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**EPIDEMIOLOGICAL METHODS
IN THE STUDY
OF CHRONIC DISEASES**

**Eleventh Report of the WHO Expert Committee
on Health Statistics**

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WHO EXPERT COMMITTEE ON HEALTH STATISTICS

Geneva, 15-21 November 1966

Members:

- Dr R. M. Acheson, Professor of Epidemiology and Medicine, Yale University School of Medicine, New Haven, Conn., USA
- Dr A. V. Čaklin, Deputy Director, Chief, Epidemiological Department, Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR, Moscow, USSR (*Vice-Chairman*)
- Dr B. MacMahon, Professor of Epidemiology, School of Public Health, Harvard University, Boston, Mass., USA (*Chairman*)
- Dr L. M.-F. Massé, Professor of Public Health Statistics, National School of Public Health, Rennes, France
- Professor J. N. Morris, Director, Medical Research Council's Social Medicine Research Unit, London Hospital, London, England
- Dr I. Shigematsu, Chief, Department of Epidemiology, Institute of Public Health, Ministry of Health and Welfare, Minato-ku, Tokyo, Japan
- Dr K. B. Westlund, Director, Life Insurance Companies' Institute for Medical Statistics at the Oslo City Hospitals, Oslo, Norway (*Rapporteur*)
- Dr A. Žáček, Professor of Social Medicine, Medical Faculty, Brno University, Brno, Czechoslovakia

Secretariat:

- Dr M. A. Akhmeteli, Deputy Chief, External Relations Board, Ministry of Health of the USSR, Moscow, USSR (*Temporary Adviser*)
- Dr G. Cerkovnyj, Chief, Epidemiological Studies, Division of Health Statistics, WHO (*Secretary*)
- Dr Ž. Kulčar, Chief, Department of Epidemiology of Chronic Diseases, Institute of Public Health of Croatia, Zagreb, Yugoslavia (*Temporary Adviser*)
- Dr W. P. D. Logan, Director, Division of Health Statistics, WHO
- Dr D. D. Reid, Professor of Epidemiology, London School of Hygiene and Tropical Medicine, London, England (*Consultant*)

EPIDEMIOLOGICAL METHODS IN THE STUDY OF CHRONIC DISEASES

Eleventh Report of the WHO Expert Committee on Health Statistics

The WHO Expert Committee on Health Statistics met in Geneva from 15 to 21 November 1966 to discuss the role of epidemiological methods in the study of chronic diseases. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General. Dr B. MacMahon was elected Chairman and Dr A. V. Čaklin Vice-Chairman. Dr K. B. Westlund was appointed Rapporteur.

1. INTRODUCTION

The serious consequences of the chronic diseases of middle and later life in many countries need no emphasis. Epidemiological methods, developed and used to such good effect in the study of the causes and control of communicable diseases, have been increasingly applied in these other conditions. The simpler techniques of analysis of the incidence of disease in relation to characteristics of time, place and person are certainly of enduring value even in this new context. In recent years, however, many modifications of older techniques and some innovations in approach or method have been made. There is a need for a review of these developments so that some of the more important of them can be commended to those concerned with the emerging problems of chronic disease in public health. These problems are most urgent in the more highly industrialized countries. At the same time, the rich sources of medical information and the administrative facilities available in these countries makes many of the newer methods readily practicable there. Even in developing countries, however, a swing towards public health concern with chronic disease has already begun; there are many opportunities for fruitful etiological studies in the rapidly changing patterns of disease and ways of life in these areas. For these reasons, WHO brought together experts experienced in the developing field of the epidemiological study of chronic disease.

Discussion was to be limited to the consideration of conditions associated with degenerative changes and metabolic or psychological disorder, e.g., cancer, diabetes, and mental and cardiovascular disorders. Methods particularly appropriate to the study of infectious disease, even those that are chronic in nature, were not considered. Thus, the aims of the meeting were :

- (1) to make a critical review of the methods presently applied in the study of the epidemiology of chronic diseases;
- (2) to indicate useful extensions of recent technical developments to fields not already covered;
- (3) to suggest how the collection of information might be improved;
- (4) to discuss the application of new methods in population surveys; and
- (5) to make recommendations for further work for both national and international studies, with special emphasis on the role of WHO.

The limited time available necessitated the neglect of certain important aspects of epidemiological work. These included, for example, the detailed consideration of the measurement of factors such as diet, physical activity and socio-cultural background. The application of the newer statistical techniques and of computer development were considered only briefly. Although their importance was recognized, the agenda excluded such areas as genetic studies in chronic disease, nomenclature and classification of disease, and collaboration in etiological inquiries with workers in other laboratory and social disciplines. The important subject of controlled trials of methods for prevention of chronic disease was also not considered.

2. ROUTINELY COLLECTED STATISTICS

A great deal of epidemiological work, in both acute and chronic diseases, depends on sources of data that are collected routinely for a variety of purposes. The basic source documents provide the starting-point for many etiological studies. In addition, the statistics routinely prepared from these documents assist in the formulation of etiological hypotheses and in the planning of detailed investigations to test them.

Ideally, for epidemiological purposes, one might wish that source documents on total morbidity in defined populations were available. In a few countries, the achievement of this ideal is aided by the form of organization of medical care services. The planning of medical care

facilities for defined segments of the population and the collection of morbidity data in such facilities for administration and patient care purposes provide unusual opportunities for epidemiological investigation. Mortality data, however, will continue to be a major resource for the chronic disease epidemiologist. Furthermore, even if perfect morbidity data were to become accurate and readily available in all areas, death will continue to be a phenomenon worthy of investigation as an end-point in the study of the natural history of disease.

2.1 Mortality

The usefulness of mortality data to the chronic disease epidemiologist lies in their universality, general availability and, in many contexts, reasonable accuracy. Their limitations must, of course, be recognized, particularly in a consideration of their application to chronic disease. Problems are posed by the unsatisfactory diagnostic information in some population sub-groups (e.g., the aged) and in some causes of death (e.g., cardiovascular disease), the long interval between etiological events and death in many conditions, and the virtual uselessness of mortality data in many chronic conditions of low fatality (e.g., mental disease, arthritis). Nevertheless, the improvement and maximum exploitation of both the source documents and the statistics derived from them are matters of considerable concern in chronic disease epidemiology. Several matters of particular importance to those working in this field were discussed.

The accuracy of statements as to cause of death should be continuously evaluated by sample inquiries to certifying physicians, by linkage to hospital reports or case registers of special diseases and by reference to autopsy findings. Whenever opportunity arises, their epidemiological relevance should be assessed by comparing differences in risk suggested by mortality data with those established by special surveys. For certain chronic diseases, such as diabetes, hypertension and pernicious anaemia, it may be worth while to conduct additional inquiries of the type in which groups of patients known to have the disease are followed up to discover how frequently the condition is mentioned on the death certificate. An important mechanism is the practice, adopted by many national statistical offices, of interrogating the certifying physician in cases of inadequate cause-of-death statements. This practice should receive epidemiological guidance.

Practices in the incorporation of the autopsy findings in cause-of-death statements vary greatly from one country to another. Considerable effort to improve such practices would be well worth while. Rather than depending exclusively or primarily on either clinical or

pathological opinions, the two should be integrated, and the epidemiologist must be concerned with the manner in which this is done.

Diagnostic information already provided by the present death certificate could be better utilized. The present convention of preparing routine tabulations according to the underlying cause of death will doubtless continue. As far as possible, however, all medical conditions mentioned on the death certificate should be coded so that the individual items could be used for special studies of their distribution, either alone or in selected combinations. Routine cross-tabulations by age, sex and area could be prepared from certificates that mention selected diagnoses, even when not given as the underlying cause, as well as of combinations of diagnoses. For example, greater confidence in the existence of time trends would be felt if it could be shown, as has been the case for hypertensive disease in some areas, that the trend is similar for the disease certified as an underlying or contributory cause. Similarly, tables based on combinations of causes may reveal epidemiological features, such as area differences, that are not apparent from tabulations of underlying causes. Finally, the occurrence of certain combinations of causes more frequently than could be accounted for by chance might give clues to the existence of disease associations. Because such combinations may result solely from current professional beliefs about likely associations of diseases, such observations would have to be confirmed by other types of study.

The present International Form of Medical Certificate of Cause of Death was discussed. The concept of a simple chain of events leading to death that is the basis of this certificate may serve excellently in deaths from, say, acute infections; but this concept is less applicable to deaths that occur during old age and even in middle age. At these ages, several pathological conditions are usually found, and it may be difficult, if not impossible, to order a series of conditions into a realistic chain of events. It may even be harmful to require the certifying physician to fit his observations into the rigid structure of the present certificate. He may, for example, be induced to put undue emphasis on a relatively unimportant aspect of the case. Preconceptions will inevitably play a large part in his decision on which of the various conditions present to include and how to arrange them on the certificate.

The ideal would seem to be to have all important disorders stated without necessarily requesting, as in current practice, the distinction between underlying, contributory and incidental conditions. At present, we do not know how fruitful, from the epidemiologist's point of view, would be the various alternative approaches that might be considered. There is a need for large-scale studies in this area. Such studies would probably involve experiments with various alternatives in the design and wording of the certificate. The final test would be the usefulness, for

instance in epidemiological studies, of the resulting information on the distribution of diseases, compared with similar tabulations based on current certificates.

Confidentiality of death-certificate records sometimes imposes barriers, not only to the use of death certificates in special studies, but also to the quality control of routine statistics. It is most important that the epidemiologist work with leaders of the medical profession and others concerned to develop procedures that will retain a satisfactory degree of confidentiality and yet not lead to loss of this valuable resource.

2.2 Morbidity

The Committee reviewed several sources of routine morbidity data. The existence of extensive population coverage for medical care can provide satisfactory morbidity statistics. The Committee regretted, however, how little transfer of epidemiological philosophy, experience and technique has taken place during the past 20 years to systems of collection of routine health data, such as school health services, hospital statistics and polyclinic attendance data. Thus, gross local differences are constantly reported that clearly have no biological basis.

The following methods of improving routine statistics, such as those relating to school health or sickness absence in industry, were suggested :

- (1) the standardization of definitions and clinical diagnosis;
- (2) more detailed examination of representative sub-samples to validate the large-scale survey results; and
- (3) the feed-back of the results of the validity tests to those responsible for the routine surveys.

Where the actual or potential sources of data are plentiful and the resources for their improvement and exploitation limited, it may be the responsibility of the epidemiologist to establish priorities. He would then press for the development and analysis in depth of only those types of data that appear to hold particular epidemiological promise. He may decide that the epidemiological exploitation of certain types of data should only be attempted in connexion with a comprehensive record-linkage scheme. Occasional analytical surveys of routine documents, such as hospital records, may be cheaper and more informative to the epidemiologist than continuing routine tabulations. Such surveys would be directed towards one or a few problems only.

As in the case of mortality statistics, every opportunity should be taken to compare, in quantitative terms, the contrasts suggested by various types of routine morbidity data with information provided by special studies. WHO might profitably assist in the collection and dissemination of experiences in this area in various countries.

Reference was made to the usefulness of having all morbidity statistics, whatever their source and whatever the degree of diagnostic detail required, presented in terms of the International Classification of Diseases.

2.3 Other vital statistics

2.3.1 Official census statistics

Comprehensive descriptive epidemiology is impossible without accurate enumeration of the population at risk of a disease. It is therefore desirable, if not essential, that :

- (1) frequent, comprehensive and accurate censuses be made;
- (2) demographic and social information be collected to permit the classification of the population by age, sex, marital status, socio-economic status, occupation of chief wage earner, domicile, etc.;
- (3) the results of the census be made quickly available in the form of detailed cross-tabulations; and
- (4) official estimates of population be made and published between census surveys.

2.3.2 Natality statistics

These are of use in various aspects of chronic-disease epidemiology. They serve as a denominator in studies, for example, of infant morbidity and mortality, and allow accurate estimates and projections of the child population to be made.

2.4 Other routine statistics related to health

Routinely collected statistics on a variety of environmental characteristics can be helpful in the identification and quantification of factors causative of disease. The following list, which is not comprehensive, merely serves to give examples of sources of data that have already been put to good use by epidemiologists :

- (1) *Demographic*: in addition to routine census data, statistics on such other demographic phenomena as population density, movement and educational level.
- (2) *Economic*: consumption of such consumer goods as tobacco, dietary fats and domestic coal; sales of pharmaceutical goods, drugs and remedies; information concerning per capita income; employment and unemployment data.
- (3) *Geological*: data on soil composition and mineral content; background radiation from rock; mineral content of water.

- (4) *Geographic*: altitude, latitude and longitude; vegetation.
- (5) *Meteorological*: natural characteristics of weather and climate such as temperature, humidity, rainfall, mean annual solar radiation; cosmic radiation; unnatural characteristics such as the chemical content of the atmosphere.
- (6) *Agricultural*: the nature of crops grown in an area; information about their quality and yield; health of livestock.

The opportunities in the study of chronic disease of correlating measures of human and animal health have been largely neglected. Data on disease in domestic animals in areas where there are different types of environment might provide information relevant to human disease.

Whatever forms of routine statistics are being considered — mortality, morbidity or environmental — it is important that the system be regularly reviewed to achieve maximum economy, co-ordination and integration, so that countries may have what they need and what they can afford.

In many countries there is an administrative separation of vital statistics and other routine health statistics. Wherever this situation exists, it is a prime responsibility of the epidemiologist, whatever his official position, to try to minimize problems of communication.

3. DISEASE REGISTERS

Registration of individuals with certain chronic diseases can be an important epidemiological tool, provided that the registration covers a defined region (e.g., a province, state or city) and that the majority of cases in the region are registered. The term "registration" implies something more than "notification". A register requires that a permanent record be established, that the cases be followed up, and that basic statistical tabulations be prepared both on frequency and on survival. In addition, the patients on a register should frequently be the subjects of special studies. Even in the absence of a defined population base, useful information may be obtained from registers on the natural course of disease in different parts of the world.

Registers for cancer and mental disease were discussed in some detail. Cancer has certain characteristics that make it highly suitable for registry work. These include the facts that the patient will usually, sooner or later, seek medical care for the condition, that the diagnosis is relatively specific and definitive and that good co-operation can be obtained because the condition is widely recognized as a problem of major importance. Mental disease, on the other hand, illustrates some of the difficulties in

diagnosis and in obtaining comprehensiveness of registration. For complete ascertainment, it is necessary to go beyond medical and psychiatric sources. Conditions such as alcoholism and behavioural disturbances in children, for example, are dealt with by a great variety of non-medical agencies. It is obviously important to develop standard procedures and definitions in this field. The current attempt by WHO to standardize the concept of schizophrenia among psychiatrists from different cultures is one example of the type of research that is urgently needed.

It seems useful for descriptive purposes to distinguish between two different situations with respect to the utilization of registers in epidemiological research. The first is the situation in which a disease register is established and maintained primarily for epidemiological purposes. The mental disease register in Croatia, Yugoslavia, was noted as a valuable example of this. To establish this register, house-to-house surveys were made on population samples by specially trained medical students, with verification of diagnosis in suspected cases by specially trained psychiatrists. A few registers of this type, based on notification from medical and other agencies rather than on survey, exist on a local basis in the USA and elsewhere. The second situation is that in which the register is established primarily for control and administrative purposes. Here, as in the case of death registration and other programmes, epidemiologists have utilized, and to varying degrees adapted, an existing resource. Thus, many cancer registers were originally established for control purposes. In the USSR and some other countries, there is compulsory reporting by various agencies to oncological, cardiovascular and mental-disease registers based on the defined areas covered by the corresponding services. Supplementary studies are often required for epidemiological research purposes; in some areas there are special cancer institutes equipped to undertake such studies.

WHO has recently initiated a review of the characteristics of known national and regional cancer registries.

Epidemiological research on cancer utilizing registry data requires considerations of standardization and of scientific method beyond those necessary for cancer control. In registries selected for epidemiological research, it will be necessary to check regularly the completeness of registration. Data on each case must be registered in a standard fashion, and observations on the characteristics of cancer cases should be compared with data on the general population obtained either by census, by special population surveys or by matched control studies. It should be noted that the epidemiological usefulness of a register increases the longer it has been in existence. It may therefore be necessary to continue careful documentation and quality-control procedures for many years before a register becomes fully productive for epidemiological purposes.

For the above reasons, caution should be exercised in opening new registers when the primary justification is epidemiological. In large countries, it may be useful to concentrate research functions on a few registers specially equipped and staffed for this purpose. These registers might be selected so that the main geographical subdivisions of the country would be represented. Competently managed registers in a few well-selected areas are likely to be more productive than if similar resources are put into broader, but more superficial, coverage.

Reporting will be improved if local physicians and health authorities, as well as the scientific community generally, are kept informed of the results of the analysis of register material. These reports will be especially effective if their relevance to problems of patient care is emphasized.

To date, there seems to have been some imbalance between the amount of effort that has gone into the collection of register data and that which has been devoted to its analysis. This may result in part from the fact, mentioned above, that only after many years of data collection is a registry fully operational for epidemiological studies. Moreover, the function of directing epidemiological research should be clearly distinguished from the administrative task of organizing complete registration; this should be reflected in the choice of staff. While confidentiality of information must be adequately safeguarded, it is important that this and other administrative considerations should not be barriers to the collaboration of the register staff with outside research workers in the full exploitation of the records.

National registers exist for some other chronic diseases, such as multiple sclerosis. A trial scheme for the registration of myocardial infarction has been maintained in a restricted area for a number of years. There are other diseases for which registers may be epidemiologically useful, particularly in geographical areas where these diseases are of special interest, for example :

- (1) chronic non-specific respiratory disease;
- (2) metabolic diseases, such as diabetes and pernicious anaemia;
- (3) endocrine disorders, such as thyroid diseases;
- (4) chronic rheumatoid arthritis;
- (5) peptic ulcer;
- (6) congenital malformation; and
- (7) renal calculus.

It would be highly desirable to have the potentialities of such registers evaluated from an epidemiological point of view. Consideration might also be given to the feasibility of registering several different diseases in one institute. Standardization of diagnoses and comprehensiveness of

reporting will be major problems. Even more serious may be the difficulty of defining and accumulating the ancillary data that may be relevant to the disease in question.

4. RECORD LINKAGE

The term "record linkage" is used to describe the process of bringing together two or more separate documents concerning a particular individual or family. The potential usefulness of this process was pointed out in the last century. However, its value has become increasingly evident in recent years as the number of individual records has proliferated and the technical capability for automated linkage on a very large scale has been developed. The value to the epidemiologist of the items concerning an individual recorded on his birth certificate, marriage certificate, hospital records, health-insurance claims, and death certificate would be greatly enhanced if the information could be collated so as to provide a serial record of his health history. Moreover, by the cross-linking of marriage and birth certificates with other health records, an extensive family history could be developed.

The linkage of hospital records is of particular epidemiological importance. At present, a number of hospitals match discharge summary sheets to permit the identification of individuals and families who are repeatedly admitted to the same hospital within a defined period of time. If this procedure is followed by all hospitals in a defined area, its value is greatly enhanced. Mental hospitals are particularly involved in this practice, which permits the creation and maintenance of a psychiatric case register. Of great importance is the example of the Oxford Record Linkage Study, in which records relating to all confinements, births, hospital discharges and deaths are being linked.

In several regions of Czechoslovakia, the matching of various types of health record has been used for a number of years to measure the levels of morbidity in samples of the population.

One of the difficulties in developing systems of record linkage is the need to preserve the confidentiality of medical and social information. In the past this has been a serious obstacle to the use of information present in census documents and it has created obstacles in some countries to attempts to relate morbidity, mortality, social security and clinical data. Epidemiologists are aware of the need to maintain confidentiality. However, concepts of confidentiality that do not preclude the transmission of information on individuals to responsible research workers have been accepted by the scientific community and the general public in many countries. Even in the absence of such a liberal outlook, computers can now be used to link the records of an individual without

disclosure of his personal identity. As already noted, the cross-tabulations thus made possible would greatly enhance the epidemiological value of data collected from both census and death-registration systems.

Record linkage is a particularly suitable method of studying associations between diseases; these associations may have etiological significance. The association between coronary heart disease and peptic ulcer and the risk of various types of cancer in diabetics have been studied by this method. In such studies, negative as well as positive associations should be sought. It may therefore be appropriate to follow up a group of patients, e.g., peptic ulcer patients, with respect to as wide a spectrum of diseases as possible.

Pre-school, school or college health records, or military documents may be linked to later morbidity or mortality records to provide information on the relevance of early habits or physiological measurements to later chronic disease. Registers of twins are now available in many countries. Information provided by linking such registers to morbidity records will be of value to chronic disease epidemiology as well as to genetics.

Whenever the death certificate is the end-point of the linkage process, the practical problem arises of how to ascertain the fact, time and place of death. A national record system, based on individual identification numbers, provides information of this type for research projects in France. Japan has an official family record, the *Koseki*, containing the *Honseki*, i.e., the legal address. Knowledge of any recent *Koseki* record is a virtual guarantee that survival status can be determined. The Scandinavian countries depend on their population registers, and in others insurance schemes or social security systems may be exploited. In some countries alphabetical lists of all deaths, giving up to three causes mentioned on the certificate, are prepared annually. In many follow-up studies the provision of this information makes a search for the certificate itself unnecessary.

In general, data obtained from registers, e.g., those for cancer or psychoses, will be more informative than those derived from death certificates, so that linkage between morbidity records is of particular value. Similarly, the utility of a disease register for epidemiological research may be enhanced by linkage to observations of diverse types on the population served by it. Migration, both within and between countries, is already a problem in many linkage studies and is likely to increase. Indeed, it may not be too early to consider methods for international record linkage.

Projects such as these would almost certainly require large-scale automatic linkage by means of a computer. The provision of a unique personal identification number, such as has already been introduced in several countries, would be essential.

In spite of the current technical progress, a single, integrated, centralized and continuing file of vital and health data, revealing simultaneously cross-sectional, longitudinal and genealogical patterns of events or diseases, will be beyond the reach of many countries. Nevertheless, more modest record-linkage projects should still be encouraged.

5. DIAGNOSTIC AND MEASUREMENT PROBLEMS IN EPIDEMIOLOGICAL SURVEYS

The definition of a "case" is particularly difficult in chronic-disease epidemiology. Here, the needs of the clinician and the epidemiologist may diverge. The clinician needs a detailed description covering all the likely or possible clinical expressions of a particular disease, so that he can be reasonably sure of making the correct diagnosis in atypical as well as typical cases. The epidemiologist, on the other hand, is more concerned with obtaining precise and consistent indications of the level of disease frequency in contrasted population groups; he is prepared to accept a certain proportion of diagnostic errors if they do not distort the comparison of estimates in these groups.

Diagnostic methods for use in epidemiological surveys must have certain properties. A useful diagnostic method should be :

- (1) sensitive, i.e., tests should indicate a high proportion of those with the disease for which a population is being surveyed;
- (2) specific, so that few unaffected individuals are classified as affected;
- (3) consistent, in that the test gives the same results on repeated application;
- (4) readily and cheaply applicable on a large scale by observers working in field conditions; and
- (5) acceptable to the population to be surveyed.

5.1 Development of diagnostic procedures

Diagnostic methods range from the eliciting of symptoms through objective clinical tests to the ante-mortem and post-mortem examination of body fluids and tissues. Some of these methods yield permanent material, e.g., in the form of electrocardiograms or biopsy preparations, which can be assessed, independently and repeatedly, by different observers without the need for the physical presence of the subject; much has been done in recent years to use such material in the improvement of diagnostic practice in epidemiological surveys. Symptoms, on the

other hand, are notoriously difficult to elicit and evaluate in a precise and consistent manner, yet they are important as indicators, often the only ones available, of the crucial early stages of chronic disease. The assessment of pain, for example, is influenced both by personal attitudes and cultural conventions. Often, no objective clinical measures of symptoms are available. Furthermore, the same symptom (e.g., pain), like the same sign (e.g., fever), may be of different disease significance in different communities.

The recognition of this problem has led to the development of standard symptom questionnaires that are designed to elicit specific sets of symptoms as precisely and consistently as possible under field conditions. In the evaluation of such instruments, questionnaire information must be compared with objective evidence of the presumed underlying disease in a sample of subjects in all of the countries, areas or cultures between which comparisons are being made. Consequently, the construction of questionnaires for use in comparisons among groups requires the collaboration of physicians who are aware of the significance of a given symptom to members of the various groups.

In field surveys of psychiatric disorder, for example, the diagnostic task consists of the observation of items such as hypermanic behaviour and depressive facies and the synthesis of these into a composite diagnosis. Attempts have been made to do this arbitrarily by giving greater numerical weights to the reputedly more important items; varying degrees of success have been achieved in different fields.

More sophisticated statistical techniques, such as discriminatory analysis, can also be used. Thus the signs and symptoms associated with thyrotoxicosis, such as palpitation, exophthalmos and hyperkinetic movements, can be assigned individual weights to form a composite index that distinguishes persons with raised basal metabolism and other objective signs of serious thyroid disease from those without such objective signs.

Useful as such composite diagnoses may be, there is often much to be learned from a more detailed study of the distribution in terms of sex, age and geography of either single diagnostic items or syndromes of two or more of them combined in different ways. In Japan, such methods have been recently used to identify a previously unrecognized syndrome involving severe bone pain, proteinuria and glycosuria, whose epidemiological distribution pointed to the possible significance of exposure to cadmium in an area where it is mined.

5.2 Validation of diagnostic methods

Before using symptom questionnaires on any scale, it is essential to see to what extent they are valid indicators of the presence of the disease in question. Where objective physiological tests of specific

dysfunction are available, e.g., measures of basal metabolic rate, the results can be used to see whether the questionnaire discriminates effectively between individuals with high and low scores. Since objective tests or tracings, such as electrocardiograms, do not always indicate the presence of a particular disease, the ultimate criterion of a questionnaire, as of the objective tests, must be its success in predicting later morbidity or death from the disease in question.

When a diagnostic test is completely valid, i.e., when it identifies all diseased persons without error, sensitivity and specificity are at their maxima. In practice, this is never the case, and the degree of compromise accepted in the conduct of a survey may be usefully stated in terms of the sensitivity and specificity of the diagnostic methods used.

5.3 Variation in diagnostic findings

Apart from validation of all diagnostic tests in this way, it is useful to ascertain the origin, nature and relative importance of different sources of variation in the results obtained. Duplicate assessments of the same individual in the same conditions will indicate the degree of precision in measurement that is being achieved. Variation in physical measures or in the reporting of specific signs or symptoms will depend on variation in the patient himself, on inconsistency in the observer and on systematic differences between observers. Much has been done in recent years to identify, measure and reduce some of these sources of bias or error in epidemiological observations.

5.4 Use of standard or clinical reference material

Radiographs and other standard case material have been used for some years to investigate the degree of observer variation in survey practice. They are also used to indicate the broad categories into which cases may be classified. One example is the series of radiographs of the progressive stages in the development of rheumatoid arthritis and osteoarthritis that has been worked out by an international group.

Attempts are now being made to develop materials that may form the basis of future standards. Physical signs such as tremor and depressive facies may be recorded on video tape or film and used as standard reference material, as in the WHO study of schizophrenia. In Japan, colour photographs of the retina have been produced for use in the epidemiological study of hypertension. In the same way, interviews with patients can be tape-recorded and played back for interpretation by different observers. Some signs, such as oedema, can not be recorded in a permanent fashion. Nevertheless, it is usually possible to develop

permanent material that covers at least some of the essential diagnostic elements in the specific chronic disease being investigated. As noted below, such materials can be used effectively in the testing and training of observers.

National differences in diagnostic standards can be assessed by a variation of this general approach. To investigate the potential importance of international differences in diagnostic conventions in determining the reported disparity in various forms of cardiorespiratory death rates between the USA, England and Wales, and Norway, a series of case histories illustrating a wide range of such conditions was prepared. These histories were then presented in turn to groups of physicians in these three countries with the request that they should "certify" the cause of death according to their usual standards. By this means it was shown that, while international differences in convention certainly existed, they were not sufficiently great to account for the differences in cause-specific national death rates.

5.5 Training and testing of observers

The use of highly trained personnel such as physicians or nurses to perform diagnostic procedures in large-scale surveys can be economically wasteful as well as destructive to their morale. It has been shown that, if the components of an examination are broken down into their individual parts, each part can often be performed more repeatably and more accurately by workers specially trained for the purpose than by skilled diagnosticians. Automated equipment is now available for the biochemical analysis of body fluids, and this, too, can function more repeatably, accurately and economically than traditional methods. If the results of studies of this kind are to be compared, however, agreed-upon standards must be used. An example of a mechanism for maintaining such standards is the exchange system developed in the USA by the Public Health Service for the measurement of such factors as serum cholesterol and serum glucose.

Careful testing and training of observers can also lead to their effective use when the diagnostic methods are not as simple and objective as, for example, in the measurement of height or weight. Training in the use of standard questionnaires may be given by listening to recordings of clinical interviews in which the subject's responses can be interpreted or classified by the trainee and scored by comparing these with "standard" classifications made by experienced observers.

These devices will reduce observer variation but not abolish it. In comparative studies in particular, diagnostic practices can best be aligned either by the interchange of personnel or by the use of an observer who is common to the units working in the two or more areas involved.

Where permanent recordings are available, as in electrocardiography or radiography, centralized coding may be essential for precision and consistency.

The usual history of many chronic diseases is long, sometimes life-long. To the affected individual, the presence or absence of the disease may be less important than the degree of medical and social disability associated with it. Recognizing this, epidemiological diagnosis must try to proceed beyond the diagnosis of the presence or absence of disease to the definition and diagnosis of disability, both social and medical, and the standardized description of relevant family situations. These newer measurements could also be valuable in the assessment of the benefits of treatment and of attempts at secondary prevention, the results of which may, in turn, affect the provision of medical and social services.

5.6 Reporting of results in field surveys

When care has been taken to ensure uniformity in observational technique, it is important to present the data in a form that allows full advantage to be taken of that effort. Demographic variables such as age, sex and marital status should be set out in a prescribed way on the questionnaire and tabulated in a standard manner. The individual record should also indicate the observer's name and his professional or technical status, so that analysis can be made to determine variation between observers, either as individuals or as members of a class. Where quantitative variables such as blood pressure are recorded, the distribution should be given as fully as possible so that differences that are not obvious in the summary statistics may be detected. The use of "cut-off" points selected without epidemiological justification to identify presumptive disease is much less satisfactory.

6. PROBLEMS IN CONNEXION WITH HIGH-RISK GROUPS

Many of the methods described above can be effectively applied to the study of the risk of chronic disorders as a problem in modern public health practice. The concept of "high risk" was discussed from several convergent points of view. These were :

- (a) identification,
- (b) mass screening,
- (c) at-risk registers, and
- (d) follow-up and surveillance problems.

6.1 Identification

The recognition of groups of individuals who are at "high risk" or are "vulnerable" is of value in the following fields :

- (1) disease causation investigation,
- (2) identification of health problems,
- (3) planning of preventive programmes, and
- (4) assessment of needs for medical care.

In assessing the degree of risk, it is necessary to consider its magnitude and the size of the group effected. For example, small increase in risk of ischaemic heart disease may be potentially more important for community health than a large one in a less common disease such as lung cancer.

Included within the wide range of variables used to classify the population into groups exposed to varying degrees of risk are : demography (age, sex, civil state, etc.), anthropometry (height, weight, etc.), family history, antenatal and natal history, childhood history, child-bearing history, habits and customs, occupational history, socio-economic factors, including size of family, environmental exposures and medical history.

Occupation is an important factor. It is possible both by the analysis of routine records of sickness and by special surveys to define occupational groups under increased risk of disease or injury. The potential bias of occupational morbidity data must, however, be kept in mind; for example, the social policies of the country and of the employing body are important in determining rates of absenteeism and may obscure disease patterns. There is a need for a classification of occupations that is more relevant to epidemiological problems than the classification commonly employed by census offices. Important methodological problems are present in the identification of workers who have left high-risk occupations several years previously and the determination of how long such workers carry with them an increased risk.

Computerization of occupational morbidity records in central offices will make it possible to scan systematically larger numbers of occupations for a wide variety of conditions. It may thus be possible, in the future, to recognize more quickly such hazards as that of bladder cancer in dye-stuff workers.

The subject of high-risk groups has been transformed in recent years by the demonstration that some clinical measures are of high prognostic value in some forms of chronic disease. Physiological measurements, such as serum cholesterol or blood pressure, have proved efficient in the prediction of ischaemic heart disease. Combined with such factors as

age, sex, occupation and smoking habits, these measurements make it possible to delineate groups currently free of ischaemic heart disease but differing greatly in the degree of risk. As in the formulation of diagnostic syndromes, this process of combining several factors may yet be further improved by statistical techniques such as discriminatory analysis.

6.2 Mass screening

Mass screening consists of the application of tests to large groups of people with a view to singling out persons who are more likely than others to have or to develop disease.

Mass screening has been used as part of epidemiological research. Increasingly, however, it is being applied by public health authorities to detect and treat the diseases discovered or to prevent disease in persons who exhibit precursor pathology. This situation presents far-reaching opportunities and obligations to the epidemiologist.

The data from the screening programme itself may give information of epidemiological value, either on the prevalence of the disease for which the examination was done or on other conditions whose presence or frequency in the community had not been previously appreciated. An example is cardiac enlargement found at routine mass miniature radiography primarily designed to detect tuberculosis.

More important, however, is the opportunity available to the epidemiologist to attach additional tests to the service programme. Examples are questionnaires, such as those on symptoms and/or personal habits relevant to health, lung-function tests, electrocardiograms, blood-pressure measurements or even blood sampling. By record linkage, highly automated long-term follow-up studies would be possible. As an example, blood pressure was measured in a standardized fashion in 70 000 people in Bergen, Norway, in connexion with a mass radiography programme directed towards tuberculosis. The mortality of the examined persons is being studied prospectively by means of automatic record linkage.

The problem of non-response in mass screening programmes is a difficult one. In routine tuberculosis case-detection surveys, for example, a low response rate may mean that the sample surveyed is not representative of the population as a whole. It may be possible to estimate the likely degree of bias from a special examination of the health and other characteristics of those who did not at first respond. However, generalizations about the whole population cannot be drawn confidently from the experience of the sample, nor can this experience be used in comparisons with other areas. On the other hand, very useful information about latent disease and the evolution of conditions such as diabetes can be extracted from such samples, particularly by follow-up inquiries.

The screening of occupational groups may be particularly useful to the epidemiologist. Advantages include a high response rate, availability of large numbers, and the prospect of effective follow-up. Such surveys inevitably generate large quantities of data, but the speed and flexibility of modern computers permit their use to ease and accelerate the process of checking questionnaires for consistency, making transformations of variables and diagnostic groupings, and tabulating results.

It is important that the epidemiologist offer his services to the public health authorities in the evaluation of screening programmes. It is necessary to determine the impact of the discovery of early disease and its treatment upon the individual involved and upon the population level of morbidity and mortality from the disease in question. In studying this problem, experience in clinical trials, with its emphasis on randomization of subjects into treatment and control groups, is very relevant. However, the task of evaluating the performance of a public health programme, is more complex than that of assessing the benefit of treatment conferred on individuals; an extensive investigation of this entire methodologic problem is urgent.

6.3 "At-risk" registers

The registration of groups believed to be at high risk of particular diseases is a rapidly growing field of interest. For example, maternity and child welfare services in the UK are trying to identify at birth infants who are particularly likely to show defects such as deafness or cerebral palsy in later life. Such infants are kept under observation with a view to assuring early diagnosis and effective treatment.

The maintenance of "at-risk" registers has encountered the difficulties that might have been predicted on theoretical grounds. The major problem seems to be that many of the criteria currently used to identify the at-risk infant are insufficiently precise and discriminating, resulting in an excessively large at-risk population, few of whom are eventually found to be handicapped.

The at-risk register should not be used to discover conditions missed in the neonatal period, such as congenital dislocation of hip, undescended testis, or Down's syndrome. It may be assumed that infants known to be at genetic risk for fibrocystic disease of the pancreas, phenylketonuria and galactosaemia will have been investigated before discharge from hospital. It may also be assumed that the dangers of haemolytic disease of the newborn and other hyperbilirubinaemias are recognized and treated. Provided that a mother who gives a history of adverse pregnancy factors is delivered in an institution where infants are closely observed, many factors, such as toxemia of pregnancy, can be disregarded once

a healthy, normal baby is born who shows no abnormal signs in early neonatal life.

If this be accepted, examples of criteria for placing an infant in the "at-risk" category would include :

- (1) family history (deafness of genetic origin in parents or siblings),
- (2) prenatal (history of maternal rubella in first four months of pregnancy),
- (3) perinatal (prematurity, defined either by birth weight or duration of gestation, moderate or severe birth asphyxia), and
- (4) neonatal (difficulty in suckling or swallowing, failure to thrive not explained by simple feeding problem, convulsions, cyanotic attacks or severe apnoeic spells, abnormal neurological signs in the neonatal period).

It is essential to quantify the risk, item by item, so that admission to the register will be on an agreed definition of above-average risk.

In the USSR and some other countries, persons with recognized hypertension, cancer, premalignant conditions, peptic ulcer and some other chronic diseases are enrolled for special medical care in the local polyclinic. This system is known as "dispensary care". Persons so assigned are regularly called up for examination and treated as required. Under consideration is the establishment of similar lists for persons with ischaemic heart disease and non-specific pulmonary disease. It is recognized that it is important to evaluate the performance of the system under various local conditions.

6.4 Follow-up and surveillance problems

Once groups at high risk of chronic disease have been identified, there remains the practical problem of effective follow-up and the ascertainment of subsequent disability and death. At the present stage in the evolution of work in this field, this is of special importance in research on the predictive value of screening procedures, but it will become increasingly important when field trials of prophylactic methods are being conducted.

The surveillance of groups of people in different risk categories may be looked at from the viewpoint of either the group or the individual. One of the best examples of the first is the collaborative follow-up study by Japan and the USA of those exposed to varying amounts of radiation during atomic bomb attacks. From this continued observation of a large population, much has been learned about the effects of radiation on all forms of disease. Another example of group surveillance is in studying the effects of a change in chemical or other processes following the identification of a specific occupational health hazard, when

it is important to know whether the change results in a lowering in risk to the group of exposed workers as a whole. In these circumstances, routine or special mortality or morbidity tabulations over the succeeding years will allow the continuing surveillance of health levels. A change from one type of retort to another in the gas industry, for example, would be an indication for such a continuing review of deaths from cancer of the lung among the workers.

From the point of view of the individual, however, the need is to maintain a close surveillance of persons known to have been exposed. The aim is to detect early disease so that, at least, treatment can be initiated at an early stage or, ideally, the process can be reversed by removing the individual from the toxic exposure. The process of surveillance will usually be successive clinical examinations, the nature and periodicity of which will depend on the risk involved. It must not be forgotten that the particular risk may remain high for many years after exposure and after the individual has left the high-risk group (e.g., is no longer employed in the hazardous occupation).

Perhaps of greater relevance to epidemiological investigation is the situation in which the high risk is only suspected, and the frequency of disease in the high-risk group is being determined for comparison with rates in some other (control) group presumed not to be at high risk. The method of surveillance will then depend on the nature of the disease under investigation. To determine frequency of certain conditions (e.g., hypertension and neurosis), there may again be no alternative to repeated clinical examinations of each individual in the group. On the other hand, if the disease is one that usually comes to medical attention, it may be possible to monitor the group by record linkage without recourse to contact with individuals. Perhaps the most frequently used method in this connexion involves searching death certificate files for the names of individuals in the groups under study. Some of the remarks concerning death certificates made earlier in this report are relevant here. The success of this method depends on the feasibility of tracing death certificates of individuals when the date and place of death are unknown and when, perhaps, it is not even known whether they are dead or not. This is not always possible, even in countries with vital statistics systems that in other respects are quite advanced. This method is extremely important to epidemiologists; where the possibility does not exist, every effort should be made to develop it.

There are other means of ascertaining the death of individuals, and although these are limited in scope, they may be useful in special groups. Such means include insurance claims (in insured populations) and various national, military or veterans' burial allowances. In the USA, the programme of follow-up of veterans by the National Academy of Sciences is an example of the use of such records in epidemiological studies. The

American Cancer Society has used volunteers to determine the fact of death or survival in a group of over one million persons classified according to various risk factors.

Disease registers (e.g., cancer registers), if they exist in the area, can be used for surveillance in the same manner as death certificate files if the disease registered is the one to which the group is thought to be at risk. The records of individual hospitals and even of physicians may be utilized if the entire medical-care facilities used by the group can be identified and covered. This last procedure, except in special local situations, will usually be laborious, and the effort involved may approach that required for individual follow-up.

The other forms of record linkage noted earlier in this report may also be useful in this context. Particular mention should perhaps be made of birth certificates and claims for medical costs or disability benefits.

7. SPECIAL STUDIES

Rapid industrialization and the movement of populations into vast conurbations have combined with the reduction in the frequency of communicable diseases to accentuate the problem of chronic disease of all kinds in middle and later life. Man is changing his own environment on such a scale and at such a pace that new problems in disease prevention demand new methods of dealing with them. There is also an increasing realization that chronic disease in later life may have originated in youth and been influenced by subsequent circumstances and ways of life. Epidemiological studies can aid in the detection of the crucial factors in chronic disease genesis and evolution; the Committee discussed several areas of special relevance to this task.

7.1 Longitudinal studies of child development

Over the past 25 years, several longitudinal studies of child development have been undertaken in the USA. Starting around 1950, research in this field was expanded by the International Children's Centre so that teams in several countries undertook to study the physical and mental development of populations of children, starting at birth and continuing until adulthood. Methods and techniques used by the teams were agreed upon at the outset and are reviewed annually. Since the origins of chronic diseases of adults are probably often to be found in childhood, the data collected in these studies may prove to be an invaluable resource in studies of the epidemiology of chronic diseases, particularly if these measurements of childhood development can be linked to disease experience in later life.

7.2 Population laboratories

Although the expression "population laboratory" has been used widely in epidemiological circles, it is not a satisfactory term. It incorporates a number of different concepts and is not clearly descriptive of any of them. No two supporters of population laboratories have quite the same ideas about their aims and structure. In addition, the word "laboratory" carries the implication of "experiment" and consequently may have unfortunate overtones. Nevertheless, several of the concepts to which the term has been applied are very important and deserve more widespread application. These include the following :

(1) An area (often a focus of disease) in which an effort is made to understand the total ecology—human, animal and plant.

(2) A geographically defined population within which observations derived from the correlation of special surveys, record linkages and overlapping clinical observations are made that would not be possible from any one source alone. The areas to which this concept has been applied vary greatly in the extent to which special censuses and surveys, efforts to improve medical diagnosis and recording, and clinical examination have been incorporated.

(3) More loosely, any population or area that is repeatedly the subject of epidemiological study. In such an area, the cross-linking of ideas or information from one study to another may produce additional information. Thus, since series of cases of both myocardial infarction and diabetes had been studied in Oslo, Norway, it was possible to combine the two sets of data to study association of the two diseases. Economies may also be introduced if the same population is used repeatedly, as in the utilization of previously collected census or control information.

There is some danger that a population that is under intensive and continuous observation may become tired of the process and that co-operation rates may consequently fall. Similarly, the mere fact of observation may cause changes in behaviour, e.g., persistent enquiring about smoking habits may prompt a change in tobacco consumption. However, this does not yet seem to have become a problem of any magnitude in most general populations used for intensive investigation. It is not likely to arise if information is derived from records; even with repeated clinical examinations, many investigators have been able to maintain satisfactory rates of co-operation.

Another possible limitation of the population laboratory is that the population requirements of different studies are seldom identical and are frequently very different, depending on the nature and frequency of

the disease under study, the distribution of suspected causal agents in the population, and the methodology of the proposed study. The existence of a convenient population laboratory may tempt an investigator to search for problems that can be investigated in his population, rather than to seek populations in which his most promising ideas can be tested. The concentration of research in selected populations may also limit the variety of experiences and disease patterns that come under investigation. This also would not yet appear to have become a practical problem.

Achievements in many of those areas that are now considered as population laboratories have been substantial, and the further application of the concepts that are embodied in them should be encouraged, particularly in areas of the world in which such correlated observations have not yet been undertaken.

7.3 Migrant studies in epidemiology

The concern in WHO and elsewhere with health hazards involved in the movement of populations, whether from rural to urban areas or from one country to another, means that special attention to the methods of investigation involved will be required in the next few years. Certainly, the large-scale migration of human populations that has occurred in the last century provides a unique opportunity for epidemiological research. Studies based on migrants are useful in measuring the effect on health of the environment, either of the place of origin or of the host country, and of changes in habits that follow migration. The mass movement of people from one continent to another has been used to make important observations on both mental disorder and malignant disease. More recently, interest has centered on cardiorespiratory diseases, such as cancer of the lung, to which migrants from the UK to other Commonwealth countries or to the USA seem to retain an excessive susceptibility even in their countries of adoption. Cardiovascular and other diseases have been foci of research in the particular context of immigrant groups in Israel, where disease frequency has been linked to place of origin and the associated dietary habits and ways of life.

Although analogous in some respects to large-scale experiments, migrant studies suffer from the usual defects of observational studies, deriving from lack of random assignment to the groups under observation. Migrants may be self-selected in that the fit, vigorous and perhaps the temperamentally unstable are more likely to move. Japanese migrants to the USA, for example, have been found to be taller than the average for the general population in Japan. The host country may also select immigrants by screening examinations designed to exclude those with major infectious or mental illnesses or defects. In general, the social-class distribution of migrants tends to differ from that of either country,

and they are likely to be housed in less satisfactory conditions than the established population of their new homeland. In order to take these sources of variation in disease incidence into account, more information is needed than is usually available on routine mortality and other official records, and, here, special enquiries among representative samples of these migrant populations about their place of origin, residential, occupational and smoking histories are helpful. Similar questionnaires also can be directed to the next-of-kin of individual migrants who die in their new country. Methods such as these have been used to demonstrate the gradient in death rates from gastric cancer, from the high level in Japan to the lower level in migrants from Japan and to the even lower levels in the descendants of migrants from Japan who were born in the USA.

Although the comparison of the experience of more than one migrant group in the same country allows the selected nature of migrants to be partly controlled, there is much to be gained by making similar observations on representative samples of the whole native-born populations of the countries concerned. An even closer degree of control over the familial and genetic background can be obtained by comparing the morbidity experience of the migrant member of the family and of those who have stayed at home. A special case is the use of twins who have been exposed to different environments as the result of migration, e.g., in rural and urban areas.

In the analysis of the data thus obtained, tabulations can be made to assess the effect of the urban environment in early life on later cardio-respiratory disease by comparing the morbidity experience of those born in urban or rural areas and now living elsewhere abroad. Similarly, the effect of length of exposure, e.g., to urban air pollution, can be gauged by comparing groups that left home at different ages. With sufficient material, other and more complex associations can be explored. Thus different gradients of disease association with social class or smoking habits, observed in people of the same family living in different national environments, may give crucial evidence on the interaction between these factors in the genesis of cardiorespiratory and other disease.

There are many opportunities for the use of such studies in the elucidation of chronic disease of obscure origin. The curious geographical distribution of multiple sclerosis throughout the world is a typical example. However, it should be pointed out that, particularly with respect to uncommon diseases, the complications introduced by the heterogeneity of the populations concerned would require the collection of large amounts of data. It is in such circumstances that international collaboration with the help of WHO might be decisive.

8. RECOMMENDATIONS

1. Because the study of populations is the basis of epidemiology, and because of the need for close international collaboration in this field, epidemiology is a subject that particularly needs the type of support that WHO is equipped to supply. It appears, furthermore, to be a subject of special relevance to the aims of WHO. The formation by WHO of a new Division of Research in Epidemiology and Communications Science is welcomed, and it is hoped that this Division will be able to strengthen WHO's role in the development of epidemiological methodology. As far as work in the chronic degenerative diseases is concerned, the following areas, in particular, are recommended for priority in this development :

- (a) methods of measuring the social and cultural environment and of standardizing description and measurement of personal habits and ways of living;
- (b) methods of measuring and describing the physical, psychological and social disability associated with chronic disease;
- (c) the integration of research in different diseases and disabilities, so that maximum use is made of investigations on populations that are of special interest and, in many cases, rapidly changing; and
- (d) the problems of record linkage, including related statistical and computer methodology.

2. There is a need to embody developing epidemiologic and statistical knowledge into routine health statistics. Improved collaboration between administrators of health services and epidemiologists in academic and other settings is likely to lead to statistics that will be of greater use both in administration and for epidemiological research.

3. For the purpose of comparing disease outcome in groups exposed to various kinds of environmental hazard, it is often necessary to search for death certificates of individuals whose date and place of death are not known. In most countries, because of considerable migration, the search will usually have to be made on a national basis. Every effort should be made to develop this capability in countries where it does not already exist. WHO could perform a considerable service by bringing the matter to the attention of the national committees and other appropriate bodies.

4. WHO and national bodies should initiate trials with different forms of death certificate designed to elicit more complete information on the pathological conditions present at death. The advisability of dropping the distinction between "underlying cause", "conditions con-

tributing to death" and "other conditions present at the time of death" should be investigated.

5. Hospital records and records of out-patients centres are frequently the most accurate source of medical information available in a community. Often, however, because of differences in record storage, indexing, and other procedures, this information cannot be fully utilized. Attention should be given to improving access to hospital information and its linkage to other sources such as death certificates and census information.

6. The Committee appreciates that WHO has long been aware of the importance of standardization in the broad field of epidemiology. However, most of this work has been concerned with specific diseases, and the Committee now recommends that WHO encourage the development of the methodology for production of properly validated standardized techniques suitable for use in chronic-disease epidemiology. The Committee further recommends that WHO consider the advisability of preparing of a list of such standards or standardized techniques as have been validated adequately on an international basis.

7. During this discussion of epidemiological methodology, problems of definition of terms arose even between epidemiologists from the same linguistic group; the difficulties are compounded in exchanges between workers using different languages. It would be desirable for WHO to consider the establishment of a glossary or dictionary, on a multilingual basis, of the terms used in epidemiology.

8. Epidemiological methods have already made important contributions in suggesting underlying causes and measures for the prevention of chronic disease, notably in the field of malignant disease and congenital malformations. Nevertheless, the bulk of the chronic-disease problem remains, and its public health significance is becoming ever more widely appreciated. At the same time, the emphasis laid by epidemiologists on problems of diagnosis and classification in this field has aroused the interest and productive collaboration of their colleagues in other branches of medicine. In the field of cancer epidemiology, for example, the need to develop methods for the uniform description of pathological specimens in making geographic comparisons has led to a better definition and classification of many forms of malignant disease.

The Committee therefore urges WHO to promote the teaching of epidemiological methods in the context of chronic disease among both medical students and graduates working in the various specialized disciplines of medicine.

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