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Report

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STUDY GROUP ON ATHEROSCLEROSIS AND ISCHAEMIC HEART DISEASE

Report

The WHO Study Group on Atherosclerosis and Ischaemic Heart Disease met in Geneva from 7 to 11 November 1955, to discuss the present status of knowledge of the etiology and pathogenesis of these diseases and to advise the Organization on means of furthering knowledge which might lead to effective preventive programmes.

Dr M. G. Candau, Director-General of the World Health Organization, in inaugurating the meeting, stated that the Study Group had been convened by WHO as a result of two recommendations. The first of these had been made by the Regional Committee for Europe at its third session, held in Copenhagen in 1953;[1] the Regional Committee had recognized the significance of cardiovascular diseases as a public-health problem and had suggested the convening of a study group with a view possibly to developing regional activity in the matter. The second recommendation had come from the Joint FAO/WHO Expert Committee on Nutrition at its fourth session in 1954;[2] it had recommended that WHO should give consideration to the important questions of the possible relationship between the character and the amount of the habitual diet, and the development of atherosclerosis and related degenerative heart disease of uncertain etiology.

Dr Candau emphasized the seriousness of atherosclerosis and related heart disease, citing evidence to show that they are among the main contributors to mortality in the more developed areas. He also pointed out that the increasing dominance of degenerative heart disease cannot be entirely accounted for by the decrease in other causes of mortality, or by the changing structure of the population. Because it was obvious, he continued, that a variety of fields must contribute to knowledge about the etiology and prevention of this disease, the members of the Group had been chosen to represent a variety of related disciplines—epidemiology, statistics, public health, nutrition, cardiology, pathology, physiology, and biochemistry.

Dr H. E. Hilleboe was unanimously elected Chairman.

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[1] Unpublished document EUR/RC3/12 Rev.1, p. 8

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1955, **97**, 44

1. INTRODUCTION

In planning its agenda, the Group felt strongly that the discussions should be focused on ischaemic heart disease as that part of the overall problem of atherosclerosis which, by its rising incidence and mortality, is of direct and growing concern to public-health authorities. Accordingly, the present report and recommendations to the Organization stress the paramount public-health importance of ischaemic heart disease.

The agenda adopted and covered by the Group was as follows : (1) definition of terms ; (2) need for standard diagnostic criteria ; (3) heredity, constitution and sex ; (4) hypertension ; (5) evaluation of environmental factors in population and statistical studies ; (6) diet and ischaemic heart disease ; (7) diet and thrombosis ; (8) physical activity ; (9) metabolic disorders ; (10) stress, strain, and mental tension ; (11) alcohol and tobacco ; (12) epidemiology and public-health importance ; (13) applications to public-health services ; (14) need for further research ; and (15) possible contributions of international agencies.

In addition to the report and recommendations growing out of the consideration of these topics, two annexes are included. One is a paper on the evaluation of environmental factors in population and statistical studies (see page 31), which was contributed by a member of the Study Group ; it is considered to be a useful discussion of the methodological problems involved in research in this field. The second, on the present status of public-health facilities and organization in the field of cardiovascular disease (see page 34), summarizes information believed to be of value to public-health administrators which could not appropriately be included in the body of the report.

2. DEFINITION OF TERMS

" 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. The two main pathological processes involved are (*a*) atherosclerosis of, and (*b*) thrombosis in, these vessels. The same processes may be responsible for atherosclerotic and ischaemic cerebral and peripheral vascular disease ; the Group decided, however, to limit its discussion and recommendations to the disorder of the heart.

" Atherosclerosis " of the coronary arteries includes several quite distinct intimal processes, e.g., fatty changes, fibrous thickening, fibrin incorporation, and calcification.

While the processes concerned in atherosclerosis—and in thrombosis—are usually concurrent, they may nevertheless be independent. This has often been insufficiently realized and the result has been a too simplified view of the problem of atherosclerosis. In ischaemic heart disease—the end product of atherosclerosis—multiple causes must therefore be considered : thrombosis and the capacity of the heart and circulation to cope with the disturbances involved. These multiple factors may operate differently and thereby produce different pictures, in individual cases and in the disease as it occurs among various ethnic and social groups.

3. DIAGNOSTIC CRITERIA

3.1 Problems of standardization

The diagnosis of ischaemic heart disease, in either the living or the dead, often raises questions of method which stand in the way of making valid comparisons among population groups. Unless methods are carefully standardized, only limited reliance can be placed on reports of differences in morbidity and mortality attributed to this disease in different localities.

For post-mortem diagnosis, the pathologist may select the number or the surface area of atheromatous plaques, the degree to which the arterial lumen is narrowed, or the presence or absence of calcifications, ulcerations, or thrombi. In assigning grades to any coronary artery disease found, different observers assign a different weight to these several factors. It seems highly desirable that a group of representative pathologists should meet and make suggestions on uniform methods for examining the coronary arteries and for recording the results. Furthermore, in applying such uniform methods to different populations, efforts should be made to reduce observer error to a minimum.

The difficulties in assuring comparable clinical diagnosis are even greater. Heart disease, occurring in the middle and older age-groups and unaccompanied by valvular disease or such specific causes as thyrotoxicosis, is commonly divided into hypertensive heart disease, ischaemic heart disease, and a less well defined category sometimes labelled " degenerative " heart disease. There is no uncertainty in the diagnosis of the patient with gross hypertension and symptoms of left ventricular failure—this is classical hypertensive heart disease. Nor is there any difficulty in labelling a patient with myocardial infarction or angina pectoris, together with arterial pressure in the lower ranges, as ischaemic heart disease. But between these two extremes is an indeterminate group that may be classified as either hypertensive or ischaemic heart disease, or heart disease of unknown cause, according to the predilection of the physicians concerned,

in the presence often of multiple pathology. In comparing morbidity and mortality rates obtained from clinical data, it is again necessary to have uniform diagnostic criteria for application to the different populations and to make provisions for reducing observer error and bias to a minimum.

3.2 Value of pilot surveys

As a guide to future investigations, as well as for the evaluation of previous studies, it would be desirable to conduct surveys of groups of patients in various countries and regions, to discover how large a proportion of actual cardiac cases are found in each of the above-mentioned categories. Surveys of this kind would indicate what percentage of the total of heart patients of different ages represents conditions that raise no special problems of diagnosis or classification. If the problem cases are only a small proportion of the total, they may offer no more than a trivial impediment to critical evaluation. If they are a large fraction, the significance of epidemiological researches based on the relative frequency of different forms of heart disease in different populations will be seriously lowered.

The certificates of death on which vital statistics are based are given as a result of post-mortem examination only in a small proportion of the total cases, even under relatively favourable circumstances. In comparing vital statistics, it would be very useful to make pilot surveys of the data on which death certificates are based.

4. ROLE OF CONSTITUTIONAL FACTORS

4.1 Interaction of genetic and environmental influences

It may be assumed on first principles that the factors concerned in the genesis of atherosclerosis and ischaemic heart disease are of two kinds, those contributed by heredity and those occurring in the environment. In practice, it is not always easy to dissociate the two, since the comparisons of morbidity and mortality in different races and social groups often involve both kinds of factor. The real problem is the extent to which heredity is a determining factor or is overborne by environmental factors.

One of the most striking and potentially important facts about ischaemic heart disease is the great difference in its incidence and mortality in different populations, even when allowance is made for age distribution. For example, it has been reported that middle-aged men in the United States, Great Britain, and Finland are more prone to die of ischaemic heart disease than are men of the same age in Norway or Denmark, and several

times more prone than are men in Italy or Portugal; the disparity is even greater when comparison is made with middle-aged males in Japan and among the Bantu in South Africa, the Mayan Indians in Guatemala, the Navajos in New Mexico, the Jews in Yemen, the natives of Okinawa, the Negroes in Nigeria, and so on. Conceivably, such differences could be primarily genetic in origin; but if they should prove to be largely the result of differences in the mode of life, this would open up important avenues of investigation which might reveal major factors operating in the production of atherosclerosis and ischaemic heart disease.

One approach to the problem would be to concentrate on the discovery of evidence showing an effect of heredity, while another would be to seek out the extent to which environment, acting on a common genetic limitation, can determine the extent of the disease. In this connexion, the comparison of the susceptibility to heart disease of identical and non-identical twins deserves special mention.

4.2 Suggested methods of investigating the role of heredity

An indication of the importance of the genetic influence might be obtained by selecting subjects drawn from the same community and comparable in age, sex, occupation, and social status, the ones with ischaemic heart disease and the others without, and determining the incidence of ischaemic heart disease in their respective parents and siblings. However, in drawing deductions from such observations, it is necessary to remember that family groups may be similar, not only in hereditary constitution, but in the environmental factors to which they are subjected.

It should also be worthwhile to study the frequency of ischaemic heart disease in national or racial groups living in their original homelands and in different environments as migrants. The Jews in Israel, the Japanese in Hawaii, and the Negroes in Chicago, as representative groups, deserve much more intensive study.

In all investigations of this kind, one is dealing with an end-result, in which more than one factor may operate. Thus, such surveys may indicate that in certain families or populations, metabolic peculiarities such as familial xanthomatosis and familial lipaemia may be present (see section 4.4, page 9), whereas in other families or racial groups these may be absent. A disturbance in neutral fat transport has also been suggested as a possible hereditary factor. It would be an important part of these investigations to discover the incidence of inherited metabolic peculiarities in ischaemic heart disease.

Another approach to the role of heredity in determining the frequency of atherosclerosis and ischaemic heart disease would be the attempt to

establish whether specific somatotypes are unusually prone or resistant to the development of these conditions. With due distinction between characteristics which are alterable—such as obesity—and more basic features—such as skeletal dimensions—a study of body types should be made in :

(*a*) patients with the most clearly recognized types of ischaemic heart disease, such as myocardial infarction and angina pectoris, and persons without these complications but comparable in age, sex, occupation, social status, and community ; and

(*b*) post-mortem material with gross or minimal evidence of coronary sclerosis, employing the same kind of criteria in selecting the sample.

Comparisons of this kind are only possible if agreement can be reached on some standards of recognition of ischaemic heart disease on the one hand, and of somatotypes on the other. Suggestions concerning body measurements for the characterization of nutritional status and skeletal form have been made by the Committee on Nutritional Anthropometry of the Food and Nutrition Board, National Research Council of the USA, and are to be published in *Human Biology*.[1] They exemplify the kind of standardization that should be sought for other types of measurements and observations required in the study of ischaemic heart disease.

A further method of examining the influence of racial background would be to study blood groups in persons with and without ischaemic heart disease in an otherwise homogeneous community.

4.3 Relation to sex

Investigations at the present time in many countries, such as the United States, Great Britain, and Sweden, show a pronounced difference in mortality from myocardial ischaemia between the two sexes in the age-group 40-59 years, males showing a considerably higher mortality than females. In populations where ischaemic heart disease is frequent, as in the United States, the ratio of male to female deaths from ischaemic heart disease is very high in young persons, and diminishes after the menopause, whereas in countries such as Italy and Portugal, the disparity in frequency as between the sexes is smaller. In Great Britain the mortality from ischaemic heart disease in married women in the age-group 45-49 years is greater in those with no children than in those having children.

Besides these differences in mortality, the course of ischaemic heart disease may tend to be somewhat different in the two sexes, the male often suffering a more dramatic and rapidly fatal development. This might account for the fact that recent hospital surveys in Sweden and the United

[1] *Hum. Biol.*, 1956, **28**, 111

States show more female patients than might be expected from the mortality statistics of the regions concerned.

These facts emphasize the necessity for paying close attention to the sex ratio in epidemiological investigations. While the sex differences found are striking, their interpretation is difficult. Men and women live differently in many ways and consideration must be given, not only to sex-linked inheritance and to differences in endocrine factors such as androgen and oestrogen levels, but also to the possible effects of differences in environmental factors such as physical and mental activity, emotional strain, diet, and the use of stimulants and intoxicants.

4.4 Involvement of specific inborn metabolic disorders

Clinicians should be alert for any associations between metabolic influences and the prevalence of atherosclerosis and ischaemic heart disease which will contribute to knowledge of the pathogenesis of these conditions. Information, largely derived from clinical observations, has accumulated to show that a number of endogenous metabolic disorders can predispose to atherosclerosis.

In familial hypercholesterolaemia, which is often associated with tendon xanthomatosis and xanthelasma, myocardial infarction is very common. This type of inborn metabolic disorder has been regarded as a relatively rare disease, but its real prevalence is not known. As the practice of the serum cholesterol determination becomes more widespread, a higher prevalence may be found.

In essential hyperlipaemia, with milky serum present in the fasting state, high cholesterol values have been reported. Some of the patients concerned had had angina pectoris and myocardial infarction. It is of interest that a low-fat diet has generally been effective in reducing the serum lipids of such patients to normal values.

In uncontrolled diabetes, the serum cholesterol and the total fat values are often high, and it is well established that atherosclerotic disease is now the chief cause of death in diabetes. It is significant that the incidence and mortality from diabetes tended to fall in parallel to the sharp drop in the death rate from ischaemic heart disease observed in certain countries during the Second World War.

On both clinical and experimental grounds, abnormal thyroid metabolism might be expected to influence cholesterol metabolism. Myxoedema is often associated with hypercholesterolaemia, and it has often been stated that myxoedematous persons are unusually prone to atherosclerosis and ischaemic heart disease. However, the way in which the thyroid hormone influences cholesterol metabolism is not well understood and there is a

definite need for more clinical and autopsy data before drawing any definite conclusions concerning the correlation between hypothyroidism and atherosclerosis. Certainly, there is as yet no justification for the use of thyroid preparations in the hope that these may prevent ischaemic heart disease.

5. RELATION TO ARTERIAL HYPERTENSION

5.1 Evidence for a relationship

The available evidence for a relationship between hypertension, essential or nephritic, and ischaemic heart disease comes from several sources. There are data from studies in both man and experimental animals which indicate that increased intravascular pressure tends to promote the development of atheromata. Post-mortem studies of the frequency of cardiac infarction show that raised blood pressure in life is frequently associated with evidence of cardiac damage, although this association is by no means universal; many individuals with higher than normal blood pressure show no signs on autopsy of excessive coronary artery disease or of infarction.

Although hypertension may accelerate atherogenesis, studies have shown that there are a number of populations in which hypertension is not uncommon, whereas the prevalence of ischaemic heart disease is nevertheless relatively low. In this connexion, it is of interest that, although the frequency and severity of atherosclerosis in both the aorta and coronary vessels generally increase with age, it does not appear to be universally true that blood pressure also goes up (populations of China, Uganda, and Panama, for instance). Expectancy of life seems to be related inversely to arterial pressure, although this correlation is barely established and expresses no more than a minimal quantitative relationship. Insurance company figures suggest that the chief source of excess of deaths among persons with the higher pressures is due to cardiovascular-renal disease. The extent to which ischaemic heart disease contributes to this excess is not yet established.

5.2 Technical problems in evaluating hypertension

Among the more important technical problems which should be mentioned are the effects of differing arm circumference on sphygmomanometer readings, and the auditory acuity of the observer. Even when these sources of error are taken into account, variations due to the environmental conditions at the time of measurement remain. The single casual measurement frequently practiced is of very limited value.

There is no scientific basis for any arbitrary division into normal blood pressure and hypertension. What is often called " hypertension " is merely an extreme value of a normally distributed variable. Current practice often designates " hypertensive heart disease " when the systolic or diastolic pressures exceed certain arbitrary values. It seems probable, on first principles, that the extent to which high blood pressure contributes to cardiac disability will depend not only on the height of the blood pressure but also on the duration of the elevated pressure levels. Clinical studies of individuals therefore require repeated readings on the same person.

Studies based on clinical cases may suffer from the difficulty of securing adequate controls; inevitably, results obtained on hospital patients or persons examined before employment are biased because of the special circumstances obtaining at the time of the examination. Comparative studies reported in the literature which seek to relate the distribution of blood-pressure readings to the incidence and mortality from cardiovascular disease in different populations face similar difficulties.

5.3 Investigations recommended

There is a need for repeated measurements on the same individual so that a measure of diurnal range of pressure and duration of various pressure levels is obtained. Such data should be related by follow-up studies to subsequent experience of cardiovascular disease. If mechanical factors in blood flow are involved, such observations may be of crucial importance.

Comparative studies in different populations should be based on frequency distributions rather than on the percentages above any arbitrary value of blood pressure reading, and they will require for success the same close attention to the standardization of techniques as the clinical and prospective (follow-up) inquiries mentioned above.

Investigations of the relationships between elevated blood pressure and the frequency of hypertensive heart disease in general, as distinguished from atherosclerotic changes in the coronary arteries, are also very much needed.

6. ROLE OF ENVIRONMENTAL FACTORS

6.1 Diet

6.1.1 *General considerations*

It is clear that there is a relationship between some aspects of the mode of life and the incidence of ischaemic heart disease. Among the factors that may be involved, a large amount of evidence suggests that

diet is directly or indirectly influential. The experimental demonstration that atherosclerosis can be produced in a number of animal species by dietary manipulation is particularly important, although these same experiments also show clearly major differences in the metabolic response of different species to the same dietary alterations. Furthermore, it has not yet been possible to produce in experimental animals the equivalent of human ischaemic heart disease; in so far as it has been possible to mimic some aspects of it, however, dietary factors have been most prominent. Manipulation of the diet is, in fact, the principal method used in the experimental production of atherosclerosis.

The concentration of cholesterol and cholesterol-bearing lipoproteins in the blood serum can be changed by dietary manipulation in controlled experiments, both in man and in animals. The findings of comparative studies of human population samples subsisting on different diets are, in general, consistent with results obtained in these experiments. The significance of these lies in the fact that much evidence from different types of research suggests that there is a relationship between ischaemic heart disease and the concentration of cholesterol and cholesterolbearing lipoproteins in the blood.

Among the kinds of information pointing to the significance of the diet may be mentioned the war-time changes in mortality rates of ischaemic heart disease in some countries where the populations were forced to change their diets; the often reported differences in the frequency of atherosclerosis and myocardial infarction among populations subsisting habitually on different diets; life insurance experience of persons of different relative body-weights who are presumed to have different dietary habits; and, perhaps, the indications of a progressive rise in ischaemic heart disease in younger men in some countries where there have also been progressive changes in the character of the diet. In none of these instances is the diet isolated as the only independent variable, but the appearance of a consistent pattern in regard to the diet suggests that it is especially significant.

In general, there are indications that habitual subsistence on an abundant, luxurious diet may tend to be associated with hypercholesterolaemia, atherogenesis, and the development of ischaemic heart disease, and that a meagre, poor diet is more likely to be characteristic of populations with the opposite tendency. In natural human populations, however, subsistence on one or other of these opposing types of diet is generally associated with other contrasts in the mode of life. Some kind of factoral analysis is required to reveal whether diet has a specific role in " natural " human ischaemic heart disease. Moreover, as indicated below, there are several different aspects of the diet to be considered.

6.1.2 *Dietary cholesterol*

The foregoing considerations have stimulated experimental and, more recently, epidemiological searches for the dietary factors that may be most directly involved. The first item studied was dietary cholesterol itself; almost fifty years ago, this was shown to be capable of producing atherosclerosis in the rabbit. It is now known that various animal species differ markedly in their response to exogenous cholesterol, i.e., cholesterol contained in natural foods or added in pure form to the diet. Man is greatly different in this respect from the rabbit and the chick, the two favourite species for experimentation. It now appears that, provided other conditions are constant, the blood cholesterol level in man usually responds little, or not at all, to variations in cholesterol intake corresponding to the range represented by the great majority of human diets.

The concentration of cholesterol in the blood is the resultant of synthesis, ingestion, degradation, and excretion. Biochemical investigations show that variations in cholesterol ingestion tend to produce compensating adjustments in the other factors in this balance, and in man and some other species (e.g., dog, rat) the last-named are highly effective in maintaining the serum level, independent of the dietary intake of cholesterol.

6.1.3 *Dietary fat*

A large number of clinical observations and controlled experiments on man as well as on animals are in agreement that the cholesterol-lipoprotein system in the blood serum, and particularly the concentration of cholesterol in the β-lipoprotein fraction in the serum, is influenced by the fat content of the diet, even where all other dietary variables are constant. Field observations on population samples likewise indicate that where the amount of fat in the habitual diet is high the serum cholesterol concentration also tends to be high, and vice versa; this association persists when the samples are matched in regard to obesity, relative body-weight, occupation, and physical activity. It is also possible that the statistical excess in mortality from heart diseases in overweight people is not related simply to an excessive calorie intake, but to an unduly high intake of some food ingredients, e.g., certain types of fats which in most "Western" countries are present in high quantities in the diets of the majority of individuals who overeat.

Among the various populations studied so far, those characterized by subsistence on a low fat diet are also those that appear to suffer a relatively low incidence of atherosclerosis and ischaemic heart disease. Examples are the men in Japan, Korea, and Okinawa, and among the Bantu in Uganda and South Africa, the Mayan Indians of Guatemala, the Yemenite Jews, the Indonesians, the Negro tribes in Nigeria, and the populations of Bolivia and Peru, as well as the general population of southern

Italy and Sardinia. At the same time, there appear to be substantial variations in mortality from ischaemic heart disease among " Western " populations, all of which have a high fat diet. No explanation is so far available for this variation.

The war-time changes in the mortality ascribed to ischaemic heart disease in some countries have been mentioned earlier (see page 12). In general, these changes followed reduction in the amount of fat in the diet and were observed to be greatest where the reduction in the dietary fat was greatest. Not only did mortality from ischaemic heart disease fall a year or two after subsistence on a low fat diet began, but the converse was also observed following the restoration of fat in the diet. Further analysis of the conditions involved in these situations shows that, in general, the major reductions in dietary fat are accounted for by fats of animal origin and, moreover, that differences in the amount of animal fat in the diet tend to be accompanied by parallel differences in the amount of protein derived from animal sources. The total protein content of the diet does not seem to be importantly involved since its range of variation is small in most human diets.

However, it must be recognized that many changes in environment occurred in the period of occupation and liberation and that some of these may also have influenced the trend in the incidence of ischaemic heart disease.

In recent controlled experiments in man, it has been shown that the several food fats do not have identical effects on the cholesterol-lipoprotein system in the blood serum. It is clear that these differences do not stem simply from the fact that the fats are of vegetable or animal origin, nor is it probable that the explanation can be found in simple differences in the degree of saturation of the constituent fatty acids.[1]

Surveys conducted in a few countries indicate some interesting features in relation to fat consumption. Firstly, fat intake generally tends to rise with level of income. Secondly, fat consumption in rural areas is usually lower than in urban areas. Thirdly, there is a tendency for heavy workers to obtain their extra calorie needs from carbohydrates rather than fat. The parallelism noted in several countries between the patterns of fat consumption and the mortality from ischaemic heart disease is very interesting, and certainly deserves careful investigation in order to establish

[1] Since the meeting of the Group was held, there has been an increased interest in the effects that certain vegetable and marine oils appear to have on the blood cholesterol level. Certain members of the Group have expressed a wish that the report, when published, should contain a strong recommendation for research in this field. Advances in knowledge resulting from recent work may be of considerable potential public-health importance. Further research may even permit of the development of easily applicable preventive measures.

its significance as a sign of a true relationship between the two orders of facts.

The importance of discovering the effects of fat consumption is emphasized when it is realized that the fat content of the diet is increasing in many parts of the world. This results from economic development, involving industrialization, urbanization, and rising incomes, and from changes in food technology and distribution that favour the use of more fats. The progressive trend towards higher and higher fat diets is clear in prosperous countries like the United States and Canada, but it may be even more pronounced, in percentage terms, in poorer countries. For example, in Japan, where little fat was used formerly, the present consumption is about five times greater than that of immediately after the war.

6.1.4 *Relation of diet to production of thrombosis*

Interest in the role of the diet has continued to be concentrated on atherogenesis because this problem is accessible to study in animal experiments and because of the possible connexion between the diet and atherogenesis through the cholesterol-lipoprotein system in the blood serum. Nevertheless, it is disconcerting that animal lesions often differ from those in humans and that thrombotic and ischaemic lesions are rarely reproduced in such animal experiments.

The influence of the diet on blood coagulation and on thrombus formation has received comparatively little attention, but there is reason to suspect that this question also may be exceedingly important. Major differences in the diet, as produced in some countries during the Second World War and as exist between various populations, appear to be associated with differences in the frequency of thrombo-embolic phenomena in general, as well as with differences in mortality from ischaemic heart disease. Although it should be recognized that intravascular thrombus formation and *in vitro* blood coagulation are not necessarily identical, there is growing experimental evidence that blood coagulation may be influenced by the diet.

Indications on mechanisms that may be involved in thrombus formation are emerging from recent studies on the heparin-lipoprotein system. The only dietary constituent that so far has received any appreciable amount of attention is the total fat in the diet. It would appear, however, that attention should also be given to the possibility that different food fats are not equivalent in this respect and, further, that other dietary elements may be influential.

Research needed

The Group was of the opinion that all these facts, and theoretical considerations as well, indicate the extreme importance of much further

research into questions of the relationship of the diet to the cholesterol-lipoprotein system in the blood serum, to atherogenesis, to thrombogenesis, and to ischaemic heart disease. The search for the necessary knowledge should be pursued by controlled experiments, clinical observations, and population studies. Epidemiological investigations offer possibilities of most fruitful results, especially if simultaneous study is made of the diet, the incidence of ischaemic heart disease, and of other characteristics of populations so differing as to present the widest possible range of variation in these items. For further discussion of this important matter see Annex 1, page 31.

Data on actual food consumption, including fat intake, in different countries are far from adequate and are lamentably deficient in showing what may be the dietary customs of different segments of the populations.

Most of the attempts at epidemiological study of a possible association between food consumption levels and mortality from ischaemic heart disease are based on data for recent years. It must be remembered that a study of the diet over a period of several years rather than on present or recent levels of consumption might be more meaningful. In most countries, comparative data over a period of several years are not available. It is therefore very necessary to obtain adequate and accurate information from now on.

The co-operation of FAO in the task of obtaining useful data on food consumption will contribute to further progress in this direction, particularly in relation to the development of uniform methods of collection, analysis, and presentation. One of the FAO nutritional studies [1] provides valuable guidance on the carrying out of appropriate dietary surveys under different conditions and on the presentation of the data on a comparable international basis.

6.1.5 *Calories, obesity, and overweight*

The dietary variable that has attracted the greatest general interest in regard to ischaemic heart disease is the calorie imbalance reflected in relative obesity or overweight. Obesity, of course, is the result of an intake of calories excessive to the energy expenditure. It must be pointed out that obesity and " overweight " are by no means identical and that almost all studies in this connexion in the past have dealt with estimates of overweight. " Relative obesity " refers to the proportion of the body mass made up of fat, and obesity means that the proportion of fat in the

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[1] Norris, T. (1949) *Dietary surveys : their technique and interpretation,* Washington (*FAO Nutritional Studies,* No. 4)

body is unduly large. Overweight refers simply to being above the " average " or " standard " for one's height, age, and sex group.

The relationship between relative body weight and obesity differs according to the skeletal type and according to the amount of physical activity. Men doing strenuous manual work tend to be heavier, at the same degree of fatness, than men in sedentary occupations. Overweight can result from large muscular development without overeating or, on the other hand, simply from overeating. The truly obese person is apt to be the one who shuns physical activity in addition to overeating, so that his body weight underestimates his fatness.

Until recently, direct estimates of obesity have been rarely attempted and suitable methods were not available. The situation is now changing and encouragement should be given to distinguishing between absolute weight and relative fatness in epidemiological work. A very considerable proportion of the total body fat is subcutaneous, and advantage of this fact can be taken for the estimation of obesity. Measurement of the thickness of skinfolds is simply made with suitable calipers, and a valuable index of body fatness is obtained. On this point the Group would refer investigators to the report of the Committee on Nutritional Anthropometry of the Food and Nutrition Board, National Research Council of the USA.[1]

The evidence indicating the importance of obesity in regard to heart disease is very largely derived from statistics in which the variable is actually overweight. There is no convincing evidence that relative obesity, of itself, is a major factor in atherogenesis or the production of ischaemic heart disease in man. Indirect indications from a consideration of the cholesterol-lipoprotein system in the blood serum are likewise inconclusive. In the active phase of rapidly accumulating body fat, the serum cholesterol tends to rise, and the reverse change is usually observed when the calorie balance is negative, as in famine or at times of subsistence on a reducing proportion of fat in the diet; hence the effect of calories *per se* is not clear. Moreover, at calorie balance, i.e., when the body weight (and fatness) is stable, the serum cholesterol level has been found to be little related to the degree of obesity or leanness in samples of men from populations characterized by a high frequency of ischaemic heart disease (as, for example, various populations in the United States and England, Europeans in Capetown, and upper-class men in Madrid).

Other evidence suggesting that obesity in itself is not a primary factor in producing ischaemic heart disease has been provided by population studies. Obesity is by no means rare in many populations in which

[1] *Hum. Biol.*, 1956, **28**, 111

ischaemic heart disease is much less common than, for example, in the United States and Great Britain. Furthermore, calculations based on United States life insurance data indicate that if all markedly overweight persons were removed from the United States population, the mortality rate from ischaemic heart disease in the remainder of the population would still be very much higher than in some other countries (Norway, Italy, Japan, for instance), even though obesity also occurs in those countries.

It appears, therefore, that the correction of obesity could at best accomplish relatively little in the control of the disease. However, it should be added at once that obesity is undesirable in many other regards and that there should be no complacency about the existence of obesity in any population. Finally, once ischaemic heart disease has developed, there is no question but that obesity, if present, should be corrected.

6.2 Physical activity

6.2.1 *Present evidence*

The relative frequency of ischaemic heart disease differs in different social and economic groups. In some countries, professional and business men seem to be affected more often than men of the same age in the rest of the population who, on the average, may be presumed to be more active physically. Moreover, it has been observed in England, among persons of the same economic class, that men whose occupations do not demand a high degree of physical activity tend to suffer from ischaemic heart disease more frequently and more severely than their counterparts in more active jobs. Evidence on this point from other countries has in some instances supported this observation but in others is inconclusive or even contradictory.

In many countries, the mode of life has been changing progressively in such a way as to reduce the average physical activity of their populations. The anatomical, physiological, and biochemical consequences of this have been little studied as yet, but it has been suggested that the apparent rise in some countries in the frequency of ischaemic heart disease among young and middle-aged men may be related to this reduction in the average level of physical activity.

The theory that physical activity is an important determinant in the etiology of ischaemic heart disease would not suffice to explain more than a part of the large differences observed in the incidence in some countries and population groups. Moreover, variations in the level of physical activity are generally associated with variations in other aspects of the mode of life, notably the diet. Serious attention should be given to the possibility that these two variables, and perhaps others, may act as additive factors in atherogenesis, or the promotion of thrombus formation, or

both. There is also a relationship between obesity and the limitation of physical activity, since exercise tends to reduce obesity and obesity to limit physical activity.

6.2.2 *Research needed*

It was the opinion of the Group that the possible role of physical activity, *per se* and in combination with the diet and other variables in the mode of life, urgently needs more research, both in regard to ischaemic heart disease itself and in experiments on other variables of relevance (e.g., the cholesterol-lipoprotein system in the blood serum, lipid metabolism, dietary habits, blood coagulation, the development of collateral coronary vessels, etc.).

The question of a possible relationship between ischaemic heart disease and emotional " stress " and " tension " is discussed below. In this connexion, it would be interesting, if possible, to explore the influence of physical activity in serving as an outlet for emotional tension.

6.3 Stress, strain and mental tension

6.3.1 *Present knowledge*

The widespread belief that psychological factors play some part in the genesis of ischaemic heart disease appears to have as yet no scientific basis. The clinical impressions which engender this belief derive from the patient's or relatives' accounts of the relation of an attack of " coronary thrombosis " to a preceding emotional event or crisis. The high incidence of ischaemic heart disease in the " Western " countries, as compared with some technically less highly organized communities, has been attributed to differences in the tempo of life, the relation between the sexes, social insecurity, and striving for dominance, all of which have their repercussions on the emotional life of individuals.

Conventional behaviour patterns which give insufficient outlet for certain emotions have been thought to cause inner tension and thereby vascular changes. The apparent concentration of ischaemic heart disease morbidity among certain occupational and social groups, particularly in recent years, is taken to reinforce this hypothesis ; until more objective evidence is available, however, this must remain an interesting conjecture. Certainly, no specific suggestions for public-health action can yet be made on this basis.

6.3.2 *Investigations required*

The Group considers that more systematic research into cultural and psychosomatic relationships in both atherosclerosis and coronary thrombosis is urgently required. In such research, clinical investigators and

epidemiologists must play an active part, together with workers from other disciplines. It should be remembered that emotions which precede acute cardiovascular episodes, even when long continued, need not necessarily produce structural changes in the cardiovascular system. Hypotheses formulated by psychiatrists as a result of their observations on cardiac patients should be checked by clinical studies. In these investigations, a clear distinction must be made between factors which may be predisposing and those which precipitate the disease.

Epidemiological researches designed for the study of other factors might be supplemented by psychological assessments of a sample of the individuals included in the surveys; e.g., by comparing cardiac patients both with healthy control groups and with patients suffering from other diseases, similar as far as possible in severity and medical and social consequences.

Psychological assessments made before the onset of clinical disease as a part of long-term follow-up studies may prove especially valuable. Similarly, such assessment might be crucial in the interpretation of differences in cardiac mortality found between occupational and other population groups. Other allied and desirable lines of inquiry are the relation of psychological assessment and contemporary personal history to the outcome of established ischaemic heart disease and occupational rehabilitation of patients, and the comparison of the incidence of the disease among groups of patients with different psychiatric disorders and among the general population.

In certain countries where different ethnic groups live according to distinct cultural patterns, it might be possible to accumulate morbidity and mortality data related to these cultural patterns, expressed in such numerical indices as can be devised, as well as to dietary habits (see Annex 1, page 31).

Special opportunities for research exist among "under-developed" communities where technical aid is now producing changes in the way of life. These changes are being observed by anthropologists, and they might be compared with the incidence of cardiovascular and other diseases and with such other measures as the level of blood pressure and blood serum cholesterol. The difficulties inherent in this type of planned observation are obvious; although the inadequate vital statistics of such communities may be supplemented by special surveys, it may be impossible to disentangle the effects of cultural and dietetic factors, as these so often occur simultaneously.

In all such studies, there is a clear need for standardization of diagnostic criteria and for the use of agreed operational definitions of such terms as stress, emotion, tension, and conflict.

6.4 Alcohol and tobacco

The evidence that alcohol is relevant to cardiovascular disease comes largely from vital statistics. Areas where consumption is high may have quite low reported mortality rates from ischaemic heart disease, whereas they seem to have an excessive death-rate from other cardiovascular and renal diseases. This is particularly evident in a number of countries, among persons whose occupations are associated with a high alcohol consumption, such as bartenders.

Two independent large-scale studies on the role of tobacco in cancer of the lung state as an incidental finding that heavy smokers have higher death-rates from coronary thrombosis. Excessive smoking and drinking may both be expressions of emotional disturbances; but whatever the mechanism, the relationship of heavy smoking to cardiovascular disease very much merits further study.

6.5 Infections

Little work has been done of late on the influence of infection on the development of arterial disease, although fatty changes in vessels are seen in many acute bacterial infections. A suggestive association has sometimes been noted between infections affecting the liver and gall-bladder functions and vascular thrombosis. This suggested to the Group that it might be worthwhile to follow up the subsequent medical histories of servicemen who had experienced infections likely to interfere with fat metabolism and of patients suffering from diseases affecting the arteries, such as typhus or polyarteritis nodosa.

7. AVAILABILITY OF VITAL STATISTICS AND EPIDEMIOLOGICAL INFORMATION

7.1 Mortality statistics

In addition to investigations aimed at determining specific etiological factors, much pertinent information of a more general nature is provided through the machinery of death registration and other vital statistics sources. This machinery has very great potentialities, but has also limitations. In utilizing vital statistics from different countries, it is important to pay attention to the lack of uniformity in : (*a*) standards of medical practice ; (*b*) criteria on which the cause of death is assigned ; (*c*) proportion of autopsies practised ; (*d*) cultural and psychological reasons for incomplete or faulty notification of certain forms of death in many countries ; and

(*e*) practices in vital statistics services. Considerable improvement can be achieved by introducing elementary notions of vital statistics into the curricula of all medical schools, by educating medical practitioners in the methods of certification of cause of death, and by improving methods of processing and analyzing the material.

With all their limitations, however, mortality statistics provide much important information on the size of the problem of ischaemic heart disease, and show a number of differences among groups that may be of potential importance. For example, they provide evidence which strongly suggests that in the United States and Great Britain there has been an increase in the death-rate among adult males from the cardiovascular diseases as a whole. At the same time, mortality from these diseases among females showed a slight decrease. This cannot simply be explained on the basis of changes in the classification procedures; it is phenomena of this kind that stimulate further investigations. Vital statistics also indicate, however inaccurately, the great differences in the death-rates from cardiovascular diseases that occur in different countries of the world. The civilian trends of mortality in Europe during the Second World War have already been mentioned.

It is essential that vital statistics services be improved in the underdeveloped countries. In many other countries, they must be amplified to provide more detailed and accurate information. In particular, it is desirable to collate and publish the distribution of deaths from cardiovascular diseases in greater detail, including more sub-grouping of the causes and more data on age, sex, and locality.

The data from death certificates have been used to provide information on the mortality rates from cardiovascular diseases by social class as this is inferred from occupation. The results are extremely interesting, but it is desirable to test further the reliability and comparability of the statement of occupations, as given on the death certificates and as reported in the census—the data from which the calculations are made.

7.2 Morbidity statistics

Mortality statistics obviously are not the only source of information of an epidemiological nature; morbidity statistics may be even more useful. It is therefore desirable to conduct, in as many areas as possible, special morbidity surveys, and if possible to repeat these at regular intervals, in order to obtain specific prevalence and incidence rates for ischaemic heart disease. Such surveys done on a community-wide basis would, in addition, provide the initial data from which the survival rates for the various groups may be determined. A start has been made on surveys among large occupation groups.

7.3 Hospital data

Similarly, useful information may be obtained from hospital statistics. Again, these have limitations, and efforts must be made to make them more useful than they are at present. One important source is the data which can be provided from hospital autopsies. However, greater attention must be given than is often the case at present to the sampling that is involved and to uniformity in procedures and reporting.

The same observation applies to statistics on ischaemic heart disease among hospital patients and on the association of the disease with such factors as occupation or race. It would probably be necessary to select a few hospitals in which a standard and uniform system of recording could be adopted. These might then form a nucleus for a larger reporting group of hospitals in the future.

7.4 Life insurance records

Besides vital statistics, other sources of information on mortality and morbidity rates ascribable to ischaemic heart disease deserve attention. In some countries, the insured population is a large and important fraction of the total and a group, moreover, about whom other information is available—on occupation, economic status, state of health at the time of issuance of insurance, body size, family status at the time of policy issuance and at the time of death, etc. Furthermore, in many regions it is customary for the insurance companies to demand, as a condition for payment of claims, further and independent information on the circumstances of death than is given in the ordinary death certificate.

It is noted that valid mortality rates require accurate data both on the number of those dying and the number of those alive, of the same age and at the same "risk" in the population. In vital statistics, the number of alive is often much less certain than the number of dead, but insurance data present no such handicap; the number "at risk" is precisely known from the policies in force, and the event of death is scarcely less accurately recorded since failure to make a claim for death payment is rare. Distinction should be made between insurance policies issued after medical examination and those which have no such qualification. It is interesting to note, however, that the mortality rates of the two types of policy-holders are substantially identical, if deaths in the first three or four years after policy issuance are excluded.

7.5 Other sources of epidemiological data

Other sources of epidemiological data on heart disease have been exploited even less than insurance data. These include the growing files of social security and pension systems, labour unions, industrial health

programmes, and such organizations as the Railroad Retirement Board in the United States, the Ente Nazionale per Assistenze Statali in Italy, the Institute for Occupational Health in Finland, etc. Some of these organizations not only have files of data on morbidity and mortality on defined sections of the population, but also have facilities and personnel for the data analysis and for the procurement of additional information.

8. PRACTICAL CONSIDERATIONS FOR PUBLIC-HEALTH SERVICES

8.1 Present status of public-health efforts

The common objective of all workers in medical science is a healthy people. The prevention of disease and of the consequences of disease is the path of greatest long-range value. To achieve this goal, public-health and medical practitioners must adjust their methodology to the state of knowledge about any particular disease at any given point of time. The present status of public-health efforts directed toward the problem of ischaemic heart disease and its complications is reviewed in Annex 2 (see page 34).

8.2 Orientation of a preventive programme

The public-health officer is entitled to ask what should be the recommendations of a programme of health education aimed at the prevention of ischaemic heart disease. The Group agreed that there is as yet no irrefutable scientific evidence to show that any particular factor causes, or contributes to, the development of ischaemic heart disease. Pending further research into the nature and causes of the disease, it might be well to remember that moderation in many things, including eating and other habits, would be very wise advice for all—the public, the medical profession, and the public-health authorities alike.

This advice of moderation has the very real value of being directed at the same time at such factors as physical activity, obesity, alcoholism, heavy smoking, and over-indulgence in many activities. The wisdom of moderation is obvious from wide varieties of experience.

8.3 Detection and handling of ischaemic heart disease

The health officer desires to know the answers to several additional practical questions:

(*a*) Can systematic health examination be useful for the prevention of ischaemic heart disease? In other words, are there any valid and easily

determined clinical or other criteria which make it possible to detect those persons who are most exposed to the risk of contracting ischaemic heart disease in the near future and, if so, what are they?

(*b*) Are there any valid and easily determined criteria for the diagnosis of mild forms of ischaemic heart disease the detection of which would make it possible to prevent a relapse or aggravation of the disease? If so, what are they and how can they be incorporated into public health procedures?

(*c*) How should the problems of re-adaptation to work be approached for persons who have had an acute episode of ischaemic heart disease?

The Group concluded that further studies of the types outlined throughout the report would be required before an attempt should be made to give sufficiently specific answers to each of these questions.

8.4 Studies recommended to public-health services

Public-health services have an important contribution to make in the establishment of the etiological factors in atherosclerosis and ischaemic heart disease. There is need, therefore, to consider the principal studies to be recommended to public-health services, particularly in the epidemiological and statistical fields.

Suggestions for further research on ischaemic heart disease are contained in the next section; other comments on the need for specific types of investigation also appear there. The Group commends to health authorities the special need for studies of the community as a whole. Health organizations can obtain information leading to a better management of this broad disease problem by studying their communities in a way analogous to clinical research by private physicians. Community projects should be in addition to the highly recommended studies on special groups, such as are now under way in many places. It is particularly important to encourage these activities in areas providing the greatest contrast in the economic and social status of the inhabitants.

An essential feature in such studies is uniformity in procedures, nomenclature, and the handling and analysis of the data. To achieve such uniformity will require both great energy and effort on the part of some co-ordinating organization and the exchange among different countries of well-qualified workers in the field of atherosclerosis and ischaemic heart disease, especially of those who are expert in epidemiology and preventive and social medicine. It is deemed highly advisable that WHO promote these activities in any possible way.

9. RECOMMENDATIONS FOR FURTHER RESEARCH AND FOR INTERNATIONAL CO-OPERATION

9.1 Need for basic research

It is clear that the control and prevention of ischaemic heart disease can be brought about only as a result of improved knowledge of the relation of environmental factors and ways of life to the pathogenesis of this disease and to the consequent morbidity and mortality. Realization of the multiple etiology and pathogenesis of the disease should stimulate research in many directions. The Group has already included in the report mention of areas in which present research activity is deficient. These will not be stated again, except to say that (*a*) the lack of information on the relation of suspected factors to coagulation and thrombosis, and (*b*) the need for adequate studies on possible psychological factors in the condition, deserve particular emphasis.

9.2 Collection of vital statistics

It is recommended that WHO should continue and expand the collection and regular publication of mortality statistics on cardiovascular and related death-rates, from various countries and from cities within these countries. Moreover, an attempt should be made to publish in monograph form relevant statistics, at least from the 1920's onward. Such a monograph should include discussion of the effects of changes in nomenclature and classification on certified mortality trends, and particular comment and information about the method of notification of death in each country.

The Group noted with satisfaction the improvements introduced in the most recent International Lists of Diseases and Causes of Death.[1] It also noted the detailed statistics on deaths from vascular lesions affecting the central nervous system and from diseases of the circulatory system, published by WHO in the *Epidemiological and Vital Statistics Report* for October 1955,[2] and heard with interest of current investigations promoted by the Organization into the problem of improving death certification in general.

The Group believes that it is necessary to develop the analysis of mortality by occupation and social class, and hopes that WHO will assist national statistical offices in this task.

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[1] The seventh revision of the International Lists will be incorporated in a new edition of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, to be published early in 1957.

[2] *Epidem. vital Statist. Rep.*, 1955, **8**, 435-466

The Group also believes that there is need for considerable improvement in the collection and recording of much of the data already routinely reported by many countries and for greater standardization of terms and procedures, so that useful comparisons between countries may be made. Sample field investigations concerning the basis of death certification should be carried out in various countries, using the same methods in each one ; these investigations should not be confined to the cardiovascular diseases. This type of study might reveal quite quickly the possibilities and limitations of the international comparisons that are now so commonly being made. WHO should initiate and co-ordinate such studies.

The Group was also agreed on the desirability of studying possible relationships between ischaemic heart disease and the various pathological processes, not necessarily mortal, occurring in other systems of the body.

9.3 Insurance company statistics

Insurance mortality and morbidity statistics are often used as evidence in medical research. Until now the experience of life insurance companies has been applied only to a very limited extent in epidemiological studies of ischaemic heart disease, the outstanding instance being the emphasis, based almost entirely on insurance experience, on the avoidance of overweight. But much greater use of insurance data, and of collaboration of insurance companies in epidemiological studies on heart disease, would seem desirable.

While the resources of individual insurance companies are largely confined to the single countries in which they have their headquarters, insurance practices are often similar and useful international comparisons may be possible by the concerted efforts of companies in different countries. It is recommended that WHO, through its Member Governments, support the adoption of an international uniform way of collecting insurance data. It also seems recommendable that a study be made of unpublished insurance information that might be used in determining the epidemiology of ischaemic heart disease.

9.4 Need for pathological and clinical standardization

The need for the standardization of both clinical and pathological criteria and terminology in respect of atherosclerosis, ischaemic heart disease, and related conditions appeared so urgent that it was hoped that WHO would give consideration to the organization of a study group, consisting of both pathologists and clinicians, for the purpose of (*a*) agreeing upon methods of examining, assessing, and reporting on necropsis with particular regard to coronary-artery and myocardial lesions, and (*b*) establishing uniform criteria for the clinical diagnosis and classification

of cardiovascular diseases in a manner that will be applicable to epidemiological and other statistical studies. Similarly, WHO should sponsor efforts to achieve uniformity in pertinent laboratory estimations, of serum cholesterol and cholesterol-bearing lipoproteins, for example.

9.5 Studies of dietary habits and food consumption

No data are available in respect of many populations that are of special interest, and existing data are often inadequate in several respects. For example, dietary information is usually collected only on a family basis, even though the results are expressed in terms of *per caput* or per consumption unit. It is essential to have data on the food habits of the individual, so that the diets of persons in different age-groups, especially of men and women in middle age and beyond, can be ascertained. Another instance is the lack of information on the nature and source of the fats in the diet, despite the interest in their relation to the general problem.

The Group believes that FAO should continue its co-operation in this field by assembling and providing appropriate data on food consumption, as recommended by the Joint FAO/WHO Expert Committee on Nutrition at its fourth session.[1] It hopes that FAO will also continue to stimulate well-planned dietary surveys to obtain as soon as possible the required dietary information for different parts of the world.

The Group noted that the Joint FAO/WHO Expert Committee on Nutrition has already drawn attention, again at its fourth session, to the possibilities of malnutrition resulting from the excessive consumption of food and to the importance of this question, particularly in regions with abundant food supplies.[1] Since ischaemic heart disease seems to be in some way associated, in conjunction with other factors, with the excessive consumption of certain foods or nutrients, it is desirable for national organizations, as well as for the international agencies concerned with these problems, to study the question of maximum limits for the requirement of calories and nutrients, especially fats. It is suggested, therefore, that FAO should be asked to consider referring this question to the forthcoming meetings of its Committee on Calorie Requirements.

9.6 Epidemiological studies

The Group has laid down in Annex 1 (see page 31) some principles affecting the conduct of epidemiological study, which is the main method of investigating the relationships between disease and ways of living. Studies of this kind offer the best hope of revealing some factors which

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1955, **97**, 44, 41

would justify suggestions for possible ways of prevention. However, the effective planning, prosecution, and interpretation of such studies require properly trained professional personnel. In the field of ischaemic heart disease, and of the metabolic and non-infectious diseases in general, there is a serious shortage of men who are familiar both with social and clinical problems and with epidemiological methods. The Group recommends that WHO should take steps to rectify the situation, especially by furtherance of post-graduate training of such workers in one or two appropriate centres. The studies already in progress are evidence of the potentialities of the epidemiological approach to these problems.

In addition to whatever epidemiological research WHO can carry out or sponsor, it seemed to the Group that the Organization could give effective assistance in the following ways :

(*a*) by drawing the attention of governments to the importance of encouraging and promoting work in this field ;

(*b*) by identifying environmental situations that offer special opportunities for study, including populations undergoing rapid social change and populations with apparently great contrasts in experience of ischaemic heart disease ;

(*c*) by making available experienced consultants to assist in the design of surveys and in the analysis of the results.

9.7 Survey of present public-health efforts

It is suggested that WHO take a co-ordinating role in a very desirable special study of how the various countries are in fact organized to meet the problem of ischaemic heart disease, particularly as regards official health agencies, voluntary health agencies, and scientific societies. The way these groups have solved any problem of joint objectives or different responsibilities will be of real value to the countries which still must meet these problems, especially if WHO, as it is recommended, would arrange for the distribution of any sort of collected information. A beginning on this task is made in Annex 2 (see page 34).

9.8 Exchange of information and experience

The Group noted the urgent need for a more extensive exchange of information and experience among workers interested in the problem of ischaemic heart disease in different parts of the world. It was felt that WHO could promote research in the field by preparing and publishing a critical monograph embodying the result of epidemiological studies carried out to date, with suggestions to research workers on the design

and interpretation of such studies, as well as on the type of additional investigations most needed.

WHO could also contribute by promoting the exchange of information and experience among workers in this field in different parts of the world. Travel grants for personal visits would be particularly helpful. The Group further draws attention to the value of promoting co-operation and the exchange of information among the various professional personnel of the United Nations specialized agencies who may be able to contribute to the solution of the problem. In particular, it hopes that medical officers, epidemiologists, nutritionists, and social scientists will all be made aware of the need for joint efforts in this field.

9.9 Promotion and co-ordination of research efforts

The Group believes that WHO should take responsibility and permanent care of the promotion and co-ordination of work in the field of cardiovascular diseases, and assist its Member States and their governmental and non-governmental agencies in dealing with this matter. Experienced consultant help should be made available in situations where such services will have special value. The results of the experiments already being made in a few countries that have health programmes aimed at the early detection and control of ischaemic heart disease should be observed. It is hoped that the outcome of these studies and additional research, as recommended in this report, will enable WHO to suggest preventive programmes to health authorities in the not too distant future.

Annex 1

THE EVALUATION OF ENVIRONMENTAL FACTORS IN POPULATION AND STATISTICAL STUDIES

The search for possible meaningful associations between ischaemic heart disease and environmental factors such as diet and physical activity is one of the most difficult tasks in medical research. Since the progress of this disease cannot generally be measured clinically, the extent of its damage can often be evaluated only on post-mortem examination. Furthermore, specific factors such as diet and physical activity, involving as they do the complexities and interactions associated with the process of living and way of life, cannot easily be disentangled and observed singly. Moreover, the investigator is often not in a position to alter specific components of the environment, quantitatively or qualitatively, and can study only such variations in these factors as are available within or among population groups.

Of necessity, therefore, the methods are most frequently indirect and the evidence is circumstantial. This means that a multiple approach must be used in order to study each specific factor from as many different and as many independent aspects as possible. At best, any one aspect is likely to suggest only a possible association which must be weighted and evaluated in the light of the findings from other types of investigations. The value of associations is, of course, greatly increased when information as to the sequence of appearance of the associated factors can be obtained.

In general, two types of problems may be distinguished: (*a*) the determination of the association of specific factors with ischaemic heart disease, and (*b*) the elucidation of relationships among the factors themselves, such as the association between the blood cholesterol level and age, or between blood pressure and obesity. Problems of the first kind are the more difficult, and the basic methodology for such investigations has not yet been established.

Two general methods would be desirable wherever they are practicable. One, which may be termed the *progressive follow-up type of investigation*, consists of selecting a representative sample of the population, classified according to a particular factor, as, for example, physical activity, and observing these persons over a long period of time to determine the frequency of occurrence of the disease in different groups. The other is the *retrospective type of study*, in which a sample of patients with the disease is selected, together with a suitable control group, and an attempt is made to compare the two groups in regard to specific factors, such as the dietary history or the use of alcohol and tobacco. The control in such a study may be

either a representative sample of the general population or one matched with the study group in one or more significant characteristics.

Either of these methods has many complications and suffers from the general defect that it is almost impossible to obtain a truly random sample of the population for investigation, and at the same time the present methods for selecting matched samples are not entirely satisfactory. There are additional complications inherent in the phenomenon under investigation. Data on many of the factors of interest are not generally available before the attack, so there is uncertainty about the pre-disease characteristics. When, for example, a high serum cholesterol level is found in persons with ischaemic heart disease, it is not possible to prove from this fact alone whether the high cholesterol level contributed to the development of the disease or whether the disease itself produced the higher cholesterol values. It is also impossible to insure that the control persons are free of coronary atherosclerosis. This is particularly true of populations in the " Western " countries.

Because of these and other complications, and especially because of the difficulty of observing large population groups for a sufficiently long period of time, it is often necessary to obtain information indirectly, by observing the frequency of various characteristics in a number of populations differing in regard to the frequency of cardiovascular disease. For example, the consumption of fat is determined for a number of population groups within a single country or in a number of different countries, and these findings are correlated with the frequency of heart disease in the same populations. Such evidence by itself can only be suggestive of causal relationships. If the factor studied and the prevalence or incidence of heart disease are found to vary in a similar fashion, it does not necessarily mean that there is a causal relationship between them. The parallels encountered may be due to other entirely unknown factors affecting both. Nevertheless, such studies can be useful, if it is understood that no conclusions of etiological relationships should be attempted unless the factor is found to be related to the disease by evidence from entirely different types of investigations.

It is highly unlikely that any single approach will identify with certainty the causal factors in the occurrence of ischaemic heart disease. Intensive investigations carried out simultaneously in a number of countries differing in the way of life of their populations, and in the frequency with which various forms of heart disease occur, are more likely to lead to success. The Group noted that the achievement of this goal can be greatly accelerated if the studies employ, as nearly as possible, comparable basic methods and definitions. It is therefore apparent that efforts should be made to obtain the co-operation of a number of investigators who are willing to adopt uniform procedures and methods of observation and recording. Although

only a few investigators in a limited number of countries may participate in the beginning, the number can be expected to grow as the advantages and results of a uniform approach become apparent.

Several examples of the type of information which must be collected can be given. Adequate, quantitative descriptions of the amount of atherosclerosis found at post-mortem is needed. This will require agreement on the sites in the coronary arteries to be examined in every necropsy. Standardized methods must also be adopted for observing patients with myocardial infarction and those manifesting typical angina pectoris. When measurements such as height, weight, body fatness, serum cholesterol and cholesterol-bearing lipoprotein levels, age, etc., are taken, they too must be obtained and recorded in a uniform manner. It should be noted that data of this kind can be used effectively only if similar information is available for the general population or for a suitable control group.

In many cases, it will be necessary for the co-operating investigators to agree on uniform methods. However, where available standards have been set up by responsible bodies, these should be adopted. An excellent example is furnished by the detailed directions for taking and recording body measurements in a standardized manner, given in the recent report of the Committee on Nutritional Anthropometry of the Food and Nutrition Board, National Research Council of the USA.[1]

It is obviously of great importance to publish, or at least to have available for distribution, detailed information on the frequency distribution of the various measurements recorded, even if only certain summaries or groupings are used in the study itself. In the case of body measurements, it is especially necessary to develop precise terminology and standards, so that the present confusion in the use of the words " overweight " and " obese " can be removed. Such terms as " optimal weight ", " ideal weight ", " normal weight ", and so on, may well be eliminated.

It is equally important to obtain reliable indices of ischaemic heart disease morbidity and mortality for the populations in which studies are carried out. These data should be made available, classified by sex, by age (employing five-year age groupings in the case of adults), and by detailed cause, within the general category of heart disease.

Unfortunately, the reliability and completeness of certifying and classifying deaths is of a relatively low order in many countries throughout the world. It may be necessary in some areas in which studies are to be conducted to obtain information separately for those deaths certified by a physician, or to use separate tabulations for deaths in hospitals.

Morbidity statistics can usually be obtained only by special inquiry. It is certain that such studies conducted on a comparable basis in widely

[1] *Hum. Biol.*, 1956, **28**, 111

differing population groups would be extremely illuminating. It would be desirable to establish a co-operative hospital reporting scheme in which previously agreed items of information would be forwarded to a central agency. The data might well include information relating to all persons having ischaemic heart disease, as well as to all necropsies performed, regardless of the cause of death. Again, even if only a few hospitals participated at the start, the information would be useful and no doubt the number would grow as the material for comparison becomes available.

As was indicated above, it is extremely difficult, if not impossible, to conduct prospective investigations on a truly representative sample of the population. Moreover, retrospective studies in this field have a number of complications.

It is important, therefore, to organize pilot investigations in a number of countries so as to determine more precisely the limitations inherent in population studies and to learn how best to carry these out.

Annex 2

THE PRESENT STATUS OF PUBLIC-HEALTH FACILITIES AND ORGANIZATION IN THE FIELD OF CARDIOVASCULAR DISEASE

The weekly *Public Health Reports* issued by the United States Public Health Service for many years carried this caption on the first page: " No health department, State or local, can effectively present or control disease without knowledge of when, where, and under what circumstances, cases are occurring."

This knowledge of prevalence and incidence of disease arises from thoughtful analyses of three main streams of information—morbidity, mortality, and census data. The first two sources of information contribute case-counts of ischaemic heart disease; the third provides the essential population base. The certainty of knowledge gained from analyses of the data is directly proportional to the accuracy and completeness of the information in these main streams.

Just as any stream of water starts with individual drops of rain, information on health and disease starts with individual human beings. The channels of flow differ only in location and time, not in basic principle, whether one deals with water or vital data.

The stream of mortality data has well defined channels all over the world. The reporting of death is generally accepted as socially desirable,

and at least rudimentary machinery for collection of such information exists and is available to most health officers. The problem in its simplest form that faces the health officer is one of improvement of data, namely, to have all deaths reported in as specific descriptive language as medical diagnostic skill permits. Emphasis must be placed on descriptive language. Only from such a base is it possible to take account of the changes which occur with time in any single area, or the differences in medical knowledge and its application among various geographic areas.

The World Health Organization, its regional offices, the national health services, and all the various health subdivisions can perform a basic service by a concerted effort to improve accuracy and completeness of death reporting. The ultimate goal is not easy to achieve, but each improvement in quantity and quality of mortality reporting adds to the general ability to use these data in serving the health needs of the living population.

Morbidity data, when viewed internationally, have at best only traces of channels. For a limited number of communicable disease only is there a world-wide acceptance of the usefulness and desirability of reporting. In ischaemic heart disease, the machinery for reporting exists only in countries with advanced public-health programmes or in those with a national programme of medical care. It should be emphasized that mechanisms for morbidity reporting are not necessarily dependent on a national medical-care programme, but that such a programme provides the mechanism as a natural by-product. In countries without comprehensive systems of medical care, the machinery for morbidity reporting can be developed (and should be developed) as a separate entity, by means of sampling processes centrally supervised which utilize the data of industrial health programmes, of insurance companies, of private physicians, of hospitals, and of other groups dealing with the sick and the apparently well.

Census data provide the denominator for the various fractions needed in any purposeful analyses of mortality and morbidity numerators. Here, the major problem is to be assured that the content of this well-defined channel, i.e., the denominator of the fraction, is systematically related to the numerators. An example of the importance of this systematic relationship can be seen in the United States. Apparent differences in ischaemic heart disease among ethnic groups have been reported in numerous clinical studies. Census data are collected in the United States in a way that prevents the obtaining of any count of the total population by ethnic origin when making clinical observations. As a result, there is no simple way to evaluate the importance of such obvious sources of bias as difference in age and sex distribution in the various groups under study.

The three information sources mentioned above are essential components in the improvement of knowledge of ischaemic heart disease. Without them, attempts at application of the results of clinical and laboratory research are at best haphazard and amateurish, and at worst can be downright harmful.

All health officers can currently collect these three types of data to a greater or lesser extent. Inadequacies that appear should provide a potent stimulus for improvement. Trained personnel speed up the rate and extent of accomplishment. If such persons are not available, recruitment and training are a first order of business for the health department.

The importance of public-health activities in cardiovascular disease is self-evident when this entity becomes the first cause of death in a country. Use of limited public funds for heart disease programmes has been questioned in countries where preventable infectious diseases are still rampant. Nevertheless, a start must be made.

A point of beginning for a heart disease programme already exists in the mortality, morbidity, and census statistics of a country. Improvement in these data from the countries where heart disease is relatively uncommon today will provide useful information for comparative purposes in others where it is highly prevalent. At the same time, this extension of knowledge, of when, where, and under what circumstances heart diseases are occurring, prepares the way for a control programme whenever the time comes that preventable infectious diseases are no longer a major problem.

The World Health Organization's role, so effectively exercised in communicable disease control, can be extended to the field of ischaemic heart disease, by surveys of needs and resources in the field of training, by help in establishing training programmes, and by temporary loan of trained personnel. The quality of the personnel will largely determine the scope and breadth of new knowledge acquired and of the application of existing knowledge.

In the meantime, day-to-day problems are being met and attempts are being made by those already engaged in public-health and other community health services to solve them. As new knowledge of the public-health aspects of ischaemic heart disease accumulates, existing programmes can be modified accordingly. Here are some practical suggestions for public-health workers to put into effect in their efforts to contribute to the prevention of onset and of progression of ischaemic heart disease.

Epidemiological studies

With the community as his laboratory, the health officer is in the position to study the development of ischaemic heart disease in relation to the defined characteristics of his population. Differences in rates of

occurrence, by age, sex, race, ethnic origin, occupation, obesity, metabolic diseases, environment (urban or rural), physical activity, dietary and smoking habits, and other such factors, need study and evaluation.

Industries with stable employment are a ready source for observation of the development of ischaemic heart disease within special population groups. The effect of environmental factors previously mentioned can be fully explored when it is possible to keep a sample group of individuals under long-term observation.

Prognosis or survival following an attack of ischaemic heart disease is another aspect that needs study in the community. Relation of prognosis to medical measures on such factors as weight reduction, low fat diet, degree of physical activity, etc., might be studied with the co-operation of physicians in the community. Pooled comparable experiences relating to prognosis should be more meaningful than currently available data from the selected experience of an individual physician or hospital.

Medical care programmes in countries with well-established systems of comprehensive services offer splendid opportunities for both cross-sectional and longitudinal studies. Insurance companies and health insurance systems possess basic data that could provide the raw material for critical studies.

Education and information for patients and the general public

Effectiveness of public-health measures to prevent disability and premature death from ischaemic heart disease will depend upon understanding and acceptance not only by physicians and government officials, but also by the general public. This applies particularly to measures that may be directed towards obesity, physical exertion, smoking, periodic health examinations, rehabilitation, or similar activities. The health officer can determine the type and appropriateness of educational activities, in collaboration with practising physicians, official and voluntary health associations, and interested community agencies.

Prevention

Various preventive measures for the avoidance of ischaemic heart disease have been suggested but, as the Group's report points out, adequate evidence does not yet exist to give scientific support to the premise that application of specific measures will prevent or delay the onset of manifest ischaemic heart disease. These measures include : prevention or reduction of obesity ; reduction of animal fat in the diet ; maintenance of a high vitamin intake ; reduction of heavy cigarette smoking ; maintenance of physical activity at a moderately active level through early and middle adult life.

If such measures are considered, it is important to embody them in a study to determine whether any measurable effect in the incidence of manifest ischaemic heart disease results.

Measures for the prevention of progression or of recurrence of ischaemic heart disease have been applied widely by the medical profession. Detection of changing character of angina pectoris may forebode impending infarction and indicate the need for the restriction of physical activity or the use of anticoagulant therapy. Diets low in total calories and in fat content are frequently prescribed for individuals who have sustained a myocardial infarction. A follow-up study of persons who maintain themselves upon such diets, as compared with control persons not under dietary restrictions, could provide information to guide clinicians in their care of patients with ischaemic heart disease.

Case-finding and screening

Individuals with ischaemic heart disease—manifested, symptomatically, as angina pectoris or, electrocardiographically, as myocardial ischaemia—can be found in most white adult population groups. Medical detection is warranted for as many such individuals as possible. Early detection leads to remedial measures and medical supervision.

Incorporation of heart disease case-finding within the existing framework of health activities is feasible and desirable. Industrial and other employee programmes can be fruitful sources of new cases. Emphasis should be laid on the fact that the findings from examinations of this kind do not jeopardize the employment status of the individual.

Chest X-ray films taken in mass surveys, clinics, out-patient departments, or at hospital admission should be read for cardiac abnormalities by experts in this field. Enlargement of the heart detected by X-ray examination is associated with increased mortality rates and is worthy of investigation. Follow-up studies of this high-risk group and of comparable controls would keep the people concerned under medical supervision and would supply information on the value of early detection and medical supervision.

Diagnostic services

Availability of adequate diagnostic facilities within the community should be a concern of the public-health physicians for the benefit of their colleagues in private practice. Confirmation of a tentative diagnosis of ischaemic heart disease is important in subsequent medical management. Ruling out ischaemic heart disease as a cause of chest discomfort is equally important to the individual with these symptoms.

Public-health nursing

Public-health nursing services have an important role in assisting physicians in the care of individuals suffering from heart disease. Physicians can use these services in order to help patients and their families in preparing menus for low caloric, low fat, low sodium, or other types of diet that may be indicated. Giving medication to home patients with congestive heart failure, or helping to see that the prescribed regimen is being followed, are other nursing functions that can reduce disability. Systematically used, these services provide follow-up information of value in epidemiological studies.

Nutrition services

Nutrition services are growing in importance as physicians increasingly prescribe specific types of diet for patients with ischaemic heart disease. Coupled with ischaemic heart disease, such conditions as obesity, diabetes, and congestive heart failure become complicating factors that require dietary measures. Direct service to patients by nutritionists and dietitians is not always possible since there are too few of these to meet the needs. The nutritionist working through the public-health nurse can often provide what is required. Group instruction has been found useful in teaching dietary regimens.

Special services

Social services offer valuable help with the social and emotional problems that arise for the cardiac patient and his family. The emotional disability created by the heart attack is often as disabling as the impairment of cardiac function. The medical social worker with her knowledge of community functions and facilities can often help the patient and family to achieve adequate readjustment and rehabilitation, following the coronary attack. The special skills of the trained social worker complement the many social services carried out by the public-health nurse.

Laboratory services

Physicians regularly need community laboratory services in diagnosis and management of the cardiac patient. Services should be available for both hospitalized patients and for patients being managed in the home or nursing home, including electrocardiograph, X-ray, and erythrocyte sedimentation testing facilities. Serum cholesterol, lipoprotein fraction, prothrombin, and serum glutamic-oxaloacetic transaminase determinations are tests the usefulness of which is being actively investigated and which

may come to have wide community uses. Critical evaluation of field experience in the usefulness of all these tests is needed.

The nursing home

There are cardiac patients who require more than home care but do not need expensive hospital care. For these patients, nursing home services are useful, when available, in meeting their needs. Maintaining optimum physical and emotional status for such patients requires a co-operative effort that embraces all the medical skills.

Rehabilitation

It appears that a high proportion of patients who have recovered from an attack of ischaemic heart disease are potentially able to return to employment with or without job modifications. Emotional disability has been found to be a factor in retarding rehabilitation.

The co-operative efforts of the health department, voluntary health association, vocational rehabilitation agency, employment service, employers, labour leaders, and other community groups are needed in developing a rehabilitation programme to meet the needs of persons who have heart disease.

The experience of cardiac work-classification units, sheltered workshops and industrial medical programmes can be a useful help and guide for rehabilitation planning in the community.

Evaluation studies

Continuing evaluation of public-health activities relating to heart disease studies and services is basic to progress in this field. In programme activities, what are the attitudes or actions that relate to favourable results? What beliefs, attitudes, customs, values are important as factors in obtaining co-operation or constructive action? What motivation is necessary to follow a weight reduction diet, to participate in case-finding programmes, to return to work following a myocardial infarction? The questions and problems are many—the answers as yet few. There are innumerable possibilities for the health officer to use his talents and resources for the investigation of some aspects of ischaemic heart disease—in clinical, laboratory, or field studies—as he combines service and research in his day-to-day activities for protecting and improving the public's health.