ARTERIAL HYPERTENSION
AND
ISCHAEMIC HEART
DISEASE

COMPARISON IN EPIDEMIOLOGICAL STUDIES

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**NOTE**

*Authors alone are responsible for views expressed in this publication.*
The World Health Organization (WHO) is one of the specialized agencies of the United Nations. Through this organization, which came into being in 1948, the public health and medical professions of more than 100 countries exchange their knowledge and experience, and collaborate in an effort to achieve the highest possible level of health throughout the world. WHO is not concerned with problems which individual countries or territories can solve with their own resources. It deals, rather, with problems which can only be satisfactorily solved through the co-operation of all, or certain groups of, countries—the eradication of diseases such as malaria, the control of cholera, plague, yellow fever, smallpox and rickettsiosis. Progress towards better health throughout the world also demands international co-operation in many other activities: for example, setting up standards for biological substances, for insecticides and insecticide spraying equipment; compiling an international pharmacopoeia; drawing up international sanitary regulations; revising the international lists of diseases and causes of death; assembling and disseminating epidemiological information; recommending non-proprietary names for drugs; and promoting the exchange of scientific knowledge. In many parts of the world, there is need for improvement in maternal and child health, nutrition, nursing, mental health, environmental health, public health administration, professional education and training, and health education of the public. Thus a very large share of the Organization's resources is devoted to giving assistance and advice in these fields to countries and territories whose health services are at an early stage of development and which are therefore weak points in the common front against disease.
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THE PROBLEM OF INTERNATIONAL COMPARABILITY

Cardiovascular diseases compete with neoplastic diseases as the leading cause of death among the adult populations of developed countries. Ischaemic heart disease and arterial hypertension are important causes even at relatively young ages; in 25 countries and territories studied in 1958 these conditions accounted for about 15% of all deaths between the ages of 35 and 39 (Table 1), and approximately 40% of deaths in the age group 50-54 (percentages for selected countries are given in Table 2).

The available statistics suggest that the highly developed industrialized nations are experiencing a persisting "epidemic" of ischaemic heart disease, associated with a high mortality, particularly among males in the productive period of life. At the same time the mortality rates for hypertension and ischaemic heart disease appear to vary widely from country to country. The USA (white and non-white males) has the highest mortality rates for "atherosclerotic heart disease"—about ten times as high as those for Japan (Table 3). On the other hand Japan shows high mortality rates for "hypertensive disease", which are exceeded only by those for non-whites in the USA.

In men between 50 and 54 years of age in a group of countries characterized by a high prevalence of chronic cardiovascular disease, namely Australia, Canada, Finland, New Zealand, the United Kingdom, and the USA, 37% of all deaths in 1958 were ascribed to atherosclerotic heart disease, (Table 2). In Japan, on the other hand, 25% of the deaths among males in this age group were ascribed to cerebrovascular disease or hypertension, and only 7% to atherosclerotic heart disease.

Research into the pathogenesis and therapy of arterial hypertension and ischaemic heart disease is pursued in many countries, and very considerable funds are sometimes available for such research within them. Nevertheless, progress in the understanding of these diseases is slow. Therapy is therefore more or less symptomatic, and there is as yet no scientific basis for effective prevention.

These diseases need to be investigated in people living in different ecological situations presenting "natural" experimental conditions. In addition, the striking differences between national statistics that have just been mentioned suggest that comparison on an international scale would be desirable. The success of international research in this field will depend on the comparability of the data obtained, and WHO is therefore concerned with the establishment of the necessary "common language", in the form of definitions, classifications, and diagnostic criteria, as well as methods and techniques. This will permit the comparison of research data in population studies, as well as in therapeutic trials, and should also improve the comparability of national morbidity and mortality statistics.

The first step towards the understanding and control of these diseases would consist in studies of the etiological factors, based on morbidity, mortality, or both, and taking into account environmental and inherent factors that may be of etiological significance.

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TABLE 1. DEATHS DUE TO ATHEROSCLEROTIC HEART DISEASE AND HYPERTENSIVE DISEASE AS A PERCENTAGE OF ALL DEATHS IN THE 35-39 AGE GROUP, IN THREE GROUPS OF COUNTRIES AND TERRITORIES, 1958

<table>
<thead>
<tr>
<th>Countries or territories</th>
<th>Percentage of all deaths due to atherosclerotic heart disease</th>
<th>Percentage of all deaths due to hypertensive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Australia, Canada, Finland, New Zealand, United Kingdom, USA</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Italy, Japan, Portugal, Sweden, Taiwan</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Group of 25 countries and territories *</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

* Australia, Austria, Canada, Denmark, Finland, Germany (Federal Republic), Germany (West Berlin), Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Portugal, Sweden, Switzerland, Taiwan, United Kingdom (England & Wales), United Kingdom (Northern Ireland), United Kingdom (Scotland), USA (white and non-white), Yugoslavia.

TABLE 2. DEATHS DUE TO ATHEROSCLEROTIC HEART DISEASE AND HYPERTENSIVE DISEASE AS A PERCENTAGE OF ALL DEATHS IN THE 50-54 AGE GROUP, BY SEX, IN SELECTED COUNTRIES, 1958

<table>
<thead>
<tr>
<th>Countries</th>
<th>Percentage of all deaths due to atherosclerotic heart disease</th>
<th>Percentage of all deaths due to hypertensive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Australia, Canada, Finland, New Zealand, United Kingdom, USA (white)</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Italy</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Japan</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Portugal</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Sweden</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Disadvantages of mortality studies

Although the appropriate mortality statistics are readily available from many parts of the world, they suffer—being based on death certificates—from a number of disadvantages, some of which are listed below.

Differences in the quality of the original diagnostic information

Medical students and physicians as a rule receive little or no formal instruction on death certification, and are not usually encouraged to attach special importance to it. Since types of medical training and fields of interest in medicine—not to mention "fashions" in diagnosis—differ widely, the same circumstances of death may lead to quite different mortality classifications in different countries and even within the same country. For example, there is a well-recognized tendency in the USA to consider sudden unexplained death as a manifestation of coronary artery disease, whereas in Japan it is more commonly attributed to cerebral haemorrhage. The degree of real difference in the mechanism of sudden non-traumatic death in the two countries remains in considerable doubt. Since cerebral haemorrhage, as classified in the International Classification of Diseases, is often rightly or wrongly viewed as a hypertensive phenomenon, these national tendencies in ascribing causes of sudden deaths could contribute to the great differences between the mortality rates from ischaemic heart disease and hypertension in the USA and Japan, though it is accepted that some real differences do in fact exist in the rates.

Shortcomings in the International Classification itself

No classification of diseases, however often and carefully revised, can keep pace with the rapid changes that occur in medical knowledge and opinion. Furthermore, the present practice of assigning a single cause of death frequently makes it difficult to take all the facts of the case into account and may interfere with the expression of well-founded medical judgment. Thus mortality data may

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TABLE 3. MORTALITY RATES (DEATHS PER 100,000 POPULATION) FROM ATHEROSCLEROTIC HEART DISEASE AND HYPERTENSIVE DISEASE, BY AGE AND SEX, IN SELECTED COUNTRIES, 1958

<table>
<thead>
<tr>
<th>Country</th>
<th>Atherosclerotic heart disease</th>
<th>Hypertensive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>35-39</td>
<td>50-54</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>32</td>
<td>346 (6)</td>
</tr>
<tr>
<td>Canada</td>
<td>21</td>
<td>172 (15)</td>
</tr>
<tr>
<td>Denmark</td>
<td>14</td>
<td>184 (13)</td>
</tr>
<tr>
<td>Finland</td>
<td>55</td>
<td>405 (3)</td>
</tr>
<tr>
<td>Germany (Fed. Rep.)</td>
<td>25</td>
<td>194 (12)</td>
</tr>
<tr>
<td>Germany (West Berlin)</td>
<td>19</td>
<td>284 (10)</td>
</tr>
<tr>
<td>Hungary</td>
<td>21</td>
<td>151 (20)</td>
</tr>
<tr>
<td>Israel</td>
<td>18</td>
<td>232 (11)</td>
</tr>
<tr>
<td>Italy</td>
<td>19</td>
<td>182 (18)</td>
</tr>
<tr>
<td>Japan</td>
<td>15</td>
<td>70 (22)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>14</td>
<td>153 (17)</td>
</tr>
<tr>
<td>New Zealand (excluding Maoris)</td>
<td>21</td>
<td>279 (8)</td>
</tr>
<tr>
<td>Norway</td>
<td>11</td>
<td>182 (14)</td>
</tr>
<tr>
<td>Portugal</td>
<td>7</td>
<td>80 (21)</td>
</tr>
<tr>
<td>Sweden</td>
<td>12</td>
<td>152 (18)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>14</td>
<td>157 (18)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>3</td>
<td>13 (23)</td>
</tr>
<tr>
<td>United Kingdom:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>England and Wales</td>
<td>27</td>
<td>272 (9)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>30</td>
<td>392 (5)</td>
</tr>
<tr>
<td>Scotland</td>
<td>47</td>
<td>343 (7)</td>
</tr>
<tr>
<td>USA:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>52</td>
<td>467 (1)</td>
</tr>
<tr>
<td>non-white</td>
<td>61</td>
<td>441 (2)</td>
</tr>
</tbody>
</table>

* The numbers in parentheses indicate the order of magnitude of the corresponding mortality rates, the highest being (1).
sometimes conceal important medical facts about a population and provide little evidence of the types of morbidity to which it has been exposed.

An individual whose most important medical problem was arterial hypertension may in fact die of renal disease or ischaemic heart disease secondary to it, and his death may be attributed to one or other of these conditions without reference to hypertension. Again, hypertensive subjects may die in accidents or from cancer or other unrelated diseases, so that their hypertension remains unrecorded in any statistics. It is to be hoped that the 1965 revision of the International Classification will permit some of these difficulties to be overcome.

Differences in coding practices in individual countries

Although the International Classification is a matter of international agreement, the rules for coding are not applied in the same way everywhere, so that diagnoses may be listed under different categories of the Classification. This has been investigated in some European countries, and the differences found in respect of ischaemic heart disease and hypertension were not important.

Validity of death certificate diagnoses

Some investigations have been carried out into the evidence supporting certain diagnoses on death certificates, including those on which death was attributed to some form of cardiovascular disease. The findings of one investigation suggested that, in certain areas sampled in the USA, approximately 80% of diagnoses of major cardiovascular-renal diseases as cause of death would stand up to critical review. In other areas, the diagnosis generally appeared to be tenable, though some other diagnosis was equally probable.

In the international field, where greater variability is to be expected, the Pan American Health Organization is at present checking the accuracy of death certification in the Americas. Such a study might provide the demographer with an indication of the limits of accuracy within which the practising physician can work, and facilitate the construction of a more practical classification.

Morbidity studies

Morbidity studies differ somewhat from mortality studies in the problems they raise, and are in some ways more difficult, especially when they concern cardiovascular diseases. Many of the types of data that are routinely available, such as hospital records, social agency records, physicians’ records, and insurance figures, suffer from limitations similar to those noted above for mortality data, and have the further disadvantage of representing selected populations. For certain acute diseases, a registration or reporting procedure is helpful. It may, for example, be assumed that diseases that are relatively rare and striking in their manifestations, such as rabies or paralytic poliomyelitis, are reported with sufficient accuracy to give a good reflection of their actual incidence in a population. In neoplastic diseases, the diagnosis is very likely to be made at some stage before death, so that worthwhile statistical information is available; moreover, cancer registration is carried out in several countries. There is little likelihood of successful registration of cardiovascular diseases in entire populations, since recognizable symptoms often occur very late in the course of the disease. Studies of representative population samples are therefore indicated, and in fact a number of such studies have been carried out.

It is probable, however, that some otherwise good surveys of cardiovascular diseases have represented a partial waste of effort and even supported erroneous conclusions because marked differences in the methods by which data were obtained have prevented valid comparisons with parallel studies in other population groups. A “common language” of comparable measurements clearly has to be found if any advance is to be made in epidemiological studies in this field. This implies international agreement on methods, to which WHO is accordingly paying special attention.

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The need for minimum standards

Diversity of approach is much to be encouraged in scientific work; standardization can become the enemy of imagination and original thought. No recipe for international research activities can or should be prescribed, since methods must always vary according to the purposes of the particular study. The first report of the WHO Expert Committee on Cardiovascular Diseases, which appeared in 1959, stated that "there was no wish among the Committee to impose more rigidity than was essential to achieve useful comparability of studies. Beyond this minimum, individual investigators and teams should be encouraged to work along lines which are most attractive to them." 6

At the same time, international studies cannot be undertaken unless there exist accepted definitions, classifications, and diagnostic criteria, and the possibility of comparing techniques. Certain cardiovascular diseases, however, differ in their manifestations from one area to another; for example, there is some reason to suspect that chest pain as a manifestation of ischaemic heart disease occurs in a very small proportion of cases in some populations, whereas it is relatively frequent in others. The emphasis in this paper will therefore be on minimum standards applicable under a great variety of conditions. Its aim is to suggest procedures which—to facilitate comparisons—may be added to or combined with those selected by the investigator. At no time is it suggested that the investigator abandon the methods of his choice in favour of those specified.

DEFINITIONS AND GENERAL PRINCIPLES *

Definitions

Many common statistical terms are understood differently in different contexts. Here are some working definitions of certain terms as used in this paper.

Validity

The term "validity" indicates a quality of data as well as of methods, valid methods being methods that produce valid data. The term is also frequently used in speaking of indices (see below). An index or body of data is valid to the extent that it measures the particular attribute it is intended to measure. For example, the waist sizes of London busmen’s uniforms were used in a certain study as an index of body-build.1 The data were available for a large number of persons over a relatively long period of time. Using direct anthropometric measurements it was established that the uniform size was a true index of body-build.2 The data and the method were thus validated. If, say, the factor “fit of uniform” had been shown to vary between the two groups compared, the index might have lacked validity.

A method of low validity, which does not directly measure the thing it sets out to measure, may still be useful for obtaining certain information. For example, the question “How many eggs do you eat per week?” may elicit incorrect replies that would nevertheless serve to distinguish between high and low fat consumers on a group basis. The method would then be of low validity with regard to number of eggs consumed but might be of high validity as an index of high or low fat consumption.

Precision

The term “precision” means the ability of a measurement technique to produce unvarying results when repeatedly applied to the same situation, irrespective of the relation-

* In the preparation of this section, valuable advice and criticism were given by the late Dr Satya Swaroop, Chief, Health Statistical Methodology, WHO Headquarters.


ship of the result to the “true” value. It implies that the method is inherently capable of marking “fine” or “close” measurements. If the heights of a study population were to be measured with a finely calibrated metre scale using a rigid right-angle arm laid upon the head, precise values might be obtained, even though the measurement might not be accurate (see below).

**Accuracy**

“Accuracy” is used to express the close-ness with which a measurement approaches the “true” or “actual” value, and is thus related to validity. If, for example, the method of measuring height just described were used, but the persons being measured kept their shoes on, a variable error would be introduced. This would impair the accuracy of the data but would not affect the precision of the measurement technique, and the same individual in the same shoes would repeatedly show the same height.

If an experienced observer were to guess the heights of a group of persons, an approximation of the correct mean height of the group might conceivably be reached, despite a widely scattered range of individual observations and probable variations in re-estimates of the height of the same individual. Though individually variable and therefore imprecise, his observations would be accurate for the group, and in this respect might be nearer the truth than the metre scale measurements of individuals wearing shoes of varying types. Accuracy in studies of groups, then, is related to the validity of the mean value, whereas precision is related to the concept of the sharpness of a measurement and reduces the standard deviation about the mean value. Measurements of low precision are characterized by large standard deviations.

**Sensitivity and specificity**

The terms “sensitivity” and “specificity” will be most frequently applied to situations where the test employed gives positive or negative results rather than continuously distributed data. The degree of sensitivity is a measure of the closeness with which the test approaches the identification of, say, all cases of a disease or possessors of an attribute. If, for example, an electrocardiographic sign were to be found which was common to all cases of left ventricular hypertrophy, the sign would have high sensitivity, i.e., “false negatives” would not be noted.

If the electrocardiographic sign of left ventricular hypertrophy were never positive except when hypertrophy was present, it would be highly specific; if it then missed some cases it might be considered to have a rather low sensitivity. A test may, on the other hand, tend to produce positive results not only when the disease or attribute is present but also when it is not. It then lacks specificity, and “false positive” results occur.

Both sensitivity and specificity are manifested in varying degrees in any method. An ideal method would be both highly sensitive and highly specific. However, such methods are not common; the more sensitive method frequently lacks specificity and *vice versa.*

Mass screening with the aim of identifying every case of a disease for treatment or preventive management may require the acceptance of false positive results. The research epidemiologist, on the other hand, is often quite willing to accept some false negative tests, provided he obtains positives in a standard or reproducible fraction of the population. Thus, in the first instance, the accent will be on sensitivity, while in the second, if a choice must be made, a high specificity will be preferred.

As far as comparability is concerned, the specificity of a measurement technique is often of greater importance than its sensitivity.

**Repeatability**

The term “repeatability” (or the interchangeable term “reproducibility”) is widely used in connexion with population study techniques and has a meaning not far removed from that of precision. Repeatability (or reproducibility) is said to be present if the reapplication of a procedure leads to the same observations under the same conditions. It involves a low variability both between observations by different observers
(inter-observer variability) and between serial observations by the same observer (within-observer or intra-observer variability). While the concept it embodies is similar to that of precision, it is often extended not only to technical procedures but to such matters as medical histories and the results of combinations of study procedures.\(^3\)

**Indices**

Kendall & Buckland\(^4\) have defined an index number as "a quantity which shows by its variations the changes over time or space of a magnitude which is not susceptible of direct measurement in itself or of direct observation in practice". Medicine—and epidemiology in particular—abounds in examples of the use of indices, one example in the field of cardiovascular diseases occurring in the study of coronary artery sclerosis. Here the underlying process is often silent and its frequency is thus not measurable during life. However, if the plausible hypothesis is accepted that increased frequency of ischaemic heart disease is a function of increased atherosclerosis in the coronary arteries, then the figures on ischaemic heart disease can be used as an index that may be suitable for purposes of comparison in population studies.

**General principles in the choice of methods**

An important basic principle in the choice of methods for epidemiological work is that the methods must be appropriate for use in unselected population groups or samples. Here the epidemiologist's approach differs markedly from that of the clinician. The epidemiologist characteristically is interested in both the presence and absence of disease in a population, whereas the clinician is concerned with cases of known or suspected disease. The material collected by the latter may still be analysed in groups, however, and he has the advantage of a close personal relationship with his patients, which permits him considerable freedom of choice in selecting methods. The epidemiologist, on the other hand, must be careful to choose methods that do not discourage cooperation if he is to obtain a sufficiently good response from the population surveyed.

Since epidemiological study is based upon comparisons, the epidemiologist is interested in methods that, as well as being used in his own particular studies, can be adapted for use by other workers investigating the same or similar problems. His methods may differ from those employed in the large-scale screening surveys carried out for practical public health purposes in an attempt to identify individuals for whom preventive or therapeutic action is advisable, since here sensitivity may be the primary consideration.

The epidemiologist will often be more interested in the repeatability of his observations than in their validity, if the two qualities cannot be combined. He will also as a rule be interested in the specificity rather than the sensitivity of the indices he uses, since he will be willing in general to discard atypical or debatable manifestations of a disease in order to obtain results comparable with those obtained by other workers. He will hope that the indices chosen will detect a relatively constant fraction of the disease present in any population, even though a fairly large number of probable cases may be discarded.

In looking for methods that will be practicable for the use of workers other than himself, the investigator will consider those that are acceptable in various cultures and applicable to a broad variety of subjects. Speed, economy, personnel requirements, available power supplies, and the portability and resistance to climatic conditions of apparatus will also need to be considered.

**The attainment and measurement of comparability**

Though it may seem obvious, it must be stressed that perfect comparability, like other forms of perfection, may be approached but can never be completely attained. For this reason, not only must the investigator seek to

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\(^3\) The term "reliability" seems to be applied somewhat loosely to a number of different concepts in different contexts. Frequently it corresponds to accuracy, precision or repeatability. Its use will be avoided in this paper.

produce highly comparable data, but he must also measure and report the extent of his success in doing so. He should proceed more or less along the following lines:

1. **The selection of methods.** Methods of known validity and reproducibility should be selected in order to achieve the maximum degree of comparability. It must however be stressed that in no case will the adoption of particular methods alone guarantee the comparability of the results.

2. **Training of personnel.** Since most studies are carried out by teams of observers, and since in any case a comparison between different studies will involve a variety of observers, it is necessary to train personnel in the use of the chosen methods. This will often involve repeated preliminary tests of observer against observer and at times the exchange of personnel between laboratories for the preliminary standardization of techniques. At other times common reference material may be made available for parallel study to permit assessment of precision and reproducibility.

3. **Measurement of actual variability.** In the design of any study provision should be made for demonstrating the actual inter-observer and within-observer variability that has taken place. This may be done by repeat observations by the same observer and by parallel observations by different observers on suitable samples of the study population.

4. **Comparability in reporting data.** It is of course an advantage to employ units of measurement in common use, such as centimetres, kilograms, and the centigrade scale for temperatures. Even when data have been collected in a fully comparable manner, their comparability may be sacrificed at the point of reporting. In general it is strongly recommended that the use of arbitrary cut-off values be avoided, and that the actual distribution of the observed data in relation to the population be reported as fully as possible.

An example from the field of blood pressure measurement will illustrate this point. If two investigators are interested in hypertension in particular populations, and one chooses to define hypertension as beginning at a level of 145/90 mm Hg, the other at a level of 150/100 mm Hg, their reports of the prevalence of hypertension based on these two definitions will give no basis for comparison. If the two investigators were to adopt a common definition, some measure of comparison might well be possible. In either instance, assuming that individual blood pressures are measured in a comparable manner, a great deal of information will be deliberately thrown away. If, however, without abandoning the investigation of hypertension, the actual distributions of blood pressure values observed in each population are reported, the maximum of useful comparability will be achieved. The distributions could of course be acceptably presented in the form of means and standard deviations or in the form of graphic representations of distribution curves. A great many observations on a population can be reported in a similar way.

Indeed, there is still some doubt as to the existence of “hypertension” as a qualitative change. Pickering, Cranston & Pears have repeatedly stressed the evidence pointing to blood pressure as a continuous variable. Until there is some agreement on this point, it would seem well to abandon the use of arbitrary cutting points for normal and abnormal values, and to report only distributions of observed blood pressure.

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Co-operative studies in the epidemiology of cardiovascular diseases are by no means new, and for a number of years there have been attempts to standardize methodology in varying degrees. We shall here confine ourselves to the steps leading up to WHO's present work in this field.

The Beaconsfield Conference

A particularly important attempt at standardization between different surveys was a two-day conference—usually referred to as the Beaconsfield Conference—held in the USA in June 1957 and attended by representatives of ten groups of investigators carrying out longitudinal studies of cardiovascular diseases. The participants reported on their own methods and study designs and, on the basis of the discussions and certain short-term studies by those taking part, some general points of agreement were reached.

The usual auscultatory technique for blood pressure measurement as specified by the American Heart Association was recommended and, despite a certain amount of disagreement, a sitting casual blood pressure was suggested as the fundamental basis for comparison. There was recognition that several observations at a single interview might furnish a better basis for longitudinal follow-up in an individual study population than a single reading. The fifth phase (disappearance of sound) was proposed as the accepted diastolic end-point and a cuff 12 cm wide was recommended for "normal-sized" arms. No consensus was reached on whether results should be recorded in multiples of 2 mm or 5 mm. While it was recommended that normally distributions of observed blood pressures should be reported, cutting points for the diagnosis of normotension, high blood pressure, and borderline high blood pressure were given.

Though some difficulty was experienced in reconciling the various views expressed on electrocardiography, codification of electrocardiographic criteria was strongly recommended, as well as the exchange of unknown and obscure electrocardiograms for standardization purposes. The difficulty of handling borderline abnormalities in a consistent way was stressed, and some preliminary suggestions concerning stress tests (post-exercise electrocardiograms) were made.

It was proposed that a central laboratory service be organized to help reduce variability in laboratory procedures. This idea was later used by the US Public Health Service Heart Disease Control Program in developing its co-operative cholesterol standardization programme.

Attempts at international standardization

A precedent for international agreement on a "common medical language" was the first publication in 1900 of the International List of Causes of Death, later somewhat extended to include morbidity data as well.

In 1939, the American Heart Association
and the Cardiac Society of Great Britain and Ireland issued a joint statement on the standardization of blood pressure readings, which has provided a basis for most later publications on the subject.

Early WHO meetings

WHO first approached the problem directly in 1955 when it convened a Study Group on Atherosclerosis and Ischaemic Heart Disease, in Geneva. The Group's report, published in 1957, stressed the need for agreement on both clinical and pathological terminology and classification. Its definition of ischaemic heart disease has been widely used:

"Ischaemic heart disease is defined as the cardiac disability, acute and chronic, arising from reduction or arrest of blood supply to the myocardium in association with disease processes in the coronary arterial system."

Details of methodology were not gone into at this meeting, but it was urged that WHO should undertake work in this field.

In 1957, a WHO Study Group on the Classification of Atherosclerotic Lesions met in Washington, D.C., to outline methods for the pathological study of atherosclerosis in accordance with the recommendations of the 1955 Study Group. This meeting reached a tentative agreement on standards for grading atherosclerotic lesions and recommended an international programme of studies in this field. Action taken on this recommendation will be discussed later (see page 19).

WHO Expert Committee on Cardiovascular Diseases and Hypertension

In 1958, a WHO Expert Committee on Cardiovascular Diseases and Hypertension met to discuss criteria and classification in epidemiological studies of hypertension and coronary heart disease. The nomenclature and classification of hypertension and coronary heart disease were reviewed, and methods constituting a “minimum” basis for comparability between studies summarized.

Hypertension. The Expert Committee made a number of recommendations on blood pressure measurement. A single casual sitting or recumbent measurement was suggested, and the use of a cuff 14 cm wide and long enough to encircle the arm completely was recommended. The selection of a diastolic end-point—i.e., whether to record phase 4 (muffling of sound), phase 5 (disappearance of sound), or both—was left to the discretion of the observer. While it was suggested that distributions of blood pressure be reported, definitions of normotension (below 140/90 mm Hg) and hypertension (160/95 mm Hg and above) were given. Hypertension was subclassified into uncomplicated and complicated types, depending on the presence or absence of cardiac hypertrophy and/or signs of vascular involvement of the brain, retinae, kidneys, or heart.

Ischaemic heart disease. The Committee accepted the term “coronary heart disease” as being synonymous with “ischaemic heart disease” as defined by the Study Group on Atherosclerosis and Ischaemic Heart Disease in 1955 (see above). A fourfold classification of the principal symptoms and manifestations was adopted: (1) angina pectoris; (2) myocardial (or cardiac) infarction; (3) sudden death (often the first clinical manifestation of coronary heart disease); (4) cardiac failure (mainly congestive in type). There were two subclassifications of angina pectoris—definite and probable—and the problems of making a fully comparable diagnosis were discussed. Whether the use of questionnaires by non-medical personnel to elicit a history of angina pectoris compares favourably with history-taking by a physician was left an open question, pending research.

The discussion of the electrocardiographic study of coronary artery disease mentioned the desirability of using more than one observer for the reading: it was felt that only patterns read as very probable or very possible myocardial infarction should be used as

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4 American Heart Association and Cardiac Society of Great Britain and Ireland (1939) Amer. Heart J., 18, 95.
evidence (an annex to the Committee's report illustrates types of patterns that could lead to the diagnosis of very probable and possible myocardial infarction). Mention was made of the desirability of the separate recording of the presence of arrhythmias, conduction disturbances, and non-specific T-wave changes to permit further study of their diagnostic significance. The Committee did not consider that the value of exercise tests in field studies had yet been proved.

The need for standardization of cholesterol measurements was emphasized, and it was observed that fully satisfactory means of studying diet, physical activity, psychological factors, and other possible etiological factors were lacking.

The Princeton Conference

Mention must be made here of the Princeton Conference held in April 1959 by the American Heart Association and the National Heart Institute of the US Public Health Service, because, although a national meeting, it discussed problems relating to international comparability. Its report reflects the work of more than 80 individuals representing many different disciplines. In addition to participants from the USA, there were four from other countries, including a representative of WHO. After an initial session on the design and analysis of studies, there was a discussion of criteria for diagnosis and clinical evaluation, followed by reports on the problems of diet, physical activity, biochemical measurements, cultural, social, family, psychological and genetic influences. The part of the report dealing with criteria for diagnosis is of particular interest. Here are some of the points in which it departs from earlier documents.

Ischaemic heart disease. The definition adopted by the WHO Study Group on Atherosclerosis and Ischaemic Heart Disease in 1955 was accepted, but the classification and associated criteria were changed to some extent. Four categories were listed:

1. Myocardial infarction
   (a) definite, defined on primarily clinical but secondarily electrocardiographic grounds;
   (b) possible.
2. Anginal syndrome
   (a) definite (this was redefined in some detail);
   (b) possible.
3. Sudden death.

The last two categories were considered unsuitable for epidemiological indices.

Hypertensive disease. This term was considered as synonymous with essential hypertension, and the definition of Goldring & Chasis was accepted. Reporting of actual blood pressure distributions was strongly advised, and the following cutting points were adopted:

1. Normotension: systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg.
2. Hypertension: systolic blood pressure 160 mm Hg or over, or diastolic blood pressure 95 mm Hg or over, or both. Under this heading systolic hypertension and diastolic hypertension were suggested as subcategories.
3. Borderline hypertension: the residual category with systolic blood pressure below 160 mm Hg and diastolic blood pressure below 95 mm Hg but not with these pressures simultaneously below 140/90 mm Hg.

*Goldring, W. & Chasis, H. (1944) Hypertension and hypertensive heart disease, New York, Commonwealth Fund. The definition reads as follows: "The term hypertensive disease is synonymous with essential hypertension and should properly be restricted to designate the as yet unidentified physiological disturbance (or disturbances) characteristic of this disease and which leads ultimately to elevation of diastolic and systolic blood pressures, anaerobic changes in the vascular tree, and functional impairment of the involved tissues. Hypertension is the earliest clinically recognizable disturbance and results from constriction of the peripheral arterioles, this constriction leading to an increase in the total effective peripheral resistance and hence to elevation of diastolic and systolic blood pressures. Hypertensive disease is considered to be a clinical entity in which an unknown pressor mechanism initiates arteriolar vasoconstriction, elevated blood pressure and vascular sequelae. Hypertension, as such, like arteriolar changes, is conceived to be a sequela appearing during the progressive development of the disease."
Hypertension was classified according to complicated and uncomplicated forms following criteria similar to those given in the report of the WHO Expert Committee on Cardiovascular Diseases and Hypertension, and the theoretical existence of a pre-hypertensive stage was noted.

**Blood pressure measurements.** The American Heart Association recommendations were, in general, accepted, but it was considered that a cuff 12-14 cm wide should be used, and that the diastolic end-points at the fourth phase (muffling) and the fifth phase (disappearance of sound) should both be recorded.

The Conference also raised the problem of the clustering of readings about certain standard values owing to observer bias. It was suggested that a coded calibration of the manometer might overcome this. In addition it was suggested that audiometric tests be performed on those expected to serve as observers.

It was also considered that the effects of position on the subjects of blood pressure measurement were as yet incompletely understood, and no statement was made as to the number of measurements to be taken.

**Electrocardiography.** The electrocardiogram was stated to play a “small and uncertain” role in epidemiological cardiovascular studies. The difficulties of going beyond a normal/abnormal decision, except in the presence of frank myocardial infarction, were mentioned. The Minnesota Code for the classification of electrocardiographic signs, without attributing significance, was presented to the Conference. This code will be discussed in a later section.

**Cholesterol estimations.** An initial report was presented on the early phase of the US Public Health Service programme on cholesterol standardization which had just then been established, partly under the stimulus of the Beaconsfield Conference.

Further WHO meetings

In 1959, a Cardiovascular Diseases unit was established at WHO Headquarters. Four meetings organized by that unit should be mentioned here.

In May 1960, a WHO Scientific Group met in Geneva to discuss the newly developed intensified research programme in cardiovascular diseases. It recognized that lack of knowledge of pathogenesis impedes the rational prevention of such conditions as ischaemic heart disease, arterial hypertension, cardiomyopathies and chronic cor pulmonale. It recommended therefore that the research programme in cardiovascular diseases should concentrate on investigating the causes of these diseases by making an international contribution to specific projects such as cooperative studies of populations in various areas of the world and research on problems that can be investigated on the local level but are considered crucial to wide advances in cardiovascular research (e.g., methods for the measurement of individual and group response to stressful stimuli).

The Group also reaffirmed the urgent need for improvements in classification, criteria, and standardization of methods. Particular stress was laid on the need for Central Reference Laboratories for biological and pathological standards. The formation of a Diagnostic Criteria Committee was considered, and it was suggested that the variations existing between different countries in the diagnosis of arterial hypertension and ischaemic heart disease might be assessed by the circulation of a group of 100 representative case histories.

There was a strong suggestion that WHO should encourage comparable epidemiological studies in the field of cardiovascular diseases, especially prospective studies of complete populations or representative samples. Clinical and experimental studies of coronary heart disease, hypertension and the cardiomyopathies were also recommended, and

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detailed suggestions made on this subject. It was thought that research on spontaneous cardiovascular diseases in animals might provide useful information, particularly if related to human population studies.

A WHO Expert Committee on Chronic Cor Pulmonale met in October 1960. While its report is not specifically concerned with hypertension and ischaemic heart disease, it considers in some detail the methodological problems involved in the diagnosis of right ventricular hypertrophy from the clinical, radiological, and electrocardiographic points of view, and some suggestions are made on the diagnosis of pulmonary diseases under conditions of population study. It is probable that in some surveys of hypertension and ischaemic heart disease it may be practical to include a study of the problem of chronic cor pulmonale.

In October 1961, a WHO Expert Committee on Hypertension and Ischaemic Heart Disease (Preventive Aspects) met in Geneva. While, as the name of the Committee suggests, it was primarily concerned with the early identification of disease at stages appropriate for preventive management, there was some discussion of methodology and recommendations were made for the classification of ischaemic heart disease and essential hypertension. Methods were not assessed primarily for comparability, however, but rather for their effectiveness in public health screening. In view of the accepted connotation in many countries, the terms “hypertensive disease” and “essential hypertension” were taken as being synonymous. The occurrence of cardiac and vascular hypertrophy was not considered strictly as a complication of hypertension but rather as a physical adaptation reflecting the severity and duration of the hypertensive state. The Committee thought it unjustified at the present stage of knowledge concerning preventive measures to screen populations solely on the basis of blood pressure readings. It was therefore felt necessary to propose a three-stage grading of hypertension:

Stage 1: High blood pressure without evidence of organic changes in the cardiovascular system.

Stage 2: High blood pressure with cardiovascular hypertrophy but without other evidence of organ damage.

Stage 3: High blood pressure with evidence of organ damage attributable to the hypertensive disease.

Criteria for identifying these stages and for distinguishing between essential and renal hypertension were presented. The importance of the electrocardiogram and of ophthalmoscopy was stressed in this connexion. A suggestion was made, subject to reservations, that an arbitrary criterion for the electrocardiographic identification of left ventricular hypertrophy be used for screening purposes (RV5 or RV6 & SV1=35 mm or more). Mention was made of the problem of the relative non-specificity of criteria showing high sensitivity.

Ischaemic heart disease was classified into four categories (not to be considered as “stages”) as follows:

1. Angina of effort.
2. Myocardial infarction (old and recent).
3. Intermediate types.
4. Ischaemic heart disease without pain: (a) Asymptomatic (b) Non-specific effects of chronic myocardial damage. This group includes cases with chronic heart failure and other manifestations such as arrhythmia, attributable to atherosclerosis.

Sudden death was stated to be a possible feature of any one of these categories and was not classified separately.

The Expert Committee discussed diagnostic criteria for the identification of these categories, stress being laid on the electrocardiogram and clinical history. Problems of methodology were left for further consideration by the Scientific Group on Comparable Methodology for the Epidemiological Study of Hypertension and Ischaemic Heart Disease, which met in Geneva in December

The discussions and recommendations of this Group will be dealt with in detail in a later section.

The WHO Regional Office for Europe, which stimulated some of WHO's early activities in this field, particularly the Study Group on Atherosclerosis and Ischaemic Heart Disease in 1955, has continued to take an active interest in the epidemiology of cardiovascular diseases. An Advisory Group convened by the Regional Office at Copenhagen in 1958 considered morbidity and mortality statistics in the European area. Subsequently the Office arranged meetings of investigators to discuss study design and methodology and to undertake some preliminary methodological testing.

The WHO Cardiovascular Diseases unit

Since its establishment in 1959, the Cardiovascular Diseases unit at WHO Headquarters has developed, with the aid of its advisory bodies, a long-term programme covering promotion and co-ordination of epidemiological and pathological studies in arterial hypertension, ischaemic heart disease, chronic cor pulmonale, cardiomyopathies, varicose veins, spontaneous cardiovascular diseases of animals, and other fields. The staff of the unit has had the opportunity to travel widely, gaining first-hand acquaintance with investigators, facilities, research activities and research potential in many parts of the world. Sixty-five distinguished scientists from 38 different countries serve on the Expert Advisory Panel on Cardiovascular Diseases, and they have been most generous in giving advice and active assistance on a variety of problems. Co-operation with the International Society of Cardiology has also proved very fruitful.

In the course of the unit's work, it has become clear that there is widespread willingness to try to develop comparable methods for epidemiological studies. At the same time, little practical progress has been made in this direction. From the papers published in this field, it is apparent that it is still difficult to make even the simplest comparison of data from two different sources, owing to differences in methodology and in the presentation of results.

There are of course many reasons why this situation should persist in spite of the expressed need for comparability. The work that has been done is largely of a pioneer nature and each investigator has developed his own procedures. To persuade intelligent, original investigators to modify their current methods, however slightly, or to adopt a specific method, factual evidence of the desirability of doing so must be advanced and this has been generally lacking.

The situation, then, seems to be that: (a) most workers wish to measure a number of agreed (but often undefined) characteristics in a comparable manner; (b) there is difference of opinion as to the most suitable method for measuring any of these characteristics; (c) evidence is lacking on which judgement of the suitability of the various methods can be based; and (d) there is a readiness to accept methods if good reasons for them are provided. Under these circumstances it seems likely that if a neutral organization would produce suggestions based on factual evidence, after taking the opinions of various workers into consideration, an acceptable comparable methodology could be achieved.

WHO has therefore sought to obtain factual data in those areas where they are, according to widely agreed expert opinion, most needed. Some of the difficulties that may arise are illustrated by attempts at comparable grading by different investigators of atherosclerosis in autopsy material. As long ago as 1955, and again in 1957, WHO Study Groups suggested definitions of atherosclerosis and indicated methods by which it might be graded. These recommendations represented the agreed, though arbitrary, opinions of experts and active workers in this field. There was, however, a lack of factual data to show that the recommended procedures were adequate. Several workers took up the suggestions of the two Study Groups; some encountered difficulties, introduced modifications, and developed new procedures. Epidemiological studies were started, using the newer procedures as well as those indicated
by the Study Group on the Classification of Atherosclerotic Lesions in 1957. Of particular interest were the studies undertaken by the Inter-American Atherosclerosis Project (PIA), which in 1962 became the International Atherosclerosis Project.

In 1960 WHO convened a meeting of pathologists interested in making comparable studies of atherosclerosis to consider how this could be done, taking into consideration the recommendations of the two WHO Study Groups and subsequent developments, in particular the studies by PIA. The group was of the opinion that there was still insufficient factual evidence to furnish a basis for definite decisions, but it arbitrarily agreed upon some definitions of characteristics to be measured and suggested methods of measurement. Most of these were similar to the definitions and methods in current use, but there were some differences. An important step taken by the group was to recommend that the suggested definitions and methods be tested. Specimens were prepared in accordance with the group’s suggestions and a grading trial arranged. It was soon found that considerable differences existed not only between the findings of different observers, but also between repeated assessments of the same specimen by the same observer. Several possible reasons for this were identified, including lack of clarity in the definitions so that they were applied differently by different observers; the use of criteria applicable to the pathologist’s usual practice, but not to epidemiological studies; and inadequacy of technical procedures.

Modifications in the definitions and techniques were accordingly made, and new sets of specimens prepared and circulated by post to 14 observers in six different laboratories. Copies of agreed definitions and criteria were circulated with the trial specimens. Each specimen was examined on two “independent” occasions by each observer. Subsequently some of the trial specimens were treated differently (stained for fat) and re-examined by 10 of the same observers; some were also examined by different methods (planimetry and electronic scanning). The results indicated that two of the three methods used were inadequate, but the third method—though crude—was shown to be useful within defined limits. On the basis of the factual evidence obtained from this trial of methods based on well-informed but arbitrary opinions, a methodology (similar to that used by PIA) was devised that was acceptable to the group and could be recommended for use, within defined limits, to other interested workers.

Mention should be made here of two points which are of general interest in connexion with comparable methodology and will be more or less applicable in considering methods for assessing other characteristics to be mentioned later. First, the comparable method rendered acceptable on the basis of the trial is neither very precise nor very accurate. It is acceptable because it is believed that, within its defined limits, it will give a definite answer to a question of interest—“is there any difference in the amount of atherosclerosis, as defined, in two groups of material?” under certain conditions judged to be of practical concern. There is no question of stating the exact amount of atherosclerosis in each group or the exact difference. Only the direction of the difference will be indicated.

The second point is that neither the validity of the observations nor the usefulness of the arbitrary definitions of “atherosclerosis” employed have so far been proved, though naturally proof is being sought. Usually, as in this case, proof is dependent upon the analysis of data obtained by the application of a comparable method. The fact that definitions of the characteristics to be measured are based on the best available agreed opinion from diverse sources makes them acceptable until proof, which must always be sought, is available.


METHODS RECOMMENDED FOR PRESENT USE

The following recommendations are based on the work of the WHO Cardiovascular Diseases unit and of WHO scientific groups, in particular the Scientific Group on Comparable Methodology for the Epidemiological Study of Hypertension and Ischaemic Heart Disease, which met in Geneva from 5 to 11 December 1961. They are neither final nor complete, and will need revision as additional data become available.

General recommendations

If comparable results are to be obtained in an epidemiological study, due attention must be paid to standardization at all stages:

1. The population studied must be defined in all relevant detail and the proportion not covered by the study must be stated.

2. The characteristics to be measured must be defined.

3. The techniques of measurement must be standardized.

4. The personnel must be adequately trained in the uniform application of the techniques.

5. Each survey should be designed so as to include its own tests of observer variability.

6. Analysis and reporting should conform to certain basic requirements and the frequency of individually specified items should be reported before they are combined in any way into special index numbers or arbitrary subdivisions. Data should be included on factors that may have influenced the observations, such as climatic conditions, time of year, high altitude, etc. In all instances, data should be given in units that are generally accepted, e.g., the metric system should be used for weights and measurements, and temperatures should be recorded in centigrade. Age and sex distributions should be given, and means, standard deviations and ranges of observation specified.

7. Sufficient data should be obtained for the establishment of diagnostic categories and differential diagnoses. For example, a prevalence study of arterial hypertension in a group with an unusual amount of urinary tract infection may not be comparable with other studies unless the associated disease is satisfactorily assessed and reported. An electrocardiographic survey of a population in which anaemia, syphilis, or "cardiomyopathies" are common may give a false indication of the frequency of ischaemic heart disease, in the absence of means of differentiation.

Ischaemic heart disease

In this field special recommendations are confined to the electrocardiogram, and the history of cardiac pain on effort.

The epidemiological uses of the electrocardiogram

Up to the point of reading and interpretation, the electrocardiogram is an objective procedure yielding a graphic record of electrical activity in heart muscle. Its use in epidemiological studies is complicated by the fact that the interpretation of this record

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1 Members: Dr D. Aleksandrow, Poland; Dr F. Epstein, USA; Dr M. Karpovanen, Finland; Dr F. Rojas Villegas, Chile; Dr G. A. Rose, United Kingdom (Rapporteur); Dr A. H. Sorour, United Arab Republic (Vice-Chairman); Dr S. Toyama, Japan; Dr H. M. Whyte, Australia (Chairman).
may vary widely according to the observer. There is also some variability in definitions of electrocardiographic signs. It is hoped that the automatic reading of simplified lead systems by electronic computers will reduce this variability; a few studies using this technique are already in progress. Nevertheless it seems likely that for at least four or five years to come the majority of studies will continue to be based on "standard" 12-lead electrocardiograms read by human observers, and the recommendations that follow are based on that assumption. For those with an eye to the future, however, it might be as well to record orthogonal leads on tape as well as standard leads on paper.

**Leads to be taken.** Nothing less than a normal 12-lead tracing, including three bipolar and three augmented unipolar limb leads plus six unipolar chest leads, can be recommended for general use at present. There may be a general improvement in the measurability of some of the smaller time intervals if at least portions of the tracing are run at 5 cm as well as at 2.5 cm per second. The placement of chest leads should conform to published standards, using the six V-type leads as a minimum. Reproducibility of placement may be improved by the use of a special caliper.

**Apparatus.** Many workers have stressed the advantages of high fidelity research-type instruments often with multiple recording channels characterized by a high frequency response. For the moment, however, only the minimum requirements for clinical instruments published by the American Medical Association can be recommended. These deal in some detail with the stability and response characteristics of acceptable machines, and specify *inter alia* that when the instrument is adjusted for a maximum deflection of 1 cm in response to a direct voltage of 1 millivolt, the deflection resulting from a sinusoidal voltage of the same magnitude varying from 1 cycle to 15 cycles per second shall not be less than 0.9 cm; from 15 to 40 cycles per second shall not be less than 0.8 cm; from 5 to 300 cycles per second shall not be more than 1 cm; and from 1 to 5 cycles per second shall not be more than 1.1 cm.

For a research-type machine, adequate response is defined as "flat response to a single square-wave input up to 200 cycles per second".

Multichannel machines have advantages from the standpoints of speed and convenience, but there is no proof that they are essential in order to obtain comparable records suitable for epidemiological studies.

**Reading of the tracing.** Several studies have shown that the classical interpretative techniques, even when used simply for normal/abnormal decisions, are too variable for epidemiological purposes. While the specific patterns associated with acute myocardial infarction are readily recognized, they are rarely encountered in field studies. Most other patterns are so non-specific as to leave room for considerable inter- and intra-observer variability.

A way out of this dilemma has been proposed by Blackburn et al. in the Minnesota Code. This code is based on the principle of studying the prevalence of observable and measurable electrocardiographic changes without attempting to assign pathological significance. For practical reasons, some arbitrary cutting points were adopted in devising the code, and certain subcategories indicative of change were developed. The system employed is adapted to standard punch-card processing.

The Minnesota Code has been tested and used in several studies by its originators. Other groups of investigators have used it, notably in the United Kingdom and the USA, but no detailed reproducibility studies by these groups have been reported.

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8 Wilson, F. H. et al. (1954) *Circulation,* 10, 564.
preliminary reproducibility test of the code has, however, been carried out by WHO, using five observers. In this test—which will be discussed in the next section of this study—it was found that several categories of the code appeared to give rise to observer variability.

There seems to be little doubt that ultimately the Minnesota Code may be improved or some alternative codes become available, but for the present it is recommended that the analysis of electrocardiographic surveys be based on this code or, should changes be necessary, on other codes readily translatable into its terms.

However good the coding system available, observers will need to be carefully trained and, if possible, "standardized" against reference electrocardiograms that have been graded by other observers. At present there is no formal general provision for this type of training and "standardization", but WHO hopes to remedy this deficiency. Its plans for doing so will be described in the next section.

The use of post-exercise electrocardiograms. Post-exercise electrocardiograms are used by some investigators, but others doubt the necessity or wisdom of including them in population studies. While the two-step test of Master and the modified double standard two-step test have been widely used, it is felt by some investigators that there is need for a more accurately controlled form of physical stimulus (e.g., one that would take the weight of the subject into account), and many, realizing that the test cannot be indiscriminately applied to all subjects, feel that it introduces a variable selection factor which would be difficult to standardize.

The slight element of risk involved in this test is felt by many observers to be a handicap, since any deaths or acute complications occurring during a survey might be attributed to the test, and this would reduce the chance of obtaining co-operation from a sufficiently high proportion of the population sample. This question should be reviewed when more data are available from investigators using exercise tests.

It is recommended that the conditions of every such test should be carefully described. The criteria for the exclusion of individual subjects from the test should be presented and the results classified according to the appropriate section of the Minnesota Code. Findings in respect of resting tracings should always be tabulated separately to permit comparisons.

Epidemiological study of cardiac pain on effort

The clinical diagnosis of ischaemic heart disease is, in the majority of cases, based on a positive history of anginal pain, which is often no less important than electrocardiographic findings. Many attempts have therefore been made to include the evaluation of cardiac pain in population surveys. The difficulty of using subjective interpretations of the type involved here is well recognized, and in international studies differences in cultural patterns, language, and even pain thresholds will increase the difficulty of attaining comparability. There is sufficient evidence of a distinctive clinical picture, however, to warrant a general recommendation that the question of cardiac pain should be investigated in all studies of ischaemic heart disease.

In an attempt to obtain comparability, standard questionnaires or check-sheets have been used by many investigators and compared with the results of interviews by a cardiologist. The effectiveness of a questionnaire or other history-taking device depends, however, on the basic definition it employs of the disease or symptom with which it is concerned. A diagnosis of angina pectoris based on the broad definitions employed in clinical medicine—which aims at the diagnosis of 100% of cases—would cover too many borderline or atypical cases to be conducive to reproducible results in an epidemiological study. While the epidemiologist does not expect to identify all cases of ischaemic heart disease, the use of a restrictive definition of "cardiac pain", as distinct from other types of chest pain, should enable him to diagnose...
a high proportion of them on a comparable basis.

The following definition of "cardiac pain" is recommended for provisional use and further study:

"A chest pain or discomfort with these characteristics:

1. The site must include either the sternum (any level) or the left arm and left anterior chest (defined as the anterior chest wall between the levels of the clavicle and the lower end of the sternum).

2. The pain must occur either when the subject is hurrying or walking uphill (Grade I), or when he is walking at an ordinary pace on the level (Grade II).

3. When the pain occurs during walking it must make the subject either stop or slow down unless nitroglycerine (trinitrin) or a similar drug is taken.

4. The pain must on most occasions disappear in 10 minutes or less from the time when the subject stands still."

A questionnaire based on the above definition has been prepared, though its validity and reproducibility within and between populations need to be tested. A modification of this questionnaire is now used in surveys at the London School of Hygiene and Tropical Medicine and is being tested for repeatability in Norway and Finland. The questionnaire is reproduced as Annex 1.

Arterial hypertension

It was stressed in an earlier section that, for purposes of comparison, it is preferable to report distributions of observed blood pressures rather than "hypertension" and "normotension" based on arbitrary definitions. Some other ways of improving comparability in studies of hypertension are discussed below.

Blood pressure measurement

Although indirect sphygmomanometry has been used for more than half a century, there are still a number of unsolved problems in this connexion. As already noted, some attempts have been made to standardize the technique, but these have usually been on a national level, and the methods still vary from country to country. There are still doubts as to the number of measurements necessary and the conditions under which they should be made, the most suitable cuff to use, the effects of differences in arm diameter, the selection of the diastolic end-point, and the way to avoid the effects of observer bias. The following standard basic technique is suggested for the sake of comparability until such time as these problems—some of which will be further discussed in the next section—have been solved.

Number of observations. While serial observations may be of interest, no specific combination of them has been shown to give superior comparability. Since at least one reading must be made in all instances, it is recommended that this initial reading be made under "standard" conditions and reported for purposes of comparison. Additional readings are optional.

Position of the subject. There is no conclusive evidence that a supine position is to be preferred to a sitting one, or vice versa. From the practical standpoint, the sitting position is suggested, since a chair and table are more likely to be regularly available than a couch.

Circumstances of observation. It is recommended—again largely for reasons of general convenience—that the initial blood pressure measurement be taken under "casual" circumstances involving no special preparation of the subject. Here certain variable
factors may come into play, such as the time the subject has to wait for the measurement, recent conditions of rest, exercise, emotional stimulation, temperature, etc. The following steps are suggested:

1. The subject should be introduced to the observer as soon as possible after his arrival, welcomed, and reassured about the purpose of the interview.

2. He should be asked to remove sufficient clothing to give adequate exposure of the arm, and should be comfortably seated.

3. The room temperature should be kept at a comfortable level and recorded.

4. Extraneous emotional stimuli (e.g., the presence of a hypodermic syringe or other possibly frightening apparatus) should be avoided. It is recommended that the pulse rate be taken, since this may give an indication of the subject's emotional state.

It must be admitted that, despite all precautions, the effects of apparently minor stimuli on the subject cannot be controlled, and perfectly standard "casual" conditions can neither be defined nor attained. Special preparation of the subject involves a number of difficulties, however, and any attempt to apply a standard pattern of preparation would probably make the results less, rather than more, comparable.

As seasonal variations in blood pressure readings have been reported, the season in which the study is performed should be indicated.

The apparatus. Though the standard sphygmomanometer is a useful tool for the individual clinician, its use in epidemiological studies has been shown to give rise to a number of errors due to observer bias. These include terminal digit preference and the clustering of determinations about certain values: for example, the findings of an individual observer might show a predominance of numbers ending in eight, or an undue number of "normal" pressures clustered about the figures 120/80. While such biases are comparatively unimportant in clinical work, they can be a serious handicap in epidemiological investigations, especially those in which the shape of distribution curves is important.

Even the special training of observers cannot satisfactorily overcome this problem. The standard clinical sphygmomanometer will doubtless remain in general use because of its lightness, cheapness, simplicity, and general availability, but most epidemiological workers would prefer a more objective system. A group of the London School of Hygiene and Tropical Medicine has developed an instrument—now available commercially—that has been shown to eliminate terminal digit preference and may also eliminate other forms of observer bias. More tests are needed, however, before it can be definitely recommended.

For standard sphygmomanometry, the mercury manometer is the basic instrument, although a well-calibrated aneroid instrument is also acceptable. While doubts still remain as to the ideal characteristics of the blood pressure cuff—work in progress on this problem will be outlined in the next section—it is recommended that investigators continue to use the size of cuff currently produced by the majority of manufacturers (i.e., an inflatable bag approximately 12 x 23 cm).

The old-fashioned tapering bandage-type fixation does not preclude faulty application of the cuff, and the more recent types with metal hooks or adhesive fabric ("Velcro") are probably to be preferred.

The techniques of measurement. There is no need to depart radically from such published recommendations as those of the American Heart Association. The following procedures are recommended.

If a mercury manometer is used, it should be placed on a level surface. The subject's arm should be supported in semi-flexion and abduction at about the level of the sternal angle. The cuff should be applied firmly and evenly to the arm, which should be adequately exposed. The lower edge of the cuff should be about 2 cm above the ante-cubital space with the rubber bag centred over the palpable course of the brachial artery. The

uninflated cuff should not compress the underlying tissue.

The cuff is then quickly inflated to 20-30 mm Hg above the pressure at which the radial pulse is no longer palpable. If there is visible venous congestion in the extremity, the recording should be made with the arm elevated. The stethoscope is applied to the area overlying the point at which the brachial pulse has been palpable, just below the edge of the cuff. Cuff pressure is permitted to fall at a rate of not more than 2-3 mm Hg per pulse beat, and the point at which the first audible pulse beat occurs is recorded as the systolic blood pressure; this is expressed as the next lower even number of mm Hg. The cuff pressure is allowed to go on falling, and it is commonly noted that the sound quite suddenly becomes muffled and dull and disappears shortly afterwards. Positive evidence on which to base the selection of a diastolic end-point is still lacking; until it is forthcoming, it is recommended that Phase 4 (the point of muffling) and Phase 5 (the point at which the sound disappears) should be recorded, again rounding off to the next lower even number of mm Hg.

The observer. All observers in an individual study should practise together in order to demonstrate and improve their ability to obtain comparable measurements on a series of individuals with varying levels of blood pressure. At present the group training of observers is the only demonstrably practical and effective means of standardization between studies. Audiograms should be made of all prospective observers, and those with less acute hearing should not be used.

Recording of data. Investigators will of course wish to collect and tabulate certain information in addition to the actual pressure values, such as age, sex, historical data, etc. Each observer’s records should be identifiable so that they may be studied for evidence of bias or systematic error.

It must be stressed again that data should not be combined into classes such as “normotension” and “hypertension” until their actual distribution and/or means, standard deviations, and ranges have been reported.

Measurement of variables of possible etiological importance

Investigators will normally wish to record a wide range of variable factors—personal, family, social and environmental—that may shed light on the etiology of ischaemic heart disease and hypertension.

Anthropometric data

Standing height without shoes (to the nearest cm), weight without clothes (to the nearest 200 g), arm circumference midway between the acromion and olecranon processes, and skinfold thickness (usually measured in the triceps and subscapular areas) are the minimum anthropometric data required. A great many different types of calipers have been produced for skinfold measurement, but their relative merits do not appear to have been studied. For the present, any of the standard calipers with provision for controlled constant pressure may be recommended. It is agreed that, for general use, there should be a constant pressure of 10 g/m² between the jaws of the calipers, whatever the width to which they are opened.

A great many anthropometric measurements might possibly be made, but the majority are too elaborate and troublesome for general use in a survey. Combined indices, such as the “ponderal index”, should not be reported in place of the frequency distributions of the original data, since there is no general agreement as to which indices are preferable.

Blood lipid measurements

The lack of comparability between different methods of blood lipid estimation—and, more specifically, cholesterol determination—is widely recognized. Moreover, there are considerable differences between the values obtained at different laboratories using the same method, and even between the day-to-day values obtained with a particular method at one laboratory.

No single method can be recommended, but it is suggested that the precision of those employed be checked by means of regular duplicate determinations on unknown sam-
amples and daily determinations on samples of a working reference standard in the form of a pooled frozen serum. The free interchange of sera with other laboratories is helpful, and "comparability networks" have grown up in some areas.

WHO's plans to assist in the standardization and improvement of blood lipid estimations will be discussed in the next section.

Pathological studies

The development of a standard protocol for studies of atherosclerosis in the aorta and coronary arteries was referred to in the previous section. It is recommended that investigators developing programmes in this field obtain copies of this protocol and conform to it as far as possible in the interests of comparability.

Family background

An attempt should be made to elicit at least the following data: parental survival and age, or age at death; size of family and sibling position; marital status and number of children.

Smoking habits

Doll & Hill, in the United Kingdom, and Hammond & Horn, in the United States of America, have shown that information elicited by a questionnaire on smoking is reproducible. The questionnaire approved by the Committee on Aetiology of Bronchitis of the Medical Research Council of Great Britain is recommended for current use, and is reproduced as Annex 2.

Physical activity

The degree of physical activity associated with various occupations has been studied in several countries, and it may therefore be useful to report on the subject's occupation. For the time being it is enough merely to record the occupation, though length of time in this occupation and the nature of previous occupations might also be taken into consideration.

Other factors

No recommendation is as yet warranted on specific methods in relation to studies of thrombogenesis and thrombolysis. The measurement of mental, emotional and personality factors, as well as data on the habitual diet, may be important, but further work is required before any practical recommendation may be made.


WORK IN PROGRESS

The electrocardiogram in epidemiology

As noted in the preceding section, efforts are being made to reduce the subjective element in the reading of electrocardiograms. The work of WHO in this field is based on the coding of measurable descriptive characteristics rather than interpretation, which is indicated only when clear-cut and recognized specific patterns exist, as in the case of myocardial infarction.

Unfortunately this approach is not so simple as it might appear to be at first sight, since it involves the use of measurements made in hundredths of seconds and tenths of millivolts. As a hundredth of a second represents only a quarter of a millimetre at normal recording speed, biased judgements may easily occur in borderline situations. It is of course easier to make close measurements of a sharply defined component such as the QRS complex than of rather slow waves with less definite onset and termination such as the P and T waves.

The coding system known as the Minnesota Code, which was devised by Blackburn and
his associates at the University of Minnesota, has already been tried out in several studies. It has been checked for reproducibility by its originators, but no reproducibility studies have as yet been published by the other workers who have employed it, either in the USA or the United Kingdom. Moreover, the validity and significance of electrocardiographic patterns are as yet uncertain.

**WHO's preliminary test**

WHO has conducted a preliminary reproducibility test of the Minnesota Code. For this purpose 100 reproductions of original tracings were assembled, including 31 pairs of duplicates. These were submitted for grading to five observers, two of whom had used the code extensively, while two had never used it at all and one had used it only a little. They were asked to classify their findings according to the code, to express an opinion whether the tracings were "normal", "abnormal", or "borderline", and to add any comments they might wish to make. The time required for coding had also to be reported.

It must be stressed that this test was intended primarily to show the points on which later, more intensive studies should concentrate, and that its findings cannot be considered as definitive, particularly as some of the tracings used were poorly reproduced.

The overall percentage of disagreement was high but, since the tracings were selected rather than representative of a random population, the disagreement was not felt to be comparable with that found in regular population studies.

Arrhythmias and abnormalities in the duration of the QRS interval occurred in only a small number of tracings, but were in general consistently coded. PR interval abnormalities, however, were never agreed upon by as many as four observers in any instance and one of the experienced observers did not note any of them, although there were 12 examples. This appeared to be due to failure of observation rather than to differences of opinion.

Of particular importance to the investigator of ischaemic heart disease are the Q waves, ST segments and T waves. In the case of Q waves, there was a disappointing lack of agreement: for 28 tracings at least one observer mentioned a Q wave or QS abnormality (Category I, 1-2-3 of the code), but in only three instances did all five observers agree on the presence of such an abnormality. These results are greatly at variance with those obtained by the originators of the code, but this may be due to the poor quality of some of the tracings. ST segment depression (Category IV, 1-2-3) was mentioned for 21 tracings, all five observers agreeing on the category in seven instances; in only three instances, however, did all five agree on the subcategory. T wave abnormalities (Category V, 1-2-3) showed similarly poor agreement on category, though agreement on subcategory was somewhat better. Again, there was rather poor agreement on Categories II and III (axis deviation and high voltage). Category IX (miscellaneous) was not studied.

The simple classification of tracings as normal, borderline, or abnormal was carried out with much more reproducibility than any single aspect of the actual coding, though this of course yields relatively little information. In a few instances all five observers agreed on coding, but disagreed on interpretation. More frequently there was agreement on interpretation, but marked disagreement on coding.

Intra-observer agreement, as tested on the 31 duplicate tracings of the series, showed approximately 80% agreement between first and second readings for each observer. The most experienced observer had a slightly better record in this respect than the others.

The conclusion drawn from the test was that further studies should be made, using better quality reproductions and concentrating on voltage, axis and especially Q waves, ST segments, and T waves.

**Arrangements for further testing**

The WHO Scientific Group on Comparable Methodology for the Epidemiological Study of Hypertension and Ischaemic Heart Disease recommended the trial of an expansion of the Minnesota Code which was submitted

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by Dr. J. T. T. Higgins, who was recently appointed Professor of Chronic Disease Epidemiology, Graduate School of Public Health, Pittsburgh. This trial was carried out during 1962 and its results are now being assessed.

In addition, WHO is assembling two collections of high quality electrocardiograms. The first is a test collection, which may be used either to study the characteristics of individual coding systems, or to serve as a reference collection against which the comparability of readings by various investigators may be tested. A further test is planned, similar to the preliminary test just described, but using a large number of observers from more parts of the world.

The second collection will be used to instruct observers in the standard employment of the code and in the interpretation of borderline measurements. It will include material illustrative of the known "trouble-spots" of the code. Before and after training, observers could be asked to grade the test collection in order to evaluate their progress.

Equipment

There is at present no reliable information to show whether a portable clinical electrocardiograph will give results significantly different from those obtainable with a high-grade research-type machine. Obviously the machines with higher frequency responses will often give more accurate expressions of QRS voltage and record more of the minor notching of the complexes as well. It remains to be shown whether and to what extent records of the same subjects made on the two different types of machine will actually lead to different sets of figures when coded for study.

WHO hopes to arrange for a co-operative investigation of this question. This might be carried out by taking parallel records of the same population sample with at least two different types of machine and giving them, thoroughly mixed, to an observer, or group of observers, for coding.

Effect of paper speed

A great many electrocardiographs, including even portable ones, now have provision for recording at double speed. It would be desirable to study the effect of using this speed (5 cm per second) for at least portions of the tracing. It is anticipated that the coding of Q waves especially will be more reproducible with tracings made at the higher speed.

Significance of electrocardiographic abnormalities

The coding of electrocardiographic abnormalities provides an excellent opportunity for studying the significance of some of the poorly understood patterns. Though many correlation studies of such abnormalities have been published, they have reached few definitive conclusions.

Some of the investigators already using the Minnesota Code are carrying out follow-up studies on population groups and will be able to observe the subsequent histories of patients who show or do not show these "non-specific" abnormalities. By observing the appearance of clinical or electrocardiographic evidence of fresh infarction, the clinical appearance of anginal pain, or deaths from cardiac disorders (especially if autopsy confirmation is available), it may be possible to shed further light on the prognostic value of certain electrocardiographic signs, and on their actual significance.

Exercise tests

The applicability of exercise tests to population studies was discussed in an earlier section. It must be stressed again that more evidence is needed on the value of the additional epidemiological data that can be obtained by these clinically useful procedures. Follow-up studies of population groups that have been submitted to exercise tolerance tests might be of some help.

Some investigators feel that unless the stimulus can be quantitatively adjusted, using a bicycle ergometer, for example, there is very little likelihood of a reproducible result. Moreover, there is the danger of a sudden heart attack or death during the test. WHO has no immediate plans for active research on this subject.
Computer techniques and simplified lead systems

A number of investigators are at present studying the application of computer techniques and simplified lead systems, but suitable apparatus is costly and complicated. The results so far suggest that it will be possible to use such techniques in field studies within the next few years. Those contemplating a large-scale, long-term study now might well consider the possibility of recording orthogonal leads on electromagnetic tape from the outset, as well as recording the standard leads. The taped records could then be stored for eventual computer analysis. As the techniques become better established and understood, it may be useful to convene a meeting of experts from different countries so that the results of the many national research efforts in this field may be made available internationally.

History of chest pain

No technique for eliciting a history of cardiac pain has been tested for reproducibility and validity when used internationally. Until an investigator has satisfied himself as to the reproducibility of a history-taking technique, he should not include it in a regular study. Furthermore, any study using such a technique should, if possible, be planned so as to include means of estimating its validity.

The questionnaire devised by the London School of Hygiene and Tropical Medicine and reproduced as Annex 1 is therefore proposed primarily for testing purposes. Investigators may of course wish to experiment with individually devised techniques, but it is hoped that they will incorporate the questions given in the Annex, since information on their use, especially in languages other than English, would be of great value. Moreover, the use of certain standard questions should yield data that would at least be somewhat more comparable than data obtained by a variety of techniques.

The chest pain questionnaire

The adoption of a standard questionnaire will not in itself ensure uniform, reproducible and comparable results, since there may be important variations in the presentation of the questions and the interpretation of the answers. Investigators planning to test the proposed questionnaire should therefore follow the standard instructions, covering the presentation of the questionnaire, the use of probing questions, and the interpretation of problematical answers. In addition, tape recordings of specimen interviews are available and may be used to train and test observers. Visits to centres already using the questionnaire would be particularly helpful, and should be encouraged.

The translation of a questionnaire into different languages raises a number of special problems. Even within a single country the popular idiom may vary from place to place, and more than one form of the questionnaire may be needed in the same language. The investigator's approach may also need to be adapted to the cultural background.

Testing the questionnaire for reproducibility and validity

In any study using a questionnaire, inter-and intra-observer variability must be determined. This will often require the questioning of some subjects after a short interval, either by the same or by another observer. Tape recordings of the interviews may clarify the reasons for any variations observed, by revealing faults in the way in which the questions were asked, or failure of the subject to understand them.

Testing for validity will take more time, since subjects both with and without chest pain will have to be followed up. The more subjects questioned initially, the sooner will some indication of the questionnaire's validity be obtained. The positive and negative replies may be compared with electrocardiographic findings, new clinical episodes, and deaths shown to be due to ischaemic heart disease.

WHO plans to facilitate validity and reproducibility tests in several countries, as well as the training of observers in comparable methods of administering the questionnaire and interpreting the answers.
Blood pressure measurements

In an earlier section mention was made of the doubts that still exist concerning cuff dimensions, diastolic end points, effects of arm circumference, effects of observer bias, etc. An international co-operative investigation of many of these problems is being planned and will be described later, but first of all the problems themselves will be discussed individually.

Cuff dimensions

In 1901 Von Recklinghausen 3 advocated a cuff width of 12 cm, and this is still the width most frequently used. Cuff length, however, has varied considerably, and according to Karvonen 4 it may have some effect on blood pressure measurements. Further intensive study of this question was recommended by the Scientific Group on Comparable Methodology, which discussed it in considerable detail.

WHO has now collected data on the types of cuff in use in at least 28 countries. In several of them government agencies have adopted standards specifying inflatable bags 12 × 23 cm; cuffs of these dimensions manufactured in the United Kingdom and the USA are widely used both there and elsewhere. Manufacturers in some other countries are employing similar standards, but in Europe alone widths varying from 9.4 to 14 cm have been reported. One manufacturer who has produced cuffs 25 cm and then 16 cm in length states that the width of 12 cm is important but that the length makes no difference in arms of normal size; this seems to be at variance with Karvonen's experience.

Whether variations in cuff size have significantly influenced normal standards for blood pressure or the comparability of statistics from one area to another remains to be established.

Arm circumference

The question of arm circumference and that of cuff dimensions appear to be closely related. The effect of large arm size on blood pressure measurements has been extensively investigated, but with conflicting results. There is little doubt, however, that arms above a certain size show an exaggeration of the auscultatory blood pressure reading as compared to the intravascular reading; this may be partly rectified by increasing the length or width of the cuff, or both, beyond the usual 12 × 23 cm dimensions. The relative importance of cuff width and cuff length is not yet known, however, nor is the extent to which they influence the readings. It is still uncertain whether more accurate figures would be obtained for a larger range of arm circumferences if the basic standard cuff were widened from 12 to 14 cm or lengthened, as recommended by the WHO Expert Committee on Cardiovascular Diseases and Hypertension. 5

Types of manometer

With proper precautions to ensure free venting of air through the filter disc at the end of the tube, the mercury manometer should be satisfactorily error-proof. The aneroid manometer produced by some manufacturers has been found dependable; with this instrument most mechanical difficulties liable to produce erroneous readings are clearly signalled by the failure of the indicator hand to return to the zero mark at zero cuff pressure. Nevertheless, if an aneroid manometer is used, it should be checked frequently against a mercury manometer.

On most aneroid instruments the scale is about half the length of that on a standard mercury instrument, and this might reduce the precision of the readings. No comparative studies of the reproducibility of readings on aneroid and mercury instruments seem to have been reported so far.

Observer bias

The greatest disadvantage of a measurement technique involving the observation of a continually moving mercury column is an unavoidable tendency to biased readings. This type of observer bias was discussed by

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the Princeton Conference, at which the possible use of "offset manometer scales to give a spurious reading later decoded by the statistician" was suggested. In the opinion of workers in the Department of Medical Statistics and Epidemiology at the London School of Hygiene and Tropical Medicine, this alone would not suffice, since the spurious calibrations would soon become familiar and the preference for particular terminal digits would be at best only partially controlled. These workers have therefore developed a special apparatus to study the effects of some of these types of bias and to improve the reproducibility of the results.

Their apparatus employs a semi-objective technique by concealing the actual reading from the observer at the moment of measurement. This is accomplished by the use of three concealed mercury manometers, the mercury columns of which are stopped by the observer when he identifies the auditory phenomena constituting evidence of the systolic and the two diastolic end points respectively. The figures are then read off the stationary columns. Provision is also made for standardization of the rate and height of inflation of the cuff, and the rate of deflation. Tests conducted in the United Kingdom and the USA have shown a virtual elimination of digit preference and some improvement in the inter- and intra-observer reproducibility of blood pressure readings. Furthermore, there has been no evidence of any tendency towards systematic error, so that it is reasonably clear that the readings are in no way less accurate than those made with a conventional apparatus. Precision appears to be improved.

The selection of a diastolic end point

After more than fifty years of auscultatory measurements of blood pressure based on Korotkov's sounds, there is still doubt whether the fourth phase (muffling) or the fifth phase (disappearance of sound) represents the more accurate and reproducible criterion of diastolic pressure. Many comparisons have been made between auscultatory and direct measurements, and the results have been sufficiently contradictory to increase rather than decrease the doubt.

In epidemiological studies, the accuracy of the value is not necessarily the important factor. For statistical handling, it is perhaps more important that the result should be reproducible. In other words, the epidemiologist, much as he would like to estimate the true intravascular pressure, should be willing to accept some error—especially if it is systematic—for the sake of a "sharp" reproducible end point.

The WHO co-operative blood pressure study

A plan for a co-operative blood pressure study was put forward by the Scientific Group on Comparable Methodology and has now been elaborated in the form of a standard working protocol upon which the participating laboratories will base their procedures.

The specific subjects of study will be: optimal cuff size and the relationship of cuff size to arm circumference; the effects—if any—of different types of cuff fixation; the accuracy and reproducibility of diastolic end points; inter- and intra-observer variability with the blood pressure apparatus devised by the London School of Hygiene and Tropical Medicine and with standard sphygmomanometers.

In addition, there will be restricted studies of the effects of variations in the rate and height of cuff inflation and the reproducibility of readings using small aneroid manometers. Simultaneous direct and indirect measurements of blood pressure are to be carried out on subjects with different arm circumferences and levels of pressure, using a set of cuffs of varying widths and types of fixation. The study will be undertaken by several observers in different countries.

Standardization and improvement of lipid estimations

As pointed out in an earlier section, there is a pressing need for standardization of blood lipid estimations in view of the impor-
tance currently attached to variations of lipid metabolism in relation to atherosclerosis. A preliminary inquiry by WHO has shown that laboratory directors in a great many countries consider such standardization desirable. The matter cannot, however, be solved simply by specifying laboratory techniques since standardization of this type would seem to be both impracticable and undesirable, and in any case would not guarantee comparable results. On the recommendation of the Scientific Group on Comparable Methodology and of other experts, WHO will base its approach on the experience of the US Public Health Service, which has operated a similar standardization programme over the past five years. It is planned to concentrate at the outset on cholesterol measurement, and it is hoped that a successful programme in this field will serve as a model for the standardization of other biochemical measurements.

A central reference laboratory will be established to offer services and technical advice to other laboratories in various parts of the world. Appropriate lyophilized reference sera will be circulated, and suitable quality control techniques established in the participating laboratories, of which there will be about six to begin with. The results will be published, and other laboratories may then judge the desirability of taking part in the programme.

Ocular fundi in hypertension

The WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease (Preventive Aspects) emphasized the role that may be played by ophthalmoscopy in classifying stages of hypertension. It appears that no reliable data exist on observer variability in this connexion. It is not at all clear whether retinal photography—which has been suggested by a number of workers—can be effectively used.

WHO has accordingly planned a study in which a group of observers will examine a selected group of subjects displaying a variety of retinal vascular abnormalities, and the inter- and intra-observer variability will be tested. At the same time changes shown in retinal photographs of these and other subjects will be studied, graded and compared.

Fields in which much additional work is needed

Further approaches to the identification of ischaemic heart disease

Sudden death. Much attention needs to be paid to the further definition and study of "sudden" death. The differences in the diagnostic assumptions made in various countries may be a factor in the variations observed in cardiovascular mortality statistics. Many workers feel that sudden deaths could provide a useful index of ischaemic heart disease in longitudinal studies.

Congestive failure. There seems to be little doubt that congestive failure frequently occurs as a manifestation of ischaemic heart disease, but practical and reproducible means of differential diagnosis are still needed. A careful study in an area where most cases of congestive failure are treated in hospital might indicate the relative frequency of ischaemic heart disease.

Direct study of the coronary arteries. The development of advanced arteriographic techniques for visualizing the coronary vessels is encouraging, and these techniques are increasingly used in clinical practice. As yet, however, there is no practical way in which they may be applied to population studies.

Additional studies of etiological factors

Thrombogenesis and thrombolysis. While a great many methods are now available for the study of various aspects of thrombogenesis and thrombolysis, none of them has yet proved practical for regular use in field studies of populations. In view of the major role which they are presumed to play in ischaemic heart disease, an effort will be made to find practical and comparable ways of applying knowledge of these processes in population studies.

Genetics. It is generally assumed that "constitutional" factors play a large part in
ischaemic heart disease. Genetics as a science is rapidly developing, and genetic studies on ischaemic heart disease and hypertension in humans should be encouraged and continued.

**Personality, stress and psychosomatic factors.** From the methodological standpoint, the personality, stress and psychosomatic factors involved in ischaemic heart disease and hypertension have been neglected, though most workers consider them to be of great importance. In spite of many attempts, no acceptable measurement technique has been worked out for any of these factors. Several workers are attempting to correlate the results of “personality inventory” tests and similar techniques with data on the occurrence of cardiovascular diseases, and some information may be forthcoming on this point. The measurement of stress due to mental factors is as problematical as its definition. Ways in which this problem might be tackled were recently considered by WHO in consultation with Professor P. C. Dell, a neurophysiologist from Paris, Professor B. Folkow, a cardiovascular physiologist from Göteborg, and Professor J. Charvat, an endocrinologist and internist from Prague. A short report is in preparation in which the basic physiological considerations are outlined and special aspects of stress provoking mental stimuli of long duration in man are described. Suggestions are made for a practical approach to the problem of measuring objective cardiovascular, endocrine and metabolic responses to such stimuli under habitual conditions over a prolonged period of time, as well as for the study of the cardiovascular system in human subjects in whom the cerebral-autonomic neural connexions are severed.

**Physical activity.** While physical activity has been postulated as a protection against the development of coronary artery disease, direct evidence on this point is lacking. Attempts have been made to estimate the activity associated with different types of work, and there is growing interest in the question of energy expenditure in leisure activity. Comparatively small amounts of total energy expenditure—in the range of 500-800 calories per day—may prove of importance. Accordingly an inquiry into possible means of estimating habitual 24-hour energy output in populations is needed.

**Diet.** A large number of methods are used to assess the food intake and nutrition of populations. Those which have been tested internationally are, as might be expected, mostly devised for the study of malnutrition. Methods for defining the food intake of well-nourished populations are not so well developed, and it is believed that attention must be paid to the types of fats and proteins consumed, as well as to the amounts. Comparable methods of assessment in this field are badly needed.

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The problems just mentioned are not the only ones on which further information is needed, but they are those considered to be of the greatest immediate importance by the Scientific Group on Comparable Methodology and the WHO Cardiovascular Diseases unit. With the help of the relevant experts WHO will continue to devote attention to these problems, since even their partial solution should increase the possibility of carrying out comparative and inclusive studies of the etiology and premonitory signs of cardiovascular disease.
Annex 1

QUESTIONNAIRE ON CARDIAC PAIN

SERIAL No .................................................................

Surname ..........................................................................
Forenames ..................................................................

Date of birth ..............................................................
Sex ..............................................................................
Civil state: ....................................................................
S M W D Sep. .................................................................

Address .......................................................................... 

Country of origin ........................................................

Interviewer ....................................................................

Put x in appropriate box

Section A: EFFORT PAIN

HAVE YOU EVER HAD ANY PAIN OR DISCOMFORT IN YOUR CHEST?  Yes No

If yes, ask next question.
If during the remainder of Section A an answer is recorded in a box marked “*”, proceed to Section A (optional) without asking any more Section A questions

DO YOU GET IT WHEN YOU WALK UPHILL OR HURRY?  Yes No *

Never hurries or walks uphill

DO YOU GET IT WHEN YOU WALK AT AN ORDINARY PACE ON THE LEVEL?  Yes No

If yes to either of last two questions:

WHAT DO YOU DO IF YOU GET IT WHILE YOU ARE WALKING?

Stop or slow down  Yes No *

Carry on

Record stop or slow down if subject carries on after taking nitroglycerine (trinitrin)

IF YOU STAND STILL, WHAT HAPPENS TO IT?

Yes No *

Relieved

Not relieved

HOW SOON?

Yes No *

10 minutes or less

More than 10 minutes

WILL YOU SHOW ME WHERE IT WAS?

Yes No *

Sternum (upper or middle)

Sternum (lower)

Left anterior chest

Left arm

Other (mark on diagram)

DO YOU FEEL IT ANYWHERE ELSE?

Yes No *

If yes, record additional information.

1 Devised by the London School of Hygiene and Tropical Medicine.
### SECTION A (Optional)

**DOES ANY OTHER KIND OF EXERTION BRING ON THIS PAIN OR DISCOMFORT?**

If yes, give details

**DOES EXCITEMENT OR EMOTION BRING IT ON?**

If yes, give details

**WOULD YOU DESCRIBE IT AS A PAIN OR A DISCOMFORT?**

<table>
<thead>
<tr>
<th>Pain</th>
<th>Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WOULD ANY OF THESE WORDS DESCRIBE THE SENSATION?**

(say Yes or No to each)

<table>
<thead>
<tr>
<th>Sensation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heaviness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tightness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stabbing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SECTION B: PAIN OF "POSSIBLE INFARCTION"

**HAVE YOU EVER HAD A SEVERE PAIN ACROSS THE FRONT OF YOUR CHEST LASTING FOR HALF AN HOUR OR MORE?**

If yes, how many of these attacks have you had?

<table>
<thead>
<tr>
<th>Date</th>
<th>Duration of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1st attack

Last attack

(N.B. Depending on the nature of the individual investigation, additional information or associated symptoms, duration of disability, means of diagnosis, etc., may be recorded here.)
Annex 2

QUESTIONNAIRE ON TOBACCO SMOKING

DO YOU SMOKE?  
Record yes if regular smoker up to one month ago

If "No" to 35:

HAVE YOU EVER SMOKED?  
Record no if subject has never smoked as much as one cigarette a day, or 1 oz. of tobacco a month, for as long as one year.

If "Yes" to 35 or 36: Fill in figures below:

<table>
<thead>
<tr>
<th>Amount smoked</th>
<th>Now</th>
<th>Previously</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes/day (average including weekends)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oz. tobacco/week (handrolled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oz. tobacco/week (pipe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigars per week (large)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigars per week (small)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age started regular smoking

Age stopped regular smoking

If smoking stopped or reduced, give reasons

INSTRUCTIONS FOR THE USE OF THE QUESTIONNAIRE ON TOBACCO SMOKING

There are unfortunately differences in the way in which smokers have hitherto been classified according to the amount smoked. More surveys of respiratory symptoms have been carried out in Great Britain than elsewhere and it is suggested that the customary British classification, given below, should be used. Since major changes of habit in present smokers are uncommon no use has been made of the information obtained in respect of previous tobacco consumption. Further investigation may show the value of some classification based on the average consumption over past years, when some standardized way of computing such averages may be proposed. The value of such averages and of finer subdivisions of tobacco consumption is a matter for further investigation.

In computing grams of tobacco, one cigarette = 1 g; one ounce of tobacco = 28 g; one small cigar = 2 g; one large cigar = 5 g. (These weights should be checked in different countries.)

<table>
<thead>
<tr>
<th>Category</th>
<th>Non-smoker:</th>
<th>No to 35 and 36.</th>
<th>Type</th>
<th>Cigarette only.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ex-smoker:</td>
<td>No to 35, Yes to 36.</td>
<td>Pipe or cigar only.</td>
<td>Mixed.</td>
</tr>
<tr>
<td>Smoker:</td>
<td>Yes to 35.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Present consumption

Light: 1-14 g/day
Medium: 15-24 g/day
Heavy: 25+ g/day

Some people distinguish a group of very light smokers with a consumption of 1-4 g/day.

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1 Reproduced by kind permission from the Questionnaire on Respiratory Symptoms (1960) approved by the Medical Research Council Committee on Aetiology of Bronchitis, Great Britain, and from the Instructions for the Use of the Questionnaire on Respiratory Symptoms (1960).
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