japan? Or does less vigorous case finding account for fewer known cases, since multiple sclerosis is difficult to diagnose? (Source: References quoted by L. Kurland, Epidemiology Branch, NINDB, 1959.)

The epidemiological surveys of the National Institute of Neurological Diseases and Blindness are credited with the direct stimulation of active clinical research centers of neurology in two Japanese universities. As more neurologists become interested in research in Japan, improvement in case finding may help to solve some of the questions raised by epidemiologists.

The newest proposed explanation of the geographic variations of MS arises from the fact that the difference in rate of MS correlates unusually well with the geomagnetic latitudes of the world. It has been suggested that the geomagnetic latitude influences the ability of high velocity cosmic particles to penetrate the earth's atmosphere.

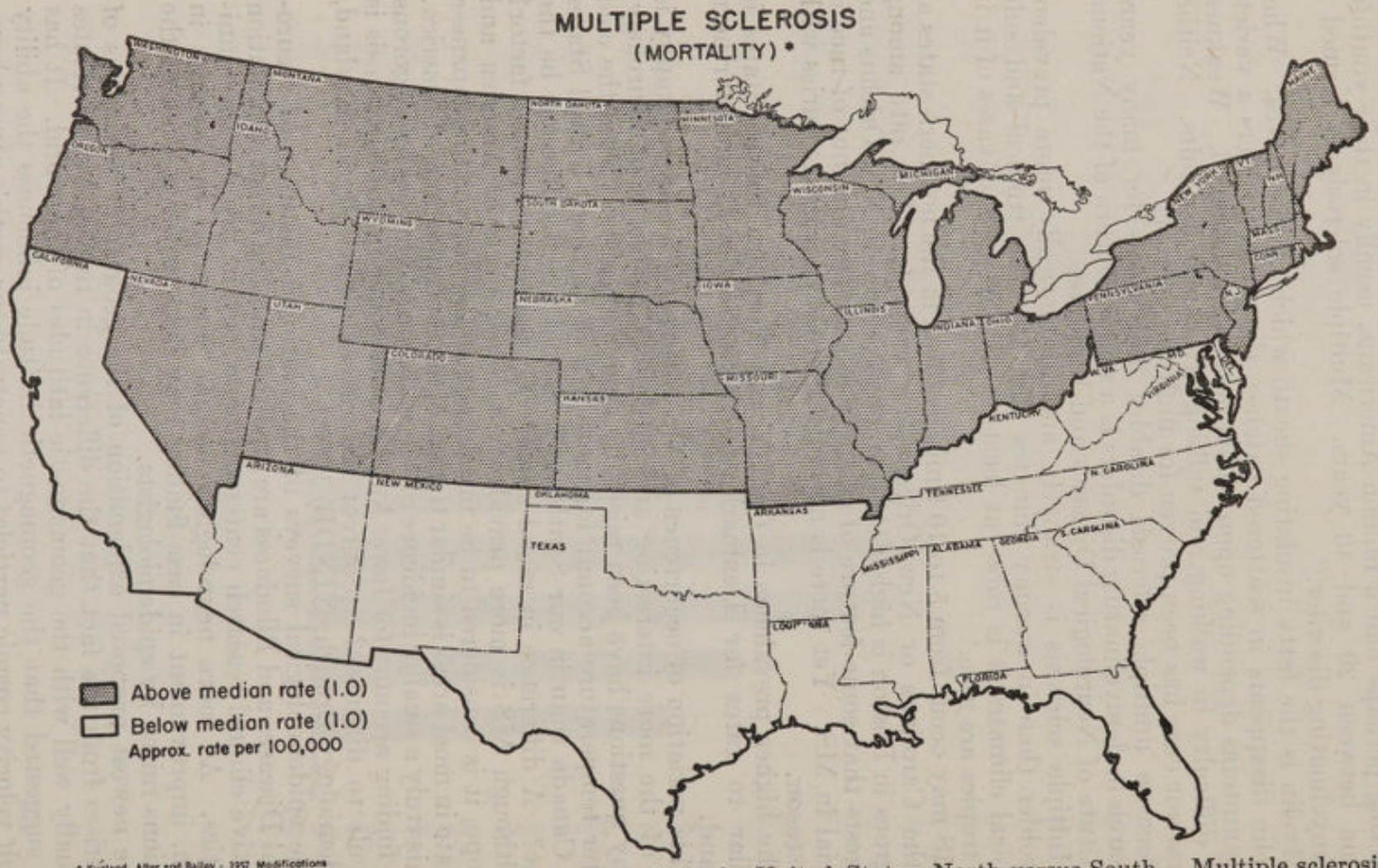
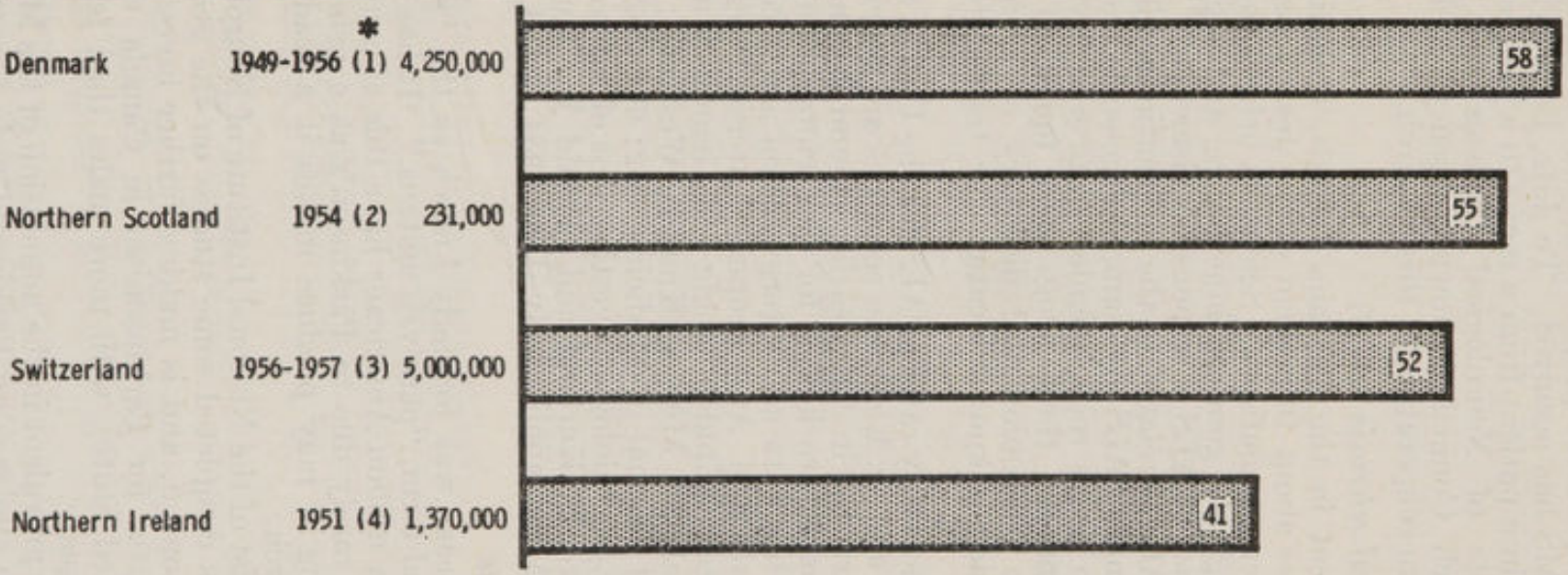


FIGURE 10.—Contrast in prevalence of multiple sclerosis in the United States, North versus South. Multiple sclerosis may occur from 5 to 10 times as often in the Northern States as in the Carolinas or Louisiana.

MULTIPLE SCLEROSIS IN SELECTED COUNTRIES



*Investigator: (1) Hyllested (2) Sutherland (3) Georgi, F. (4) Allison & Millar

FIGURE 11.—Multiple sclerosis in selected countries.

And by some unknown mechanism possibly an increase of cosmic particles may account for an increase in the prevalence of MS. This hypothesis is being tested further.

A long-term cooperative project continues on the effect of change of climate after MS has occurred. To date, little evidence indicates an improvement in a patient from a move to a warmer climate. The National Institute of Neurological Diseases and Blindness, the National Research Council Followup Agency, and the Veterans Administration are cooperating in this research.

Amyotrophic lateral sclerosis (ALS)

ALS is prevalent in the Mariana Islands, including Guam. On Guam, ALS causes about 10 percent of the deaths, or more than 100 times that of other populations. Scientists believe most Guam cases are carried through the genes of inheritance, and suggest the theory that a similar cause of ALS is responsible elsewhere.

Treatment of ALS is related to the international picture. Because of the high incidence of ALS in Guam, a large-scale study was possible there to test two drugs recommended from a study in the United States. Unfortunately, these drugs were found to be ineffective. Nevertheless, the epidemiological discovery of numerous cases in Guam has provided a known location for testing future potential cures.

Age-adjusted mortality rates of ALS for the United States, Canada, Australia, Japan, and six European countries are suprisingly uniform. No geographic variation in ALS deaths is found in continental United States. Official rates are higher for the white population than for Negroes, but further data and interpretation are needed. (Sources: "Multiple Sclerosis and Amyotrophic Lateral Sclerosis—Etiologic Significance of Recent Epidemiologic and Genetic Studies," Leonard T. Kurland, Donald W. Mulder, Knut B. Westlund; reprinted from the New England Journal of Medicine, 252: 649–702 (April 21 and 28), 1955. (2) "Epidemiologic Investigations of Amyotrophic Lateral Sclerosis," Leonard T. Kurland and Donald W. Mulder; reprinted from Neurology, Minneapolis, May–June 1954, vol. 4, No. 5–6.)

Parkinson's disease

Parkinson's disease was formerly known as the "shaking palsy," and by the medical term, "paralysis agitans." It has been estimated that as many as a million Americans have this ailment.

While death is rarely due to Parkinson's as a primary cause, the long-term crippling it may produce makes it a leading concern in neurological research.

An epidemiologist of the National Institute of Neurological Diseases and Blindness has completed some studies on the geographic distribution of Parkinsonism, and is making further investigations. The reported death rates for Parkinsonism in Canada were similar to those in the United States, with more males than females reported as dying of the disease.

Parkinsonism is prevalent in the population of the Mariana Islands. A series of genetic analyses on Parkinsonism in Guam is being completed, with results anticipated during 1959.

Sporadic cases of Parkinsonism are still being seen which resemble the many cases which followed the 1918 epidemic of influenza and encephalitis and various later encephalitis epidemics. The nature of

the virus, if one is responsible, has not yet been determined. The study of encephalitis offers some hope of clarification of this confused situation. A worldwide investigation of encephalitis might help to solve its connection with Parkinsonism.

A careful study in Denmark revealed that a significant number of Parkinson patients had relatives with Parkinson symptoms. This also has been noted in America where records have been compiled of families where a number of members in several generations have been affected. To determine whether this was due to hereditary influence, or similarity of environment, further investigation must be made.

(Source: Unpublished data, Epidemiology Branch, NINDB, 1959.)

Neurological disorders of childhood

Several European reports have offered data indicating that some congenital abnormalities of the central nervous system may occur more commonly in some population groups than in others. Other studies have indicated that some brain damage may occur more commonly among infants born in winter than in summer months. Certain studies in the United States have suggested that expectant mothers may tend to choose a protein-deficient diet during the warmer summer months. But these suggestions are yet to be proven.

Now that increased emphasis is being placed on congenital abnormalities in this country, it would be most unfortunate if advantage were not taken of this work to project certain phases on an international basis. With a little more effort and a relatively small expenditure of money, it is possible that certain causes of brain damage might be uncovered through an international approach which might not be found in this country.

An international approach would afford a chance to compare rates of cerebral palsy and other neurological disorders of childhood in the United States with those of other countries. Some of the factors which could provide the basis for comparison might be the difference in procedures of delivery and handling of the newborn, variations in the practice of using X-ray, and the diverse factors related to nutrition and infections during pregnancy.

Hereditary muscular and neuromuscular disorders

There are several useful national and international population reports available of muscular dystrophy, myotonic dystrophy, myotonia congenita (Thomsen's disease), infantile progressive muscular atrophy (Werdnig-Hoffmann's disease), and peroneal muscular atrophy (Charcot-Marie-Tooth). This is one of the areas of great need, and perhaps untapped sources of new scientific information could be gained from further epidemiological investigations on an international basis.

Information concerning the genetic characteristics of population groups may also have a number of practical applications related to estimation of gene frequencies and mutation rates. For example, in the case of childhood progressive muscular dystrophy, which is inherited in a sex-linked recessive manner, it is important to know the rate at which these genes mutate in the population if their control or elimination rate is to be made effective. Cases of one form of muscular dystrophy develop in the population as a result of spontaneous mutation from normal parents. Investigators studying this disease ex-

tensively in Utah estimated a mutation rate of 1 per 10,000 male births.

Muscular dystrophy, which appears to be comparatively common in parts of Utah, has been traced back to an early pioneer, born in England in 1775, who settled in the Salt Lake area in the early 19th century and reared a large family.

It was estimated that the minimal prevalence rate for muscular dystrophy in North Carolina was about 4 cases per 100,000 population. In surveys in Northumberland and Durham Counties in England, 84 cases were found in a population of about 2,262,000 (also a prevalence of about 4 cases per 100,000 population). Fifty-eight cases of one of the three described clinical types have been reported to have occurred in 1,249 individuals in a single kindred.

Surveys of myotonic dystrophy in England reveal a prevalence rate of almost 1 per 100,000 population. No adequate mortality statistics are available for this disorder. Population studies and prevalence figures of the other muscular disorders mentioned above have been reported for England, Canada, Denmark, and Guam. Some mortality statistics are available in these areas. However, in view of the confusion in diagnosis of amyotonia congenita and infantile progressive muscular atrophy, for example, it is uncertain how valid mortality statistics would be. (Source: "Descriptive Epidemiology of Selected Neurologic and Myopathic Disorders With Particular Reference to a Survey in Rochester, Minn.," L. T. Kurland, Journal of Chronic Diseases, St. Louis, Vol. 8, No. 4, pp. 378–418, October 1958.)

In areas such as these, where a need for research definitely exists, international epidemiological studies would contribute toward greater unification in methods of identification, classification, and diagnosis of these hereditary muscular and neuromuscular disorders.

The first approach to these disorders in this country has been a neuropathological one—the anatomical study of nerve and muscle tissue in normal and diseased states. Careful studies of infants suffering from muscle weakness have indicated that this disorder is comprised of several different diseases which have often been confused as a single entity.

Further, it is now clearly evident that there is an abnormal protein content in dystrophic muscle. Through an international epidemiological approach and with continued research in this country, it may be possible to determine with accuracy the actual abnormal molecules in the diseased muscle, and hopefully to determine ways in which these elements can be modified.

Kuru

Epidemiological studies have led to the discovery and documentation of kuru in New Guinea. This rapidly fatal disease of the nervous system has been discovered in an isolated population living in the inland plateaus. It bears many resemblances to certain disorders of the nervous system known in the civilized world, but has certain distinctive features.

Within the isolated valley where this disorder exists, the investigators have ferreted out and recorded most of the cases. The disorder has an extremely high incidence, affecting approximately 2 percent of the population each year, and probably accounts for over 50 percent of all deaths. For each examined case, detailed history has been

recorded. (Source: "Kuru: Clinical Study of a New Syndrome Resembling Paralysis Agitans in Natives of the Eastern Highlands of Australian New Guinea," V. Zigas and D. C. Gajdusek, The Medical Journal of Australia, November 23, 1957.)

The successful acceptance of the research team among this primitive tribe has made possible the conduct of over 30 autopsies, and a number of brains have been forwarded to several neuropathologists for special examination. A thorough report of the pathology of kuru has been published.

In searching for the cause of kuru, the geographical characteristics of the region were mapped and the distribution of the disease was charted. Its distribution corresponds closely to an isolated ethnic group called the Fore Tribe. This lends strong support to a genetic origin.

A number of laboratory studies have been completed. Examination of blood serological specimens from patients and nonpatients both in affected and nonaffected areas has demonstrated the existence of an abnormality of the protein fraction, but the relationship of this to kuru has not been defined.

Abnormalities of adrenal hormone compounds also have been demonstrated, and these have been associated with abnormalities of sodium and potassium levels in the blood serum, strongly suggesting the existence of some endocrine imbalance in this disease. The existence of some hormone imbalance is further suggested by a preponderance of the disease in small children and in women.

In a further effort to establish a genetic relationship, blood grouping in this population is also being conducted, and over 2,000 specimens of blood serum have been obtained for this purpose. This serum is also being subjected to antibody studies in order to obtain information on the virus exposure and experience of this previously untouched population.

In the kuru study and in the other investigations mentioned above, the expanding medical-statistical discipline of epidemiology has become a significant part of research programs. It is being used to study incidence, geographic distribution, and population selectivity in a way which may stimulate and support clinical and laboratory research efforts toward etiology and control of the noninfectious neurological diseases.

Part 3

CONCLUSION

The effective epidemiologist is above all an opportunist in the finest sense. In order to isolate various genetic and environmental factors which influence the incidence and severity of disease, he must carefully select groups which show (*a*) marked differences with respect to incidence and severity of the disease under study, but (*b*) marked similarity in all genetic and environmental factors except those being considered. The laboratory scientist can usually control these factors at will; he can also introduce modifications into his experiment. The epidemiologist, however, cannot modify either subject or environment. Instead he must seize upon the "experiment of opportunity," those fortuitous natural modifications which can be studied and analyzed in the same way as laboratory sequelae. Fortunately, the world abounds in such opportunities.

Of these opportunities, Dr. Paul Dudley White has said:

> Nature has for centuries been conducting gigantic experiments as to the effect of climate, of type of work, of diet, and of local or worldwide diseases on men, women, and children of different races, that are spread out before our very eyes for us to record and to analyze, quite readily yielding information that might never be obtainable by our own experiments on man, although certain tests could be added to enrich the findings. Under the most exacting conditions animal experiments of this sort cannot be completely applied to man; important clues and discoveries can result from experiments on animals, but if we rely only on them we are letting go to waste an equally important source of information about disease.

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Selected Diseases and Disease Factors

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