PUBLIC HEALTH PAPERS **34**

PRINCIPLES AND PRACTICE OF SCREENING FOR DISEASE

J. M. G. WILSON & G. JUNGNER

WORLD HEALTH ORGANIZATION
GENEVA

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PREFACE

The object of screening for disease is to discover those among the apparently well who are in fact suffering from disease. They can then be placed under treatment and, if the disease is communicable, steps can be taken to prevent them from being a danger to their neighbours. In theory, therefore, screening is an admirable method of combating disease, since it should help detect it in its early stages and enable it to be treated adequately before it obtains a firm hold on the community.

In practice, there are snags. In developing countries there is as a rule such a vast burden of overt disease that the medical services are overwhelmingly occupied with the treatment of patients coming to them with often advanced stages of communicable disease. With so much curative work to do, they have little time, let alone resources in manpower and money, to spend on looking for disease in its incipient stages, and their preventive work consists largely of attempting to improve environmental conditions.

In the developed countries, the communicable diseases have become less important as killers than chronic diseases, often of insidious onset, such as cancer and the cardiovascular diseases. The developed countries have much greater resources than the developing countries, and can call on more qualified staff. And the diseases that have now come to the fore are of such a nature that, if detected early, they stand a reasonable chance of being cured, whereas if not diagnosed until the patients come to the doctor with clear-cut symptoms they may be incurable. In developed countries, therefore, it would seem that the practice of screening for disease should be widespread. That it is not so to the extent that might be expected is due to a number of factors, among them the cost of screening and the tendency in the medical profession to wait for patients rather than actively to look for disease in the population. Another factor undoubtedly is inadequate knowledge of the principles and practice of screening for disease.

This book attempts to set out the principles and practice of screening for disease in a clear and simple way. It was commissioned by WHO

from its authors because screening for disease is now a subject of growing importance in developed countries, as is evidenced by the controversies over, for example, cytological testing for cancer of the uterine cervix or regular medical check-ups of key executive personnel. The book is concerned mostly with the chronic diseases of adults in developed countries. As communicable disease comes under control in the developing countries, however, the chronic diseases that occupy the limelight in the developed countries may be expected to increase in importance in them; in some of the developing countries this trend has already become apparent. It may therefore confidently be expected that screening for disease will grow in importance with time. Some knowledge of its principles and of what it entails in practice should form part of the intellectual equipment of all concerned with the control of disease and the maintenance of health.

INTRODUCTION

The subject of early disease detection is vast and it would clearly be beyond our capacity to be comprehensive. This account, then, represents only our personal viewpoint of a rapidly developing aspect of medicine and the examples we have chosen are ones that have, for one reason or another, appealed to us personally. There may well be other examples, equally good or better, that we have omitted. (We have not, for instance, included the practice of early disease detection in the maternity or child welfare field, largely because that practice is already so well established.) In other words, we have made a number of preliminary sketches and have not attempted to present a complete picture. We are also aware that the subject is controversial and that much still needs to be learned. If anywhere we have appeared dogmatic, we hope this may serve to stimulate discussion, since, in the end, real development depends on an exchange of views.

The subject is dealt with under three main headings: the basic principles of early disease detection; practical considerations, including the application of screening procedures in a number of different disease conditions; and, finally, present techniques and possible developments in methodology.

For the purposes of this study the definition of "screening" proposed by the United States multi-sponsored Commission on Chronic Illness (CCI)[1] (see Chapter 1, page 11) and accepted by the WHO Regional Committee for Europe,[2] is adopted. Periodic physical examination is also included in the review, and we refer to both screening and periodic physical examination generically as "early disease detection". Epidemiological surveys to establish the prevalence and incidence of conditions, as well as to study longitudinally the natural history of developing disease, are not considered to fall within the terms of reference, which we have confined to case-finding (see Chapter 1, page 11). However, frequent reference is made to surveys that throw light on our attitudes to case-finding.

Screening for the chronic non-communicable diseases prevalent in the more advanced countries forms the main subject of the report; but the problems facing countries at other stages of development and with different standards and types of medical care are also discussed, and because of this communicable disease detection is also dealt with to some extent.

CHAPTER 1

DEFINITIONS

SCREENING

The CCI Conference on Preventive Aspects of Chronic Disease, held in 1951, defined screening as "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment."[1] It should be noted that, by definition, unrecognized symptomatic as well as pre-symptomatic disease is included; also, physical examination is considered part of the procedure, so long as it can be classed as rapid. The term "other procedures" may also embrace the use of questionnaires, which are assuming an increasingly important place in screening. Finally, tests may be "diagnostic", though not necessarily so intended; for example, a gynaecological examination could be covered by this definition provided it were rapidly carried out. In general, we have taken the definition to imply a relatively simple (though not necessarily unsophisticated) method of case-finding.

MASS SCREENING

This is a term used to indicate the large-scale screening of whole population groups. We have used it to refer to screening where no selection of population groups is made.

SELECTIVE SCREENING

We use this term for the screening of selected high-risk groups in the population. It may still be large-scale, and can be considered as one form of population screening.

MULTIPLE (OR MULTIPHASIC) SCREENING

This procedure has evolved by combining single screening tests, and is the logical corollary of mass screening. Where much time and effort has been spent by a population in attending for a single test (e.g., mass radiography) it is natural to consider the economy of offering other tests at the same time. Multiple (or multiphasic) screening has been defined as "the application of two or more screening tests in combination to large groups of people".[1]

SURVEILLANCE

This term is often used as a synonym for screening and essentially, in the sense the term is used, it does have the same meaning. However, a useful and important distinction can perhaps be made between the two terms. Webster's *Third New International Dictionary* (1966) defines "surveillance" as "close and continuous observation", while the definition of "to screen" is "to examine... methodically in order to make a separation into different groups". "Screening" tends to be thought of as (and in practice often is) a cross-sectional, short-term operation on a population at risk (e.g., "health weeks", "health fairs"); while "surveillance" conveys rather the sense of a long-term vigil over the health of an individuals or of a population.

In this report "surveillance" has been used to convey the idea of a long-term process where screening examinations are repeated at intervals of time.

CASE-FINDING

Throughout this report this term is applied to that form of screening of which the main object is to detect disease and bring patients to treatment, in contrast to epidemiological surveys (see below).

POPULATION OR EPIDEMIOLOGICAL SURVEYS

While screening tests may well be used in population surveys (e.g., sphygmomanometry for blood pressure or tonometry for intra-ocular tension), the principal aim of surveys is not to bring patients to treatment but to elucidate the prevalence, incidence and natural history of the variable or variables under study, though case-finding is a natural by-product of surveys. A good example of an epidemiological survey is the Framingham study of ischaemic heart disease.[3]

EARLY DISEASE DETECTION

It is sometimes useful, we think, to use a term that refers to all forms of early detection whether by screening, physical examination or other means; and this is meant when we use the term "early disease detection".

CHAPTER 2

PRINCIPLES

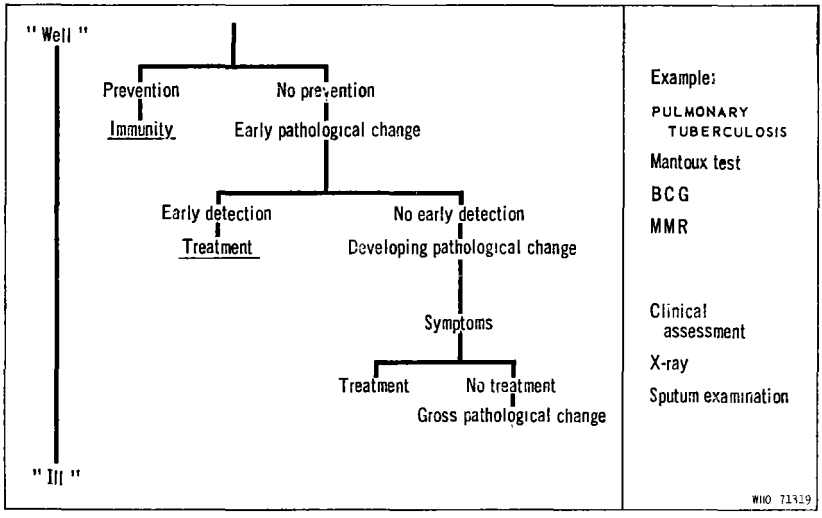
GENERAL CONSIDERATIONS

The aim of early disease detection

The aim of early disease detection (sometimes called secondary prevention) is simple. Primary prevention seeks to abolish disease by protecting the individual and the population from attack before the challenge has been made. Early detection (case-finding) aims at discovering and curing conditions which have already produced pathological change but which have not so far reached a stage at which medical aid is sought spontaneously. These stages are shown diagrammatically in Fig. 1.

For screening, as defined, there is the second, economic, aim of achieving more for unit expenditure by saving the time of highly trained professional people. Part of their work can be performed by less highly trained personnel able to carry out screening tests, whether by

FIG. 1. STAGES IN EARLY DETECTION OF DISEASE



hand or by automated means (see Fig. 3, page 65). However, it seems likely that the total cost of screening in a community is higher, not lower, than the cost of conventional medical care since more people will be found to be in need of treatment (and these will be mainly elderly persons and liable to be under care for a long time). We shall say more about the economic aspects of screening in a later section (see page 35). However, it is worth noting here that in some circumstances screening may be altogether uneconomical. A condition (e.g., helminth infestation) may be almost universally prevalent, and under these conditions mass treatment without screening may be the course to pursue, thus avoiding the high cost of preliminary confirmation of a virtually certain diagnosis.

Pattern of screening development

Sociological factors have been important in the development of screening. These relevant factors are closely related to the degree of sophistication of the population at risk—for example, the level of education and awareness, the amount and form of medical care available and the general standard of living. In highly developed societies an improvement in social conditions has been accompanied by a decline in communicable disease and by an apparent or real increase in degenerative and genetically determined disease. Under these circumstances, also, there is a tendency towards diagnosis at an earlier stage than in the past. In less developed countries, however, the communicable diseases remain largely paramount and the diagnosis of chronic illness is often made at a later stage; while living conditions, nutrition, public education and medical care all need to be greatly improved. For these reasons the early detection of illness presents different problems in highly developed and less developed countries.

The historical development of screening can best be examined by observing the measures taken to control endemic communicable disease —measures which are now to a large extent no longer needed in well-developed areas, but which are still vitally important in many less developed countries. Table 1 sets out the progressive stages of screening, whether in time or in terms of development. A study of the reasons behind these earlier forms of screening is helpful to an understanding of the later developments introduced in highly developed countries for the screening of chronic disease.

In tropical and subtropical areas of the world parasitic diseases such as malaria, schistosomiasis and ancylostomiasis have long been the subject of mass detection. One of the main reasons has been the need to control these major causes of disease by attempting to stamp out the

TABLE 1. PROGRESSIVE STAGES OF SCREENING

Screening era	Examples of conditions sought
Early	Malaria Nematode infestations Leprosy Trachoma
Middle	Pulmonary tuberculosis Venereal diseases
Late	Diabetes Ischaemic heart disease Iron-deficiency anaemia

human reservoir. Similarly, chest radiography was first introduced primarily as a public health measure to help in controlling the spread of pulmonary tuberculosis; prolonging the life and health of the individual was at that time a secondary objective. A further example can be found in the attempt to control the spread of syphilis by mass serological examination of the population.

Only when the prevalence of endemic communicable disease has been reduced to a minimum has early detection been directed chiefly towards the secondary aim of chronic disease detection. Clearly, economic factors play a large part: controlling the spread of disease is vital to economic prosperity and even survival, while prolonging individual life and health is less essential from an economic point of view. These differences are important when considering the principles upon which population screening should be based, for the relative importance of individual considerations varies in the two cases.

In a smaller way the same story can be told of industrial health examinations. In the early days of industry there were endemic industrial diseases, such as mule spinners' cancer, for which primary prevention was developed (in that case by removal of the causative agent). In other conditions—for example, silicosis and lead poisoning—where the cause could not be wholly eradicated, early detection techniques were developed (chest X-ray, blood film and urinary lead content). With advancing sophistication in industry the idea grew not only of monitoring the health of workers in relation to known environmental health risks but also of anticipating non-industrial hazards to the health of individuals by periodic health examination. These two types of examination are comparable to the two stages of growth of general population screening.

While the benefits of the first type of mass detection (to control the spread of communicable disease) have been, at least to some extent, demonstrated (e.g., in tuberculosis), the value of the second to a large extent still needs to be ascertained (e.g., in diabetes mellitus and chronic simple glaucoma). Why this should be, and how answers to outstanding questions might be found, will be examined later.

Much screening practice evolved in the USA during the 1950's in the form of multiple screening programmes has been reviewed elsewhere[4–9] and will only be discussed briefly here. A useful bibliography was issued by the Bureau of Chronic Diseases of the California State Department of Public Health.[10] The motivation for screening has been dealt with at some length in three papers, respectively by Chapman,[11] Mountin[12] and Smillie,[13] published between 1949 and 1952, at the time of maximum growth of this concept in its application to chronic diseases. Some of the chief points made in these papers were:

(1) Case-finding by multiple screening is a technique well suited to public health departments, whose role is changing.

(2) Provision for diagnosis, follow-up and treatment is vitally important; without it case-finding must inevitably fall into disrepute.

(3) Tests must be validated before they are applied to case-finding; harm may result to public health agencies' relationships with the public (not to mention the direct harm to the public), and with the medical profession, from large numbers of fruitless referrals for diagnosis.

(4) There is a danger that multiple screening might lead to the neglect of other aspects of community medical care because of the competing cost and possibly also because a false sense of security might be propagated.

(5) The effect of multiple screening needs to be evaluated in terms of reduced morbidity and mortality.

In 1957 the Commission on Chronic Illness accepted the value of multiple screenings as "contributing to good medical practice" and considered that it "constitutes a practical means for early detection of a number of important chronic diseases and impairments". The CCI considered at that time that screening might profitably be carried out for the following conditions:

pulmonary tuberculosis
visual defects (including chronic glaucoma)
hearing defects
syphilis
diabetes
cancers of skin, mouth, breast, cervix and rectum
hypertensive disease
ischaemic heart disease (possibly).

In 1960 the American Public Health Association strongly endorsed multiple screening in a publication entitled *Chronic Disease and Rehabilitation: a Program Guide for State and Local Health Agencies.*[7] While recognizing that screening should, where possible, take second place to periodic health examination as an effective technique for early disease detection, the authors of the *Program Guide* considered that "the sheer weight of economic reality . . . dictate[s] recourse to procedures that conserve the time and energy of highly trained personnel such as physicians and dentists".

With the formation, in 1961, of the Chronic Diseases Division of the United States Public Health Service came the ability to provide State services with project grants for setting up demonstration screening programmes. A relatively large number of these projects have been carried out, but for various reasons it has been difficult for them to satisfy all the above points.

The use of different forms of screening

Selective screening. Screening tests can, of course, be used in different ways, varying from single examinations applied to individuals to batteries of tests offered to whole populations. They may also, as already indicated, be either indiscriminate or selective.

From the viewpoint of both the individual and the economy there are obvious advantages in combining a number of tests and applying them all at the one examination, providing each has been shown to be medically worth while. However, in practice, there may be drawbacks to combining certain tests—for example, when each test gives reasonable yields only in selected population groups of different age, sex or occupation.

Much screening is selective, of long standing and well established. This type of screening is practised, for example, at antenatal, post-natal and infant welfare clinics, where conditions such as pre-eclamptic toxaemia, the anaemias of pregnancy and congenital conditions are sought by the application of simple tests.

Mass public health screening. More recently, public health agencies have tended to extend their screening activities from these kinds of clinic to the general public. Multiple screening has been offered at *ad hoc* clinics staffed by auxiliary workers, positive results being notified to general practitioners. However, it has been recognized that this approach gives rise to difficulties (some of which are discussed below), and of late it has declined in popularity as a means of early disease detection.

Surveillance. A third method of screening is the individual approach, as opposed to mass screening. At first sight there is little difference between screening the individual and the ordinary good practice of clinical medicine. The physician examining his patient's urine or blood pressure, or even weight, when he has no special reason to suspect illness related to these findings is simply complying with an accepted standard of good diagnostic practice. He may, in fact, include other examinations such as haemoglobin determination or electrocardiography. If he also arranges for these examinations to be carried out by an auxiliary helper, he may then be regarded as submitting his patients to a form of multiple screening, which may or may not be selective, according to whether only those patients consulting him over some complaint are examined, or whether the physician has made arrangements for all his patients to undergo these tests.

The essential difference between this form of screening and ordinary good medical practice is that in the first instance the person examined is presumptively well, or at least not complaining of the disease or diseases for which screening if offered, while in the second he or she comes to the physician as a patient with a complaint. There is really a good deal of difference between these two concepts; the economic implications for a general practitioner in terms of time, auxiliary help and the use of records, as well as premises, are very different if he is aiming to carry out selective screening in his practice, in contrast simply to applying a number of tests to patients reporting with a complaint. However, as a development in medical care, there are clear potential advantages in this form of positive surveillance. The general practitioner would, in this way, be enabled to practise personal preventive medicine; and, secondly, the normally close contacts between the physician and his practice would largely avoid communication difficulties over the results of tests.

Screening hospital patients. A particular form of screening special groups of the population is the screening of hospital patients. There are at least three aspects to this type of screening. Firstly, hospital patients in general, whether in- or out-patients, constitute a specially high-risk group of the population and are likely to give a high yield for conditions such as diabetes mellitus, cancer of the cervix and simple glaucoma. Secondly, patients come to hospital with a complaint of which the diagnosis may be either in doubt or erroneous. It is then usual to request laboratory and other tests in a sequential fashion, one request often depending on the result of the previous one. Submitting the patient to a number of laboratory tests routinely without exercising individual choice is a form of screening that may prove its worth in

leading to diagnoses that would otherwise have been delayed or even missed altogether. This performance of a number of laboratory tests on one blood and/or other body-fluid specimen at the same time is now becoming quite feasible with the introduction of laboratory automation (both in carrying out the tests themselves and in the equally onerous matter of processing the data). It may well prove more economical than the traditional method of *seriatim* laboratory requests. Thirdly, as a consequence of performing a number of tests simultaneously, there may be an economic gain in hospital stay. One of the most costly items of medical service is the upkeep of a patient in a hospital bed. Rationalizing medical care in hospital so as to minimize the length of stay is one of the chief ways in which the cost of health services can be kept from mounting disproportionately to other expenditure. It is possible that the screening of hospital patients could shorten length of stay or lower costs in some other way—for example, by reducing the number of hospital consultations called for. It must be admitted, however, that as yet evidence for a shortening of hospital stay is lacking and that, equally, automation used for screening may prove to prolong hospital stay. Work aimed at elucidating these questions has been carried out in the USA and Canada, and trials are in progress in Great Britain and Sweden.

Screening in industry. Lastly, industrial populations may offer special advantages for screening, especially in industrialized countries where there is no universal general practitioner service. It is important to remember, of course, that industrial screening examinations are of two sorts: one kind is for special industrial risks, of which examples have been mentioned above; the other kind of examination is aimed at the early detection of diseases that may impair the general efficiency of the worker. This subject is discussed in Chapter 3 (page 66).

EVALUATION OF RESULTS OF SCREENING

General

The evaluation of screening may be considered from two separate aspects, which yet have a certain connexion with each other. These aspects are, firstly, the evaluation of tests or examinations and, secondly, the evaluation of results. The important connecting link is the need to use standard criteria for tests, as well as for the variables measured, when comparing the results of case-finding or survey operations. Associated with these standards is the difficult problem of the "in-between" or "border-line" patient, which will be considered in this chapter.

Evaluation of screening procedures

The Conference on Preventive Aspects of Chronic Disease considered the evaluation of case-finding tests and programmes in 1951 and the matter has been dealt with at some length in the CCI publication *Prevention of Chronic Illness*.[14] The following criteria were discussed:

(1) Validity
(2) Reliability
(3) Yield
(4) Cost
(5) Acceptance
(6) Follow-up services.

In this section we deal only with validity, reliability and yield; the other criteria are discussed later, under the heading "Principles of Early Disease Detection" (see page 25).

Validity. The CCI defines the validity of a screening test as the measure of the frequency with which the result of that test is confirmed by an acceptable diagnostic procedure—i.e., the ability of the test to separate those who have the condition sought from those who do not. Applying a screening test to a population will produce four categories of result, provided that the whole population is also examined definitively to establish the actual prevalence of disease. These four categories are shown in Table 2.

An ideal test would, of course, detect only those persons in a population suffering from the condition looked for (as defined by agreed criteria) and would not fail to detect any of them. The ability of a test to classify as positive those persons with the disease is termed "sensitivity" and the ability to class as negative those without the disease "specificity"; that is, sensitivity is a measure of the false-negative rate and specificity of the false-positive rate.

Sensitivity and specificity can be varied reciprocally according to the "setting" of the test. Take, for example, the detection of iron-deficiency anaemia by determination of the haemoglobin content of the blood. Let us say that the aim is to diagnose and treat all women in a population with a haemoglobin level of 10 g/100 ml or less. A screening level of 10 g/100 ml will miss a number of cases owing to the errors of the test, and the sensitivity will be low though the specificity will be high. By raising the screening level to 12 g/100 ml the sensitivity will be raised so that few cases will be missed; but the penalty must be paid of lowering the specificity and having to accept a rise in the number of false positives. The example shown in Table 3 illustrates this point.

TABLE 2. THE EFFICIENCY OF A SCREENING TEST*

Screening result	True disease classification of apparently well population	
	Diseased persons	Persons without disease
Positive	With disease and with positive test (true positives)	Without disease but with positive test (false positives)
Negative	With disease but with negative test (false negatives)	Without disease and with negative test (true negatives)
Total	Total unknown cases of disease	Total persons without disease

$$\text{Sensitivity}^a = \frac{\text{Diseased persons with positive test}}{\text{All persons in population with disease}}$$

$$\text{Specificity}^a = \frac{\text{Non-diseased persons with negative test}}{\text{All persons in population without disease}}$$

[a] These values are often expressed as percentages.
* Adapted, by permission, from Remein & Wilkerson.[15]

Reliability. Providing the test selected is a good index of the disease sought, two factors are involved in the reliability or efficiency of the test: the variation of the method and the variation of the observer. For example, in measuring the arterial blood pressure with an inflatable cuff sphygmomanometer there are the variations connected with the indirect relationship between the method and the true intra-arterial blood pressure and with the variability of the blood pressure itself; and there is also the error of the observer (which has recently been shown to be much more significant than was previously supposed).[16,17]

In considering screening techniques there is scope for research into methods. Ideally (as has been said) a test should be highly sensitive and should miss very few persons with the disease, though a relatively high proportion of false positives can be accepted; it should be as simple as possible and able to be carried out rapidly, often under improvised field conditions (though in some instances there is also a case for a firmly based unit to which the population comes or to which specimens are sent); thirdly, a test must be acceptable and cause minimal disturbance to the subject in its performance. Pain and discomfort, much undressing or the need for a large blood sample may rule out an otherwise useful test.

TABLE 3. EFFECT ON SENSITIVITY AND SPECIFICITY OF VARYING SCREENING LEVEL OF HAEMOGLOBIN IN DETECTING ANAEMIA

Total population	Anaemic patients	Screening level							
100	20	10 g haemoglobin/100 ml blood				12 g haemoglobin/100 ml blood			
		Positive		Negative		Positive		Negative	
		True	False	True	False	True	False	True	False
		15	2	78	5	19	10	70	1
Sensitivity		$\frac{15}{20}\times 100=75\%$				$\frac{19}{20}\times 100=95\%$			
Specificity		$\frac{78}{80}\times 100=98\%$				$\frac{70}{80}\times 100=88\%$			

Lastly, the test should be as cheap as possible. Speed tends to diminish efficiency and *vice versa*, though automated laboratory techniques are now proving more accurate than hand methods. The local need will probably determine which factors are the more important. For example, in detecting diabetes mellitus, urine testing may be chosen for its simplicity, cheapness and minimal disturbance to the population. However, testing for glycosuria is inefficient, and blood-sugar screening on the spot using capillary blood might be chosen instead. This may be preferable to obtaining a venous blood sample, which has the drawback of being costly, since it involves the taking, transporting and chemical analysis of many specimens of blood. Recent commercial research has produced a quick glucose oxidase blood-sugar screening strip, though it has not, as yet, been validated by full field trials. Another example of research into methods is in screening for anaemia. Here simplicity is usually obtained at an unacceptable sacrifice of accuracy. There has been need for comparison of available methods and at least one has now been published.[18] It should soon be possible to make a rational choice related to need.

Yield. The yield from screening may be regarded as the measure of previously unrecognized disease (whether overt or latent), diagnosed

as the result of screening and brought to treatment. Other forms of yield are provided by persons with known disease who have previously lapsed from treatment.

The yield is clearly primarily related to the prevalence of disease in the population and to the availability and use of medical care facilities. The highest yields from screening will be obtained from screening for a highly prevalent condition in a population where medical care facilities are minimal—e.g., for malaria carriers in a poorly developed tropical area. Where medical care is good, though a condition may be relatively common, less new disease will be discovered through screening.

A further important factor in yield is the efficiency of the test itself. Thus urine testing for glycosuria will miss large numbers of diabetics in a population, thereby giving a poor yield.

The "border-line" problem

The need for epidemiological surveys is perhaps best emphasized by referring briefly to one of the important findings resulting from work of this kind.

Measurement in probability samples of a population is tending to show that many physiological variables are continuously distributed round the mean, conforming to a normal, or skewed normal, curve. Whether there is a discrete, diseased part of the population or not cannot always be determined from the data; but in considering the separation between "border-lines" and "diseased" this point may not be of prime importance, as Fig. 2(i) shows: in either case there may be an area of doubt. Nevertheless, such variables as blood pressure, blood cholesterol, blood sugar and intra-ocular tension—to give a few examples —all appear to favour a continuous distribution. The "diseased" part of the population occurs at the extreme end of the distribution curve and this, as can be seen in Fig. 2(ii), means that the "border-line" group in a population may be far greater than the "diseased".

There is, however, theoretically at least, a difference between the outcome of surveys, depending on the distribution of the variable or variables measured. If the distribution is bimodal, as might be expected in the case of some genetically transmitted characteristics, such as, for example, phenylketonuria, the "border-line" group will in fact comprise a mixture of persons with the disease and persons without the disease whose level of the variable falls within the same range (between A and B in Fig. 2(i)). On the other hand, if the distribution is unimodal the "border-line" group will comprise a homogeneous sample of persons, the question being whether the point between "disease" and "normality" should be set at C or D (Fig. 2(ii)). We may note, in passing, that the

FIG. 2. DISTRIBUTION OF A VARIABLE IN A POPULATION

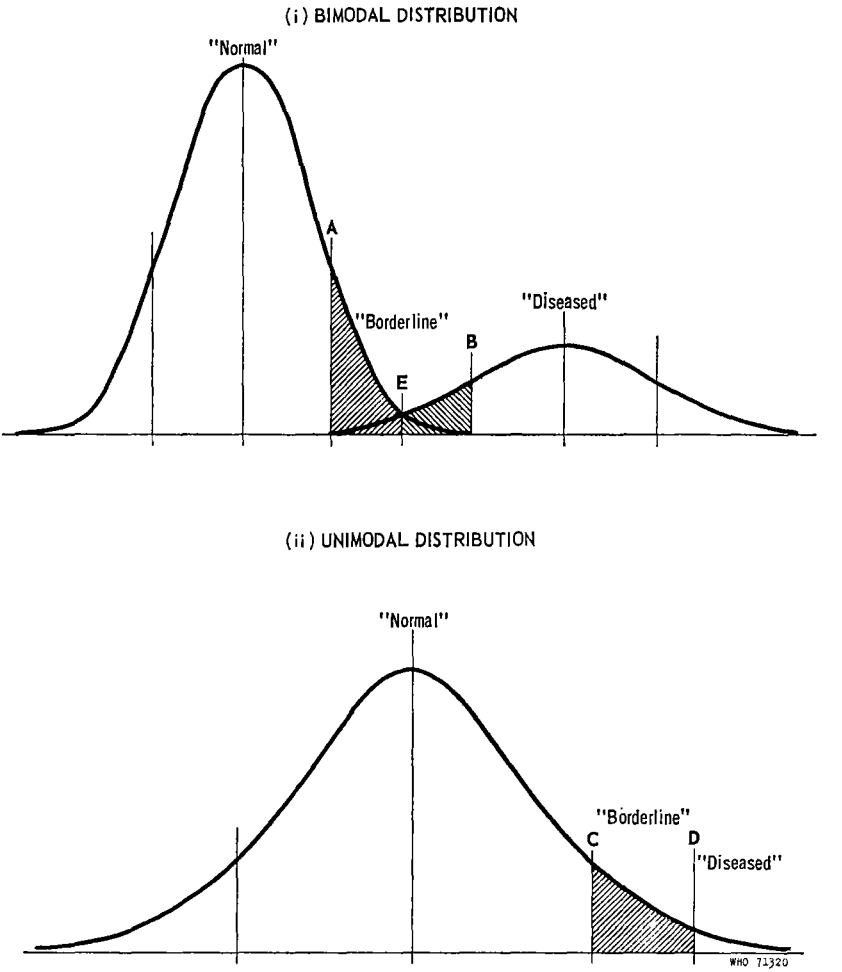


figure illustrates graphically the concepts of sensitivity and specificity. A screening test giving a positive reading at the level of A (Fig. 2(i)) or C (Fig. 2(ii)) would be highly sensitive, missing few cases, but yielding many false positives; by contrast, the "cut-off" points at B and D respectively indicate a very specific test. In practice it seems likely that a trial by randomization of treatment should enable a reasonable decision on the "cut-off" point to be made between those considered in need of treatment and those who may be reassured that they are healthy. Some false negatives would need to be accepted in a bimodal example

for the sake of the specificity of the test (e.g., a "cut-off" at E), while in the unimodal example a similar arbitrary choice would need to be made, based on the response to treatment of the "border-line" patients.

It is perhaps worth noting here that the terms "sensitivity" and "specificity", while having a clear meaning in the case of the bimodal distribution, have theoretically no meaning for a unimodal distribution. Thus, supposing a "cut-off" level at E in Fig. 2(i) (the bimodal distribution) to be used, both true and false positives would occur at that level. But with the unimodal distribution, once a "cut-off" level has been adopted, all persons above that (e.g., above level D in Fig. 2(ii)) would be regarded as diseased, and there would be no false positives. In practice, sensitivity and specificity remain important because an indirect index of disease is usually adopted, subject to variations between observers and within patients from one occasion to another, as well as to the error of method. This index will only have a certain power in diagnosing patients and will miss some and falsely include others.

For a fuller discussion of sensitivity and specificity, as well as the reproducibility and accuracy of a test, the United States Public Health Service Monograph *Principles and Procedures in the Evaluation of Screening for Disease*,[19] may be consulted.

PRINCIPLES OF EARLY DISEASE DETECTION

The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy. For this reason we have devoted this section to a reasonably full discussion of a number of points that might be regarded as guides to planning case-finding. This is especially important when case-finding is carried out by a public health agency, where the pitfalls may be more numerous than when screening is performed by a personal physician. For ease of description rather than from dogma we have called these points collectively "principles". The following is an attempt at elaborating at least some of these principles:

(1) The condition sought should be an important health problem.

(2) There should be an accepted treatment for patients with recognized disease.

(3) Facilities for diagnosis and treatment should be available.

(4) There should be a recognizable latent or early symptomatic stage.

(5) There should be a suitable test or examination.

(6) The test should be acceptable to the population.

(7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.

(8) There should be an agreed policy on whom to treat as patients.

(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

(10) Case-finding should be a continuing process and not a "once and for all" project.

It is now necessary to discuss each of these headings in some detail.

Importance of the problem for the individual and the community

To be considered an important problem, a disease need not necessarily have a high degree of prevalence, though that would be a usual requirement. Thus diabetes mellitus is relatively highly prevalent in the populations of developed countries, though frequently of mild degree, with a lengthy course not known, as yet, to be greatly influenced by treatment. On the other hand, phenylketonuria is extremely uncommon but warrants screening on account of the very serious consequences if not discovered and treated very early in life.

Clearly the importance of the problem needs to be considered from the point of view both of the individual and of the community. Thus conditions with serious consequences to the individual and his or her family in general may warrant relatively uneconomic screening measures; while certain individually mild conditions, but having serious consequences for the community if not discovered early and treated, will justify screening on these grounds. An example of the latter kind might be the finding and control of overweight in a population.

Accepted treatment

Of all the criteria that a screening test should fulfil, the ability to treat the condition adequately, when discovered, is perhaps the most important. In adhering to the principle of avoiding harm to the patient at all costs (the *primum non nocere* of Hippocrates), treatment must be the first aim. For declared disease there is, of course, the ethical obligation to provide an accepted treatment whether or not this is of scientifically proved value; but, when new territory is being explored by the earlier detection of disease, it is clearly vital to determine by experimental surveys whether a better prognosis is given by treating

the conditions found at an earlier stage than was previously the practice. Unless this is so, there can be no advantage to the patient and, in fact, in alerting him or her to a condition that has not been shown to benefit by treatment at an earlier stage actual harm may be done.

This matter resolves itself into two questions:

(1) Does treatment at the pre-symptomatic border-line stage of a disease affect its course and prognosis?

(2) Does treatment of the developed clinical condition at an earlier stage than normal affect its course and prognosis?

Question (1) is referred to more fully below (see page 32), in a discussion of the need for adequate survey work. However, it might be mentioned here that without well-planned surveys, carried out in advance of the main body of medical opinion, the view that early diagnosis and treatment successfully improves the outlook for the condition in question is likely to become generally accepted. This in turn automatically renders unethical planned randomized trials of intervention by treatment, following early diagnosis; with the result that ideas about the effect of treatment pass into the realm of folklore rather than that of scientific knowledge. Thus we are still in ignorance of the effect of treating the lower range of high blood pressure. If the use of drugs for mild hypertension became general it would probably no longer be thought ethical to randomize treatment, and we should have to rely on the unsatisfactory long-term evidence of mortality and the age at which morbid changes appear. Border-line diabetes mellitus, ocular hypertension and asymptomatic bacteriuria are other examples of conditions in this class. Until the needed information has been obtained there is, we submit, no case for alerting border-line persons by case-finding programmes. If persons in the border-line range are to be informed of their results they should presumably be told they are not diseased.

Coming to question (2) we enter the field of accepted clinical practice and the course to be followed is largely pre-determined. For example, it is reasonable to seek in a population persons with signs of clinical diabetes (possibly confined to an unequivocally elevated blood-sugar level) and treat them, even though they may have no symptoms. It is not known whether early treatment in fact alters the outlook, but this is the accepted assumption (although there is evidence that renal and neurological changes may follow a course independent of treatment). The same argument applies to the early treatment of established chronic glaucoma (where the course of the illness is also long and the treatment unpleasant, and where doubt must arise as to the proportion of those prescribed treatment who adhere to it). Medical opinion accepts the value of treatment and there is no ethical alternative.

There are also conditions where evidence shows that the prognosis is unaffected, or practically unaffected, by early recognition and treatment. Lung cancer is one example, mass radiography being the standard method of early detection. In at least one survey it has been demonstrated that the prognosis for life in patients detected at an early, unreported, stage of bronchial carcinoma was little if any better than that of patients detected later who had made their medical contact on account of symptoms (see chapter 4, page 106). The same kind of findings have resulted from early detection by the cytological examination of sputum. While there is a good case for continuing efforts to detect lung cancer early in selected groups, such as heavy smokers, in the knowledge that a few patients will benefit, it is doubtful whether any useful purpose is served by advocating mass case-finding specifically for lung cancer (though, of course, mass radiography carried out for other purposes produces a steady run of cancer cases). At present it seems likely that greater efforts should be directed towards educating the public about the risks of cigarette smoking and the need for investigating persistent cough.

It is axiomatic, therefore, that case-finding should only be undertaken when the prospects for treating the condition are at least reasonable.

Facilities for diagnosis and treatment

Clearly, in planning to detect some condition, or group of conditions, in a population it is a prerequisite that persons found in need of treatment should be able to obtain it. In general, the larger the scheme the more this proviso assumes importance. Thus, in introducing on a national scale cytological screening of all women with a risk of developing uterine cancer, a major part of the scheme must consist in ensuring that services are available for the definitive diagnosis and treatment of those found positive on exfoliative cytological examination. Of even greater magnitude is the problem of providing effective treatment and care in a developing country, where medical services may be extremely thinly distributed, for conditions detected by mass screening. In this context pulmonary tuberculosis may pose a difficult question.

Recognizable latent or early symptomatic stage

In order usefully to detect and treat disease at an early stage there must clearly be a reasonable period in the natural history of the condition during which symptoms are either not present or at any rate not clamant.

There is, in fact, a latent stage in many chronic diseases that can be recognized, and also in the carrier state of some acute communicable diseases. However, certain chronic diseases such as multiple sclerosis

and arteriosclerotic cerebrovascular disease, though there must be a precursor stage, do not have a clinically recognizable latent period. Rheumatoid disease, for example, though there is an early symptomatic stage, has no certainly recognizable presymptomatic state.

Suitable test or examination

A number of factors have to be considered. Tests may be divided into diagnostic and screening, but this is a matter of degree rather than of kind; the screening test (which of its nature should be easy and quick to perform) is allowed to possess a higher margin of error and may be less valid than a diagnostic test.

For some conditions that do have a recognizable latent stage there is at present no suitable screening test. For example, barium-meal examination for carcinoma of the stomach has been tried but found impracticable, on the grounds of radiation exposure, discomfort to the subject, and time needed. (Recently, in Japan, intra-gastric photography has been developed as a screening technique and this may prove satisfactory if used selectively in areas where there is a high incidence of gastric disease.)

Similarly, Addisonian anaemia could probably be detected at a preclinical stage if an easy test for parietal-cell antibody were available.

On the other hand, some tests are accepted as suitable for screening because of their simplicity and ready application, though they may not, in fact, be very good indices of the condition being looked for—for example, tonometry in the detection of chronic simple glaucoma. It is important to remember that most of the tests we use are indirect indices of the pathological process we are seeking. In general, it is reasonable to suppose that the less direct the index the greater is the liability of error in diagnosis. For example, examination of the haemoglobin—the actual pigment that is decreased in anaemia—is a highly precise measure of anaemia (regardless of type), provided the error of the technique of measurement is small. On the other hand, the chest X-ray film in chest disease, the glucose level of the blood in diabetes and the intra-ocular tension in glaucoma are all indirect indices of the conditions sought and, in these instances, there is likely to be an error not only of observation but also of interpretation. Thus the shadow, the blood-level or the pressure may not always provide a valid guide to the clinical condition.

It is the task of the investigator always to seek more direct and more valid techniques, without sacrificing convenience and speed. It would be difficult to replace chest X-rays in the diagnosis of lung cancer,

though ultimately development of a reliable automated cytological technique applied to high-risk groups of the population may prove a valuable adjunct; while there is a possibility that fatty acid or other variable biological levels in the blood might prove a more reliable index of the clinical state of diabetes than is the blood sugar. Regarding chronic glaucoma, there is now evidence that intra-ocular tension may not be a reliable index; in a recent survey as many patients with glaucoma were found within the normal range of tension as were found with raised tension.[20-22]

Finally, there is the question of the validity of the test, indicated by the proportion of those examined found to give false-positive results, and the proportion found to give false-negative results—i.e., having the condition looked for but giving a negative response to the test. In case-finding work a fairly high false-positive rate is acceptable but the false-negative rate should be very low, since missed cases may lead to individual disasters and, in the case of a communicable disease such as tuberculosis, to the undetected spread of the disease.

Acceptability to the population

Clearly a test or series of tests must be acceptable to the population to which it is offered. Acceptability is, of course, related to the nature of the risk and to the way in which the ground is prepared previously by health education. For example, the risk attending uterine cancer is by now well known to the more educated sections of Western society, but we are still pretty much in the dark about the attitude of women in the lower socio-economic groups towards prophylactic vaginal and cytological examination.

Work is being undertaken (see chapter 3, page 72) on this particular aspect of vaginal cytology, both in Great Britain and in the USA, but there is scope for much more investigation of this kind. As an example of suiting the test to existing public attitudes, Davis[23] reports a higher degree of acceptance (nearly 80%) in a Maryland county for the self-taking of exfoliative cytological preparations using the irrigation-pipette[24] than for conventional cervical smear-taking methods. This illustrates the importance of paying special attention to making a test as easy and as little trouble to perform as possible.

There are other forms of examination which, the evidence shows, could usefully be carried out in the search for early disease and its prevention, but which are so unpleasant as to be quite unacceptable for general population screening, though they have a place in screening selected populations. One of these examinations is proctosigmoi-

doscopy, the usefulness of which in detecting pre-cancerous conditions of the rectosigmoid is accepted. The application of this examination is virtually limited to medical clinics and periodic health examination centres.

Need for surveys

We have already emphasized, in the Introduction and in Chapter 1, the important difference in concept between case-finding and epidemiological surveys. The need for maintaining this distinction is not always clear, since the distinction itself tends to become blurred unless we look at the matter historically. We are apt to assume that, because it is possible to carry out useful case-finding by screening for one condition (subclinical pulmonary tuberculosis, for example) without the need for preliminary surveys, the same principle applies to other diseases, such as diabetes or chronic glaucoma. In making this assumption we forget that much survey work has been carried out on pulmonary tuberculosis in the past (and is still being carried out) and that the natural history of the early stages of the disease has gradually become established over the course of many years of study. However, when we turn our attention to attempting to control the new epidemics of chronic non-communicable disease by similar case-finding techniques, we are likely to run into difficulties unless we are first able to view clearly the natural history, and especially the precursor stages, of these diseases. The most important questions that need answering for conditions such as high blood-pressure, ischaemic heart disease, diabetes mellitus and chronic simple glaucoma are:

(1) What changes should be regarded as pathological and what should be considered physiological variations?

(2) Are early pathological changes progressive?

(3) Is there an effective treatment that can be shown either to halt or to reverse the early pathological changes?

It has already been noted (see page 28) that we do not know the answer to the last question, even for some established clinical conditions of which diabetes mellitus (in the progress of its clinical complications) and chronic simple glaucoma are examples. An important reason for this ignorance is that controlled trials of treatment were not carried out at a time when such a procedure might have been considered ethical (this applies specially to glaucoma), the controlled trial technique not having been developed at the appropriate time. The lesson for pre-symptomatic disease detection is surely clear: randomized controlled trials of early treatment need to be carried out as speedily as possible,

while they are still considered ethical. Once it is regarded as normal practice to treat latent disease, whether this has been shown to be beneficial or not, the opportunity for carrying out randomized trials will have passed. Since much treatment is both unpleasant and, in chronic illness, of lifelong duration following diagnosis, it is clearly important not to treat people unnecessarily. In enthusiastically attacking disease at an early stage the Hippocratic principle, previously mentioned, of *primum non nocere* should not be neglected.

Where it has been decided that a survey of the natural history of a condition and controlled trial of treatment is needed, there is a strong argument against trying to combine the survey with case-finding (as defined in Chapter 1, page 12). For the sake of the clarity of the results it is usually considered proper that during the course of a survey it should clearly be understood by all taking part—public and investigators alike—that the work is experimental and devoted to finding the answers to certain questions as a preliminary to embarking on the next stage, that of case-finding. Naturally, all persons discovered in the course of a survey to be suffering from clinical disease would be referred for treatment. The border-line group alone would be asked to submit to a randomized trial of treatment.

It may be asked why surveys and case-finding should not proceed together at one and the same time. Of course, to the extent that surveys discover patients with undiagnosed clinical disease (as we have just noted) they do proceed together. But in general the aims are different, and mixing them may lead to confusion. Where case-finding, with its implication of treatment, is planned it is necessary to be quite clear who is to be advised to undergo treatment and who not. This means that a decision has to be taken about the criteria that constitute disease. Making this decision begs two vital questions that the survey side of the programme would be trying to answer—namely, the question about pathological significance or physiological variation, and the question of whether these early pathological changes are progressive. One way out of this difficulty, in case-finding, is to set high criteria for the diagnosis of disease in need of treatment. The classification of border-line patients by diagnostic techniques, and the arrangement of a controlled randomized clinical trial (which would constitute the survey side of the mixed programme), entail much clinical and administrative work, as well as long-term scientific follow-up. University departments and other scientific institutions are well placed to carry out clinical trials of this nature, and have two major advantages over the personal practitioner or public health physician: they have the necessary multidisciplinary approach within the organization (or at least within easy reach), and they are detached enough from the day-to-day clinical scene to

remain objective. By contrast, it can be argued that it is hard for general practitioners to organize randomized trials among their own patients, and on their own unaided responsibility.

The recent findings of a diabetes survey by Butterfield et al.[25] emphasize the need for randomized trials of treatment on probability samples of the population at risk, before advocating case-finding on other than the strictest criteria of clinical diagnosis. A blood-sugar survey of all persons over 21 years of age found that some 16% have "diabetes" if the commonly accepted criterion of a blood-sugar level of more than 120 mg/100 ml two hours after the taking of 50 g of glucose by mouth is used. If these figures are extrapolated to the age/sex structure of the population of England and Wales as a whole, there would be found (on the above criteria) a prevalence of "diabetes" of approximately 13%. The survey by Butterfield and his colleagues took the form of case-finding (in the first place, by urine testing for glycosuria) and did not comprise a random probability sample of the general adult population (there was a 67% response). The figures may therefore be to some extent biased. However, it seems unlikely that they are far wrong, since they are supported by data from the National Health Survey carried out by the National Center for Health Statistics of the United States Department of Health, Education, and Welfare.[26] According to these findings, 15.5% of persons aged 18 to 79 had a blood-sugar level of 160 mg/100 ml, or over, one hour after taking 50 g of oral glucose (see Chapter 4, page 85). Whether some 13%-15% of the entire adult population of a country of this type is in need of treatment for diabetes, and, if so, which kind of treatment is required, urgently need discovering. Since the treatment of border-line diabetics (see page 83) is not at present known to affect prognosis it seems reasonable in case-finding to advise treatment only for declared, or established, diabetics until the outcome of surveys, at present in progress, is known. (The question of what should be regarded as declared, or established, diabetes is discussed on page 85.)

Groups to be treated in case-finding programmes

The border-line problem has already been discussed (see page 24). It is important, in designing a case-finding programme, as opposed to a scientific survey, to have a clearly defined policy about border-line subjects. If it is agreed that only patients with established disease (wherever the demarcation line of the test used may be drawn) shall be treated, the management of the border-line patient largely depends on the design of the case-finding programmes and on communications. When a personal physician examines a patient, whether in the form of a routine medical examination or by using one or more screening tests,

there is no real problem; the results are recorded on a case-sheet and the patient need only be informed if there is definitive disease needing treatment. The physician in fact makes his own personal decision between what amounts to disease and what merits expectant observation, in the light of his personal knowledge of the person in question, the family, and the environment. With a community health scheme, however, great care needs to be taken in passing on information without harm resulting to some of the persons examined. In any given scheme there may or may not be personal physicians taking part, according to the local system of medical care. In either case, as long as a clear policy has been agreed, no confusion should result. But if persons with doubtful results are referred to their own personal physicians who have not taken part in deciding on the protocol of the case-finding programme, confusion may result; either those considered to be in need of treatment may not be treated, or else those with equivocal changes may be placed under long-term treatment, or both.

Arrangements are clearly desirable for the follow-up of the border-line cases; this might preferably be done by the personal physician as part of a routine examination, so as to avoid segregating this group into a special population, which is, however, by definition, not considered in need of treatment. Clinics do exist, of course, for the management of persons not suffering from frank disease but for whom it is believed that preventive treatment is indicated. For example, there are clinics for persons with a high risk of ischaemic heart disease.[27-29] But in these instances there is at least a measure of agreement that expectant treatment is effective. Apart from this type of clinic, it seems likely that clinics for following up border-line cases should be confined to surveys.

Economic balance of the cost of case-finding in relation to total expenditure on medical care

It is often considered that the detection of disease by screening will be economical of a country's resources. In order to examine this question it is perhaps worth looking at some of the reasons why screening (specifically, as opposed to other methods of early disease detection) is considered in principle worth while. There appear to be two main aims, the one medical, the other economic. The CCI, for example, states that: "multiple screening, by combining several disease-detection tests, is a streamlined process assuring speed, efficiency and economy. Multiple screening contributes to good medical practice".[30] The medical aim, therefore, is to improve the health of a population by the early detection and treatment of illness; while the immediate economic aim is

to spare the time of highly trained people by using technicians, and perhaps automated methods, as a first line in disease detection. Mass radiography, for example, not only saves the time of the personal physician by making good use of his high index of suspicion and eliminating preliminary history-taking examination; it also may help to attain the goal of better health by finding (among other conditions) latent pulmonary tuberculosis. The long-term economic aim is, by preventing or treating early disease, to lengthen the productive life of the population at risk, and in this way to improve the over-all economy. Thus malaria control may, for instance, lead to a quite dramatic change in a country's economic situation and, conversely, failure to control endemic disease may bring about economic deteriotation.

However, this goal may prove expensive, as even highly developed countries find, and there comes a point of diminishing returns. In the case of mass radiology, for example, once the backlog of undetected tuberculosis has been dealt with, the economics of advocating mass routine screening is open to question. On the other hand, the very economy of a developing country may be threatened by uncontrolled communicable or parasitic disease, and it may be necessary to carry out a mass programme with priority over medical care needs.

It would be helpful to compare the economics of medical care provided through screening with the results obtained for similar expenditure on conventional medical care. The probability is (at any rate during the early period when prevalent disease is being discovered) that, though screening might save physicians' time, the total load of medical diagnostic and therapeutic work would be increased by screening, not lessened.

As an example, the rates of new cases discovered for certain conditions (using the given criteria) in the CCI screening survey in Baltimore[31] are shown in Table 4. In all, 32% of those screened were classified as having one or more "major" abnormalities, not necessarily leading to a new diagnosis ("major" meaning conditions unconnected with height, weight, hearing or vision). Another example is the screening programme carried out on longshoremen (dockers) in the San Francisco Bay area in 1951,[32] where screening led to over 19% new diagnoses. When repeated in 1961 there were still 14% new diagnoses. As in the Baltimore survey, the commonest conditions found were high blood pressure (5%), raised blood sugar (4%), and abnormal electrocardiogram (3%).

Fully to diagnose and treat all these patients must add considerably to the total screening cost. Only a prospective survey to determine whether morbidity has been reduced and working life improved, in comparison with a non-screened population, could indicate the saving

TABLE 4. DISCOVERY RATE FOR CERTAIN CONDITIONS IN BALTIMORE SCREENING SURVEY

Condition	No. per 1 000 adults
Cardiovascular disease	20
Abnormal electroencephalogram	41
High blood-pressure	37
Raised blood sugar	27

Adapted, by permission, from Commission on Chronic Illness.[31]

in cost, or otherwise, to the community. One of the many difficulties in carrying out a trial of the kind is, of course, the need to compare like with like; this means that the sample under study needs to be randomized into screened and control groups. In practice this is extremely difficult to carry out in one population, since those allocated to the control group are likely to be influenced by the screened group (there is good evidence that screening is popular with the general public) and to demand screening tests too. Another real difficulty is that the necessarily long-term nature of trials of this kind leads to significant losses over time in both study and control groups.

One brief comparison is perhaps of interest. The Cortland County (New York) screening project[33] in 1960 offered nine different tests: self-administered questionary, haematocrit, height and weight, blood sugar, chest X-ray, urinary albumin and sugar, blood pressure, oral cytology and a 12-lead ECG. It cost $14.55 per head; while the average general practitioner in the United Kingdom was paid (in 1962-63) about $3.0 per patient seen in the course of one year to cover all medical services (amounting to about $0.80 per consultation). Thus, superficially, screening can be a costly rather than an inexpensive method of providing medical care. However, with the arrival of automation both for carrying out tests and for data processing, the cost may soon be greatly reduced.

The need for case-finding to be a continuing process

Much screening in the past has taken the form of single-occasion "drives", "weeks", or "fairs". Impetus has been given to arranging for a number of persons to be examined once, but the momentum necessary for making full use of the organization thus created, by carrying out continuing examinations, has not been generated. The single-occasion examination is clearly only of limited value, since (*a*) only a small proportion (often those at least risk) is likely to be

examined, and (*b*) the screening picks up those persons in the population who happen at that particular time to have the conditions sought; it cannot touch the future incidence of disease at all. Thus continuing examinations have great advantages. An organization can be built up which can gradually become more efficient and economical, and which can take its place as an accepted part of the normal medical services. Regular offers of examination are likely (with the help of health education) gradually to cover more and more of the population at risk, including, by re-examination, those persons presenting with new disease.

Concept of "surveillance". As we have already noted, many of the difficulties stemming from screening examinations are connected with problems of continuity and of communication between those initiating examinations and the physicians who have personal responsibility for patients. Much of this difficulty may be avoided if arrangements can be made for screening to be carried out under the auspices of the personal physician himself. This type of care would amount to the routine examination of patients in particular high-risk groups for certain conditions, at regular intervals, as contrasted with the usual arrangement at present, whereby the patient reports a departure from normal health to his own physician. The routine examination may take the form of a number of preliminary tests, including the completion of a questionary, followed by an interview and examination by the physician in the event of any abnormality being suggested by the tests, or by reassurance that nothing abnormal has been detected. It is important to make it clear that a screening examination is not equivalent to "a clean bill of health", and to emphasize that symptoms still need to be reported to the physician as soon as they occur.

This kind of regular, repeated surveillance suggests at first sight the hopeless involvement of the general practitioner in unproductive routine examinations at the expense of his important clinical function. Indeed, were this the only possibility, surveillance of this sort would be quite impracticable. However, in many countries health centres or group practices of one kind or another exist or are being developed, and it is in this environment that routine surveillance has the most favourable prospect of developing. Auxiliary workers, both laboratory and secretarial, can carry out and record screening examinations, having first selected from patients' records those persons due for examination. To do this, a well-organized system of records is clearly of the first importance and, for large numbers, automatic data handling and processing are mandatory in order to sort persons for examination by age, sex, marital status, parity, etc. On the laboratory side, advances in automating tests and in handling and processing large quantities of data are

already having a noticeable effect in changing traditional practice. Looking back to the past, it is interesting to note that where specialized data handling was not necessary in order to examine high-risk groups of the population (as, for example, in maternity and child welfare work and school health services, where the high-risk groups are self-selected), screening for abnormalities developed at a very much earlier date.

This kind of surveillance has the great advantage, where a family doctor service exists, that continuity of examination and care can be maintained (the personal medical record following the patient who moves from physician to physician). Moreover, only the personal medical adviser need be concerned in the interpretation of tests (though he can seek the assistance of specialists if he wishes), so that, in the event of doubtful findings, he can record these for future reference but is not put in the position of having to divulge them to the patient.

It seems likely that the future development of screening may well be along these lines (so long as a personal physician service is available) with public health services playing an important part through the provision of premises, auxiliary services and data-processing facilities. Laboratory services are, of course, an absolute necessity. These may be provided at a relatively simple level, on the practice premises, or the services of a hospital laboratory (with or without automated facilities may be employed, arrangements being made for sending specimens and reports to and from the laboratory.

CHAPTER 3

PRACTICE

AUTOMATIC DATA HANDLING

Health investigations result in the amassing of a considerable amount of data. The main problem is to handle all detailed information in a way that offers possibilities both for surveying the results and for picking out details from each individual screening. The difficulties are much the same as in sick care, although the need for this type of handling is comparatively greater in screening. In the past the results were, for practical reasons, often not treated very extensively; data based on vast experience have been buried in hospital medical records and have not been easily available for such purposes as research. The use of computers has changed the situation rapidly. It is now generally agreed there should be no large screening projects without automatic data processing. Important trends may be uncovered through statistical analysis, and new knowledge accumulated for medical science and medical practice alike.

The particular needs of screening

Screening is demanding in some respects. The data-handling equipment has to be chosen for the special needs that arise from the special circumstances: for example, when work is carried out in the field under primitive conditions, or when several facts have to be collected on different occasions, to be collated at a later stage or when circumstances occur that are seldom encountered in usual data processing.

Of the particular demands, it should be noted that the recording of primary screening results must be extremely simple. The method used should be easy to work with, because the heavy load makes it necessary to reduce the manual work as much as possible. The manipulation must be easy to learn at different educational levels, so that those given *ad hoc* training can produce reliable results and save the time of highly trained personnel. The data-collection method should aim at recording the results of screening in such a way that they can be machine-read

as early as possible. It should nevertheless allow for visual reading and checking at every step of the procedure.

A very large capacity is often necessary, demanding high speed and a large-size computer memory. It is sometimes useful to make arrangements for the selective sorting out of records with results suggesting the need for further investigation.

Basic concepts

Adapting computer techniques to screening is mainly a problem of selecting the proper methods for the practical work. The basic components are *collecting*, *manipulation*, and *storing* of data.

For screening purposes, the *collection of data* is the most important part of data management. The choice of methods and means must depend on the particular circumstances of the screening programme. For instance, the need for temporary storage of primary results until further data are available for completion of the information may determine the choice of method.

The *processing of data* can be done in a conventional way. Although conversion between different media may be determined by the special needs of the screening procedures chosen for the particular project, actual manipulation of screening data—the data processing—is done by customary computer technique.

The *storage of data* is also concerned with much the same problems as administrative data handling, and is mostly associated with the difficulties of storing large amounts of data and still ensuring that the details are retrievable within a sufficiently short space of time. Technical evolution is proceeding rapidly in this field. The necessary volume for a given amount of data is decreasing, as is the cost.

Data collection

The problems inherent in data handling for screening are concerned with the collection of data and with obtaining the information in a form suitable for machine processing.

In general, the conventional means of recording information can be used—e.g., punch cards, paper tape or magnetic tape. The choice is, however, dependent on the particular properties of the media. An elementary idea of these properties will illustrate the point.

The punch card is easy to handle and can be punched, checked and sorted by simple machines. For screening, highly effective combinations can be used by combining the uncoded text with the punched holes.

A definite advantage is that punch cards allow new information to be added whenever needed—for instance, during different steps in a multiphasic health examination. In order to get enough information on every card (which ordinarily means 80 alpha-numerical signs) a reduction of data is often adopted, for instance, by coding classes of values instead of the individual digital values. Sometimes the vulnerability to damage by handling may be a serious drawback to the use of punch cards for screening; under primitive conditions it may be difficult to avoid such damage.

There are many ways of changing punch cards to adapt them for special needs that are of interest for screening purposes. For instance, a combination card—the *dual card*—offers the possibility of connecting visual information, etc., to the coded punch card.

Punching is somewhat tedious work and needs well-trained personnel; it also introduces errors. Duplicate punching is often necessary, because errors in digital information may be misleading and dangerous. The checking of duplicates can be done automatically by machine (a "verifier").

Another technique of special interest in primary data collection for screening is the use of *mark-sensing cards.* Instead of punching holes, marks are made on special areas by ordinary lead pencils, or by special ferrite pencils. The marks can then be read by machine. The mark-sensing cards have less capacity, since the marks need more space. They are easy to handle, but it is easy to make faulty notations. For certain purposes, the IBM "Port-A-Punch" is useful. The cards are partly perforated, and a clear hole can easily be made with a pencil. The error inherent in mark sensing must always be borne in mind. However, the technique has been adapted for laboratory work, etc., with highly satisfactory results.

Paper tape as a medium is increasing in popularity. However, a special punch is needed, which is inconvenient. One of the main drawbacks is that, of their nature, paper tapes store sequentially arranged information. Therefore, addition of data (or sorting, etc.) cannot usually be done without retyping.

There are also paper tapes with extra space for adding, for example, the uncoded text and identification. Paper tape is somewhat unwieldy to handle in quantity. It is nevertheless a cheap and convenient way of storing information, especially for later data processing.

Special edge-punched cards provide a simple form of data recording, and are convenient on a small scale in circumstances where, for instance, identification, standardized information or procedures are needed comparatively often. The data can easily be extracted with a minimum of errors.

Electric typewriters combined with punch and reader for paper tape (Flexowriter, Teletypewriter, etc.) constitute self-contained equipment. Such equipment can serve as a "terminal", and is handy and not too costly. Simultaneously, it gives the uncoded text for visual checking of the information stored on the paper tape. When needed, the information can then be sent to a distant computer centre by using a modulating unit and ordinary telephone connexions.

Magnetic tape and other magnetic media, such as discs, will presumably dominate the future scene. The advantages are striking, with high capacity and readily available information. On a large scale, they are economical. For health screening, however, the use of these media is of interest only for the processing and storage of information in a data centre where factors other than screening needs will be decisive. Today, recording on magnetic tape is still somewhat complicated, and requires special equipment. For a considerable time hence, it will be easier to use other media, such as cards and paper tape.

Data processing

There is a discernible trend to use large and fast computers centrally located, instead of smaller ones working at a lower speed. By means of a time-sharing technique, a large computer can perform many different operations concurrently, and is more economical. It is true that small desk-size computers are now available, which are comparatively inexpensive and not too slow. However, they are used mostly for data collection on line and as terminals, or for data reduction. They will presumably not replace large computers to any appreciable extent, especially since the development of data-transmission technique has been very rapid.

Data storage

Generally speaking, extremely large memory capacity can be achieved today only by magnetic tape. This is a comparatively cheap method and not too space-demanding, but it has the disadvantage of a long access time. The production of large disc memories with a very high capacity and a very short access time is a promising development.

In the future, it can be expected that computer centres will be able to store enormous amounts of data, and also to distribute them automatically to desired terminals. For a considerable period, however, it may be necessary to work both with easily accessible data that are carefully selected and with cheap means (such as magnetic tape) with a comparatively long access time.

PRESENT SCREENING PRACTICE (INCLUDING MULTIPLE SCREENING)

Introduction

As we have seen earlier, screening developed in the control of endemic communicable diseases; indeed, preventing the spread of conditions such as malaria and syphilis still depends in part on screening measures. The development of interest in screening for chronic non-communicable diseases since the Second World War has resulted, in the USA particularly, in a large number of "programmes" in which varying combinations of screening tests have been employed.

In Table 5 we have listed the principal conditions for which screening has been carried out, subdivided into communicable (infectious and parasitic) and non-communicable, and categorized by selective screening by age and type of country (degree of development).

Comparison of studies

It would greatly lengthen this report without, in our opinion, being correspondingly profitable, to attempt a detailed review of all this work. The tropical and subtropical diseases are a specialized field and might well be treated as the subject of a separate study. Case-finding for the chronic non-communicable diseases has been reviewed in the past (see below) and the difficulties have thereby become apparent. These are in the main twofold: firstly, the difficulty of evaluating the results of these programmes because of the inability, in general, to follow up the result of screening and determine the effect of early treatment on those diagnosed; and, secondly, because the methods employed in different programmes are rarely comparable. A study of multiple screening was made some years ago by the American Medical Association[4] which illustrates these points clearly. Table 6 adapted from a paper by Breslow,[6] gives an example of the type of results obtained.[a] It must be noted that the criteria used for diagnosing "new cases discovered" may have varied, the inclusion of more or less border-line cases depending finally, perhaps, on the judgment of the physician.

Examples of multiple screening projects

Of the many multiple screening programmes carried out in the USA three have been particularly highly organized on a research basis: two under the auspices of the Commission on Chronic Illness (an urban one

[a] The issue of the *Journal of Chronic Diseases* in which Breslow's paper appears also contains other articles on screening for asymptomatic disease, including heart disease, cancer, diabetes, anaemia and glaucoma.

TABLE 5. CONDITIONS SCREENED BY AGE AND TYPE OF COUNTRY (DEGREE OF DEVELOPMENT)

Condition	Selection by age					Degree of development of country		
	Infancy	Child-hood	Adult	Middle age	Elderly	High-est	Middle	Least
Hearing	×	×		×	×	×		
Vision	×	×		×	×	×		
Phenylketonuria	×					×		
Congenital dislocation of hip	×					×		
Rheumatic heart disease		×	×	×		×		
Congenital heart disease	×	×				×		
Hernia	×		×	×	×	×		
Overweight		×	×	×		×		
Diabetes mellitus			×	×	×	×		
Anaemia	×		×	×	×	×	×	×
Chronic glaucoma				×	×	×		
High blood pressure			×	×		×		
Renal tract disease		×	×	×		×		
Ischaemic heart disease				×	×	×		
Rheumatic diseases			×	×	×	×		
Cancer of lung			×	×	×	×		
Cancer of skin				×	×	×	×	
Cancer of bladder			×	×	×	×		
Cancer of rectum				×	×	×		
Cancer of mouth				×	×	×	×	
Cancer of cervix			×	×		×		
Cancer of breast			×	×		×		
Mental illness			×	×	×	×		
Malnutrition	×	×					×	×
Pulmonary tuberculosis		×	×	×	×	×	×	
Venereal disease:								
Syphilis			×	×		×	×	×
Gonorrhoea	×		×			×	×	×
Urinary tract infection		×	×	×		×		
Non-specific lung disease			×	×	×	×		
Infective hepatitis		×	×	×		×	×	
Histoplasmosis		×	×	×		×	×	
Coccidiomycosis			×	×				
Trachoma			×	×				
Yaws		×	×	×	×			×
Carrier conditions:								
Streptococcal infections		×	×			×		
Dysentery		×	×	×	×	×		
Typhoid			×	×		×		
Diphtheria	×	×				×		
Poliomyelitis	×	×	×					
Malaria	×	×	×	×	×		×	×
Filariasis	×	×	×	×	×		×	×
Schistosomiasis		×	×	×	×		×	×
Trypanosomiasis		×	×	×			×	×
Ancylostomiasis		×	×	×			×	×
Kala-azar		×	×				×	×
Hydatid disease		×	×	×			×	
Trichinosis	×	×	×	×	×	×	×	
Tinea capitis		×	×				×	

TABLE 6. EXAMPLES OF MULTIPHASIC SCREENING RESULTS IN CALIFORNIA, 1948-54

Nature of test	Number of persons tested	Positive screening test		Diagnosis confirmed		New cases discovered	
		No.	Rate per 1 000	No.	Rate per 1 000	No.	Rate per 1 000
Serological test for syphilis	3 974	412	104	159	40	23	6
	21 733	1 949	90	425	20	188	9
Chest X-ray	1 755 001						
(i) For tuberculosis		(i) 55 210	32	18 939	11	[a]	[a]
(ii) For heart disease		(ii) 10 899	6	3 388	2	697	0.4
(iii) For lung cancer		(iii) 3 500	2	339	0.2	339	0.2
	3 990						
		(i) [a]	[a]	29	7	13	3
		(ii) 21	5	9	2	3	0.8
		(iii) [a]	[a]	1	0.3	1	0.3
	4 167						
		(i) 157	38	32	8	3	0.7
		(ii) 40	10	[a]	[a]	[a]	[a]
		(iii) 15	4	4	1	4	1
Blood sugar	3 124	54	17	18	6	11	4
	14 863	259	17	127	9	73	5
	3 966	156	39	56	14	34	9
	2 162	31	14	20	10	9	4
	3 543	53	15	5	1	5	1
	2 856	87	30	27	9	16	6
Urine sugar	3 132	16	5	11	4	4	1
	3 987	199	50	54	14	29	7
Electrocardiogram	2 250	395	175	110	49	[a]	[a]
	3 984	666	167	301	76	182	46
Blood pressure	3 989	837	210	369	92	207	52
Haemoglobin	3 986	5	1	1	< 1	1	< 1
Urine albumin	3 988	92	23	35	9	16	4
Vision	3 972	944	238	395	99	205	52
Height and weight:							
Overweight	3 992	360	90	241	60	74	19
Underweight	2 860	90	32	90	32	[a]	[a]

[a] Not available.
Adapted, by permission, from Breslow.[4]

in Baltimore[34] (already referred to) and a rural one in Hunterdon County, New Jersey,[35] and one in San Francisco sponsored by the Kaiser Foundation, the Longshoremen's Union, and the California State Health Department, also referred to above.[32,36,37]

Baltimore. Tables 7 and 8 demonstrate the main findings of the Baltimore screening programme, from which it may be seen that the largest number of previously undetected conditions were found by elec-

TABLE 7. ABNORMALITIES FOUND IN THE BALTIMORE SCREENING PROJECT, 1957

Number of abnormalities present	Number	Percentage of:	
		Total	Total with major abnormality
Total number of persons screened	2 024	100.0	—
No abnormalities	743	36.7	—
Minor abnormalities only	629	31.1	—
One or more major abnormalities	652	32.2	100.0
Occurrence of major abnormalities:			
One major abnormality	434	21.4	66.6
Two major abnormalities	140	6.9	21.5
Three major abnormalities	55	2.7	8.4
Four major abnormalities	17	0.8	2.6
Five or more major abnormalities	6	0.3	0.9

Reproduced, by permission, from Commission on Chronic Illness.[24]

TABLE 8. RESULTS OF TESTS ON ADULTS EVALUATED AND DIAGNOSES BY PHYSICIANS, BALTIMORE SCREENING PROJECT, 1957

Test	Number of persons (unweighted)	Test results		Confirmed by diagnosis		
		Negative	Positive	Total	Previously known to patient	Previously unknown to patient
		Relative rates per 1 000 persons screened				
70-mm chest X-ray:						
Tuberculosis	537	984.4	15.6	3.9	0.5	3.4
Cardiovascular disease	537	943.6	56.4	32.9	12.9	20.0
Other	537	976.0	24.0	5.1	1.3	3.8
Electrocardiogram	571	874.3	125.7	70.3	29.7	40.6
Blood pressure	608	887.9	112.1	105.5	68.9	36.6
Blood sugar	601	936.9	63.1	39.5	12.4	27.1
Urine sugar	586	995.1	4.9	4.7	4.3	0.4
Urine albumin	572	991.6	8.4	4.7	3.9	0.8

Adapted, by permission, from Commission ou Chronic Illness.[24]

trocardiography, sphygmomanometry, blood-sugar estimation and chest radiology. Some 63% of the sample population had some abnormality discovered by screening, of which half were "major" (i.e., unconnected with height and weight, hearing or vision, as tested). The most frequent disorder previously unknown to the person screened was heart disease (with electrocardiograph changes and raised blood pressure as the indicators). A critique and follow-up of this screening programme has been carried out by Wylie.[38,39] He found that only 29% of the invited sample attended for tests. The participants represented that part of the population less likely to be in need of medical care. The five-year mortality of those screened, age for age, was the same or higher than the five-year mortality experience of the non-participants, varying from 6 per 1000 at risk for those less than 35 years of age to 149 per 1000 for those aged 50 and over. There was no evidence in the secular trend that the persons screened experienced a lower-than-expected mortality in the first years after screening. Moreover, Wylie found that the age-adjusted mortality of those screened with "major" defects was nearly twice as high as that for persons with "minor" defects, and over 18 times as high as that for persons with negative tests. This is, of course, not unexpected and only demonstrates that people who are ill die sooner than those who are not. It does *not* show whether or not earlier diagnosis improves the prognosis.

Hunterdon County. In the Hunterdon County survey a sample of the population was examined clinically ("clinical evaluation sample") and a second sample was submitted to multiple screening procedures, as was done in the Baltimore survey. There was, however, a difference between the Hunterdon County project and the Baltimore survey in that part of the "clinical evaluation sample" was also examined by multiple screening, so that it was possible to compare the results of screening with the known prevalence of disease.

The findings are interesting, though difficult to interpret because of the clinical "border-line" problem raised by the use of the screening technique. Table 9 (reproduced from the relevant report[35]) shows the proportion of abnormal findings from screening discovered in the "clinical evaluation sample". It is noticeable, as with the Baltimore survey, that cardiovascular abnormalities are the commonest, even though only 40% of the sample was aged over 44 years. Table 10 (adapted from Table 11-1 of the report) gives the most complete analysis available of the Hunterdon screening and clinical evaluation comparison.

Examination of the table raises some doubts as to the economy of multiple screening: where the yield of positive tests is reasonably abundant the contribution to an early and clinically useful diagnosis seems

TABLE 9. PERCENTAGE OF ABNORMALITIES FOUND BY SCREENING THE CLINICAL EVALUATION SAMPLE OF THE HUNTERDON COUNTY SURVEY

Screening test	Abnormal findings (weighted percentage of screened persons)
VDRL	Less than 1
Mazzini-lipoidal antigen test for syphilis	1
X-ray for chest disease other than tuberculosis (70 mm)	1
Chest X-ray for tuberculosis (70 mm)	3
Blood glucose above 130 mg	3
Urinalysis for albumin—positive or doubtful	4
Urinalysis for sugar—positive or doubtful	5
Diastolic blood-pressure—level of 100 mm	6
Audiometer	11
X-ray for cardiovascular disease (70 mm)	12
Weight status	18
Far vision	18
Electrocardiogram (12-lead)	19
Systolic blood-pressure—level of 150 mm	19
Haden-Hausser test for haemoglobin	19
Electrocardiogram (lead 1)	22
Near vision	29

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not to be high—e.g., the 255 abnormal or border-line electrocardiographs; but where the test might be considered to be clinically of value its sensitivity and specificity appear to have been low—e.g., the 98 positive haemoglobin tests missed 2 out of 3 cases of iron-deficiency anaemia, while the other positive tests occurred either in the presence of non-specifically related disease (56 tests), or where there was no ascertained disease at all (34 tests).

San Francisco longshoremen. In 1951 nearly 4000 longshoremen (dockers) were examined by a multiple screening technique in San Francisco.[32] In 1960 the mortality and morbidity of the original group (of whom the records for over 3000 were available) were followed up and a repeat examination was given to a sample of 818 persons. In the 1951 screening (which included hearing and vision tests, 70-mm chest X-ray, ECG, blood pressure, serology for syphilis, haemoglobin estimation, urinary albumin test, post-prandial glucose tolerance test, measurement of height and weight and a self-administered questionary), 63% of persons examined had positive tests, which led to the finding of 35% with clinical disease. Of these, over half (19%) had previously undiagnosed disease. In other words, about one-fifth of those examined were found to have previously undiagnosed disease.

TABLE 10. MULTIPLE SCREENING RESULTS IN THE HUNTERDON COUNTY SURVEY

Screening results according to final diagnosis		Infective and parasitic diseases		Neoplasms		Allergic, endocrine system, metabolic and nutritional diseases			Diseases of blood and blood-forming organs		
Type and total number of tests	No. of positive tests	Total (002-138)	Syphilis (020-029)	Total (140-239)	Malignant pulmonary neoplasm (163)	Total (240-289)	Diabetes mellitus (260)	Obesity (287)	Total (290-299)	Pernicious anaemia (290)	Iron-deficiency anaemia (291)
Weight judgment Overweight Underweight No. of tests 597	123 6	1 —	1 —	1 —	— —	107 —	11 —	96 —	3 —	— —	— —
MMR-tuberculosis Suspicious findings No. of tests 758	43	8	2	2	1	6	1	5	3	—	—
MMR-chest diseases Suspicious findings No. of tests 672	17	—	—	1	1	3	2	1	1	—	—
MMR-cardiovascular Suspicious findings No. of tests 746	154	3	1	1	—	47	13	33	6	1	—
Electrocardiogram Abnormal/border-line No. of tests 737	255	3	1	2	—	94	23	70	6	1	1

Diastolic pressure Over 100 mm No. of tests 824	114	1	—	—	—	61	10	50	1	—	—
Systolic pressure Over 150 mm No. of tests 824	253	4	2	1	—	102	26	75	4	1	1
Haemoglobin < 14 (M) or 12 (F) g% No. of tests 808	98	5	3	—	—	6	3	3	8	—	1
Syphilis-Mazzini Pos. or doubtful No. of tests 756	6	4	4	—	—	2	—	2	1	—	—
Blood glucose Above 130 mg% No. of tests 750	40	—	—	—	—	31	20	11	1	—	—
Urinalysis-sugar Pos. or doubtful No. of tests 823	47	2	1	2	1	30	22	6	5	—	—
Urinalysis-albumin Pos. or doubtful No. of tests 820	50	—	—	—	—	17	6	11	1	—	—
TOTAL NO. OF CONDITIONS DIAGNOSED		10	4	4	1	202	32	167	18	1	3

TABLE 10. MULTIPLE SCREENING RESULTS IN THE HUNTERDON COUNTY SURVEY *(continued)*

Screening results according to final diagnosis		Diseases of the circulatory system									
Type and total number of tests	No. of positive tests	Total (400-468)	Rheumatic fever (400-401.3)	Other rheumatic heart disease (416	Arterio-sclerotic heart disease including coronary disease (420)	Arterio-sclerotic heart disease (420.0)	Acute coronary occlusion (420.1)	Angina pectoris (420.2)	Essential benign hyper-tension (444)	Hyper-tension with arteriolar nephro-sclerosis (446)	Other hyper-tensive disease (447)
Weight judgment Overweight Underweight No. of tests 597	123 6	103 3	1 —	4 —	19 2	10 —	4 —	2 —	7 —	— —	23 —
MMR-tuberculosis Suspicious findings No. of tests 758	43	25	—	—	2	6	7	—	2	—	6
MMR-chest diseases Suspicious findings No. of tests 672	17	16	1	1	3	2	—	2	2	—	3
MMR-cardiovascular Suspicious findings No. of tests 746	154	163	2	24	32	28	6	2	6	—	17
Electrocardiogram Abnormal/border-line No. of tests 737	255	259	1	18	67	35	10	8	13	—	34

Diastolic pressure Over 100 mm No. of tests 824	114	159	—	2	26	11	4	7	5	1	44
Systolic pressure Over 150 mm No. of tests 824	253	295	2	13	61	35	11	10	22	2	57
Haemoglobin < 14 (M) or 12 (F) g% No. of tests 808	98	30	—	1	9	10	—	1	2	—	2
Syphilis-Mazzini Pos. or doubtful No. of tests 756	6	4	—	—	2	—	—	—	1	—	—
Blood glucose Above 130 mg% No. of tests 750	40	35	—	—	10	7	2	2	1	—	4
Urinalysis-sugar Pos. or doubtful No. of tests 750	47	31	—	2	6	7	1	2	2	—	5
Urinalysis-albumin Pos. or doubtful No. of tests 820	50	46	—	4	10	5	2	3	—	2	6
TOTAL NO. OF CONDITIONS DIAGNOSED		434	2	39	95	50	14	12	37	2	83

TABLE 10. MULTIPLE SCREENING RESULTS IN THE HUNTERDON COUNTY SURVEY *(continued)*

Screening results according to final diagnosis		Other respiratory diseases				Diseases of the digestive system		Diseases of the genito-urinary system			Congenital malformations (750-759)
Type and total number of tests	No. of positive tests	Total (510-527)	Other chronic interstitial pneumonia (525)	Bronchiectasis (526)	Emphysema (527.1)	Total (530-587)	Hernia of the abdominal cavity (560-561)	Total (590-637)	Pyelitis, etc. (600.0)	Cystitis (605)	
Weight judgment Overweight Underweight No. of tests 597	123 6	6 —	1 —	2 —	2 —	— —	— —	6 2	1 —	2 —	2 —
MMR-tuberculosis Suspicious findings No. of tests 758	43	16	2	2	8	—	—	2	—	1	1
MMR-chest diseases Suspicious findings No. of tests 672	17	4	—	—	3	—	1	—	—	—	—
MMR-cardiovascular Suspicious findings No. of tests 746	154	9	1	1	5	3	2	3	—	—	3
Electrocardiogram Abnormal/border-line No. of tests 737	255	18	2	1	10	3	2	6	—	1	4

Diastolic pressure Over 100 mm No. of tests 824	114	6	1	1	3	—	—	—	—	—	1
Systolic pressure Over 150 mm No. of tests 824	253	20	2	3	12	2	1	6	—	2	2
Haemoglobin < 14 (M) or 12 (F) g% No. of tests 808	98	7	—	—	4	2	2	1	—	1	1
Syphilis-Mazzini Pos. or doubtful No. of tests 756	6	2	—	—	1	—	—	1	—	1	—
Blood glucose Above 130 mg% No. of tests 750	40	2	—	1	1	1	1	—	—	—	—
Urinalysis-sugar Pos. or doubtful No. of tests 750	47	4	—	1	3	1	1	—	—	—	—
Urinalysis-albumin Pos. or doubtful No. of tests 820	50	5	—	1	3	—	—	4	—	2	—
TOTAL NO. OF CONDITIONS DIAGNOSED		45	5	7	26	5	3	32	1	17	9

TABLE 10. MULTIPLE SCREENING RESULTS IN THE HUNTERDON COUNTY SURVEY *(concluded)*

Screening results according to final diagnosis		Symptoms, senility and ill-defined conditions				
Type and total number of tests	No. of positive tests	Total (780-795)	Albuminuria, unqualified (789.0)	Albuminuria, orthostatic (789.1)	Glycosuria (789.6)	Uraemia (792)
Weight judgment Overweight Underweight No. of tests 597	123 6	1 —	— —	— —	— —	1 —
MMR-tuberculosis Suspicious findings No. of tests 758	43	1	—	—	1	—
MMR-chest diseases Suspicious findings No. of tests 672	17	—	—	—	—	—
MMR-cardiovascular Suspicious findings No. of tests 746	154	2	1	1	—	—
Electrocardiogram Abnormal/border-line No. of tests 737	255	3	1	1	—	1

Diastolic pressure Over 100 mm No. of tests 824	114	2	1	—	1	—
Systolic pressure Over 150 mm No. of tests 824	253	1	1	—	—	—
Haemoglobin < 14 (M) or 12 (F) g% No. of tests 808	98	—	—	—	—	—
Syphilis-Mazzini Pos. or doubtful No. of tests 756	6	—	—	—	—	—
Blood glucose Above 130 mg% No. of tests 750	40	—	—	—	—	—
Urinalysis-sugar Pos. or doubtful No. of tests 750	47	1	—	—	1	—
Urinalysis-albumin Pos. or doubtful No. of tests 820	50	6	4	1	—	1
TOTAL NO. OF CONDITIONS DIAGNOSED		7	4	1	1	1

Chicago Board of Health. More recently, the Chicago Board of Health has initiated a Demonstration Chronic Disease Project on three city housing-sites, under the direction of Dr J. Stamler.[40] This project combines a battery of screening tests with a physical examination, and should provide useful information on the contribution to diagnosis and prognosis made by screening as an aid to physical diagnosis.

Common conditions for screening. In this chapter we do not propose to discuss in any detail conditions for which it is common to screen; some of the more important of these conditions are dealt with in some detail in Chapter 4. It will suffice here simply to note the chronic conditions for which screening is commonly carried out, either singly or as a multiple operation, and to see to what extent they satisfy the main criteria we have noted under "Principles of early disease detection" (page 25). An analysis is set out in Table 11. In deciding in any given instance about the value of screening, local circumstances of course play a large part. Naturally, as indicated in Table 5, selective screening by age-groups will in all cases give higher yields, and in certain instances (e.g., phenylketonuria and congenital dislocation of the hip) this is necessary in order to be of any use at all. In individual instances, also, it is possible to avoid some or all of the objections indicated in Table 11 and it would, of course, be wrong to dogmatize. Allowing, however, for the objections to current case-finding, the conditions that score most heavily in favour are seen in Table 12.

This is not a very long list and it will at once be noticed that certain conditions—glaucoma, for instance—have been given a low priority despite the fact that they may constitute more of a public health problem than some of the conditions listed. This kind of variation from the more usual emphasis placed on certain conditions is explained by selection in the above list on grounds of all-round feasibility. The pros and cons for screening for some of the major conditions listed in Table 11 are discussed subject by subject in Chapter 4.

EPIDEMIOLOGICAL STUDIES

Having stated that much of the practice of case-finding poses problems that have not been solved (and this can be discerned from a study of the case-finding projects already briefly mentioned), it is, we believe, worth while considering at this point what is being done to remedy this situation. Making decisions on the value of early treatment and on the policy to be adopted regarding the border-line patient involves, as we have stressed earlier, epidemiological surveys (see under "Evaluation of

TABLE 11. SCREENING OF CHRONIC CONDITIONS: ABILITY TO MEET CRITERIA

Conditions for which early detection is employed	Public health problem	Natural history of precursor stage delineated	Recognizable latent stage	Suitable test available	Test acceptable to public	Accepted treatment available	Approved policy on latent stage
Diabetes mellitus	+	?	+	+	+	+	—
Heart disease:							
ischaemia	+	?	+	+	+	?	—
rheumatic	+	?	+	+	+	+	+
congenital	?	—	+	+	+	+	+
High blood pressure	+	?	+	+	+	?	—
Overweight	+	?	+	+	+	+	+
Lung disease:							
tuberculosis	+	+	+	+	+	+	+
non-specific	+	?	?	+	+	?	?
cancer	+	?	?	+	+	+	+
Renal disease:							
nephritis	?	?	+	+	+	+	+
bacteriuria	+	?	+	+	+	+	?
Anaemia (iron-deficiency)	+	+	+	+	+	+	+
Arthritis:							
rheumatoid	+	—	+	—	[a]	?	—
gout	+	?	+	+	+	+	+
Breast cancer	+	—	+	+	+	+	+
Uterine cancer	+	?	+	+	?	+	+
Rectal cancer	+	?	+	+	—	+	+
Oral cancer	+	+	+	+	+	+	+
Bladder cancer	+	+	+	+	+	+	+
Skin cancer	+	?	+	+	+	+	+
Hearing (inherited and acquired deafness)	+	?	+	+	+	+	?
Vision:							
glaucoma	+	?	?	+	+	+	—
cataract and senile macular degeneration	+	—	—	+	+	+	[a]
Hernia	+	—	—	+	+	+	[a]
Congenital dislocation of hip	+	—	—	+	+	+	[a]
Varicose veins	?	—	—	+	+	+	[a]
Phenylketonuria	?	+	+	+	+	+	+
Venereal diseases:							
syphilis	+	—	+	+	+	+	+
gonorrhoea	+	—	—	+	+	+	[a]
Mental illness	+	—	?	—	[a]	?	—

[a] Not applicable.

TABLE 12. CASE-FINDING OF CONDITIONS AT THE VARIOUS AGE PERIODS: ESTIMATE OF RELATIVE WORTH

Relative worth	Pre-natal and pregnancy	Neonatal	Infancy	Childhood	Adult	Old age
Greater	Toxaemia	Locomotor (congenital dislocation of hip)	Anaemia		Anaemias	
	Rh factor		Vision (amblyopia)			Vision (cataract—senile macular degeneration)
	Anaemia	Inborn errors of metabolism (phenyl-ketonuria)	Hearing (congenital deafness)		Hearing (otitis—conduction deafness)	
			Mental development			
	Syphilis				Syphilis	
	Asymptomatic bacteriuria	Congenital defects (heart)			Gonorrhoea	
						Locomotor (arthritis)
						Hernia
					Cancers – uterus – bladder – skin – mouth	
				Pulmonary tuberculosis		
	Diabetes mellitus			Diabetes mellitus (strict criteria)		
				Overweight		
Lesser					Cancers – breast – lung	
					Chronic bronchitis	
					Ischaemic heart disease (strict criteria)	
					Mental illness	
					High blood pressure (strict criteria)	
					Chronic simple glaucoma (selective screening only)	

screening procedures", Chapter 2, page 20). We have attempted to set out in Table 13, in the form of examples only, some of the work at present in progress in different fields. In the column "Comments" we have tried to indicate where there are gaps in our knowledge that might be filled by further studies. Much of this work is still in progress and at the moment unpublished. It is more than possible that the choice of examples may appear unbalanced and, if so, this can be attributed to the fact that we have chosen them from our own knowledge only and have not sought to be exhaustive.

PERIODIC HEALTH EXAMINATIONS

Introduction

It will not have escaped notice that some of the conditions mentioned under the heading of early detection are detectable not by means of specific screening tests but by physical examination. Rectal cancer and, to a lesser extent, uterine cancer fall into this category; so do hernia and cataract. Other examinations, such as blood pressure and electrocardiography, may or may not form part of a general physical examination.

The idea of the periodic health examination goes back a long way. In 1861, for example, Dobell published a monograph advocating "periodical examinations", and in 1925 the American Medical Association published a manual for physicians. More recently, the Commission on Chronic Illness[41] has expressed itself in favour of "all persons having a careful health examination including selected laboratory tests at appropriate intervals". The Commission has advocated screening tests only as a substitute for personal medical examination, recognizing that the shortage of medical manpower has made universal routine medical examinations impossible.

The difference between these two types of examination is quantitative rather than qualitative. With the periodic health examination the individual attends the physician, who examines him, determines what (if any) laboratory tests are needed, and arranges for a second interview and re-examination if necessary—in which case there are two physician interviews and one set of tests. With screening the individual undergoes a set of tests, and then sees a physician (only if necessary, the preliminary sorting of abnormal from normal having already been carried out by the screening tests); the physician may then order more laboratory tests, and examine him once again. With the periodic health examination the physician sees everyone and himself acts as a selective screening

TABLE 13. EXAMPLES OF CURRENT STUDIES ON THE EPIDEMIOLOGY OF CHRONIC DISEASES

Condition	Work in progress	Comments
Diabetes mellitus	(1) Boston study of maternal pre-diabetes (United States Public Health Service)[84] (2) Bedford study of borderline diabetics[83,84] (3) Study of border-line diabetics (College of General Practitioners)[66] (4) Randomized trial of treatment in potential and subclinical diabetics (British Diabetic Association)	Search for other disease indices should be continued. Further trials of rapid blood-sugar screening technique are needed.
Ischaemic heart disease (IHD)	(1) Framingham survey of IHD in a defined population (United States Public Health Service)[8,113,117,118,134,135,136] (2) Studies of IHD questionnaire (London School of Hygiène and Tropical Medicine)[108,138] (3) Tecumseh study of epidemiology of IHD in a defined population[85,105,106] (4) Co-operative studies (World Health Organization)[137] (5) Numerous studies of blood lipid levels in populations; comparisons between populations[106,132] (6) Work on computer analysis of ECG with increase in diagnostic power (7) Work on emotional factors in IHD (8) Co-operative dietary trial (USA) (9) Trial of polyunsaturated fats in IHD patients (Medical Research Council Social Medicine Research Unit and London hospitals) (10) Trials of steroids in IHD (11) Study of diet in prevention of IHD (United States Public Health Service)	Work is required on reliable screening tests for individual, rather than group, diagnosis. More controlled work is needed on personality and emotional factors in IHD. More work would be useful on factors acutely influencing blood lipids and clotting time.
Essential hypertension	(1) Study of propositi and relatives in South Wales (Medical Research Council Epidemiological Research Unit, Cardiff)[145] (2) Framingham survey[147] (3) Tecumseh project[105] (4) Study of sphygmomanometry (London School of Hygiene and Tropical Medicine)[143]	A randomized trial of treatment for early essential hypertension has not so far been carried out.
Chronic bronchitis	(1) Prospective survey of clerical workers and men working in the engineering industry) Postgraduate Medical School, London) (2) Prospective survey of infants and young children in London (Department of Social Medicine, St. Thomas's Hospital, London) (3) Prospective survey of schoolchildren in Kent (Department of Social Medicine, St. Thomas's Hospital, London) (4) Study of steel workers, South Wales (Department of Social and Preventive Medicine, Welsh National University) (5) Prospective study of medical students at St. Bartholomew's Hospital, London, for early correlates of chronic bronchitis (Medical Research Council Air Pollution Research Unit)	Special study in progress of sensitivity to tobacco. Trial of antibiotics ready for publication. Studies are being started of trials of intensive anti-smoking propaganda in high-risk groups identified in the population. Work is in progress aimed at achieving international agreement on definitions with the object of making vital statistics and research comparable between countries (e.g., WHO European Symposium Report[170]).

TABLE 13. EXAMPLES OF CURRENT STUDIES ON THE EPIDEMIOLOGY OF CHRONIC DISEASES *(continued)*

Condition	Work in progress	Comments
Cancer of lung	(1) Philadelphia Chest Clinic study[177] (2) Baltimore study[180] (3) Albany, New York, study (4) London factories study	More studies of motivation in cigarette smoking are needed.
Cancer of uterus	(1) Memphis survey[190,191] (2) San Diego Survey (3) St Louis Survey (4) British Columbia survey[188] (5) Cardiff survey (6) Aberdeen survey[194] (7) Manchester, study of public and professional attitudes[64] (8) Copenhagen, Baltimore, Stockholm, London, Manchester, and Birmingham, study of irrigation pipette[33,84,193,196] (9) London, study of enzyme test for cytological diagnosis[197,198] (10) US study of computer scanning for cytodiagnosis (11) Study of prognosis in relation to biopsy diagnosis and treatment of cancer of cervix (Royal College of Obstetricians and Gynaecologists)	There is room for more international studies of morbidity and mortality in relation to the utilization of exfoliative cytological services. The problems of the use of exfoliative cytology by the public could be studied more intensively. Development of diagnostic scanning by computer is being undertaken.
Cancer of breast	(1) Study of X-ray mammography in population screening in New York[217] (2) Prospective study of endocrine status in relation to development of breast cancer, Guernsey (Guy's Hospital, London) (3) Studies in clinical mammography at Albert Einstein Center[215,216]	To determine its value, population screening by X-ray mammography is being done with randomization, so that one group is treated at early diagnosis and one treated at normal clinical diagnosis, with histological comparison and morbidity-mortality survey. Material should be available for co-operative studies of survival from early detection clinics (e.g., University of Minnesota Cancer Detection Center).
Asymptomatic bacteriuria	(1) Boston[234] (2) Jamaica[231] (3) Rhondda, South Wales[235] (4) Edgware, Middlesex (5) Charing Cross Hospital, London	Despite all the work done, there is still a great need for studies to determine the importance of bacteriurias (asymptomatic) in the etiology of pyelonephritis by randomization of treatment. Prospective surveys to determine the prognostic effect of treatment over the long term are lacking. The possible relationship of vesico-ureteral reflux to infection and onset of pyelonephritic changes is not settled
Rheumatoid disease (including other arthritides)	(1) British Empire Rheumatism Council Survey[241] (2) Tecumseh Survey[238] (3) University of Pittsburgh (4) United States National Health Survey (5) Other prevalence studies—in Scandinavia, Brazil and New Zealand[237] (6) Studies of rheumatoid factor in various populations, Leiden[237]	Further survey work is to be expected on the lines suggested at the CIOMS Symposium in Rome, 1961, and by the Technical Conference on the Public Health Aspects of Chronic Rheumatoid Arthritis and Related Diseases, Rome, 1963.

TABLE 13. EXAMPLES OF CURRENT STUDIES ON THE EPIDEMIOLOGY OF CHRONIC DISEASES *(concluded)*

Condition	Work in progress	Comments
Mental illness	(1) Institute of Psychiatry study of prevalence of reported mental illness in general practice[348] (2) Study of mental illness in Camberwell, London (Medical Research Council, Social Psychiatry Unit) (3) Prevalence of psychiatric symptoms in relation to social attitudes in a South Wales rural population (Medical Research Council Social Psychiatry Unit)	There is room for studies of unreported mental illness in a community, with randomization of treatment.
Anaemia (iron-deficiency)	(1) Prevalence study (Medical Research Council Epidemiological Research Unit)[351,352] (2) Trial of haemoglobinometry in general practice (Medical Research Council Epidemiological Research Unit)[354] (3) Trial of preventive treatment in adolescent girls (Medical Research Council) (4) Trial of prevention in adults by addition of iron to bread (Medical Research Council Epidemiological Research Unit)	Extension of field surveys is very much dependent on the developments of suitable haematological techniques for use in the field. There are contradictiory views on the value of adding iron (and, for instance, vitamins) to food for prevention of iron-deficiency anaemia.
Chronic glaucoma	(1) Survey of intra-ocular tension and glaucoma (Medical Research Council Epidemiological Research Unit)[20,21,28] (2) Bedford Survey of intra-ocular tension and glaucoma[328] (3) Study of patients' attitudes to medication (Medical Research Council Epidemiological Research Unit) (4) Randomized trial of treatment of ocular hypertensives (Medical Research Council Epidemiological Research Unit)	Finding a better index to early chronic glaucoma than tonometry would facilitate case-finding, as contrasted with surveys of intra-ocular tension. There is a lack of material on randomized trials of medical treatment of chronic glaucoma and of ocular hypertensives.

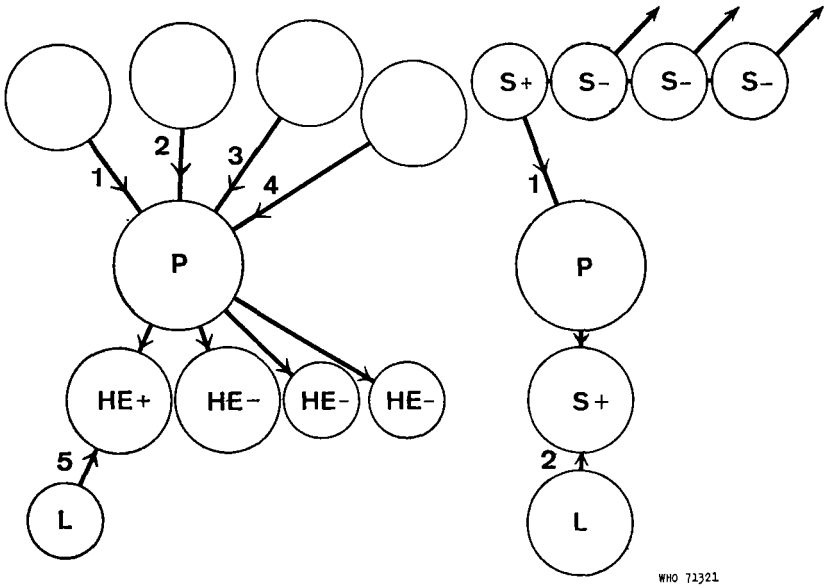
Much of the work referred to in this table is mentioned in the text and the relevant references are given. For permission to cite the work that is as yet unpublished we should like to express our gratitude to the authors and organizations concerned.

agent ordering what laboratory tests he deems necessary. Finally, he sees the selected individuals yet again, with the results of the laboratory tests in front of him. The sequence of the two types of examination is represented diagrammatically in Fig. 3.

The advantage of the periodic health examination is, of course, the intervention, at each examination, of the trained analysing brain of the physician, which is without doubt a more efficient selector mechanism than a battery of tests, rigidly forechosen (however ingeniously) on general probability grounds. The disadvantage is equally clearly the impracticability of routine physical examinations for all. There is a second drawback to consider—namely, the blunting of clinical acumen that may occur in certain circumstances of repetitive physical examination, particularly where the yield of abnormal results is expected to be low.

School physical examination, without selection, is an example. On the other hand, the yield of abnormalities reported from the examination of other groups—middle-aged male business executives, for example—is high.[42,43]

FIG. 3. SEQUENCE OF PERIODIC HEALTH EXAMINATION AND OF SCREENING EXAMINATION



HE+ = positive examination
HE— = negative examination
S+ = positive screening
S— = negative screening
P = physician
L = laboratory

Numerals denote number of physician contacts

The subject of periodic health examination has been dealt with in some detail elsewhere,[44] and it is not intended to consider the matter in any way exhaustively in this report. However, two differing aspects of this kind of examination in relation to medical care are worth noting.

Relationship to general practice

The first aspect of interest is in relation to the development of general practice. Where general practice has become relatively highly organized, whether by concentration in health centres or into group practices, or

by voluntary limitation of the number of patients cared for (facilitated, perhaps, by a high per capita financial reward), there has been a tendency towards the elaboration of routine medical examination. Apart from actual physical examination, there may be a full examination of the blood, X-ray of the chest, ECG, proctosigmoidoscopy, as well as testing of the urine and examination of the faeces for occult blood. There is special scope in this kind of environment for the development of relatively sophisticated tests. The various biochemical estimations possible with the Gray wedge photometer are a case in point, the recent development of an electronic apparatus for recording the knee jerk (as an index of thyroid function) is another. With the development of laboratory automation an increasing number of sophisticated examinations are steadily becoming more freely available to the general practioner. While information is available on the number and type of abnormalities revealed by this kind of search for early disease, we do not have comparisons with the results of finding and treating disease by more conventional methods. Perhaps all that need be said is that it is clearly better to diagnose developed disease at the earliest possible stage and that the only comparison ethically feasible would be that of the proportion of patients under treatment, by condition, in otherwise comparable general practices.

The industrial health examination

The second aspect of interest is the commercial or industrial periodic health examination. In this context we are considering examinations for the general health of the worker and not statutory examinations for industrial hazards such as silicosis, lead poisoning, industrial X-ray exposure or extensive noise.

General medical examinations have, of course, been demanded for a very long time by bodies that set their own terms of entry—for example, insurance companies, the armed forces, railways and air lines. In this case there is either a commercial interest in the medical findings, based on actuarial calculations, or an interest in the public safety, or both. Thus it is surely perfectly legitimate, and desirable, that a man seeking to become an air pilot should be rejected say, on the grounds of equivocal abnormalities in his ECG, though these changes would not be considered adequate causes on which to base a prognosis in civilian life. Again, if changes develop and are found at the routine examination of a pilot employed as such, this may well be a reason for taking him off flying duties. In industry, too, it is necessary that specific medical examinations should be made on persons at special risk. For example, the periodic routine

cytological screening of the urine in persons who have in the past been exposed to beta-naphthylamine is obviously needed; and other industrial examples can be thought of. It is when, as often happens, industrial firms offer medical examinations as a "fringe benefit" to their employees that doubts must arise. The question *cui bono* may be asked in these instances, and it is well to make sure that the employee who submits to the examination derives at least as much benefit from it as does the employer. That both sides may benefit from periodic staff medical examinations is probably true; as a result of such examinations persons with early disability are sometimes found more suitable occupations, but there may also be the chance that the employees will incur a loss of earnings and responsibility because of a risk that never materializes. It is salutary to remember that the Olympic 100-metre record was once held by a man with an aortic regurgitation that led to his rejection for military service.

In some countries periodic health examinations are carried out on all employees every year. In other countries such examinations are carried out only on selected groups, such as those exposed to occupational hazards and groups with special work demands (for example, crane operators, truck drivers, foremen and executives), or groups with higher morbidity, such as middle-aged and older people, young workers (below 18), and those with numerous long-term and short-term sickness absences, or employees who, according to their supervisor, deviate from normal behaviour, showing poor attendance or low productivity.

While medical care arrangements vary greatly from country to country there may be special advantages in industrial health examinations. The industrial physician is often well placed to follow the same individuals for a long time and thus can detect early deviations from health because he is able to compare the results of the physical examination and screening with the findings of pre-employment health examinations.

Industrial health services offer certain particular advantages for studying early disease detection in that it is possible to ensure the regular attendance of a relatively large population and that continuity of attendance is usually of a high order.

The interest and full support of both management and employees have been achieved in several countries through national or local agreements on industrial health services or through legislation. (The International Labour Office Recommendation on this subject (No. 112, 1959) should be mentioned in this connexion.)

Routine examinations through life

We should not forget, of course, that in most developed countries there is already a well-established pattern of routine medical examinations, extending through life. If these are wisely spaced the individual can probably be given the maximum protection with the minimum interference in his normal pattern of life. After ante-natal, post-natal and infant welfare examinations, the child is next examined at or soon after school entry and again before leaving school. After school there are pre-employment examinations, as well as examinations before entering certain specified careers. In industry it would seem reasonable to ask for medical examination at key points in a person's career as part of the selection for promotion, considering the high degree of investment in the individual necessary for senior appointments. However, the results of these examinations need interpreting with latitude, taking into full account all that has been said about border-line conditions and giving the individual the benefit of any doubt that may arise in a particular case.

Finally, as Williamson and his colleagues,[45] among others, have shown, many remediable defects are to be found in the elderly and aged by routine physical examination. Defects of the special senses and of locomotion constitute some of the greatest handicaps of old age and these tend, in the elderly, to fall short of a level of clinical urgency necessary to compel the patient to seek medical advice. There seems to be considerable scope for clinics for the elderly where special attention is paid to their medical needs. Certainly some of these clinics appear to be filling a real need.

THE PLACE OF SCREENING IN THE PROVISION OF MEDICAL CARE

Justification within a country

At the start of this report we gave some space to a discussion of the aims of the early detection of illness. These aims need considering along with the policy aims that are central to any system for providing medical care. With greater prosperity more money will become available for personal health services. This means that greater efforts can be made to extend the disease-free period of life by all possible means, including the detection and correction of early departures from normal health. Poorer countries, on the other hand, must needs manage with the minimal medical services necessary to prevent the major epidemic disasters and to maintain the working population in as fit a state as possible.

The specific aims of early disease detection are, firstly, the control of communicable diseases such as pulmonary tuberculosis or schistosomiasis and, secondly, the promotion of better health and the reduction of human suffering resulting from disease. Both aims are governed by the economic situation. In the first case, it may well be in the national interest to control a disease or group of diseases, and a national campaign may be mounted. In the second case, the advance to better health may be marginal only, and may be left to local effort, where that is forthcoming. Ideally, and in areas where the economic aspect is all-important, the cost to the community of early detection and treatment of a condition should be less than the cost of treatment at a later stage. For example, it has been calculated that the cost of diagnosing and treating one patient with pre-symptomatic pulmonary tuberculosis costs about $400, a sum which, in relation to the cost of treating a developed case, represents a worth-while saving, even without taking into account the probable liberation of a family from anxiety and suffering. On the other hand, serological screening of certain communities for venereal disease, which used to be considered economically worth while, may no longer be so considered. Similarly, the returns on screening patients for lung cancer are so poor (see Chapter 4, page 106) that this procedure is probably no more to be recommended on economic than on medical grounds.

In working out cost a large number of factors may need to be taken into account. One important factor that comes into the calculation is the possible saving of the time of highly trained people, bearing in mind the cost in time and money of their education and experience. If a screening procedure can, by automation or by employing a less highly trained person, partly replace the work of a highly skilled person, there will then be a saving. However, it must be remembered that the over-all cost to the community is usually greater than before, because something is being done that was not being done previously. For instance, the detection, treatment and rehabilitation of previously unascertained disability among the elderly undoubtedly costs the community extra, even though the ascertainment may be carried out by questionary or auxiliary workers rather than physicians.

An example in which the over-all cost may be lowered can be found where the treatment of a condition is in any case essential. Thus, taken together, the detection and treatment of carcinoma-in-situ of the cervix uteri should cost considerably less than the diagnosis and treatment of established invasive cancer; for while the diagnosis of carcinoma-in-situ may cost more than the diagnosis of the invasive lesion, the cost of treating it is much less. But, again, it should be remembered that there is a period when the over-all cost is increased, from the time of admission

to hospital both of the newly detected carcinoma-in-situ patients and of the normal quota of invasive cancer patients until the moment when a fall in the incidence rate of invasive lesions becomes apparent.

Cost of multiple screening

The actual cost of multiple screening programmes naturally varies with the examinations made. A typical programme—that of the San Francisco longshoreman—is estimated by Breslow to have cost $5.04 per person screened.[6] In this case, 12 tests were carried out (as cited above). Breslow also quotes two other schemes, in which only chest X-ray and blood-sugar determination were done, where the cost lay between $1.50 and $1.75 per person. Other costs are given in the American Medical Association's study of multiple screening[4] already referred to.

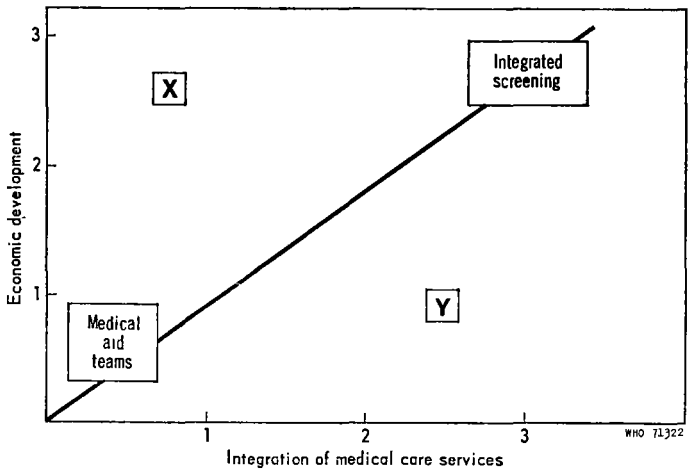
What is difficult, however, is to relate costs like this to the benefits that would have been derived from spending the same sums on other forms of medical care. It is perhaps of interest to consider these services in relation to what is spent generally on medical care. In terms of US dollars, an average British general practioner earned, in 1962-63, about $7300 per year from all sources, and he looked after, on average, 2300 patients. This allows approximately $3 per head for all general medical services. The cost of the whole National Health Service for England and Wales in 1962-63 (excluding welfare costs) was £876 million, which allows an expenditure of about £19 (or $53) per head of population over the year for all services—hospital, public health and general medical. California, the wealthiest state in the USA, had a total health budget (Federal and State) of over $43 million in 1960-61.[46] This allows expenditure on health and welfare services of about $3 per head in the year (of which 36% was spent on hospital construction and 7% on preventive medical services, about $0.20 per head). We must remember, too, that this health budget is for public health only (apart from the contribution to hospital construction), and personal medical services are supplied under private contract. Thus, in relation to total health expenditure, multiple screening is costly and its use would need to be judged on the benefits to health that it could provide.

Inter-country differences

Besides requiring justification on economic grounds in individual countries, screening procedures need to fit into existing systems of medical care, and the variation of these between countries may influence the pattern of screening. Unlike the usual sequence in clinical medicine,

when the patient, feeling unwell, consults a physician and thus submits to diagnostic examination, early detection entails an appeal to the public to come to be examined. An appeal of this kind is most easily organized through the public health services, and not through the clinical services (though it may be to clinicians that the public go for their actual tests, as, for example, cervical smears). Where there is no unification of the medical services, and where these are financed in different ways, the efficient practice of screening becomes difficult. Moreover, there is the twofold danger of a failure in communication and of a failure to follow up—possibilities that have been discussed earlier in this report. On the other hand, where there is a unified medical service it is relatively easy to carry out the whole screening operation, beginning with an appeal to the public, through screening tests, definitive diagnosis, treatment and follow-up, without breakdown in communications at any point. Figure 4 represents the two dimensions of economic development

FIG. 4. RELATIONSHIP OF MEDICAL CARE SYSTEM TO ECONOMIC DEVELOPMENT



and unification of the services for medical care, and the straight line passing through the point of origin indicates an average axis of development of the two variables. Near the point of origin of the curve is the area of poor countries with little in the way of organized medical services. In this area is indicated a medical aid team, which might visit the country at its government's request for some special screening operation (for example, the control of schistosomiasis). At the other end of the curve

is the area of wealthy countries with highly organized systems of medical care, where integrated screening operations carried out under national arrangements may be expected. At the opposite extremes are countries "X" and "Y". "X" is wealthy but has non-integrated medical services, and expensive sporadic screening exercises may take place here, with poor communication and follow-up. Country "Y" on the other hand, is relatively poor but has a unified system of medical care. Thus "Y" would offer ideal conditions for the control of those endemic diseases that remain a problem in the less prosperous parts of the world—for instance, pulmonary tuberculosis. Unfortunately, there are few economically underdeveloped countries that have as yet achieved integrated medical services, since this in itself is costly.

Example of gynaecological cytology

Some lessons on the medical care problems and economics of screening can perhaps be learned from experience with initiating gynaecological cytology services in England and Wales, where there is a tripartite, decentralized, national health service consisting of general practitioner, public health and hospital services. Here the responsibility for the examination is regarded as primarily belonging to the general practitioner, by virtue of his practice of personal preventive medicine. Either he, a public health authority physician or a physician from a voluntary family planning organization may, in the case of "well" women, actually take the cytological material, and it is generally considered preferable that this examination should be carried out by a physician. This poses one problem of screening; ideally, examinations should be carried out by a physician, since women have considerable confidence in the examination and are likely to believe that a negative test indicates that they are not only free from cancer but unlikely to develop it. While a trained auxiliary—a nurse or assistant of similar standing—can easily learn to take cytological material, she is not so well trained in observing local pathological changes. Yet, if physicians alone were to carry out this examination, not only would a heavy economic burden have to be borne, but the service would be likely to remain limited owing to a shortage of medical manpower. If screening for uterine cancer (taking material) is to be carried out by non-medically-qualified people—as to some extent it almost certainly has to be—it is extremely important that the public should understand that a screening examination is provisional and can in no way guarantee the exclusion of cancer of the cervix, much less of the body of the uterus.

A problem, in a way similar to the above, has to be faced in the examination of cytological specimens. It is of the first importance that those

responsible—both pathologists and technicians—for deciding whether specimens are negative or positive should be well trained. Inadequate training may easily bring a whole service into disrepute; wrong decisions on smears and biopsy material will have far-reaching effects, since the definitive treatment for intra-epithelial (carcinoma-in-situ) cervical lesions is normally total hysterectomy. However, insistence that training in cytology shall be limited to generally trained laboratory technicians, while admittedly ensuring a high standard of technical service, is liable to clog the rate of development of the service. The USA and some British Commonwealth countries (among others) have successfully adopted the procedure of *ad hoc* training in cyto-technology for university graduates or persons with similar education. This is important because, in all advanced countries, competition for manpower has become extremely keen from all sides, and an over-insistence on formal qualifications prior to training in cyto-technology could be an important factor in slowing up the development of a service. The number of technicians needed for carrying out not only primary examinations but also regularly spaced re-examinations is considerable, as the following rough calculation will show. There are approximately 15 million adult women in England and Wales. Supposing cytological examination were carried out, on an average, at three-yearly intervals by technicians who could examine 10 000 women/specimens per year, a total of 500 technicians would be needed. (This makes no allowance for sickness absences, holidays and part-time work, nor for the fact that working attendance is, at best, only of the order of 70%-80%.)

The problem of the future may well be that of persuading those women at greatest risk to attend for examination (and, incidentally, perhaps of promoting health educational measures likely to diminish the chances of developing cervical cancer); and it is likely that a rather large proportion of the population will fail to submit to regular examination. Even with smaller numbers the recording and efficient recall, with follow-up if necessary, of all these women present formidable problems. A possible means of recall that is being explored is the central registration of all cytological examinations in an area, followed by automatic data processing and the issue of recall appointments. Such a central registration system clearly has great epidemiological potentialities, in addition to the advantages to be derived from its routine use.

By reason of the manpower shortage the search for automated techniques for cytological screening is clearly of great interest, and such techniques would be acceptable even with a high false-positive rate. Provided that the cost per examination could be kept low, automation could be combined with a high degree of centralization of screening services, with a consequent saving in overhead costs. However, it must

be remembered that the lengthened lines of communication would become more vulnerable, and it seems likely that on-the-spot re-examination of reported positive specimens would still be necessary.

It still remains to be seen whether cytological screening will be accompanied by a significant reduction in the number of deaths from uterine cancer, though it does appear that the incidence of invasive cervical cancer may be lowered by this technique. Where it is economically possible, exfoliative cytology is being provided as a service on the grounds that finding and removing in-situ lesions offers the best hope of reducing mortality from invasive cervical cancer. It is perhaps of some interest to examine briefly the consequences of such a policy on hospital-bed usage, and the following simple calculation may give some idea of the effects of widespread population screening for uterine cancer. At present in England and Wales there are about 10 500 discharges from hospital annually for carcinoma of the cervix and the average duration of stay is 21 days, giving a total of 220 000 hospital days.[47] These discharges refer to admissions and not to persons. The approximate total time spent in hospital as an in-patient by a woman with carcinoma of the cervix during her lifetime is in the region of 50 days. The average length of admission for cone biopsy for a patient with carcinoma-in-situ is in the neighbourhood of 7 days, or roughly one-seventh of 50 days. On the other hand, perhaps twice the number of women who would ultimately have developed invasive cancer would be subjected to cone biopsy. Supposing cervical screening to be nearly 100% effective, this would still cut down total hospital-bed usage by a factor of 3 or 4. However, admission for biopsy during the early years of a screening programme would occur simultaneously with the same number of admissions for invasive cancer as previously experienced. From the Hospital In-Patient Enquiry reports of England and Wales it can be estimated that in a population of 250 000 there would be roughly 35 admissions for cancer of the cervix per year. If one-fifth of the female population over 20 years of age were screened annually, according to the findings of the Memphis, Tennessee, survey 50-60 carcinomas-in-situ would be discovered, thus nearly trebling the existing admission rate. At 10 days in hospital for each case this would need, on average, an extra 2 beds for a population of 250 000, over and above the 2-3 that would be needed in any case.

Conclusion

Clearly some method is needed for measuring the value to a community of the early detection and treatment of both pre-symptomatic and declared disease. The value may consist either in the provision of better

standards of health or comfort to individuals, or in the creation of economic benefits for the community. Obviously, in terms of health, the two sorts of value cannot be fully separated—the man or woman who enjoys better physical or mental health can work better, though it may be impossible to measure the difference in output between less healthy and more healthy people.

The most important point, perhaps, in determining whether a particular measure for early disease detection is or is not worth while is the degree to which the medical value of screening for particular conditions has been established. For example, it seems doubtful whether it is of value to screen a whole community for high blood pressure, other than what is already done by the clinical services, in the absence of good criteria and of a proved and acceptable form of early treatment. On the other hand, as we have seen, it does seem possible that the early detection and treatment of cancer of the cervix may lead to a very great reduction in suffering from the disease; and this, in terms of benefit to the individual woman, is well worth while. However, the economic cost of a campaign to eradicate cervical cancer must, if it is to succeed fully, inevitably be relatively high. The cost must therefore be considered by any community in terms of its own particular economy. If there is a limit to the health budget (as in practice there always is), the benefit and effectiveness of the proposed programme need to be compared with other desirable objectives. For example, an intensive campaign to prevent young people from starting to smoke, or a nationwide attempt to prevent overweight, could, if successful, improve the life and health of a far larger number of persons in the active span of life than could a cervical cancer programme. In the event, communities often decide that every feasible form of early disease detection and prevention must be offered to the population, with the result that the over-all cost cannot satisfactorily be met, and a substantial number of programmes are carried out in a less than effective way, instead of a few that are well planned and well executed.

THE PLACE OF EDUCATION IN THE EARLY DETECTION OF DISEASES

Education of the medical profession

Undergraduate medical education is traditionally disease-oriented. Education in public health has in the past been largely concerned with environmental health and the primary prevention of communicable disease. The teaching of hygiene and public health in Europe has been

reviewed in a WHO monograph by Grundy & Mackintosh.[48] The dominant role in teaching medical students is still to too large an extent filled by the clinician, whose training, in turn, has not been greatly concerned with preventive medicine. At present there remains a tendency for a self-perpetuating system of teaching that allows too little emphasis on new ideas about preventive methods.

In recent years there have been signs of a new approach, consisting in the teaching of both the preventive and the clinical aspects of medicine at the same time. The preventive side of medical practice in the community needs to be learned both in the undergraduate course and in the pre-registration and post-graduation periods. Thus a WHO Expert Committee[49] considered that the preventive aspects of medicine should be taught at all stages in the curriculum, including the basic medical sciences and pathology courses. Interest in the earlier detection of disease must largely stem from an understanding of the epidemiological approach. As the WHO Expert Committee points out, a number of new and special subjects are needed in training for preventive medical services, of which the epidemiological method takes first place, and which should include medical statistics, the social sciences, genetics and the organization of health and welfare services. These subjects are best taught by participation (involving some degree of personal responsibility) in laboratory work, field surveys, out-patient and peripheral services, domiciliary care and rural health programmes. For fostering the idea of early disease detection it is important to introduce the student to a type of general medical practice organized in such a way as to make this work feasible—e.g., a well-organized group practice or health centre. Similar views have been set out in a WHO study,[50] which particularly emphasizes the value of the health centre for this type of teaching.

It is, in fact, now realized that it must be for the physician practising in the community to undertake the first-line prevention of disease, whether at the primary or at the secondary stage. He is best placed to see the beginnings of illness and to be aware of local genetic and environmental factors. University faculties of general practice are now springing up, and their role in relation to early disease detection may fruitfully be exploited in association with their fellow departments of epidemiology, social medicine and medical statistics. The place of the general practitioner in the prevention of disease was recently considered by the College of General Practitioners.[51]

It is important to remember that, in addition to physicians, there are other workers in the practice of medicine in whom more positive attitudes to the early detection and treatment of illness need to be inculcated —for example, nurses, health visitors, chiropodists and pharmacists.

Education of the public

In order to carry out successfully the early detection of disease it is not only essential to have an alert and prevention-oriented medical profession; the public must also co-operate in the operation. We know from experience that, for example, in the reporting of symptomatic cancers, the public tends to defer seeing a doctor until the condition is relatively far advanced. Knowledge about the value of early diagnosis and treatment, based on sound scientific studies, needs to be spread to the community. Thus it is accepted that education of the public is essential; what is not always known is the form that this health education should take, both in its content and in its application. In order to succeed, early disease detection as a means of prevention in the community should reach all, or nearly all, those at risk regardless of cultural and economic differences between the various parts of the population. A common experience is that persons with the best general education make use of facilities of which they may perhaps, in reality, be in little need; while others, at a much higher risk of disease but with a less good education, fail to utilize a service out of ignorance of their special need (the example of high-risk groups in cancer of the cervix is briefly referred to in Chapter 4, page 110). Planning health education so that it will reach all kinds of people is therefore essential and, in order to do this, special studies of public attitudes to disease may be needed in the first place. Studies of this kind have, for example, been carried out for gynaecological cytology in California,[52] and nationally in the USA,[53] and one is in progress in Manchester.[54]

No doubt much still needs to be learned about the best ways of reaching populations in providing health education. One point of importance is the need for proper organization. "Delivering the message", whether in print or by direct speech, radio or television, is a specialized technique and, if carried out in an amateurish way, can lose most of its potential impact. There is a place in public health administration for specialist health education officers to assist the medical and nursing staff. In addition to local officers, the central planning and teaching of health education may be valuable, as suggested by the Central Health Services Council in Great Britain.[55]

Apart from the staff employed by public health authorities to spread health education, other specially trained persons have an important part to play in educating the public. General practitioners are well placed to induce their patients in particular high-risk groups to attend for examination; and nurses and health visitors, for example, can influence the public beneficially during the course of their work.

CHAPTER 4

ILLUSTRATIVE EXAMPLES OF SCREENING FOR DISEASE

The previous chapters have dealt almost entirely with the general considerations of early disease detection. It now seems useful to consider some specific conditions in rather more detail. In the present chapter we have therefore chosen certain examples to illustrate specific points made in the earlier chapters.

DIABETES MELLITUS

General

Diabetes detection, according to Joslin et al.,[56] goes back to 1909, when Barringer reported the findings on over 70 000 persons examined for life insurance purposes. However, the concept of population screening for diabetes dates from the survey carried out by Wilkerson & Krall in 1947[57] on the people of Oxford, Massachusetts. Post-prandial blood-sugar estimation, together with glycosuria testing, was carried out. Since that time an increasing amount of case-finding, either by urine examination or by blood examination, or by both, has been practised in the advanced countries of the world. (For typical examples, see Walker & Kerridge.[58]) Despite all this work it is still difficult to evaluate the results in terms of benefit to the populations screened. Some of the criteria for case-finding discussed above remain unsatisfied. This question will be dealt with later in this chapter.

There is little question that the best documented case-finding has been carried out during the past decade in the USA. Under the Diabetes and Arthritis Program of the Chronic Diseases Division of the United States Public Health Service, information has been gathered together and published. Thus McDonald and his co-workers[59] give figures for 1958-63; during 1963 nearly 530 000 persons were screened by blood-sugar estimation, as compared with 190 000 in 1959, an increase from 1 per

1000 of the total population to 3 per 1000. Of 338 500 screened in 1962, 10 300 tests were positive; 9000 (2.7%) of these were referred to their physician, and of these 2500 (0.7%) were known to be diagnosed as diabetic. The United States National Health Survey finds a rate of 9 per 1000 population of all ages for known cases of diabetes, while the estimated rate for unsuspected diabetes is 8 per 1000 for all ages.[60] This would yield a total of 1 500 000 known and 1 400 000 unknown diabetics in the USA, so that screening, even in a country where a relatively large amount has been done, has still a long way to go.

In general, blood-sugar examination has superseded urine testing, rapid screening being possible using either the Clinitron apparatus or the simpler, slower (but much cheaper) Glover-Edwards kit, both employing the Wilkerson-Heftmann screening test.[61] These methods have the advantage that the needed equipment is relatively mobile. Fully automated techniques, on the other hand, while considerably more accurate, rely on more delicate and less readily portable apparatus. In favour of the Wilkerson-Heftmann type of test is its immediacy, making it possible to notify people on the spot if further action is needed, and the fact that only a small sample of capillary blood is required. The fully automated methods usually employ a sample of venous blood, and are better suited to a system where specimens are transported to a centralized laboratory, with a corresponding loss of immediacy.

Table 14 shows the specificity and sensitivity obtained for blood-sugar and urine screening respectively in a study by Remein 8 Wilkerson[15] on 580 persons of various ages and races.

TABLE 14. EFFICIENCY OF SCREENING TESTS

Test	Sensitivity % positive	Specificity % negative
Blood (Somogyi-Nelson) 160 mg/100 ml, 1 hour after test meal	52.9	99.4
Urine (Dreypack, glucose oxidase) 1 +, 2 hours after test meal	45.9	90.3

Adapted, by permission, from Remein & Wilkerson.[15]

It is clear that neither technique is good at picking up a high proportion of persons with diabetes, though the blood-sugar method has the advantage of finding very few false positives.

As a practical example of the application of the above blood-sugar sensitivity and specificity, in a population of 10 000 with a true prevalence of 150 diabetics there would be 70 false-negative results (i.e., 70 missed cases) and 60 false-positive tests.

The practice of case-finding is discussed by the CCI in *Chronic Illness in the United States*,[62] the Baltimore screening survey providing an interesting example. The urine was first tested 30-50 minutes after the administration of 50 g of glucose, given as a drink. The venous blood-sugar was screened at a level of 160 mg/100 ml, using the Wilkerson-Heftmann technique, 45-75 minutes after glucose ingestion. If positive, a two-hour specimen of blood was screened by the same technique at 130 mg/100 ml blood. Of 1916 persons of all ages over 16 years, 33 (14 males and 19 females preponderantly in the 45-64 age-group) were found with positive one- and two-hour values (in a few cases blood for sugar estimation at two hours could not be obtained). In 13 persons only was follow-up completed; 7 were confirmed as diabetics, and of these 5 were previously undetected.

The rate for abnormal findings in both tests (numbering 33 in all) was 8 per 1000 persons examined. This is fairly typical of a low yield of previously unknown illness from mass case-finding. The cost of this type of operation (excluding overheads and publicity) is estimated by the United States Public Health Service as being in the neighbourhood of $0.84 per person screened (i.e., $1600 for screening the 1916 persons), provided the project is carried out by an adequately staffed local health department.[61] Thus the cost per diabetic diagnosed in the Baltimore screening project works out at $123, or $320 per previously undiagnosed diabetic.

A difficulty in comparing case-finding programmes has been that the criteria for diagnosing diabetes have differed from place to place. The United State Public Health Service *Diabetes Program Guide*[61] lists nine different sets of criteria. The Committee to the Public Health Service Diagnostic Study recommends the criteria shown in Table 15, with a point value allotted to each reading. A total of two or more points is considered to indicate a diagnosis of diabetes.

Despite these attempts at defining diagnostic criteria, it is still very difficult to know in practice which criteria are being used in a particular case-finding programme. Where separate forms of medical care exist side by side, the follow-up to diagnosis of screened positive persons may be fruitless, and it is not very uncommon for such follow-up to consist only of a urine examination following a positive blood test. Reid's report on diabetes detection in the USA[63] makes a number of cogent points:

(1) Differences of opinion exist about the value of generalized, as opposed to selective, screening.

(2) In the case of selective screening, the question arises of the criteria that should be used for selection.

(3) The relative merits of urine as opposed to blood screening are a matter of discussion, although opinion seems to have hardened in favour of the latter.

(4) Screening is carried out under varying conditions. Thus it is sometimes undertaken on the basis of random blood samples; sometimes on tests carried out at special times in relation to meals; sometimes with prior carbohydrate loading; and sometimes with a substantial period of dietary preparation.

(5) There is a wide divergence of opinion about the interpretation of screening levels; and, of course, standards vary according to whether a true glucose or another type of blood-sugar estimation is carried out.

TABLE 15. CRITERIA FOR DIAGNOSING DIABETES

Time	Minimum blood-sugar level considered positive	Point value for positive result
Fasting	110	1 point
1 hour	170	1/2 point
2 hours	120	1/2 point
3 hours	110	1 point

Reproduced from United States of America, Department of Health, Education, and Welfare, Public Health Service.[81]

(6) Follow-up arrangements for those who give positive results are variable, and many of the persons concerned are not adequately investigated.

(7) Even if full tolerance tests are arranged, there are again variations in such matters as dietary preparation, carbohydrate loading, and the interpretation of results.

(8) There may be further confusion because many of the medical publications reporting diabetic screening campaigns do not give enough information to permit judgments to be formed. For example, no details may be given of the preparation of the patient for testing, of the type of blood used, or of the kind of quantitative estimation employed.

(9) Practically all the surveys that have been carried out point to the conclusion that diabetes mellitus is difficult to define in terms of blood chemistry, since the examination of the blood-sugar level in a population

shows, at one end of the scale, those who are clearly not diabetic, and at the other, those who are definitely diabetic; but in the middle, a substantial group falls into neither category. In many ways the position resembles that pertaining to the diagnosis of hypertension, and greater knowledge is required of the natural history of diabetes before anything of a more definite nature can be said about the intermediate group.

(10) This last point is, in turn, related to the problem of the preventability of diabetic cardiovascular complications. This again is a question that has not yet been finally answered; indeed, it is unlikely to be decided for another ten years or so, by which time randomized studies of treatment of border-line groups should have been completed.

Before advocating a general policy for diabetes screening, therefore, more needs to be learned about the disease and the results of treatment. This will be discussed in the next part of this chapter. However, the detection of overt diabetics is to be encouraged, and high blood-sugar screening levels could be agreed on as an interim measure, so as to exclude border-line cases. Selective screening of the high-risk groups should be more economical than mass screening, since the yield is greater, but a real difficulty (the solution of which might prove expensive) is to make contact with these groups. What is also needed is better education of the public and of the medical and nursing profession. As Reid[64] has pointed out, inquiry shows that public knowledge of the symptoms of diabetes is extremely vague; and, according to the findings of Redhead,[65] Wilkerson & Krall,[57] and the College of General Practitioners,[66] a proportion of diabetics diagnosed in surveys have already had symptoms for some time. In the USA emphasis is now being given to educating the medical profession itself in the diagnosis and control of diabetes. Auxiliary workers are trained as "public health representatives" to organize local detection work. They are based on local health departments and visit local physicians or other professional personnel.[63] In some United States projects self-selection plays a part and as much as an 8% yield of diabetics may be obtained in this way. Another high-risk group is that of patients attending hospital. The Dundee workers[67] have shown a surprisingly high proportion of undetected diabetics in hospital wards, and there is scope for increasing the awareness of physicians and nurses of the sad fact that admission to hospital is in itself no guarantee that the asymptomatic diabetic will be diagnosed.

In screening populations for diabetes it is important to ask whether the criteria discussed in Chapter 2 under "Principles" have been fulfilled. In this connexion, two questions merit further discussion:

(1) whether it can be accepted that early treatment is valuable, and
(2) the problem of diagnostic criteria.

Value of early treatment

The effect of early treatment can be considered at two stages: firstly, in early clinical diabetes and, secondly, at a later stage of the condition.

It is not possible to obtain irrefutable evidence for the value of early (or late) treatment of developed clinical diabetes, because it would be unethical to withhold treatment from a control group. However, clinical evidence has accumulated that carefully controlled diabetics experience less complications than poorly controlled patients. Rundles[68] has noted that neuropathy is particularly prone to develop in the latter. Garland[69] states that amyotrophia is totally reversible with full diabetic control. In Ashton's view[70] "good control" of diabetes over many years may have some beneficial effect on retinal microaneurysms. Both Dunlop[71] and Marble[72] have reported that diabetics under good control are much less likely to develop nephropathy than poorly controlled patients; while Johnsson[73] found significantly less nephropathy and severe retinopathy in a series of patients treated by strict dieting, with an attempt to keep the urine sugar-free, compared with a series allowed a more liberal diet, in which only control of polyuria and ketonuria was attempted. Wolff & Salt[74] found, in acute experiments, that hyperlipaemia returns to normal in children when diabetes is controlled, thus suggesting a possible causal relationship between diabetes and early arteriosclerotic changes; and Keen[75] has reported that cataract is more common in poorly controlled diabetics who are also arteriosclerotic. Newburgh & Conn,[76] among others, have pointed out that weight reduction in the obese middle-aged diabetic may result in a return of the glucose tolerance test to normal. The relationship between diabetes and obesity has recently been briefly reviewed.[77] Finally, as a general finding, patients still living free of complications after a 25-year history of diabetes have been found by Joslin's clinic to be those who had controlled their diabetes meticulously.[78] The subject has been ably reviewed by Beckett,[79] who urges the need to lessen delay in the diagnosis of diabetes.

There is therefore a considerable body of evidence (though open to the objection of selection between groups) in favour of the benefits of treatment in minimizing diabetic complications. It must also be allowed that there is some evidence to the contrary, particularly on the progress of retinopathy and renal changes.[80–82]

When treatment at the earlier, pre-clinical, stage is considered the matter becomes in one sense more complicated because of the difficulty in deciding where to draw the arbitrary line between "health" and "disease"; however, this also means that investigation is made simpler by the real uncertainty that exists about the value of treatment, thus

ethically allowing randomization into treated and control groups. Hoet[83] has shown that "pre-diabetic" women put on insulin during pregnancy have significantly more live births following treatment than before; and Wilkerson[84] finds insulin in "pre-diabetic" women prevents overweight in the infant, with a probable reduction in perinatal mortality. Reid[63,64] reports on a visit to the United States Public Health Service Diabetes Field Research Facility in Boston, Massachusetts, where this work is being carried out, that more members of the control group of "pre-diabetic" women (not treated with insulin) have developed clinical diabetes than have women in the treated group, though the numbers are not statistically significant. "Pre-diabetic" women are defined by Wilkerson as a group characterized by "a high incidence of big babies, stillbirths, neonatal deaths, spontaneous abortions, premature deliveries, toxaemia and congenital abnormalities", as well as by "transient abnormalities of carbohydrate metabolism during pregnancy". Fajans & Conn[85] regard the "potential" diabetic as a person with a normal oral glucose tolerance curve but showing a positive response to the cortisone-glucose tolerance test. They advocate applying this test to those with an increased risk of diabetes—i.e., the women in the categories just cited, as well as the relatives of diabetics.

Diagnostic criteria

This question is connected with that of the value of early treatment, inasmuch as the criteria adopted determine the stage of blood-sugar abnormality at which the diagnosis of diabetes is made and thus the stage at which treatment should be started.

An important factor in considering the nosology of diabetes mellitus is the part heredity plays. The familial aggregation of diabetics has been attributed to the inheritance of a Mendelian recessive gene.[86,87] Ford & Glenn[88] found the prevalence of unrecognized diabetes five times as high among relatives of known diabetics as in the general population. Other surveys have confirmed these findings, but it is not, of course, necessary to invoke a single gene to account for this. Harris[89,90] considers there is insufficient evidence to determine the type of transmission. Recent blood-sugar surveys[25,91] have demonstrated a continuous distribution of this index with no visible tendency to bimodality, though this could be present but concealed. On balance, present evidence probably favours a multifactorial inheritance. The question has been reviewed recently in the *British Medical Journal*.[92] Whether single-gene or multifactorially transmitted, the index blood sugar fails to segregate a discrete group of "diabetics" from "non-diabetics"

and therefore the problem of the border-line case illustrated in Fig. 2(i) arises. This is the problem that lies at the root of any discussion of diagnostic criteria and of "pre-diabetes". The best diagnostic criteria are based on the experience of those treating diabetic patients, and one such group has advised the United States Public Health Service on the set of criteria already cited.[61] It should, however, be noted that these criteria are not the same as those adopted by the American Diabetes Association and there is no general agreement as yet. International agreement on a set of criteria could be a valuable contribution to the comparability of survey work. Recently, a WHO Expert Committee has reviewed current knowledge about diabetes mellitus and has recommended working criteria for single blood-sugar levels after glucose loading.[93]

While it must be agreed that a diagnosis based on a glucose-tolerance curve is arbitrary, the separation of "diabetics" from "non-diabetics" by means of a single blood-sugar examination, or—worse still—urine test, is even more arbitrary and subject to doubt. Apart from patients actually found with the symptoms of diabetes, there will be at one end of the scale those with such high blood-sugar levels that there can be little if any doubt of the diagnosis; while at the other end there will be those persons with low blood-sugar levels, in whom there can be no suspicion of diabetes. The intermediate group, as studies in Birmingham[66] and Bedford[25] and by the United States National Health Survey,[91] have shown, comprise a formidable proportion. In the National Health Survey, for example, 15.5% of subjects had a blood-sugar level of 160 mg% or more one hour after taking 50 g of glucose by mouth (see Table 16), a level that Remein & Wilkerson[15] showed to be 99.4% specific for diabetes by the accepted criteria of their advisory panel. This proportion increased greatly with increasing age, as Table 16 shows: thus, nearly half the women over 65 could be classified as diabetic by this criterion. Similar findings have been reported from Birmingham and Bedford. The National Health Survey report suggests that current standards for a normal blood-glucose level are unrealistically low. As the report says, it is outside the scope of the survey to answer this question but within its scope to raise it. A follow-up of the border-line group found in the Bedford survey is in progress, with randomization of treatment, so that in due course information should become available on the criteria to be adopted for diabetics in need of treatment. Until that time comes it might be legitimate to screen at a higher blood-sugar level of, say, 180-200 mg% at two hours after the administration of 50 g of glucose, in order to detect only unequivocal diabetics. There are hints, however, that relatively mild hyperglycaemia is associated with cardiovascular changes;[94,95] though it remains to be seen whether measures

TABLE 16. PERCENTAGE OF ADULTS HAVING BLOOD-SUGAR LEVEL OF 160 mg% OR MORE ONE HOUR AFTER 50 g OF ORAL GLUCOSE, BY AGE

Subjects	Age groups (years)							
	Total	18-24	25-34	35-44	45-54	55-64	65-74	75-79
Males	11.8	1.3	5.0	11.0	13.2	17.7	27.4	24.7
Females	18.8	5.1	7.3	11.0	19.6	34.5	43.0	58.2
Total	15.5	3.4	6.2	11.0	16.5	26.4	36.0	41.5

Adapted from United States of America, Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics.[91]

aimed at lowering the blood-sugar level are able to prevent or delay these changes. Blood-sugar screening may be greatly facilitated in practice if the newly available glucose-oxidase strip-paper technique proves its worth. This technique would greatly simplify the screening by individual practitioners of the high-risk patients known to them. A large-scale field trial of this method has yet to be published; at least one is in progress in the United Kingdom.

There has been hope that other and better diagnostic indices than the blood sugar might be found—for example, non-esterified fatty acids (NEFA). But so far nothing more reliable than blood sugar as a clinical index has been demonstrated.

HEART DISEASE

Rheumatic heart disease

In developed countries rheumatic fever and its consequences appear to be diminishing, though convincing figures are not available. Satisfactory proof can only be provided by incidence figures, which in turn depend on the condition's being notifiable; and notification has only been carried out in localized areas. However, the declining number of deaths from chronic rheumatic heart disease provide some evidence of this recession. In England and Wales, for example, the crude death rate fell from 255 to 130 per million persons between 1950 and 1964.[96,97] Some of this decline is, of course, likely to be due to improved treatment.

In developed countries, again, the prevalence rate for chronic rheumatic heart disease is relatively low. We do not know what it may be in developing parts of the world. The British general practice survey[98]

gives an annual patient-consulting rate of 1.4 per 1000 persons of all ages (2.3 per 1000 aged 45-64). On the basis of examinations carried out on a national sample between 1961 and 1962, the United States National Health Survey[99] found a prevalence rate of 1.1% of persons aged 18-79 with rheumatic heart disease, the highest rate (3.8%) occurring in men aged 75-79. In women aged 45-54 the rate was 1.8%. (In spite of many inquiries set on foot by WHO, data on the world prevalence of rheumatic heart disease are not yet available.[100,101])

Preventive measures can be taken at two stages: firstly, by treating prophylactically all persons who have had at least one attack of rheumatic fever; secondly, by administering continuing prophylaxis to persons who have developed rheumatic heart disease. In areas where the prevalence of sequelae is not high it is probably not economic to attempt mass detection (by measuring antistreptolysin titres, by taping heart sounds and by electrocardiography), and detection and prophylaxis can safely be left to the personal physician. An example of detection by taped heart sounds is the study of heart disease in children attending Chicago public schools.[102] In this instance the yield proved so small that the cost per case found would surely have been prohibitive. The heart sounds of 27 000 children in elementary schools were recorded on magnetic tape and interpreted by two physicians. Cases of organic heart disease were discovered at the rate of 2 per 1000 children, of which 1 per 1000 were previously unrecognized. Of these previously unrecognized cases 0.2 per 1000 were due to rheumatic fever and 0.8 per 1000 to congenital heart disease. Mass detection and prophylaxis may be more economically worth while in circumstances where many young people are living communally, as in schools and the armed forces. Trials of mass prophylaxis have, for example, been carried out in the United States armed forces, but it has been found extremely difficult to maintain continuous prophylaxis.

It may well be that much higher rates for acute rheumatism and rheumatic heart disease prevail in Africa and Asia, for example, and that prophylaxis in these areas should be tried, despite the difficulties of dispersion and supervision that would be met. We understand that a trial of case-finding for rheumatic heart disease is in progress in the USSR, based on the National Rheumatological Institute in Moscow.[101]

Congenital heart disease

Little need be said here about congenital heart disease. Serious cases will normally be discovered at an early stage in life at infant welfare examinations, whether carried out by the family physician or at health authority clinics. At a later age the school health service takes on this

screening role. Whether so much medical manpower should be used in carrying out repeated routine health examinations is a matter of current discussion. The answer may perhaps lie partially in streamlining the examinations and partially in cutting their number to the minimum, restrincting them to key times in the life of the schoolchild —e.g., at school entrance, at puberty and at school leaving.

Ischaemic heart disease

Mortality. Of all diseases in developed parts of the world arteriosclerotic and degenerative heart disease accounts for the greatest number of deaths, by far the largest number having specified involvement of the coronary arteries (category 420.1 in the *International Classification of Diseases*). The death rate has been steadily climbing. For example, in England and Wales,[103] the crude death rate per million living, for this assigned cause, rose from 808 in 1940 to 2731 in 1962, for men, and from 374 to 1613 over the same period, for women. There is thus not only about a threefold rise for both sexes but an approximately two to one male to female ratio (the ratio diminishing the later the year). The evidence that this recorded increase is real is reasonably firm.[103]

Morbidity. For ischaemic heart disease (IHD), too, reasonably good measures of prevalence and incidence are provided by a number of prospective surveys.

Different studies give mean incidence figures (which, of course, rise with age) that vary from 2 to 12 per 1000 (for men) with 7 per thousand as the mode; while prevalence estimates vary even more widely, from over-all rates of 24 per 1000 for men aged 30-59 (Framingham study)[3] to 24 per 100 for men aged 55-64 (Annandale study).[104] A recent publication of the United States National Center for Health Statistics[99] finds an over-all prevalence for definite IHD of 38 per 1000 in a probability sample of white males aged 18-79 years. Epstein and his coworkers,[105] in a survey covering 90% (8641) of all persons over the age of 16 in the town of Tecumseh, Michigan, measured a prevalence of IHD (including probable disease) of 49 per 1000 for males and 33 per 1000 for females. The prevalence for white men between 65 and 74 years was 12.2% with definite IHD and a further 5.1% with suspected IHD. The diagnosis was based on a medical history and cardiovascular examination, including a 12-lead ECG and a full-scale chest X-ray. The subject has recently been well reviewed by Epstein.[106]

In 1963 the WHO Regional Office for Europe held a Technical Meeting on surveys of the prevalence of IHD in certain European countries.[107] At this meeting Rose reported on IHD prevalence in

workingmen in England aged 35-59. An over-all prevalence of 10% was found, using his questionary,[108] and ECG's read by the Minnesota Code. If diagnostically weaker ECG items (ST depression and T inversion) were included as indicating IHD the prevalence increased to 20%. This variability according to the ECG criteria used may account for much of the difference between the prevalence rates cited above. At the same meeting Horstmann and Thomsen reported findings for IHD symptom prevalence in men from Odense, Denmark. They found an over-all prevalence of coronary symptoms of 5.6% for men aged 45-59, 9.6% for men aged 50-54, and 10.4% for men in the 55-59 age-group.

Screening. One of the primary reasons for screening—a high prevalence rate—is therefore satisfied. The next important question is whether a recognizable pre-symptomatic stage exists. This question will be examined in two ways; firstly, whether there is a latent stage of myocardial ischaemia; secondly, whether a satisfactory high-risk group can be defined. (This distinction is referred to in a WHO report on preventive aspects in arterial hypertension and ischaemic heart disease.[109])

(1) *The latent stage of myocardial ischaemia.* The development of the cardiovascular questionary[110,111] has led to the recognition that many people have symptoms of IHD without being under medical care. Rose found that 4% of the men aged 35-59 who were examined by questionary had symptoms of angina pectoris and 4.5% had symptoms of possible myocardial infarction. About three-quarters of this angina had been previously undiagnosed.[112] Thus, in the symptomatic group alone, there is scope for this type of screening. Electrocardiography is the other chief screening technique. Routine examination by ECG shows that in a high proportion of people there are changes consistent with IHD in the absence of symptoms, quite apart from the appreciable proportion of those developing actual myocardial infarction without pain (21%) in the Framingham series.[113]

In the Annandale series, already referred to,[104] in 10 of the 24 men aged 55-64 found to have IHD there was ECG evidence only. In the Achesons' group of 53 men aged 65-85 with IHD, 27 had ECG changes only.[114] The United States National Health Surveys found that 5% of persons aged 18-79 years had either definite or suspected IHD. In addition, there was a further 6.4% who had electrocardiographic abnormalities falling "just short of the rather severe survey criteria for myocardial infarction".[99] In the series quoted by Rose[108] of 1848 English manual workers aged 35-59, 2% had definite ECG changes in the absence of symptoms (as elicited from answers to the questionary) and a further 10% had the less definite ST depression and/or T inversion. It should

be noted here that Hinkle and others,[115] in studies on the variation of the ECG under conditions of daily life, report that changes in the ST segment and T wave occur so frequently in people of all ages in association with ordinary activities, that they believe it would be hazardous to assume that these changes necessarily indicate a pathological process. However, the prognostic significance of some of these ECG changes in the absence of other signs of IHD can be accepted from the results of prospective studies.[116]

We may ask how successful is the ECG in only detecting disease when it is actually present—i.e., what is its specificity—, and what proportion of false positives we may expect. This question cannot properly be answered because we do not know enough about series of persons having abnormal ECG's who later died and were found not to have myocardial disease post mortem.

Regarding the sensitivity (indicating the proportion of false negatives) of electrocardiography, there is more evidence. The six-year follow-up of the Framingham survey revealed that 88 men had developed myocardial infarction; of these, 15 (all of whom died suddenly) had had no previous evidence of IHD.[117] An earlier report from Framingham showed that of 44 ECG's taken on patients with IHD 22 were normal.[118] Findings of this kind indicate the limits of the ECG in diagnosing the presence of IHD. Moreover, as with other tests, the ECG is subject to the drawback of variability in interpretation between observers.[119] The Minnesota Code[120] is certainly a help in improving observer agreement. A further help will be the training of observers (who need not be medically qualified) on the set of reference tracings being prepared by the Cardiovascular Diseases unit at WHO headquarters, Geneva.[107] The within-observer variation of selected observers may be rewardingly low, while inter-observer variation is about twice as great as the variation in readings by the same observer.[110, 111]

We may conclude, then, that the ECG, though highly significant when positive, is far from being a certain diagnostic technique when used by itself.

A third method of screening for IHD (as well as for other forms of heart disease) is by mass radiography. Mass radiography is sometimes used in case-finding for heart disease, including arteriosclerotic disease. A good example is the study by Thompson and his colleagues, carried out in Oklahoma.[121] When screening for pulmonary disease, the search for heart disease in addition is undoubtedly worth while and is perhaps best done in this way. Carried out by itself, the yield for all heart disease is small—very small, if compared with other methods of finding IHD. Nor is radiography likely to find early IHD or hypertensive disease. In Thompson's Oklahoma project 8126 persons over

the age of 15 were screened by mass miniature radiography—about one-quarter of the whole population of Carter County in this age-group. There were 917 (11%) "suspect" films, of which 302 (4%) were confirmed by a physician. Fifty-two of these cases proved to be previously undiagnosed (0.6% of the population examined). Of these 52 cases, 45 were either arteriosclerotic or hypertensive, or both.

Lastly, screening for IHD is sometimes carried out by estimation of the serum lipids (usually the serum-cholesterol level). The predictive value of a high cholesterol level, while closely correlated with IHD for groups of the population, is not of a high order in the individual and is therefore not of great value, by itself, as a screening test (though, of course, the occasional very high level may indicate the presence of disease). Epidemiological studies of the significance of raised serum-lipid levels in different populations are in progress. A WHO standardization programme is centred on Atlanta, Georgia, under the direction of Dr G. R. Cooper.[122] A review of cardiovascular survey methods has been prepared for WHO by Dr Henry Blackburn of the Laboratory of Physiological Hygiene, University of Minnesota, and Dr G. A. Rose of the London School of Hygiene and Tropical Medicine.[123]

(2) *High-risk groups.* A number of definite risk factors can now be recognized as a result of the various studies, prospective and otherwise, of the epidemiology of IHD. These factors will be discussed briefly.

(*a*) *Age.* The death rate from IHD increases with age and so does the evidence of disease. For example, in the Framingham survey,[117] the six-year incidence for men aged 30-44 was 24.9 per 1000 population, and 90.6 per 1000 for men aged 45-62.

(*b*) *Sex.* As is well recognized, the incidence of IHD is higher in men than in women. In the Framingham study the male to female ratio of incidence at ages 30-44 was 25: 2, while at ages 45-62 it was 91: 45. The tendency for this ratio to approach unity with age is well recognized and is considered to be related to the hormonal changes at the menopause.[124,125]

(*c*) *Physical activity.* Morris and his co-workers [126,127] have shown that IHD probably develops more frequently in those whose work is physically inactive than in those with physically active occupations.

(*d*) *Occupation.* There is a gradient among men (not at all evident among married women) in mortality by social class. The Registrar General's Decennial Supplement for England and Wales (1958)[128] gives a Standardized Mortality Ratio (SMR) gradient from 147 for males in Social Class 1 to 89 for males in Social Class V, and the range is even

greater for specific occupations (registered medical practitioners, 159; farmers, 62).

(*e*) *Serum lipids.* The findings of the Framingham survey, among much other evidence, clearly relate group susceptibility to IHD to the serum-cholesterol level. These is no evidence of bimodality in the distribution, except perhaps for the very small group of familial hypercholesterolaemias. The risk of IHD has been shown to increase with a rising cholesterol level.[117] Even more, perhaps, than with other continuously distributed variables, the predictive value of the serum cholesterol in the individual is low for myocardial infarction.

(*f*) *Blood pressure.* There is a firm relationship between high blood pressure and IHD. The Framingham survey shows that the risk of developing IHD increases as the level of the blood pressure (both systolic and diastolic) rises, the observed incidence of IHD being not far short of twice the expected incidence in persons with definite hypertension (systolic blood pressure over 159 mm Hg or diastolic blood pressure over 95 mm Hg).[117] When left ventricular hypertrophy was present the ratio was more than trebled.

(*g*) *Body-weight.* The independent contribution of overweight as a factor in IHD is not supported by evidence from the Framingham survey.[117] The Framingham work, and also that of Doyle and collaborators[129] (but not that of Paul et al.[126]) does show a positive correlation between IHD and gross overweight: but it appears that this contribution to morbidity is mainly due to the cross-correlation of overweight with serum-cholesterol level and blood pressure. Excess weight is also associated with diabetes mellitus, which in turn increases the liability to IHD. Again, the association may be indirect. However, since overweight is more readily identified than high blood pressure or raised cholesterol level, weight remains an important correlate (even though indirect) for IHD. Apart from body-weight itself there is certain evidence that body-build may be directly correlated with IHD, in that mesomorphic persons are at higher risk than exomorphic or endomorphic.[130] Spain[131] found a higher prevalence rate for IHD in endomesomorphic persons, which was not altered by excluding hypertensive individuals. Paul,[116] while noting no significant difference in weight between IHD patients and controls, did find a significant difference in skinfold thickness, the IHD patients having a higher fat content.

(*h*) *Smoking.* There is ample evidence that cigarette smoking is in some way correlated with an increased risk of IHD. The study of Doll & Hill[132] on British medical practitioners and the prospective surveys of Hammond & Horn,[133] of Dawber and his associates[134] at Framingham,

and of Doyle et al.,[135] as well as the follow-up of the San Francisco longshoremen,[29] all support this conclusion. The important points are:

(i) that the excess risk of IHD increases with the number of cigarettes smoked;

(ii) no relationship between risk and the duration of exposure to cigarette smoking has been shown;

(iii) there appears to be no excess risk from pipe and cigar smoking; and

(iv) there appears to be a rapid reversion of the excess risk of IHD to normal in persons who have given up cigarette smoking.

No causal factor in cigarette smoke has been identified, but it appears probable from these findings that the excess risk of IHD may be due to the repeated adrenergic effect of the nicotine content of cigarettes. The Framingham workers estimate that, if cigarette smoking ceased, mortality and morbidity from IHD might be reduced by almost one half.[136]

Towards the end of 1965 a WHO Working Group, meeting in Prague,[137] considered the present possibilities for preventive measures in IHD and outlined the high-risk factors, in order of importance, as:

high serum lipids
high blood pressure
diabetes mellitus
cigarette-smoking
overweight
stress.

Conclusion. We have seen that more studies have been made into the epidemiology of IHD than into most other non-communicable chronic diseases and that a considerable amount is now known about the early natural history of the condition (though tantalizing gaps in our knowledge of causation still exist). Much is also known about the available early diagnostic tests (though we do not yet know the sensitivity and specificity of the cardiac questionary).

We should now ask whether, in the light of this knowledge, enough is known with sufficient accuracy about the natural history of early IHD, the tests for its detection *in the individual*, and its treatment to justify case-finding programmes.

We have noted above that the practical possibilities for early detection and treatment have been recently reviewed by WHO.[137] At present we must perhaps regard the value of early diagnosis in IHD in a tentative manner in view of our ignorance of causation and of methods of prevention. However, there appear to be at least three risk factors that can, through individual effort, be reduced: cigarette-smoking,

overweight and sedentary habits. It is possible that, with the development of a simple cardiovascular questionary, combined with electrocardiography, blood-pressure recording, chest X-ray and weighing in older persons, a particularly high-risk group of the population could be identified for whom there would be a special incentive to stop smoking, reduce weight and increase physical activity. At least one trial on these lines is in progress.

The other line of prevention that has received much attention is the reduction of serum-lipid levels by dieting. At present reliable information is lacking on the value of diets low in saturated fats with or without added polyunsaturated fats in preventing myocardial infarction. However, the adoption of such regimens is regarded as a reasonable clinical preventive measure in persons at particular risk, and it has been recommended on a large scale in some countries—for example, in Norway, in Sweden (by the Swedish Board of Health), and in the USA (by the American Heart Association). Whether or not it is justified on present knowledge as a general recommendation, alteration (where necessary) of the diet in persons identified in the population through screening measures as being at particular risk may well appear reasonable.

In conclusion, the matter of communication with the public, and how this is to be handled, is of great importance. A health education policy that presents the public with a reasonable and balanced view of the risks of IHD and what can be done about them needs to be evolved at the same time as the epidemiological work is carried out, and not left until actual case-finding is being widely practised. It might be disastrous if persons knowing themselves to belong to a high-risk group were to take too gloomy a view of what could be done about this situation; it would be equally, if not more, disastrous if people tried radically to alter their way of living on the basis of inadequate epidemiological evidence. Though light-heartedly humorous, Myers' "Thumbnail sketch of the man least likely to have coronary heart disease", cited by Groom,[138] does point a lesson.

HIGH BLOOD PRESSURE

Sphygmomanometry is usually carried out as part of a screening programme. It is, of course, of value to diagnose severe degrees of hypertension as early as possible. Undoubtedly cases of severe hypertension occur in the absence of symptoms, or with minimal symptoms only, though this must be the exception rather than the rule.

Perhaps the most valuable reason for taking the blood pressure is in the case of the young person with a high pressure in whom the condi-

tion may be remediable, such as coarctation of the aorta or phaeochromocytoma. Even when the cause lies in the kidney, remediable measures may well improve the outlook. There is evidence, too, that treating severe essential hypertension improves the prognosis and may reverse retinopathy.[139,140] Overshadowing this relatively small group, there is, however, a large number of persons with moderately "raised" blood pressure for their age and sex for whom the value of treatment has not yet been established. This is work that needs to be done. It may well turn out that drugs, while lowering blood pressure and marginally improving prognosis, are so unpleasant to take for the rest of the patient's life, and induce such a sense of invalidism, that the over-all benefit cannot be considered worth while, despite the incontrovertible evidence that life expectation in the actuarial sense diminishes with rising blood pressure.[141] The postural hypotension and sexual impotence induced by some modern drugs are severe disabilities in themselves.

Apart from our present ignorance of the value of treating the early essential hypertensive (and of what criteria to adopt), there is the methodological difficulty of the blood-pressure recording itself. Two factors contribute to this difficulty;

(1) Interpretation of the level in relation to the circumstances under which the reading was taken (casual, resting, circumstances of the examination). Recent work relating average casual pressures to average continuous recorded pressure in normal and hypertensive persons carrying out normal duties indicates that there are wide departures from the average relationship in individual instances, and that the average recorded pressure is considerably lower than the average casual pressure.[16,142]

(2) The observer variation in recording blood-pressure. Sphygmomanometers are now becoming available which remove this source of error.[43]

These points are clearly important in practice since they may seriously affect the validity of blood-pressure examination. Recently, the subject of measuring blood pressure has been well reviewed in the *Lancet*.[17]

We do know that "high blood pressure" is common, increasing with age. There is argument as to whether transmission might be by a single gene or whether it is multifactorial. Population surveys by Boe et al.,[144] Miall & Oldham,[145] Hamilton et al.,[146] Kagan et al.,[147] and the United States National Health Survey[148] indicate a skewed normal distribution of blood pressure with no sign of the segregation of a "disease" group of hypertensives. The Framingham workers arbitrarily define "high blood pressure" as reading by two examiners of 160 mm Hg or over, systolic, or 95 mm Hg or over, diastolic. By these criteria 391 out of 2024 men aged

29-62 (19%) and 410 out of 2445 women in the same age-group (17%) were hypertensive. Using the same criteria the National Health Survey found a total of 15% males and 16.7% females between the ages of 18 and 79 years with blood pressure at or above these levels. The numbers with high blood pressures rose with age in the proportions shown in Table 17.[148]

TABLE 17. PERCENTAGE OF ADULTS WITH BLOOD PRESSURE OF AT LEAST 160 mm Hg SYSTOLIC OR 95 mm Hg DIASTOLIC, BY SEX AND AGE, USA, 1960-62

Sex and age	Systolic at least 160 mm Hg	Diastolic at least 95 mm Hg	Systolic at least 160 mm Hg or diastolic at least 95 mm Hg
Both sexes—18-79 years	11.3	10.0	15.9
Men			
Total—18-79 years	9.3	10.5	15.0
18-24 years	0.2	1.6	1.6
25-34 "	1.0	4.5	4.8
35-44 "	5.2	12.6	13.4
45-54 "	8.9	15.7	18.9
55-64 "	17.1	13.6	23.3
65-74 "	29.0	14.5	30.3
75-79 "	40.7	13.8	41.6
Women			
Total—18-79 years	13.0	9.6	16.7
18-24 years	0.1	1.1	1.1
25-34 "	1.1	3.0	3.1
35-44 "	3.8	7.5	8.4
45-54 "	12.8	13.4	18.2
55-64 "	26.1	18.3	31.8
65-74 "	46.9	18.9	49.9
75-79 "	44.0	13.0	45.9

Reproduced from United States of America, Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics.[148]

Epstein and his collaborators,[105] in the Tecumseh, Michigan, survey, found an over-all prevalence of hypertensive heart disease (HHD) of 7 per 1000 for males and 9 per 1000 for females (defining HHD as a systolic blood pressure of 160 mm Hg or more, or a diastolic pressure of

96 mm Hg or over, or both together with suggestive evidence of left ventricular hypertrophy). As would be expected, the prevalence rises steeply with age and was higher in females than in males; for example, in the age-groups 60-69 it was 39 per 1000 for males and 71 per 1000 for females.

We do not yet known whether treatment would be effective and worth while in improving prognosis. It is difficult, as Pickering has pointed out,[149] to compare the prognosis in hypertensive patients with that expected for the whole population because of the almost inevitable selection in the case of the hypertensive series. Bechgaard,[150] however, has compared a group of persons with raised arterial blood pressure with the total population of Denmark and shows that the mortality for men in the age-group 40-49 with a systolic blood pressure of over 180 and less than 200 is nearly five times greater than that for the whole population. (The corresponding mortality for women is only one and a half times greater than normal.)

The records of insurance companies also show the relationship between levels of blood pressure and mortality. There are therefore good grounds for treating mild essential hypertension, provided it can be demonstrated that this is effective at the lower levels of blood pressure and does not interfere unacceptably with the normal enjoyment of living. What is evidently needed is a controlled trial of early therapy to answer these questions, including that of the acceptability of long-term drug administration in the absence of symptoms.

OVERWEIGHT

In multiple screening programmes it has been usual to record the weight and height and to determine, by reference to standard weight tables, whether the subject is "overweight". If so, he is told of the risks of overweight and advised about weight reduction. This advice is normally based on the judgment that the excess weight is due to obesity, since above-average muscle or bone mass may not be associated with a reduced life expectation.

Life tables, such as those published by the American Society of Actuaries[151] show that expectation of life falls with increasing degrees of overweight when weight is standardized for height, build, age and sex, and that expectation can in fact be improved by weight reduction.[152] The main risks associated with overweight are cardiovascular disease (only with gross obesity, according to Doyle et al.[129]), diabetes, chronic respiratory disease and degenerative arthritis. But, as with other continuous distribution conditions, there is difficulty in deciding what

should be regarded as overweight; anything from 10% to 30% above the mean has been regarded as the lower clinical limit in different studies. Kemsley and his co-workers[153] suggest the upper and lower quartiles as reasonably practical limits for overweight and underweight. An important factor, not fully allowed for in most standard tables, is the relative adiposity—i.e., the ratio of fat deposits to total body overweight. Measuring this adds to the complication of the examination, though it may be done relatively simply with an instrument such as the Harpenden calipers[154].

Another difficulty about using tables is that normal weight (and, of course, height) for men and women varies from country to country and within the same country at different periods of time. For example, comparison shows that the average height and weight of persons in the USA[155] has been increasing during the present century and weights (in relation to heights) were greater than those in some other countries (Canada and Norway). In the CCI Baltimore study,[156] in the physician evaluation of a sample by physician interview, the prevalence of obesity as judged by observation was 129 per 1000 population, or nearly 1 in 8 persons. Of the sample submitted to screening 40% of males were 10% or more above the Canadian normals used, 18% were 20% above and 8% were 30% above. As the report says, "the high prevalence of obesity . . . points up the need for further research to clarify the relationship between obesity and health . . . The size of the problem suggests that the approach may need to be directed to the public at large as well as to the individual obese patients". Strong motivation is indeed required to persuade obese people to reduce their weight by dieting, as those who have had clinical experience of this particular problem know. To some extent this recommendation, made in 1956, is beginning to be translated into action. Norway, for example, has recently issued a public statement, through the Norwegian Board of Health, advising moderate dieting, primarily aimed at lowering the intake of polyunsaturated fats but also recommending keeping to a moderate total calorie intake. The problems of definitions and of weight control in obesity were reviewed in the *British Medical Journal*,[157] where the need for further longitudinal studies of the effects of treatment was pointed out. There is no doubt that weighing is one of the simplest and most precise screening tools available and that the information it gives is important for health; what we still need to learn is how best to act on the information thus acquired.

RESPIRATORY DISEASES

Pulmonary tuberculosis

Although mortality from pulmonary tuberculosis began to fall dramatically with the introduction of streptomycin and other chemotherapeutic agents,[158] the number of notifications has not decreased at anything like the same rate; indeed, in the older age-groups it has even tended to rise. This effect may be attributable to improvement in methods of detection and especially to mass radiography (MR). Having reached low levels in developed countries there is a tendency for the notification rate to level off. In England and Wales at the end of 1963 there were 340 000 persons under supervision for pulmonary tuberculosis —a rate for the population of about 0.75%. The Director-General of WHO has pointed out[159] that not a single country has reached the point of control where there is less than 1% prevalence of natural reactors to tuberculosis among 14-year-old children—a criterion set by a previous WHO Expert Committee on tuberculosis as indicating that tuberculosis is no longer a serious public health problem.

Pulmonary tuberculosis is perhaps the classical condition for early, often pre-symptomatic, detection (as well as primary prevention with BCG) and it meets the screening criteria well, in that:

(1) Pulmonary tuberculosis is an important public health problem.

(2) Facilities for diagnosis and treatment should be available, otherwise there is no benefit, only harm, from screening.

(3) The natural history of the precursor stage of the disease has been elucidated; early infiltration does lead to overt disease.

(4) There is a recognizable latent stage (positive tuberculin reaction and infiltration).

(5) Suitable tests are available—the tuberculin reaction and mass radiography (MR).

(6) The tests are acceptable to the population.

(7) There is an accepted (and effective) treatment.

(8) Persons without recognized disease (small fibrosed infiltrations) are not treated as patients.

(9) The cost is tolerable when MR is used, because the expense involved in treating a florid case of tuberculosis is thereby avoided.

(10) Long-term follow-up is an essential part of schemes for the control of tuberculosis.

This brief summary makes no attempt to review the bulky literature on the early detection of tuberculosis. The subject has been examined recently by a WHO Expert Committee on Tuberculosis.[159]

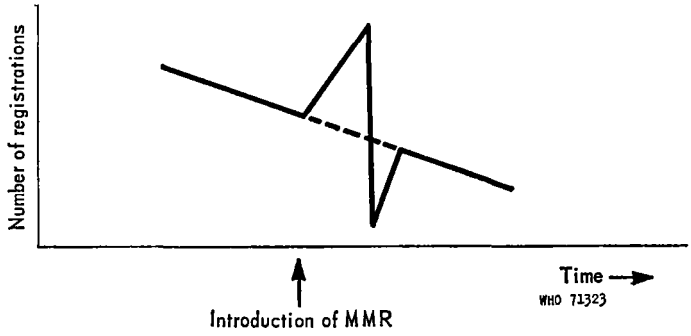
Only a few salient points will be discussed.

(1) Unlike cancer, there is evidence that small tuberculous lesions in the lung indicate early lesions.[160] In a five-year prospective survey of civil servants and other workers in the London area the size of lesion at first X-ray has proved of the greatest prognostic significance.

(2) Small infiltrative lesions can only be ignored at peril; persons with these lesions are in fact in need of treatment and between 70% and 80% will have further trouble if the lesion is ignored.

(3) Proof of the effect of early treatment is very difficult to demonstrate, since it would be necessary to show that the rate of decrease in the number of registrations was influenced by earlier detection and that a significant change in the slope of the curve in a downward direction had occurred. What has in fact occurred as a result of introducing MR (and this has been seen best in intensive surveys, such as those carried out in some Scottish cities) is an early rise in the number of registrations at the time of introduction, followed later by a compensatory fall, and then a relatively rapid swing back to the level of the falling base-line, after which the fall in registration continues at its "original" rate (Fig. 5).

FIG. 5. EFFECT OF INTRODUCTION OF MASS MINIATURE RADIOGRAPHY ON REGISTRATIONS OF TUBERCULOSIS



Thus in England and Wales in 1938-39 the mean annual notification rate per 100 000 persons was 88; in 1947-50, following the impact of MR, it rose to 100 per 100 000, and this was followed by a fall in 1954-55 to 80 per 100 000 persons.[158]

(4) As with other tests, radiological screening gives rise to the problem of sensitivity and specificity, which is linked with that of observer variation. Yerushalmy[161] found a false-negative rate (a missed lesion of some kind) of nearly one third, in addition to a false-positive rate of about 2%. By dual reading, one third of the lesions missed by a single reader could be picked up, but, of course, the double reading of X-rays necessarily adds to the cost of case-finding.

(5) As radiological screening progresses the number of persons needing continuing supervision increases cumulatively: few are discharged and additions are always being made. This need for keeping the intermediate type of patient under surveillance further adds to the expense. The experience of the Danish Tuberculosis Index[162] is that for every one person requiring treatment between 5 and 10 will need to be kept under observation. Similarly, Styblo[163] has some 20 000-30 000 persons under supervision in Czechoslovakia, in whom the natural history of the border-line lesion is being followed. (Thus screening criterion (3) above (page 99) has not been completely met: there are early pulmonary stages that require watching rather than treatment.)

(6) Economics. (*a*) In a developed country the yield from MR rapidly declines. The question then arises of whether to make MR more and more selective; or whether to continue offering it to the whole adult population in the expectation that the rare missed case might otherwise go longer undetected than if MR had never been introduced (because of the very rarity of the disease), thereby prolonging the period when contact cases might occur. One alternative is to make MR selective for high-risk groups in the population (adolescents, the elderly, the economically depressed, persons exposed to special industrial or professional risks, and persons with a cough); another is to link MR with Mantoux testing so that all contacts of Mantoux-positive children are X-rayed.

(*b*) In countries where the cost of a countrywide service might be prohibitive, medical services are unlikely to be adequate to carry out extensive follow-up of border-line cases. In the first place, it goes without saying that the prerequisite for a detection programme is an adequate medical service for the definitive diagnosis, treatment and aftercare of the patient. There is clearly no point in making a diagnosis if facilities for treatment and for the prevention of contacts are not available. Secondly, the stage at which tuberculosis is diagnosed may be varied according to resources. MR is expensive and, as we have noted, produces a large number of border-line patients for costly follow-up. There is a case, now that chemotherapy is so effective, for passing over the earliest stages of the disease and endeavouring only to detect the condition when the sputum has become positive[164]. Clearly, with this

technique there is an associated risk of increasing the number of contact cases, but it is perhaps the most economical secondary preventive measure available and therefore capable of being widely used.

In summary, it should be noted that symptoms provide a much more selective criterion for achieving high yields than do other epidemiological screening criteria, single or combined. Where pre-symptomatic case-finding is considered justifiable and feasible, screening procedures dictated by the epidemiological situation can increase the efficiency of a community examination, but the contribution of such examination to the total case yield will always remain marginal. Follow-up may well be the most important consequence of screening, since there are indications that it yields, in the long run, quite substantial returns.

Non-specific respiratory disease

Chronic non-tuberculous disease of the chest presents rather different problems from those discussed under tuberculosis. By far the largest contributor to this category of illnesses is chronic bronchitis, and it is with this condition that the present section will be concerned.

There is now overwhelming evidence that the prevalence of chronic bronchitis is associated with the twin factors of atmospheric pollution and cigarette-smoking—so-called macro- and micro-air pollution.[165] Wide international differences in mortality and prevalence are found and much of this appears to be related to the factors just mentioned. Undoubtedly, also, the diagnostic customs in the countries concerned play their part. For example, the mortality attributed to bronchitis in England and Wales in 1958 for all persons was 65 per 100 000, compared with a rate of only 2.3 per 100 000 persons (Caucasian) in the USA. However, it is doubtful whether differences in diagnostic habit or coding of the cause of death could account for such large differences. Comparative studies of pathology are now in progress, in Chicago and London, and these should help to resolve these doubts.

As an example of the type of epidemiological work needed in order to understand the real meaning of international differences, the study by Mork[166] of comparative prevalence of respiratory disease in England and Wales and in Norway should be mentioned. Mork found that, while the prevalence of minor symptoms was nearly the same in the two countries, the prevalence of severe symptoms of chronic respiratory illness was considerably higher in England and Wales. Studies of similar working groups of postal and telegraph workers in London, rural England and cities in the USA have been carried out by Holland[167], with results comparable to those of Mork.

In England and Wales chronic bronchitis appears to be more prevalent than in any other country. A survey by the College of General Practitioners[168] showed a prevalence of 17% in men aged 40-64; and in an earlier survey bronchitis was found to be the second commonest reason (after the common cold) for consulting a physician in general practice (260 consultations per 1000 patients per year).[98]

Though much has still to be learned about the etiology of chronic bronchitis, a great deal of epidemiological work has by now been carried out which has enabled us to identify some at least of the precipitating factors. Use of this knowledge, largely by abating atmospheric pollution and by persuading people not to smoke cigarettes, should go far towards preventing the disease. However, it will take a long time to achieve these aims, and meanwhile many young persons are insidiously developing chronic bronchitis. We should try to discover what might be done to arrest the course of this pathological process and, if possible, to reverse it.

In the absence of a specific etiological agent or of specific pathology the assessment of chronic bronchitis has to depend on recording symptoms and on measuring sputum volume and such functions as the forced expiratory volume (FEV) and the peak expiratory flow rate (PEF). Records have proved their worth in cross-sectional epidemiological studies. Work is now in progress on prospective studies aimed at identifying personal factors of susceptibility to chronic bronchitis. Preliminary evidence[169] seems to incriminate atmospheric pollution at a much earlier stage of life than has previously been recognized. If it proves a practical proposition, say, by using a short respiratory questionary and a simple measurement of lung function, to identify a high-risk group of individuals at a very early stage of respiratory function abnormality, the next stage would be to conduct a trial of treatment. In this particular case the most effective method we know is to stop smoking, and a comparison between early chronic bronchitics who are still smoking and those who have stopped smoking should give helpful information about the reversibility of the condition. A difficulty would certainly be that of obtaining test groups comparable in other respects. At the same time, naturally, it would be useful to study the effect of the cessation of smoking on the incidence of ischaemic heart disease (see page 92). Studies of this kind are now getting under way, but it will be some time before we can expect the results that are needed to indicate whether a high-risk group of persons can be identified who would specially benefit from intensive preventive measures, over and above those normally advised.

Finally, industrial risks should also be considered. The precise relationship between certain industrial hazards—for example, in the

steel industry—is not fully understood. Here again work is needed to discover whether a high-risk group exists which could be identified and advised on suitable employment. At least two studies of this kind are in progress in the United Kingdom.

The need for an internationally comparable nomenclature and methodology in chronic non-specific lung disease, and for further epidemiological studies, was discussed at a WHO European Symposium, held in Moscow in 1962.[170]

CANCER

Lung cancer

We do not possess accurate morbidity data on lung cancer that would indicate the size of the problem. Nevertheless, an idea can be obtained from the general practice survey carried out by the College of General Practitioners and the General Register Office in England and Wales in 1955-56,[98] since it is likely that all patients with lung cancer consulted their family doctor at least once during the observation year. The rate for "patients consulting" for neoplasm of the lung, bronchus and trachea is 0.5 per 1000 persons (1.0 per 1000 for males and 0.1 per 1000 for females); for men between the ages of 45 and 64 the rate is 2.1 per 1000. In this high-risk group lung cancer is found, therefore, at a rather lower prevalence rate than is carcinoma-in-situ of the uterine cervix in all adult women (3 per 1000). However, lung cancer is so lethal that deaths from this condition are more than five times as frequent as those from cancer of the cervix. Moreover, mortality has been increasing annually at an alarming rate in the highly developed countries, in step with earlier cigarette-smoking; in England and Wales the number of deaths due to malignant neoplasms of the trachea, bronchus and lung has increased in males by nearly two-thirds between 1954 and 1964, having risen from 14 000 to 24 500.[171] Such is the nature of lung cancer, therefore, that if early detection could be made effective, mass screening of the adult population in highly developed countries would be indicated.

Unlike the accessible cancers (cervix, lip and skin) lung cancer is customarily at an advanced stage when diagnosed with the help of X-rays and the prognosis is nearly always bad. The corrected survival rate at five years for males in England and Wales registered during 1945-47 was only 14% for early cases submitted to radical treatment.[172] For all early cases, whether treated or not, the five-year survival rate was only 2%. Seven out of eight cases were in men and of these only 13% were classified as early at diagnosis, while nearly one-quarter had metastases. The median duration of symptoms was about six months

for the early cases but only four and a half months for those already with metastases. The five-year survival rate of both early and late cases treated radically was unaffected by the duration of the symptomatic history, being 12% for persons with symptoms of from 0 to 2 months duration and 10% for those who had had symptoms for 12 months and over.

This is a gloomy picture, but it is necessary to remember that it is based on persons developing the disease 20 years ago. Since then mass radiography (MR) has been practised widely and it is necessary to study its effect in combination with advances in thoracic surgery. MR was, of course, developed for case-finding in the epidemiological control of pulmonary tuberculosis. With the decline of tuberculosis in many countries, attention has turned towards the possibility of using MR mainly for diagnosing other lung conditions, of which cancer is the most important, rather than just for seeking out tuberculosis. We therefore need to see as clearly as possible what is the evidence for benefit so that a sensible policy can be evolved.

Four surveys will be considered: that of Posner, McDowell and Cross in Birmingham;[173] Cuthbert's review of the Glasgow X-ray campaign;[174] Waddington's comparison of the Liverpool survey with his own and Gifford's routine hospital admissions;[175,176] and Boucot, Cooper & Weiss's experience with the Philadelphia Pulmonary Neoplasm Research Project.[177]

Birmingham. Posner and his colleagues analysed all cases of lung cancer diagnosed by mass miniature radiography (MMR) units in the Birmingham Hospital Region during one year (1955-56), 238 in all being investigated. As with the Glasgow series, patients diagnosed by "conventional" MMR ("routine MMR cases") were compared with patients referred to the units by general practitioners ("referred cases"). There were rather more older patients in the group referred by general practitioners. At one year the survival of the routine MMR group was better than that of the referred group—50% compared with 36%—, though this difference is not significant. More of the routine MMR cases proved to be resectable than the referred cases—44% compared with 30%; also there was a higher proportion of lobectomy as opposed to pneumonectomy in the routine MMR group, which is usually considered to equate with a better prognosis. As with the Glasgow series, 85% of the routine MMR group had had symptoms at the time of presenting for examination. Posner et al. concluded that the smallest cancers were very easily missed and recommended the selective screening, by static 100-mm camera units, of men over 35 referred by their own doctors, irrespective of symptoms. They considered it would be a major mistake

if the relatively high cost of a programme of this kind were to be allowed to deflect attention from the importance of primary prevention.

Glasgow. Forty-eight patients with proved bronchogenic carcinoma were found through the operations of one of the city chest clinics, and these patients were compared with 48 consecutive patients referred to the same clinic by general practitioners. The average age of the two series was about the same with a similar range, most of the patients being between 50 and 65. Of the 48 MMR cases, 36 were found to have had one or more of the cardinal symptoms of chest illness; but on several counts the disease in the patients referred by general practitioners was more advanced. As might be expected, the patients in both series who were considered suitable for surgery had the better survival at 18 months; but the MMR group did better than the referred group, 13 of the MMR group surviving at 18 months compared with only 8 of the referred group.

Liverpool. Of more than 450 000 persons over the age of 15 X-rayed in the Liverpool campaign of February-March 1959, 235 were admitted to surgical wards for investigation. Of these, 163 were suspected of suffering from bronchial neoplasm—a rate of 0.36 per 1000 persons examined (0.5 per 1000 males), which is somewhat lower than the general practice survey rate quoted above. Of the 163 suspects, 118 were proved to have a primary bronchogenic carcinoma, and Waddington compared these with his earlier series of patients admitted to the Liverpool Thoracic Unit. Of the 118 from the Liverpool campaign, 80 (68%) were resected, which amounted to 90% of all those surgically explored. This is a rather higher rate than was found in the hospital series, where only 70% of those explored could be resected. Moreover, a higher proportion of the Liverpool campaign patients could be treated by lobectomy (as opposed to pneumonectomy) than in the hospital series. However, at the time of compiling the report, while only 61% of all the operated patients from the MMR campaign (who had survived the first two months) had survived one year, 67% of the hospital series had so survived. There therefore seems to have been no advantage, at the time of writing, for those presumptively diagnosed earlier by MMR.

Philadelphia. In this well-known project 6137 men of 45 years of age or more were enrolled in an experimental prospective survey with the aim of following them up by means of six-monthly 70-mm chest X-rays and a short medical history. A previous MR campaign in Philadelphia had shown a prevalence rate for lung cancer of 2.7 per 1000 men over 45, which is rather more than was found in the survey carried out by College of General Practitioners in a similar age-group.

During the course of the study, 26 men, in whom no radiological evidence of neoplasia had been discovered on entry to the project, developed lung cancer. Only 5 were without symptoms up to the time of the first positive X-ray and only 2 were asymptomatic actually at the time of the examination. The other finding of direct interest is the period of survival: only 2 of the 26 had survived to the time of writing the paper, which could have given a maximum survival time of seven and a half years, though there is no statement as to actual survival times.

From these surveys it is clear that the prognosis of lung cancer is little influenced by detection by routine radiography and that, in fact, most of those who are detected in this way are symptomatic at the time of their X-ray. It seems probable that, as at present carried out, routine chest X-ray at any interval greater than six months would be of little use. More frequent X-ray examination not only would be uneconomic but would also pose problems of persuading subjects to attend and of causing possible harm from radiation exposure. The best use of routine radiology at present is likely to be for the selective screening of middle-aged persons, particularly males, with a persistent cough.

In considering the results of these (and other) early detection surveys it is important to remember that like is not being compared with like; and that the slightly better prognosis in the screened, as compared with the routinely diagnosed, series of patients is probably accounted for by the fact that the disease in the screened group was discovered earlier in its course. It is therefore unwise to attribute, without better evidence, the improved prognosis to the effects of treatment. Truly to compare two series in this way, it is necessary to follow the treated patients over a much longer period, in order to observe the long-term effect of earlier diagnosis on the cure rate.

Another point of importance in comparing series in this way is the need for random allocation of the population into screened and control sections. Without this precaution there is the real danger that the patients diagnosed early by X-rays may differ in important respects (which might affect the prognosis) from the routinely diagnosed group.

The examination of sputum by exfoliative cytology has also been employed as a means of detecting early cancer of the lung. Compared with the use of exfoliative cytology for cervical cancer there are drawbacks. The bronchus is not as accessible as the cervix; and examining the sputum is considerably more time-consuming than examining cervical smears if the results are to be at all reliable. At the Johns Hopkins Hospital, Baltimore,[178] the positive sputum rate in patients with bronchial carcinoma rose from only 20% when one sputum specimen was examined to 56% when 5 specimens (3 smears of each—i.e.,

15 slides) were examined (or from 42% to 95% when suspicious as well as definitely positive reports were included). In another series of 144 patients with suspected lung cancer at St Bartholomew's Hospital, London,[179] 10% of the results obtained from examining 3 smears from one specimen of sputum were false-negative. The time needed to achieve this degree of accuracy was unacceptably long. A rapid sputum cell concentration technique is needed to shorten examination time, and work on these lines is proceeding.

Lilienfeld[180] has reported on a comparison between sputum cytology and radiology in the early detection of lung cancer in persons living in United States Veterans' Administration homes. Up to 1960 over 12 000 persons, aged 45 and over, had been submitted to a six-monthly X-ray and sputum cytological examination at least once, and some 4000 had been screened three or four times. Of 43 cases of lung cancer diagnosed by follow-up, cytological screening contributed to the diagnosis in 15, and this diagnosis would have been missed if X-ray screening alone had been used. On the other land, if cytology alone had been used, 21 of the 43 would have been missed. Unfortunately survival at six months was no better than that observed on previous occasions, where repeated screening was not carried out.

It appears, therefore, that while sputum cytology is complementary to chest X-ray, its use does not improve the prognosis by earlier diagnosis in lung cancer; and that the technique is too time-consuming for it to be economically justifiable as a mass screening measure.

Clearly the prevention of lung cancer would be far better than early detection, and it is interesting that the American Cancer Society and Veterans' Administration study just referred to showed that 1% of present smokers had positive or suspect sputum cytology as compared with 0.35% of those who had never smoked and 0.47% of past smokers.

Cancer of the cervix

The evidence for the value of detecting cervical cancer early is relatively strong. The earlier the stage at diagnosis the better is the survival rate. It is also reasonable to suppose that diagnosis and treatment at the pre-invasive, carcinoma-in-situ stage would very greatly improve the existing survival rate, though it is as yet too soon for the relevant statistical data to have accumulated; nor is there evidence of a reduction in the death rate directly attributable to diagnosis and treatment of the pre-invasive lesion (though mortality from cervical cancer is in general decreasing at a slow but steady rate in advanced countries). It is, indeed, probably too soon to expect to see this effect, since intensive

community screening for cancer of the cervix has only been practised for a few years, and then only in relatively few centres. A considerable fall in the incidence of invasive cervical cancer has, however, been observed in British Columbia and other centres since the introduction of widespread screening by exfoliative cytology, which may or may not be attributable to such screening.

Unfortunately, the relationship between so-called intra-epithelial carcinoma of the cervix, or carcinoma-in-situ, and invasive cervical cancer has not so far been clearly elucidated beyond the shadow of a doubt. Now, because the evidence is highly suggestive that the one is a precursor of the other—if not always, at least frequently—it can no longer be considered ethical to carry out a definitive trial. Were it feasible, the ideal trial would randomize between two groups of women in a large population. One group would be screened and re-screened at intervals for carcinoma-in-situ (as well as for pre-clinical, micro-invasive cancer) and those women found with lesions would be treated by surgery; while the other, control, group would not be screened, but clinical cancer of the cervix would be diagnosed and treated in the conventional way. Such a trial should demonstrate whether incidence and mortality were lowered and survival lengthened in the screened group, as compared with the controls. It might still be ethical for a trial of this kind to be carried out where facilities for screening, diagnosing and treating uterine cancer are as yet strictly limited by the degree to which medical care is advanced. The nature of the evidence required for a rigorous appraisal of the relationship between carcinoma-in-situ and invasive cervical cancer has recently been reviewed by Knox.[181]

Short of such a definitive randomized trial, the natural history of pre-invasive cervical cancer has been reasonably closely studied. Firstly, there is relatively good evidence that the in-situ lesion of the cervix may become invasive cancer of the cervix. The direct evidence for this is both retrospective[182] and prospective.[183–186] There is also indirect evidence based on the age-specific distribution of in-situ and invasive cancers.[187–188] Secondly, estimates are available of the proportion of in-situ lesions that become invasive,[183–185,188–190] though these estimates vary widely (from one-quarter to two-thirds).

Another important feature of the pre-symptomatic lesion about which there is incomplete information is its duration. Dunn[190] has done useful work on this point, based on his study of the United States Public Health Service survey in Memphis, Tennesee. He and his colleagues[191] now estimate an average duration of about 10 years (calculated from the age-specific prevalence and incidence rates). This accords reasonably well with the estimate of Boyes, Fidler & Lock[188] of 12-13 years, based on mean age of onset of both in-situ and clinical invasive carcinoma.

Some of the picture presented by pre-invasive cancer of the cervix has therefore been filled in, but there are still important gaps in our knowledge. We need to know about the effect on mortality as quickly as possible since it is possible that incidence could fall without a reduction in the death rate. To obtain this information, mortality data related to numbers of examinations in populations screened are needed. It is also important, for practical purposes, to discover how frequently cytological examinations need to be carried out. To learn this it is necessary to note the time elapsing between the last negative examination and the first positive one in as large a number of reported screenings as possible, the screening interval being varied in different groups of women. In this way it should be possible to construct a frequency distribution of the rate of progression from cytology negative to invasive cancer in the small number of women in the population who develop cancer of the cervix. Depending on the shape of this distribution curve, it may be possible to select an optimum screening interval at a point where there is a steep increase in the number of invasive cancer cases. Registration of cytological examination and linkage with invasive cancer registration are one way in which this can be done.

There are other practical problems associated with population screening, the solution of which depends on epidemiological knowledge. One of the problems is that of ensuring that examination is offered to women at greatest risk. The evidence shows that the incidence of cervical cancer increases with age; that it affects married rather than unmarried women; that early coitus is an etiological factor rather than parity; that there is a sharp social-class gradient, with the higher incidence in the lower social classes; and that there are marked cultural and geographical differences.[192-194]

It is therefore important, in organizing population screening, to take steps to ensure as far as possible that married women, particularly those who married young, and women in the lower socio-economic groups are not only offered, but accept, examination. This means a "free" service and organized health education along lines planned according to prior attitude studies. Without this approach it is doubtful whether merely providing facilities will in practice achieve results. It is also necessary to plan health education, based on a knowledge of the fundamental attitudes of the public, both women and men, to cancer of the cervix and cervical cytology, so as to reach that part of the population most in need. The surveys with this aim in view, in Alameda County, California,[52] on a national sample of the population of the USA,[53] and on a sample of the population of Manchester, England,[54] have already been referred to (see Chapter 3, page 77).

A recent development, at present still in the evaluation stage, shows

signs of overcoming the difficulty of persuading women at high risk to undergo cytological examination. This is the irrigation pipette,[24] a plastic pipette that can be inserted by the woman herself into the posterior fornix of the vagina. The pipette contains fixative, which is expelled into the vaginal pool and sucked back together with exfoliated material. The pipette is then placed in a container and mailed to the laboratory, where smear preparations of the material are made. Davis[23] has reported a nearly 80% rate of acceptance of this technique among "semi-indigent" women in Washington County, Maryland; and a similar acceptance rate has been found both by F. Koch[195] in Copenhagen and by Elizabeth MacGregor and her colleagues[196] in general practices in Aberdeen—to give only three examples.

With the general acceptance of the value of cytological screening for uterine cancer, attention has naturally turned to the possibility of developing automated techniques. Two may be mentioned.

A number of workers are examining the value of estimating the 6-phosphogluconate dehydrogenase (6-PDG) level in vaginal aspirate as an index of the presence of malignant cells. So far this technique has proved too unreliable for case-finding. Though apparently reliable as regards sensitivity as a test for invasive cancer of the cervix, it has a false-negative rate in the region of 50% for carcinoma-in-situ.[197] The false-positive rate is also high—between 20% and 40%. The value of varying the technique is now being examined.

The development of an automatic electronic scanner of preparations of vaginal cells has been in progress since the 1950's. A practicable instrument has not so far been developed, but work employing the principle of scanning with a flying spot microscope is advancing. There are numerous possible uses for an instrument of this type and more than medical interests are involved. The cost of developing a prototype instrument is considerable and there might well be a case for co-operative effort in this field. More recently, the possibility of detecting cervical cancer cells in vaginal aspirate, using the Coulter Counter, has been reported.[199] The technique is still being critically investigated.

Breast cancer

In England and Wales carcinoma of the breast in 1964 accounted for 20% of all female cancer deaths and for nearly 4% of all female deaths.[200] It is easily the commonest cause of death from cancer in the female, and mortality has remained steady from year to year regardless of treatment. Thus the death rate for all females in England and Wales per million living (standardized) was 158 in the decade 1901-10, and 182 in 1950-54. This trend is carried through all age-groups, as rates for

1936-54 demonstrate.[201] Nulliparous women are more prone to the disease than women who have lactated and there is evidence that some tumours are hormone-dependent; in one group of tumours the peak registration rate is reached at the time of the menopause and is followed by a temporary fall, though another group shows a steady increase in the registration rate throughout life.[202]

There is no question, therefore, that a high-risk group involving large numbers of middle-aged women does exist, at least in certain countries. (Some countries—Japan, for example—have an extremely low prevalence of breast cancer.[203]) Unfortunately the results of treatment are discouraging; the corrected five-year survival rate for all stages in England and Wales, 1945-47, was only 37%, though it was 67% for the earliest stage when radically treated.[204] Breast cancer appears to a large extent to run its own course and to be not greatly influenced by treatment, whether surgical or radiotherapeutic. Park & Lees[205] have estimated that, at most, treatment accounts for cure in no more than 5%-10% of women. Lewison,[206] from the breast cancer clinic at Johns Hopkins Hospital, Baltimore, found little difference in survival when different forms of surgical treatment, carried out at different time periods, were compared. Berg & Robbins,[207] in a 20-year follow-up of breast cancer at the Memorial Hospital, New York, estimated the cure rate by surgery for anaplastic duct carcinomas at 12%.

For a highly prevalent and lethal condition that tends to run its course whatever the treatment, the question of early diagnosis, with a view to more complete eradication of the tumour and consequent improvement in the prognosis, assumes high importance. We should inquire whether, if breast cancers can be brought to treatment at an earlier stage than at present, by health education, frequent self-examination of the breast, or screening by soft X-rays (or possibly by infra-red or ultrasonic scanning), the prognosis is likely to be improved. Delay among women at risk may occur for two main reasons: firstly, fear, and, secondly, failure to be aware of a small lump in the breast. Another cause of delay is a lack of awareness by the medical profession of the importance of early diagnosis.

The first of these reasons for delay is gradually diminishing *pari passu* with a rising level of general education. Better general education enables people to reason more clearly and to plan rational steps to meet a situation. More specifically, ignorance and fear go cheek by jowl, and health education, in seeking to overcome ignorance, at the same time aims to dispel the fear that may prevent a woman from consulting her doctor as soon as she notices something wrong.

The second reason for delay—the fact that the lesion is small enough to escape attention at all unless looked for in a special way—can be

overcome by organized mass screening. Screening may take the form of physical examination, examination by the woman herself, or an externally applied technique, such as mammography or thermography. Some of these methods are costly, use up valuable resources, both human and material, and involve the female public in a co-operative effort that may have bad, as well as good, effects on morale. Therefore, before advocating case-finding, it is necessary to examine the merits of detecting breast cancer when the lesion is as small as possible.

The question of the value of detecting the lesion when small may be examined in two ways. Firstly, it is worth looking at some of the evidence for the benefits of diagnosing breast cancer at an early stage in its course (which is linked with the grade of malignancy). Secondly, the evidence for the relationship between size of lesion and stage and degree of malignancy needs to be examined.

Prognosis by stage

(1) There is a considerable correlation between stage at registration of breast cancer in the female and duration as reported by the patient.[208] Nevertheless, in a series of registrations in England and Wales, in nearly 20% of women with a history of more than two years the growth had neither spread nor apparently invaded the lymphatics; while in over 25% of those with a declared duration of less than one month the growth had invaded extra-mammary tissue or produced distant metastases. Therefore, length of history alone will not account for the facts; there must also be a wide variation in the degree and nature of malignancy between tumours.[208]

(2) The average prognosis for breast cancer is poor: the Registrar General's Supplement[204] finds, as we have seen, a corrected five-year survival rate of 37% and concludes that the chances of survival depend almost entirely on the clinical stage when treatment is begun, and that neither the duration of the tumour before diagnosis nor the age of the patient seriously affects survival.[209] Among others, Bloom, in a recent report,[210] has demonstrated, by grading breast carcinoma according to histological type, that survival correlates well not only with stage but also with grade. Among patients with stage two cancers, for example, there is a five-year survival rate of 71% for grade I tumours, decreasing to a 26% survival rate for grade III tumours.

Relationship between size of lesion and stage and degree of malignancy. This question has been reviewed by Sutherland.[211] There is evidence that women with small tumours experience better survival rates. Hawkins,[212] for example, in a series of over 3000, found a five-year survival of 86%

when the lesion was less than 1.5 cm in diameter; and Taylor & Wallace[213] have reported an inverse relationship between the size of the primary growth at operation and five-year survival, varying from 89% when the tumour was less than 2 cm in diameter to 18% when it was over 4 cm. Unfortunately, however, small size of tumour has not uniformly been found to relate to a good prognosis. Kreyberg & Christiansen[214] considered, in a review of nearly 1000 patients, that small cancers did not have a specially favourable prognosis. They concluded that more than half the patients who present with tumours no bigger than 1×2 cm are likely to die from their cancer. The evidence therefore supports the case for a degree of correlation, well short of absolute, between size of lesion and prognosis.

What, then, can be said about the over-all value of early treatment? We have seen that, though little affected by duration of symptoms, survival depends on age, stage and tumour grade. The effect of age can be accounted for mainly by the later clinical stage at registration in these patients; and this, in turn, is associated with the longer duration of history found in older women. There is also evidence that, to some extent, the smaller the lesion the better the prognosis (though not to an extent that could be considered satisfactory). The conclusion is, therefore, that a proportion of patients could in fact be treated at an earlier stage if delay in duration of symptoms could be reduced; but this proportion may not be very high, because so many patients are found to have a late stage of cancer or a highly invasive type, even when the history is very short.

Physical examination and self-examination of the breast. While physical examination by a physician is to be encouraged whenever a woman at risk presents as a patient for whatever cause, we must realize that this may be risky. The danger is that women may be falsely reassured and that, during the probably long intervals between examinations, breast cancer may develop with symptoms, and perhaps signs, that are ignored. For this reason it is advisable always to teach self-examination of the breast at the time of the first physical examination, so that early danger signals are not disregarded through ignorance or fear. Naturally, teaching breast self-examination is only a part (though an important part) of health education. It is likely that physical examination of the breast will keep its importance in early cancer detection, since mammography and examination by a physician appear to be complementary, and not mutually exclusive.

X-ray mammography. Mammography was first developed as a clinical diagnostic technique to assist the clinician when diagnosis was difficult. For example, Gershon-Cohen & Borden[215] discovered 28 can-

cers in 1100 women over the age of 35 examined every six months for eight years. Again, in a hospital series of 2500 women with unrelated breast pathology Egan detected 58 malignant growths.[216]

For the reasons we have already considered it has been suggested that earlier diagnosis of breast carcinoma at a pre-clinical and perhaps impalpable stage by population screening using mammography should improve the prognosis. This is a reasonable hypothesis but one that is difficult to test.

In order to determine the value of X-ray mammography in population screening a controlled trial on a defined population is needed, with a comparison of the results of standardized treatment in a randomized group of women diagnosed by X-ray mammography with those of a second group in whom the diagnosis of breast cancer has been made in the usual way. A very large population is needed in order to provide adequately sized treatment groups. The annual incidence of carcinoma of the breast in England and Wales is of the order of 64 per 100 000 women aged between 35 and 74, so that a population of 100 000 women between these ages, representing a total population of some quarter of a million persons, would only yield annually individual treatment groups of 30 patients each, regardless of age, clinical stage and histological type. Further difficulties in a therapeutic trial of this kind are its very long-term nature (follow-up for a comparison of mortality between the two groups is essential, with consequent loss to the trial from migration and deaths from causes other than cancer), and the large amount of apparatus and of skilled radiologists' and radiographers' time that need to be available. However, a survey of this kind is being undertaken in the State of New York, in association with the Hospital Insurance Plan of Greater New York.[217] Preliminary findings show, as we have just noted, that mammography and physical examination appear to be complementary.

Until it can be discovered whether there is value in pre-symptomatic diagnosis by screening in this way, it would seem that X-ray mammography should be limited to its use as an adjunct to diagnosis.

Other techniques are being explored besides that of radiology. Infra-red photography (thermography) is one possible method at present being evaluated, and it has been shown that outlines of tumours can be produced from their increased blood flow compared with the surrounding tissue by means of an infra-red scanning device (thermovision). Another possibility is the use of ultrasonics, and this field, too, is being explored though the technique has not as yet reached a practicable stage. The technique of xerography is also under investigation, its advantage being that it can give sharper detail on the photographic film than can mammography alone.

Other cancers

Screening for other cancers has been shown to be of value in certain groups of the population who are at special risk. Of these, perhaps the foremost are workers in certain industries, of which the rubber and electric-cable industries are the most important. In the past, benzidine and beta-naphthylamine or allied substances were used in the manufacture of rubber articles and electric-cable insulating material. These substances are now known to be highly carcinogenic, especially for the bladder. Pre-cancerous polyps and early cancers of the bladder can be accurately detected by means of exfoliative cytology. For those at risk routine cytological examination of the urine at six-monthly intervals is recommended.

Exfoliative cytology has also been shown to be valuable as a diagnostic aid in the early detection of cancers of the oro-pharynx. Dental inspection often shows small lesions of the tongue or cheek that would not normally be suspected of malignancy. However, by routine scraping of these lesions and cytological examination of the material a proportion can be shown to be carcinomatous and radically exterminated. This is probably the best present use for oral exfoliative cytology. It is sometimes suggested that mouth washings of scrapings from the cheek should be routinely examined for all persons undergoing dental inspection, but it is likely that the yield of unsuspected malignancy would be very low and the use of resources in this way uneconomic.

There are some 14 000 deaths annually in England and Wales from gastric cancer, mainly in persons over the age of 55. This is second only to carcinoma of the bronchus and lung as a cause of death from cancer. Methods for its early detection can be employed, though they are difficult to apply. Unfortunately, the prognosis for stomach cancer is appallingly bad when diagnosed by normal clinical means, at whatever stage. Indeed, it is a paradox that the shorter the history of symptoms the worse is the prognosis in terms of survival. The best hope of improving the results of surgery is by diagnosis at a pre-cancerous stage and this may be done either by gastric cytology or by gastric photography, or both. However, the stomach is inaccessible and any kind of mass screening is hardly practicable. The exfoliative cytological technique for examining the stomach requires particular skill and needs to be carried out under hospital conditions; its use is therefore virtually limited to aiding clinical diagnosis in patients with suspected lesions. Both exfoliative cytology and gastric photography are used for screening high-risk populations, particularly elderly men—for example, in Japan, where there is a high incidence of carcinoma of the stomach. Perhaps these techniques will be found to be of particular use in special high-risk

groups of persons who have already given positive results in a preliminary screening test. Haemoglobin estimation could be used in this way, applied selectively to the elderly members of the population, since persons with gastric atrophy tend to develop macrocytic anaemia. Another possibility is tubeless gastric analysis for the presence of free hydrochloric acid, using an electrolyte-combining resin. In the future, it may prove possible to develop a simple test for gastric parietal cell antibodies.

In England and Wales, in 1963, there were 5393 deaths from cancer of the rectum, which accounted for 5.3% of all cancer deaths. In addition, there were over 9000 deaths from intestinal cancers, many of which must have arisen in the sigmoid colon. This therefore constitutes a very considerable cancer problem. Although during the past 20 years operative mortality for colon and rectal cancer has fallen considerably, it is an unfortunate fact that survival is still about the same as it was 20 years ago.[218] The best hope of improving the outlook may therefore lie in earlier detection. Routine proctosigmoidoscopy, as part of a general medical examination, offers the possibility of detecting not only early invasive rectal and lower sigmoid cancers but also probable pre-cancerous lesions, such as polyps. Kendall Elsom and his co-workers,[219] for example, at the University of Pennsylvania Diagnostic Clinic, found, on routine proctosigmoidoscopy of 1006 persons, that 105 (10%) had rectal polyps. Carcinomatous change in the polyp was established by biopsy in 3 cases. Similarly, Hertz and others[220] reported from the Strang Cancer Prevention Clinic in New York City a finding of cancer in 2.2 per 1000 out of 26 000 persons over the age of 45 examined by proctosigmoidoscopy (1.8 per 1000 in women and 3.1 per 1000 in men); 52% of the patients were asymptomatic and 48% had only minimal symptoms (persons with definite preceding histories having been excluded).

More needs to be learned of the risk of cancer developing in polyps. The risk in familial generalized intestinal polyposis is known to be very considerable; the conversion rate to invasive cancer of the various forms of sporadic polyp is at present not so well known.

There are, however, difficulties in offering proctosigmoidoscopy to persons undergoing routine health examinations. In the first place it is difficulty to ensure that faeces do not obscure the view at the time of examination; and, in the second place, there is reason to believe that the nature of the procedure deters people from attending. Whatever the difficulties may be at routine "preventive" physical examinations, there is little doubt that routine proctosigmoidoscopy is to be advocated in older persons (say, over 50) who are undergoing medical examination at a clinic or in hospital.

Lastly, the importance of searching for early pre-cancerous and cancerous skin lesions needs to be remembered. This is particularly true in countries where the sunlight is strong and the population largely of Caucasian stock and employed in agriculture. Australia is an example of a country where skin cancers due to exposure of the skin to sunlight are common.

DISEASES OF THE EYE

Chronic glaucoma

It is only in the last two decades that chronic open-angle glaucoma, or glaucoma simplex, has come to be recognized as a separate nosological entity from angle-closure glaucoma. Chronic simple glaucoma, which for practical purposes may be said to occur only after the age of 40, has been said to attack "like a thief in the night" because of the long period during which physical signs gradually progress, and the perhaps equally long period when subjective visual changes are minimal and only detected by careful examination. For all glaucoma patients registered as blind, Sorsby[221] found only 0.4% below the age of 40 at registration, and 65% were between the ages of 60 and 79. Glaucoma (both acute and chronic) accounted in England and Wales, during the period 1951-54, for 13.6% of cases of registered blindness (4200 persons). There is reason to believe that registration of blindness is incomplete and it is likely that there are far more persons in England and Wales either blind or with impaired eyesight on account of glaucoma. There is a considerable literature on the prevalence of chronic glaucoma and its distribution is apparently world-wide.

The accepted treatment of chronic glaucoma is by miotic drops administered daily for an indefinite period, starting if possible in the early stage of the disease. If interference with vision becomes serious an operation aimed at increasing the aqueous outflow can be carried out. It is commonly accepted that miotic and other drug therapy effectively stops the progress of chronic simple glaucoma. One guide to glaucoma screening states that "Almost every case of chronic simple glaucoma can be arrested if it is diagnosed early. Many miotics are available..."[222] Unfortunately, a difficulty is that the value of this medical treatment has not been effectively assessed. It is also an uncomfortable treatment, and may be dangerous in that it severely limits night vision, so that there must be real doubt about the degree to which patients follow treatment instructions.

Established chronic glaucoma is diagnosed by finding characteristic visual-field changes, cupping of the optic disc and retardation of the normal outflow capacity of the aqueous fluid, as measured by tono-

graphy. A rise in intra-ocular tension is regarded as the usual accompaniment of chronic wide-angle glaucoma and this has been the accepted a sign by which early glaucoma is detected.

Intra-ocular tension is measured by tonometry, the Schiotz Tonometer being the most popular instrument used in screening. The principle followed in screening is that a rise in intra-ocular tension is the first sign of early glaucoma, preceding the onset of other signs by some years (perhaps by 10-20 years). A population is examined by tonometry and perhaps 6% or 7% are found to have pressures in the higher range (over 25 mm Hg). Of these, about 2% are considered to have probable glaucoma, with an intra-ocular tension of over 30 mm Hg.[222]

A United States Public Health Service publication on screening for disease[19] illustrates the bimodal distribution of a disease attribute and takes the intra-ocular tension in glaucoma as a possible example, showing separate normal distributions for diseased and non-diseased populations. There is no good evidence that this is so, and population samples of intra-ocular tension that have been recorded[20,21,223] do not support the bimodal model. Evidently, as with height and weight (and probably blood pressure and blood sugar), there is a continuous distribution of intra-ocular tension, with the probability of glaucoma increasing in the higher range of pressures. As with other conditions, such as diabetes and arterial hypertension, therefore, the border-line problem occurs, giving rise to the question: "Does ocular hypertension indicate an early, pre-symptomatic, stage of chronic glaucoma?"

A further question is posed (the parallel of which does not arise with diabetes or high blood pressure): "Does chronic glaucoma occur in the absence of a rise in intra-ocular tension?". An authoritative body of ophtalmological opinion answers this question in the negative (e.g., Goldman[224]). However, there are those who disagree[225] and their view is supported by the results of a recent survey in the Rhondda Valley, South Wales.[20,21,22]

In the Ferndale (Rhondda) survey 13 cases of chronic simple glaucoma were found in the 4246 people aged 40-74 years who were examined (equivalent to 92% of the total Ferndale population in that age-group); this is a total glaucoma prevalence of 0.28%. Six of the 13 cases were already known glaucoma patients and only 7 were newly discovered. All persons underwent not only applanation tonometry but also examination of the optic fundus; in addition, visual-field perimetry was applied to a one in three random sample. Glaucoma was diagnosed by finding a characteristic visual-field defect with optic disc cupping. Seven further suspected glaucoma patients were found to have intra-ocular tensions of less than 21 mm Hg but were diagnosed as cases of glaucoma on the basis of optic disc cupping and visual-field defects alone.

Of these 7 cases, 2 have since been observed to have raised pressure. Adding these 7 low-tension glaucoma cases to the 13 found by tonometry raises the prevalence rate for chronic simple glaucoma in this population to 0.43%, which is low compared with other recorded rates but similar to the findings of Strömberg.[223] If these findings are confirmed on a larger sample the inference is that if tonometry alone is used for the early detection of glaucoma, a false-negative rate of more than 50% will have to be accepted. It seems likely, therefore, that we need to search for other, more satisfactory, methods for early glaucoma detection. Visual-field screening, which only detects patients when undoubted early clinical glaucoma is present (though its course, before subjective interference with vision begins to be noticed by the patient, may well be as long as 10 years), is an obviously attractive screening technique. Unfortunately there are two important drawbacks: firstly, plotting the visual fields, even with a new electronic flash apparatus (the Friedmann or the "Globuck" field screener[226,227]) takes up to five minutes for each examination; and secondly, the number of false-positive results found by this technique and needing full ophthalmological investigation is unacceptably high. However, many non-glaucomatous defects have been found by visual-field screening (13% in the Ferndale survey, though this result was obtained with the Friedmann, not the "Globuck", Screener).

Apart from the possible need to look for other methods of diagnosing chronic glaucoma early, there is the practical problem for any community of the ability of the local eye services to meet an increased load of examinations. The Ferndale survey (the only survey, so far as the writers are aware, carried out either on a complete, defined population, or on a randomly selected population sample and therefore representative of that population) has demonstrated a prevalence of 0.43% confirmed chronic simple glaucoma (previously diagnosed plus newly discovered), a considerably lower rate than that reported from other, non-representative, population surveys. One reason may well be that the rate is spuriously raised in most detection programmes by weighting with persons having an increased likelihood of glaucoma (e.g., relatives of glaucoma patients). Another, artificial, factor of definition that may account for the low prevalence found at Ferndale is the use of the term "ocular hypertension" by the authors of this survey. This in itself would tend to decrease the prevalence compared with other surveys by transfer of "glaucoma patients" to this less well-defined group. In contrast to this low true prevalence rate for glaucoma found by tonometry, the false-positive rate was high—8.6%. A rate of this magnitude, implying a large number of persons in need of further investigation by an ophthalmologist, would throw an impossible strain on any country's eye services. Perkins,[228] for example, has calculated that in England and

Wales this might mean a load of 4500 persons to be investigated by each consultant ophthalmologist in the country. Assuming that by some means all the persons with early glaucoma in a population have been diagnosed, the question of treatment next arises.

We have seen that the efficacy of medical treatment is in doubt and that there is a harmful element in such treatment. Work is urgently needed to help elucidate the following questions: (1) do patients in fact do as they are advised and (2) if they do, (*a*) does the treatment prevent them from developing more advanced glaucoma and (*b*) has it deleterious effects—e.g., do those on miotic drug treatment suffer more accidents than the rest of the population. It might well be worth assembling all the evidence on the value of the medical treatment of early chronic glaucoma and deciding on the evidence whether a randomized trial of treatment would be justified.

Lastly, there is the problem of the border-line cases—those persons with intra-ocular tensions at the high end of the distribution without symptoms or signs of glaucoma. In some surveys (for example, Perkins's study[228]) persons with a diminished aqueous outflow, as measured by tonography, are regarded as belonging to the "glaucoma" group and are excluded from the border-line group. In the Ferndale survey, by contrast, only those with optic cupping and a field defect were regarded as glaucomatous. The border-line cases comprise a group of individuals to whom a randomized trial of treatment can ethically be offered; there is real ignorance as to: (*a*) the risk to the individual of developing chronic glaucoma, and (*b*) whether prophylactic medical treatment will reduce such risk as exists, and, if so, to what degree. A trial of this kind is in progress as part of the Ferndale survey, but of course it will be several years at least before significant results can be expected.

Looking to the future, it would be good to see work in hand aimed at discovering more about predisposing factors in chronic glaucoma. Besides the relationship with a raised intra-ocular tension, we know there is a familial trend; it is possible that there may be some correlation with iris colour. This is little enough to go on. Chronic glaucoma is one of the conditions in which useful correlations with other physiological variables or with other morbid processes might be revealed by wide-fronted prospective study on the lines of the Tecumseh, Michigan, experiment, where a complete population is followed over time and its disease experience correlated with recordings of as many variables as possible. There is obvious scope for biochemical and digital automation in making feasible this form of large study.

On the technical side, it was found in the Ferndale survey that, while the coefficient of variation of the Goldman applanation tonometer was greater than that of the Schiotz instrument, neither was considerable in

terms of mean pressure levels. Applanation tonometry was more acceptable to the population than the Schiotz technique. The Mackay Marg tonometer is commercially available and it is claimed that this can be used without anaesthetizing the cornea. If reasonably accurate readings can be obtained in this way it would clearly be a great advantage, since using a local anaesthetic on the cornea inevitably adds some element of risk to the procedure.

Until the answers to some of the problems discussed have been provided by experimental work, what can usefully be done for the detection of chronic glaucoma?

It seems that tonometry is the only practicable screening method we have at present. In order to avoid an uneconomic and unbalanced use of the eye services available in most advanced countries, it would seem wise for the present to concentrate on those at highest risk—i.e., persons over 40 related to patients with known glaucoma, since a familial tendency to glaucoma has been demonstrated.[229] What is done in practice will depend a great deal on the type of medical care prevailing in the area in question. In the USA much glaucoma screening is at present carried out and efforts are being made to abandon the "drive" type of campaign in favour of a continuing programme. In the San José, California, programme for 1961, for example, 3286 persons were examined; of these, 27 were found to be suffering from glaucoma, the cost per case found amounting to $ 175. This sum can be compared with the estimated cost of $ 1200 per year needed to support one blind person under the United States "categorical aid program for the blind". This report[264] states that "it is apparent that early case discovery is of significant economic benefit to the taxpayer". But this is only true if early detection and treatment do in fact prevent or delay blindness— a point that still needs to be ascertained. In countries where health services are unified it is even more mandatory than in countries where medical care is largely financed by the individual that the facts be ascertained before formulating a country-wide policy and undertaking universal glaucoma detection.

Other eye diseases

While glaucoma accounts for 13.6% of the registered blindness in England and Wales, cataract is responsible for 26.2% and senile macular lesions for 21.6%. "Congenital abnormalities" account for a further 4.2% of blindness, 38% of it in children under 4 years.

Much of this blindness, as well as impairment of vision that stops short of blindness, is remediable. In infancy the condition of amblyopia, present from birth, may lead, unless corrected, to blindness in one eye.

Detection of the condition needs to be carried out early in life, usually before the child can read, so that orthoptic measures may be instituted. In California, for example, the public health nurse service is used to provide information and instruction to parents on screening young children at home for amblyopia.

At the other end of life, impairment of vision from cataract, senile macular degeneration or other causes can be detected by a visual acuity test and by examining the lens with a slit lamp. Cataract is, of course, remediable by surgery, and senile macular degeneration can be alleviated by providing the patient with a visual aid. As with glaucoma, the medical care aspect needs examining carefully. The proportion of hospital beds available for eye surgery is usually small and waiting lists for cataract operations are long. Examination in the elderly, as in the young, might well be carried out by the home nursing service after special training.

DISEASES OF THE URINARY TRACT

General

Urine specimens are relatively easy to obtain in screening projects and urinalysis is simple. Its results may be indicative of a number of conditions, of which diabetes and kidney disease are the most important; also, as an index of subclinical icterus in epidemic jaundice, uribilinogen examination may be extremely useful. However, we are here concerned with the urine in renal disease only.

In the Baltimore screening study a prevalence of albuminuria of 8.4 per 1000 persons examined was found. In 4.7 per 1000 this was confirmed by further diagnostic tests; and of these only 0.8 per 1000 had been previously unknown to the patients concerned. In his five year follow-up Wylie[38] found this test of high prognostic significance.

Asymptomatic bacteriuria

In screening for diseases of the urinary system the etiology of the condition sought is of great importance from the preventive point of view. While patients with chronic glomerulonephritis can indeed be helped (particularly, perhaps, by guarding against recurring streptococcal infection), interest has in the past decade turned to chronic pyelonephritis and especially to its possible source in recurrent attacks of urinary infection, whether accompanied by symptoms or asympto-

matic. Here again is the classical screening situation: a potentially lethal condition preceded by a possibly latent and reversible stage. What is not yet certain is the role played by asymptomatic bacteriuric infections, particularly in the female, both in childhood and in adult life. The natural history of these infections (which are certainly common) still needs to be worked out in relation to the development of kidney damage, hypertensive disease and functional and anatomical abnormalities of the urinary tract such as vesico-ureteric reflux and malformations of the urinary collecting system. Clearly the matter is potentially one of great public health importance. Accurate prevalence figures for pyelonephritis are not available. A survey conducted by the College of General Practitioners[51] showed a patient consulting rate of 13 per 1000 persons for urinary tract infections.

The possible precursor of much pyelonephritis—asymptomatic bacteriuria in pregnancy—has been found in a number of surveys to be prevalent in about 5% of pregnant women; the incidence of acute pyelonephritis in those women with persistent bacteriuria has been discovered to be 10 times greater than in women without initial bacteriuria[230] Miall & Kass and their colleagues[231] have found a bacteriuria prevalence of 4.4% in the general female population aged over 15 years in Jamaica, but re-examinations show that, while the prevalence remains the same, different women are affected at each survey. So far, the evidence for an etiological connexion between asymptomatic bacteriuria and later chronic pyelonephritis appears to be incomplete. What is needed is a prospective trial or treatment; though the evidence for the immediate value of treatment in pregnancy, in preventing attacks of symptomatic urinary infection, prematurity and fœtal loss, is now considerable.[232,233]

The work of Kass[234] suggests that untreated asymptomatic bacteriuria in pregnancy is accompanied by increased fœtal loss and low birth-weight, and that treatment reverses this trend. Should these findings be substantiated there are grounds for widespread case-finding, both in the female child and in pregnant women. The means for doing this are already being worked out; the triphenyl tetrazolium chloride (TTC) screening test, described by Simmons & Williams,[235] shows promise of providing a useful technique for use in the field, provided facilities for refrigeration of urine specimens are available. Catheterization is not required and indeed is contraindicated;[236] a "catch" midstream specimen of urine, passed into a sterile container and immediately cooled by refrigeration, is probably the best form of collection. Doubtless, a wider evaluation of the TTC test and the possible development of improved tests are needed, since other workers have been unable to obtain results comparable with those of culture methods.

RHEUMATIC DISEASES

Rheumatoid arthritis

Arthritis and rheumatism account for a large part of the illness dealt with by the general practioner. In the British general practice inquiry,[51] it accounted for a patient consulting rate of 65 per 1000 (not including acute rheumatism), second only, in order of prevalence, to acute nasopharyngitis and, of course, causing far more disability. Population surveys for rheumatoid arthritis and for the presence of rheumatoid factor have been relatively extensive.[237] The prevalence of definite rheumatoid arthritis in different sample populations in Northern Europe varies from 2% to 3.5% for persons aged 55-64, with an additional 1%-6% of persons probably affected. In North America the Tecumseh, Michigan, project finds a prevalence rate in all persons over the age of 6 years of 0.39% definite and 0.85% probable rheumatoid arthritis.[238,239] The world-wide distribution of this disease has not yet been defined by clinical surveys and in many case the value of international mortality data is known to be limited. However, serological testing for rheumatoid factor shows its distribution to be widespread in both Africa and Asia; though the exact relationship of the presence of positive tests (latex fixation and Waaler-Rose) to the development of rheumatoid arthritis has still to be determined.

There is therefore good evidence that rheumatoid arthritis has a high prevalence (its diagnosis being based on the American Rheumatism Association criteria). This provides a strong *prima facie* case for early detection. However, the other criteria for justifying screening are not fulfilled, notably: (1) there is no clear pre-symptomatic stage (despite the somewhat obscure relationship with positive tests for rheumatoid factor); and (2) there is no specific treatment. The best accepted treatment for the early stages of rheumatoid arthritis is to protect the affected joints from excessive use.

Case-finding before the patient presents with disability does not therefore appear to be possible at present. We still need to learn more about the etiology of the condition, as well as about its early treatment. Apart from basic work on a possible etiological factor, continuing survey work can add to our knowledge of the relationship between the various factors so far uncovered and the disease process itself. A possibly useful contribution to survey work might be a concomitant continuing population survey of biochemical variables in blood. This is feasible with automated laboratory facilities. In this way early deviations from the "normal" biochemical pattern might be noted in relation to early rheumatoid changes.

Gout

Although gout is not a highly prevalent condition, the patient consulting rate being only 0.8 per 1000 persons in the British general practice survey[51] (though this rate reached 4.5 per 1000 in the prevalence studies quoted by Kellgren[240]), it is a condition (*a*) with a recognizable preclinical stage (hyperuricaemia), (*b*) in which there is a high-risk group in the population (relatives of gouty probands), and (*c*) for which an effective treatment exists (low purine diet, avoidance of excess dietary fat and alcohol and the use of uricosuric drugs). There is therefore a good case for screening for this condition, possibly in a selective manner.

Gout appears to be one of the few clinical conditions that is almost certainly transmitted by one or, at most, two genes and where a bi- or tri-modal distribution of serum uric acid levels is found in a population. Kellgren[240] has suggested that an intermediate peak in the distribution curve, at 6 mg/100 ml, may represent the heterozygotes in the population, the gouty homozygotes having a peak distribution in the gouty range, at about 8.5 mg/100 ml. A subcommittee of the Council for International Organizations of Medical Sciences (CIOMS), at a symposium held in Rome in 1961, agreed that a serum uric acid level of over 7 mg/100 ml in males and of over 6 mg/100 ml in females should be regarded as one of four criteria for the diagnosis of gout.

It seems likely that in those at genetically high risk the condition may become clinically manifest through variations in habit, perhaps reflecting the dietary habits of the general population. A high purine diet, excessive intake of dietary fat and alcohol (as experienced by well-to-do city dwellers as compared with poorer country dwellers) and the use of drugs such as salicylates in low dosage, hypotensive agents and diuretics may promote a higher prevalence of gout; while restrictions in the diet and in the use of drugs (as occurred during the Second World War) tend to cause the prevalence to wane.

Biochemical screening of the uric acid level will indicate those persons at high risk; this risk can then be lowered by alteration of the diet and advice on the use of drugs. In Great Britain a survey by Lawrence and his colleagues[241] showed a prevalence of 5.5% in males over the age of 15 with serum uric acid values of 6 mg/100 ml or more, in the rural area of Wensleydale, Yorkshire. Among males aged 55-64 with serum uric acid levels above 6 mg/100 ml in the town of Leigh, in Lancashire, the prevalence rate was as high as 18%. Thus selective screening could give a high yield of persons to whom useful advice could be given.

MENTAL ILLNESS

On grounds of magnitude the early detection and treatment of mental illness in a community should have a high priority. In the British survey of general practice[51] the rate of patients consulting their family physician for psychoneurotic disorders ranked next only to the consulting rates for acute nasopharyngitis, rheumatic disorders and bronchitis in frequency; the annual patient consulting rate was 46 per 1000 and the total consulting rate 166 per 1000—or more than 4% of the total consulting rate for all causes. In a survey directed specifically to mental illness in general practice, Shepherd[242] found, in a random sample of London practices, a total patient consulting rate for psychiatric morbidity of 140 per 1000 persons (176 per 1000 females and 98 per 1000 males) over a 12-month period. Of these, neuroses accounted for by far the greatest number (89 per 1000), while psychoses were diagnosed in 6 per 1000 persons. For women, psychiatric disorders ranked as the third commonest cause for consultation after respiratory diseases and orthopaedic or traumatic conditions.

A review of 50 surveys carried out in different parts of the world showed rates for all mental disorders varying from 1 to 370 per 1000 population. The differences are mainly due to variations in the techniques employed in the surveys.

It is clear, therefore, that mental ill health imposes a great burden on society, and it is reasonable to aim at early detection and treatment as a buttress to conventional methods. However, when the question is examined more closely, difficulties appear.

In contrast to most other forms of illness, it has not so far been possible to reach an etiological classification of mental disease, and for this reason there are very few specific treatments (the therapeutic measures used in neurovascular syphilis and phenylketonuria are exceptions). Thus there is no clear agreement about the diagnosis and treatment of much overt mental disease. "Treatment" may consist of drug therapy, as in depressive illness, but it also includes the management of the patient in relation to his total social situation and his immediate family and social group. In certain conditions it is not clear what would be the "best" treatment of the whole situation. It may be in the immediate interest of the patient himself to carry on as a member of the community. On the other hand, this may lead to a breakdown of the family situation, in which circumstances diagnosis and removal for a time from the social environment is the treatment of choice. It is therefore not necessarily beneficial for the psychoneurotic, say, to be the subject of early diagnosis; his best treatment may be that of continuing the struggle to integrate himself into society.

After a fashion, this is the same problem of border-line disease met with elsewhere—namely, the problem of what to regard as "disease" in need of treatment, allied to the question of whether early treatment will be beneficial. When all this has been said, it still appears that there is a group of persons with relatively mild depressive illness who could benefit from early diagnosis and treatment with modern ataractic drugs, among other methods. There is a shortage of evidence of the value of various treatments in depressive illness, especially in its earlier stages. The British Medical Research Council is now conducting a trial of treatments (including drugs and electroconvulsive therapy) for more advanced depression;[243] but evidently a great deal of mild depressive illness is not referred for specialist advice and is treated by general practitioners with ataractic drugs. A trial of treatment of this milder illness might be valuable and could be combined with a survey of early, unreported mental illness in the community. Work has recently been published on ascertained mental disease in general practice (Shepherd[242], cited above), but there is perhaps need for further work to identify persons who might be helped by early treatment (including social adjustment within their family group) and for a trial of such treatment. This would entail a trial, *inter alia*, of the benefits of using social workers in the pre-breakdown stage of psychiatric disease.

Population surveys of psychiatric illness in the community are being undertaken (e.g., by the Medical Research Council in Camberwell, London, and South Wales), and at least one trial of the early diagnosis and treatment of unreported mental illness is being initiated in the London area.

Mental retardation: examples of specific conditions where screening is carried out

A detailed critical review of a number of community-wide surveys on mental retardation was made by Gruenberg in 1964.[244] Remarkable variations are found both between and within age-groups. At the age of peak prevalence—about 14 years— Gruenberg found a 10-fold variation, from about 1% to 10%. Such variations may be largely accounted for by differences in the limits and scope of studies, diversity of definitions and availability of measuring instruments. Some type of screening of school-age children has been widely carried out in countries with a well-developed school system, based largely on the criterion of ability to keep up with the classwork, but frequently supplemented by the use of IQ tests. Where suitable services exist, the children suspected of retardation are often referred to school psychological services for further testing and investigation of the possible cause of the retardation. Stress

is increasingly being laid on the importance of using batteries of tests combined with socio-psychiatric investigation, since failure to keep up with the school system has frequently been found to have causes other than low level of intelligence; moreover, most specialists now doubt the prognostic value of IQ tests used alone.

An example of the screening of a school-age population is that carried out by Jaeggi & Jaeggi in Geneva[245] as a preliminary to the reorganization of the cantonal socio-medical educational service for the mentally retarded. The primary screening was carried out through consultation of institutional, educational and medical registers and reports. It was considered that practically all suspected cases could be found by this means, these reports being very thorough and kept up to date. (An indication of the reliability of the data is given by the fact that, in 1964, 10% of the total school population of the Canton was seen by the socio-medical service.) A detailed questionary was then completed for each suspected case, providing information on social, psychological and medical conditions as well as on educational achievement. It was found that 0.8% of the children of school age were in need of special social, medical or educational services.

Phenylketonuria (PKU)

PKU is one of the few disorders leading to mental retardation of which the causation is understood—a genetically transmitted metabolic abnormality. If the defect is detected very early in life mental retardation can be prevented or favourably modified through a special diet low in phenylalanine. A bacterial inhibition assay screening test for blood phenylalanine (Guthrie test) was used routinely by state health departments in the USA in 1962 and 1963 on more than 400 000 newborn infants born in about 500 hospitals. The frequency of PKU was found to be 1 per 10 347. Such routine testing has now become compulsory in some states (e.g., New York and Massachusetts). Urine testing is also used widely in the United Kingdom and some other countries. Obviously neither type of test can be used in areas without a wide network of health services.

Galactosaemia

This disorder is also caused by an inborn error of metabolism, but, unlike PKU, if untreated it leads to early death. A diet low in galactose prevents the development of the clinical condition, which includes severe mental retardation. Promising attempts are being made to

devise simple screening methods—e.g., paper-strip tests. By quantitative biochemical screening procedures it seems possible to detect, with some measure of accuracy, the heterozygous state of galactosaemia, thus making it possible to detect parents who might produce galactosaemic children[246].

ANAEMIA

There are, of course, many causes of anaemia but iron deficiency is by far the commonest, and only this form of anaemia is considered here. This deficiency is essentially an imbalance between intake and absorption and excretion or loss in other ways; it can be prevented by correcting either deficient intake or abnormal loss. Thus one of the principal criteria for screening is met, in that the condition can be prevented by treatment (whether primary or secondary).

A second feature of iron-deficiency anaemia as far as screening is concerned is the test for its detection. Measurement of the haemoglobin level is one of the few examinations that directly estimate the variable in question. There is therefore no doubt about the significance of what is being measured (as there is, for example, in measuring intra-ocular pressure as a test for pre-symptomatic glaucoma) though the other difficulties of definition and the variability of the method and or the observer are the same as for other tests.

Prevalence

Iron-deficiency anaemia was the subject of discussion by a WHO Study Group in 1958.[247] After considering the haematological data on apparently normal persons throughout the world the Study Group adopted criteria for haemoglobin values below which anaemia could be considered to exist (Table 18).

The Group's report reviewed the available studies of prevalence and considered that more of these studies were needed. It pointed out that in some parts of the world anaemia constitutes a major public health problem. An investigation in Mauritius had shown that 50% or more of certain groups of the population were probably affected. In more highly developed countries the prevalence is clearly much lower. Using the above criteria, the survey by Berry and others[248] of London housewives in 1951 showed that 9% of the women had haemoglobin levels of less than 12 g/100 ml. Kilpatrick & Hardisty,[249] in a study in South Wales and the North of England, of men and women in age-groups 35-64 and 55-64 respectively, found that 14% of the women had haemo-

TABLE 18. HAEMOGLOBIN VALUES BELOW WHICH ANAEMIA CAN BE CONSIDERED TO EXIST

Age (years)	Sex	Haemoglobin (g/100 ml)	
0.6- 4		10.8	11.5
5 - 9		11.5	
10 -14		12.5	
Adutls	Male	14.0	
	Female	12.0	
	Pregnant female	10.0	

Adapted from WHO Study Group on Iroa Deficiency Anaemia.[247]

globin levels of under 12 g/100 ml and 3% of the men had levels of less than 12.5 g/100 ml. Kilpatrick & Hardisty's female group were over the age of menopause. Iron-deficiency anaemia is, of course, most prevalent in women who menstruate, and it is likely that women in the age-groups concerned would be found to be anaemic much more frequently. For this reason iron-deficiency anaemia is a condition specially suited to the selective screening of women between the ages of, say, 20 and 44.

More needs to be learned, however, about the criteria determining anaemia and the relationship of haemoglobin levels to symptoms. Though we may have a reasonable idea of what is clearly anaemia, we do not know much about optimum levels of haemoglobin. Further survey work is needed:

(1) to ascertain with the greatest possible accurary the distribution of haemoglobin levels in a probability sample of a large population;

(2) to relate carefully, and without observer bias, symptoms to haemoglobin levels in iron-deficiency anaemia, as well as symptoms to the effects of treatment;

(3) to discover the cheapest and most effective way of treating and preventing the recurrence of iron-deficiency anaemia.

Fourteen years ago Berry[250] carried out a small survey demonstrating an absence of association between haemoglobin level and symptoms of "anaemia". More recently a well-planned survey has been completed under the auspices of the British Medical Research Council's Epidemiological Research Unit by Elwood & Wood.[251,252] These studies have failed to demonstrate a correlation between symptoms of "anaemia" and haemoglobin level, down to 10 g/100 ml; nor was there a significant improvement in symptoms when the haemoglobin level was raised with

iron compounds. Further studies in this field are being undertaken by the Epidemiological Research Unit, and, of course, other institutions may be conducting similar research.

Methodology

When samples of venous blood are being withdrawn for other purposes, there is advantage in centralizing the estimation of haemoglobin, so that it can be carried out on an accurate calibrated photo-electric instrument. On the other hand, collection of venous samples in tubes specially for this purpose is expensive and in many field circumstances it may be both cheaper and more convenient to estimate the haemoglobin on a sample of capillary blood. The simplest and cheapest way of screening for anaemia is the Phillips-Van Slyke specific gravity method (which is used by the British National Blood Transfusion Service for screening potential blood donors). However, its accuracy for use in general or selective screening is open to question.[253] A recent trial carried out by the British Medical Research Council's Epidemiological Research Unit (South Wales)[254] has shown that the American Optical Company's Spencer haemoglobinometer compares well with the Council's Gray Wedge, the EEL photo-electric photometer and the Sahli method. The Spencer haemoglobinometer has the advantage that it works without dilution of the blood sample; a drop of blood is simply placed on a special slide, haemolysed with a stick impregnated with saponin, and covered with an optical coverslip. The slide and coverslip are optically prepared so as to present a standard depth of blood between them, the colour of which is compared with a standard.

Another, and reasonably accurate, screening technique for capillary blood is the micro-haematocrit method. This method, of course, requires a centrifuge and is therefore best when it is laboratory-based.

Screening

Screening for anaemia gives the highest yield, as we have seen, when it is carried out among women in the menstrual age-groups. Many women of child-bearing age attend maternity and child welfare clinics, which offer an excellent venue for screening. The causes of anaemia other than menstruation, such as other blood diseases, malignant disease, peptic ulceration and other gastro-intestinal disease, rheumatic and renal disease, can also be picked up by haemoglobinometry. Routine haemoglobin estimation is therefore probably one of the most profitable screening tests for all ages in pointing to unsuspected disease; Jungner

& Jungner[255] found that 1.4% of 30 000 persons in the Värmland project were confirmed as being anaemic, the commonest previously undiagnosed condition.

Other than part of a case-finding population screening programme, haemoglobinometry is clearly a most useful addition to the normal examination of patients in a general practitioner's work. It can easily be carried out by an auxiliary helper. Fry[256], for example, has reported the results of routine haemoglobin estimation in an Outer London general practice. He took a 10% sample of all his adult patients and found 18% had haemoglobin values of less than 12 g/100 ml, which was 10 times the rate of "clinical" anaemia in his practice.

Conclusions

In conclusion, therefore, anaemia is probably one of the more acceptable conditions for screening under present circumstances; it is highly prevalent, can be sufficiently accurately detected and, when due to primary iron deficiency, responds excellently to treatment. The haemoglobin level is also a sensitive index to a number of other conditions, of which anaemia may be one of the earlier signs. Naturally, once anaemia is discovered, it is of the first importance that a complete haematological investigation should then be carried out, leading to a definitive diagnosis.

CHAPTER 5

METHODOLOGICAL TRENDS IN SCREENING

In this chapter, we shall consider some common procedures and tests that have been applied in case-finding or in similar screening surveys in a population. There seem to be certain interesting trends in the techniques that may predominate in the future, in contrast with the wide variations in present-day methods and ideas.

CLINICAL OR TECHNICAL SCREENING

Firstly, there is a strong tendency to use automated methods, particularly for chemical tests. The extensive use of laboratory methods has, however, been criticized, and the value of impersonal and highly standardized methods may be questioned. Only if resources (particularly of personnel) are limited can the medical value justify the cost and effort of automated or mechanized techniques with high capacity. Evolution may occur stepwise, when laboratory tests and certain clinical examinations may first be applied in "drive" campaigns, but are later used as special facilities at the practitioner's disposal for periodic health examination.

Another obvious trend is the increasing use of data-processing machines. This matter will not be considered here. Although health services generally adapt principles that have been evolved for actual sick care, in certain cases—e.g., data registration and storage—the work involved in health examinations may lead to earlier development in the relevant field.

PARTICIPATION BY PHYSICIANS

The most essential and decisive factor in the extent and organization of case-finding has been whether or not medical examination by a physician has been included. It is debatable whether a physical examination is to be regarded as a screening procedure.

On this basis, we can divide health investigations into two groups. One group takes the form of a complete examination, which includes a physical examination by a medical practitioner; the other group is composed mainly of a battery of clinical and laboratory tests, in which the contribution of physicians is limited to evaluating certain tests, or is completely lacking.

Inclusion of the physician's findings, as well as his interview and evaluation, greatly widens the scope of screening and makes it comparable to a general medical examination. As an important part of the final medical conclusion, examination by a physician is extremely valuable. The signal factor is the time that is devoted to the check-up. Simple inspections and fast examinations, as well as comprehensive physical examinations, have been practised.

Physical examination by a medical practitioner

This normally comprises inspection, palpation and auscultation, and includes blood-pressure measurement and rectal examination.

Physical examination is sometimes carried out as one of the first steps in a screening programme, together with checking the questionary and ordering special tests, which are not carried out on all patients. The final evaluation is made by the physician after all tests have been completed.

Obviously, there is not always a sharp distinction between the technique used in examining the healthy and that used in sick care. For example, when seeking such conditions as malnutrition, the technique may be similar to methods used for the general care of children, as may be seen, for instance, from the report of the WHO Expert Committee on Medical Assessment of Nutritional Status.[257] It can be expected that some of the work that today is done by the physician may be taken over by auxiliary technical personnel using special equipment. By means of proper organization, many clinical tests can be done more easily and on a fairly large scale. This will make the goal of a complete medical examination in every instance easier to reach.

Cancer detection is sometimes one of the main objects of health screening—despite the fact that no guarantee of freedom from malignancy can be given and that the possibilities of detecting cancer in an asymptomatic stage are extremely limited. Several suggestions have been made about how to perform cancer-detecting examinations most effectively. One example is the well-known description by Day.[258] In the report of a WHO Expert Committee[259] the following examination is mentioned: inspection of the entire skin area and all accessible body cavities, urine tests, chest X-rays and proctoscopy; in males prostatic

examination, in females cervical smears and palpation of the breast. Sputum cytology, gastro-intestinal radiography, blood counts, colposcopy, and possibly mammography may be added.

History-taking by a physician or specially trained auxiliary medical staff

The medical history is very important, and can be obtained by appropriate questionaries. It has been reported from many investigations that the medical history and the physician's physical examination make the greatest contribution to the diagnosis. However, most of the diagnoses are then known *before* the screening procedures. How much medical value is afforded by the notation of earlier known disease remains to be seen. Obviously, the information is most useful the first time an examination is undertaken. The history is of immense value and the advantage of questionaries is great.

Questionaries

Many useful questionaries have been suggested. Best known is the Cornell Medical Index—a simple checklist medical history form ("self-screener"), which has been used as a basis for many other questionaries. The size and contents of the questionary depend on the purpose and the facilities available. Although the number of questions may be very small, a general survey of the state of health may require 200-500 questions, arranged in groups. Some workers use still more comprehensive systems, where positive findings, if any, are more carefully investigated.

As a rule, the questionary is checked by a physician or by specially trained hospital staff. The gain in time is also appreciated in connexion with the physical examination.

It is important to remember that the effectiveness of a questionary is strongly linked to the social culture of the population for which it is intended. A good deal of the wording needs to be based on local custom and the jargon used to describe diseases. Thus it is difficult, if not impossible, to transplant effectively a questionary such as the Cornell Medical Index, devised in the USA, for use in a population in Great Britain.

Clinical methods and laboratory tests used for screening

Screening examinations originate from and resemble in many ways the traditional visits to a medical practitioner's office. This was natural when health examinations started. There has, however, been a gradual

change in some respects, depending on the lack of definite signs of a disease.

Looking at the procedures adopted, it is obvious that conventional diagnostic methods or functional tests will be used for a long time to come. In Table 19 an attempt is made to give a rapid idea of the examination programmes used. A comparison is drawn between more conventional and traditional screening programmes (column 1) and some new attempts (columns 2 and 3). In the first column the frequency of the test is apparent from the numbers given, the data being taken from a study of 33 screening surveys[4] in the USA during 1946-54. The table shows that none of the tests was used in all 33 surveys, but that the most popular were chest X-ray or MMR, simple serology, and blood-sugar determination.

The other two colums in Table 19 give specific examples of more recent projects, according to somewhat different principles. The first (column 2) refers to a Swedish study in the county of Värmland, where 100 000 people were offered a screening examination in connexion with a traditional survey for tuberculosis by MMR.[255] Apart from MMR, the basic examination consisted of blood-pressure measurement, urine analysis and a multiple blood examination with a number of tests: haemoglobin, haematocrit, serum analysis of serum iron, creatinine, the transaminases GOT (glutamic-oxalacetic) and GPT (glutamic-pyruvic), cholesterol and beta-lipoprotein, zinc sulfate test for gamma-globulin, thymol turbidity test and, finally, determination of total protein-bound hexoses and determination of sialic acid, both of which are non-specific tests indicating many kinds of non-specific inflammatory reactions.

The screening was carried out by a field group, who also took the blood samples. Analysis was done in a centrally located automated laboratory, and the results were handled by computer. This kind of investigation was performed to find objective grounds for recommending examination by a physician. In such an investigation the methods chosen are obviously less diagnostic, but sensitive to various diseases. The taking of the blood samples—as well as supplementary clinical tests—is simple and can be done under primitive conditions, using disposable material (sterile needles, sample containers, etc.).

The last column (column 3) gives an example of a periodic health examination carried out by the Kaiser Foundation in California[260,261] (see page 61). It indicates the methods selected using advanced techniques on a large scale.

From the examples given it can also be determined how often studies are restricted to detecting only certain diseases. Although the variation among different projects is considerable, the main procedures are common to all the studies surveyed in Table 19. One of the striking charac-

TABLE 19. COMPARISON OF SCREENING PROGRAMMES

Test	(1) Number of studies using the test (from 33 surveys in USA, 1946-54)	(2) The Värmland study, in Sweden, 1962-64	(3) Multiphasic screening by Collen et al., 1965
Physical examination	4		+
History taking or questionary	15	+	+
Oral and/or dental examination	5		
Intra-ocular tension, tonometry	1		+
Visual acuity	18		+
Retinography			+
Hearing tests	12		+
Proctosigmoidoscopy			+
Biometric measurements, such as height, weight, skinfold measurement	20	+	+
Blood pressure	19	+	+
Electrocardiogram	13		+
Lung function tests			+
Cytology: vaginal smear	5		+
Chest X-ray or MMR	32	+	+
X-ray mammography			+
Serology:			
VDRL, etc.	30		+
blood groups, Rh factor	3		+
Haematology:			
haemoglobin	23	+	+
haematocrit	1	+	
cell count, differentials count	1		
Blood in faeces	5		
Erythrocyte sedimentation rate	4		
Chemistry:			
urine, sugar	16	+	+
urine, protein	16	+	+
urinary deposit	3		
bacteriuria			+
Blood sugar	30		
Blood sugar after test load			+
Protein-bound hexoses, sialic acid		+	
Cholesterol		+	+
Beta-lipoproteins		+	
Serum albumin and/or total protein			+
Gamma-globulin (Kunkel)		+	
Thymol turbidity or similar test		+	
Transaminases		+	+
Creatinine and/or blood urea nitrogen		+	+
Uric acid			+
Calcium			+
Serum iron and/or iron-binding capacity		+	

The examples chosen were taken from: (1) a summary of 33 studies in the USA;[4] (2) a Swedish pilot study with a battery of chemical blood tests;[855] and (3) a multiphasic study in California by Collen et al.[860, 861]

teristics of the development of screening is that the more the cost can be reduced per test the greater is the number of investigations made. Whatever the reason, there seems to be a wish to extend such studies. The willingness to follow up the investigations is not increasing to the same degree, however, although today some serious attempts to do so may be noted.

DEVELOPMENT OF SCREENING FACILITIES

Technical evolution will have a drastic influence on all these factors connected with screening. Generally speaking, the considerable efforts to improve health screening by technical means may be said to follow two different lines of evolution:

(1) the use of simpler techniques for laboratory tests, and
(2) laboratory automation.

Simplification

The first trend consists in the use of tests that are extremely simplified —for instance, paper-strip tests. Such techniques will certainly be greatly improved, and will increase in number. The simplification of complicated methods, such as those for determining sugar and urea in blood, also seems to be a promising development. There are, however, definite limitations to such procedures, as well as certain difficulties in getting reliable registration and sample identification and accuracy in the reporting of results, etc.

The cost of analyses decreases when complicated procedures are done by extremely simple methods, although by no means to the degree that might be expected. Manual handling and sorting are too time-consuming to be economical on a large scale. So far, the cost of the material is not negligible.

A good example of simplification in another respect is the laboratory routine worked out by Suchet in Paris.[262] Using a well-planned routine, it is possible for one technician in a working day to perform 100 of each of the following analyses: erythrocyte sedimentation rate, haematocrit, lipoproteins, antistreptolysin titre, urinary sugar, protein and blood, and urea in serum, in addition to 300 serological tests for syphilis.

The techniques may be regarded as semi-quantitative. In some instances, it may be permissible to sacrifice some accuracy in order to obtain a high capacity at low cost. Although it remains to be decided how precise methods should be for screening purposes, it is certainly not necessary to aspire to the same degree of accuracy as in hospital

laboratory work or research. There are so many difficulties in sampling and handling specimens in large-scale investigations that a semi-quantitative level might well be justified.

Automation

The second important trend is laboratory automation, on which intensive work has been done with promising results. The first clinically important analytical robot was the AutoAnalyzer. In screening, the most usual way of achieving sufficient capacity has been to arrange for several AutoAnalyzers to work in parallel. In such a way extensive systems have been assembled, capable of carrying out a large battery of well-known tests.

Many improvements that are of interest in screening have been made on AutoAnalyzers. With the multi-channel equipment now available a number of drawbacks have been overcome that were troublesome in large-scale investigations. Examples are: patient identification with numbering of samples, peak detection and reading, calibration, analogue-digital conversion and automatic print-out.

Analytical programmes have gradually become directed towards screening needs, and for AutoAnalyzers there is now a large variety of procedures to choose from.

In Sweden, experience of an automatic system for chemical mass analysis—partly based on AutoAnalyzers—led to the devising of new equipment, called the AutoChemist, working with discrete samples and including a small computer.[263] The AutoChemist has a very high capacity, being designed for mass analysis. Theoretically it can process some 500 thousand to 1 million samples per year, with 20 or more analyses on each sample. In practice, factors other than the analytical work-load are usually decisive for normal operation, but with a fixed analytical programme—as in screening—conditions are especially favourable. The maximum efficiency—up to 150 specimens per hour and up to 40 different analyses on each sample—is likely only to be needed periodically, but it is advantageous for managing a high load temporarily. The AutoChemist has 24 fixed analytical channels for different tests—chemical, as well as bacteriological and serological.

Handling such an apparatus is extremely simple and personnel-saving. Loading is done on one side of the apparatus, and the samples are returned on the other side, on a similar transport belt, after analysis. The inclusion of a small, desk-size computer is very useful for screening purposes—e.g., editing the format, sorting and checking. Recording takes place "on line" by automatic print-out on a teletypewriter with a paper-tape punch.

TABLE 20. SURVEY OF SCREENING PROCEDURES

Test	Manual method available for large-scale use[a]	Fully automatic procedures available with high speed[a]	Comments on automatic methods
BACTERIOLOGY			
Growth (selected media)	+	+	Turbimetric
Bacterial count	(+)	+	Indirect counting
CHEMISTRY			
Urine:			
Sugar	+	+	Automation economically reasonable only on a large scale
Ketone bodies	+	+	
Protein	+	+	
Urinary sediment	(+)	—	
Bacteriuria	+	+	
PKU (see also phenylalanine in blood)	(—)	+	Fluorimetric
Blood, carbohydrates:			
Sugar	+	+	
Galactose	(—)	+	Enzymatic
Total protein-bound hexose	—	+	
Sialic acid	(+)	+	
Blood, lipids:			
Cholesterol	+	+	
Beta-lipoprotein	+	+	Turbidimetric
Total lipids	+	+	
Phospholipids	—	(+)	
Non-esterified fatty acids (NEFA)	—	(+)	
Triglycerides	(+)	(+)	Fluorimetric
Serum protein:			
Total protein	+	+	
Albumin	(+)	+	
Zinc sulfate (gamma-globulin)	+	+	Turbidimetric
Electrophoresis	(+)	—	
Haptoglobin	(+)	+	
Transferrin	(+)	+	
Thymol turbidity	+	+	
Ceruloplasmin	—	+	Non-specific test, still on research level
Enzyme activities:			
Transaminases	+	+	
Phosphatases	(+)	+	
Lactic acid dehydrogenase	(+)	+	
Non-protein nitrogenous compounds:			
Creatinine	+	+	
Urea, blood urea nitrogen	(+)	+	
Non-protein nitrogen	(—)	—	
Uric acid	(—)	+	
Phenylalanine	(+)	+	Fluorimetric, better than urine test

TABLE 20. SURVEY OF SCREENING PROCEDURES *(concluded)*

Test	Manual method available for large scale use[a]	Fully automatic procedures available with high speed[a]	Comments on automatic methods
Electrolytes, etc.:			
Sodium/potassium	(+)	+	Of little value for screening
Calcium/phosphorus	(—)	+	
Serum iron	(+)	+	As supplementary haematological test
Iron-binding capacity	(+)	+	
CYTOLOGY			
Vaginal smear	(+)	(+)	Results from electroscanners still experimental
Urine	(—)	(+)	
Cancer cells in blood	(—)	(+)	
Sputum	(—)	—	
HAEMATOLOGY			
Haemoglobin	+	+	
Cell counts	+	(+)	
Differential count	(—)	—	
Erythrocyte sedimentation rate	(+)	—	Can be replaced by protein-bound carbohydrate tests
Haematocrit	(+)	(—)	Semi-automatic —electronic— methods available
SEROLOGY			
Wassermann reaction	(+)	(+)	Large-scale automatic methods may be available at high cost
VDRL, etc.	+	(+)	
RA (rheumatoid arthritis factor) test	+	+	
Antistreptolysin, etc.	+	(+)	
MISCELLANEOUS			
Blood (faeces, urine)	+	—	Semi-automatic methods have been tried
Protein-bound iodine	—	(+)	
Polarography	—	+	Non-specific test
6-phosphoglucose dehydrogenase (vaginal washing)	(—)	+	Still on a research level

[a] (—) denotes that by expensive means and special organization a fairly high degree of effectiveness can be attained;
(+) denotes that under certain circumstances large capacity can be reached.

It seems likely that technical evolution in the domain of automatic analytical apparatus will aim at an increasingly high speed of analysis. The essential feature, however, appears most likely to be an increase in the number of types of analysis. There seems to be a distinct tendency to erase the frontiers between chemical, bacteriological, serological, haematological and other procedures. This implies that equipment, basically an electro-mechanical device for automation of analyses, will be relatively similar for very different tests. The decisive factor for the apparatus system will be the choice of tests or screening.

Theoretically, almost any method can be automated. The analytical technique may be based on well-known procedures but needs to be modified and adjusted to the automatic machine. In practice, however, the difficulties and costs often become so great that other ways are sought to evolve equipment, and completely different methods of getting the desired information are tried.

In order to give an idea of what might be of interest for screening purposes, various methods are listed in Table 20. The list is by no means complete, and important advances are continually being made.

In some cases, screening needs may promote automation. For instance, microbiological determination of vitamin B_{12} may be used on a large scale as a screening procedure.

AUTOMATED MULTITEST LABORATORIES

The most important methodological progress in this field has been made by Dr Morris F. Collen and his collaborators. Automated multitest laboratories in the Kaiser-Permanente medical centres in California have been arranged when advanced examination techniques have been adopted for periodic health examinations on a large scale.[260,261] In many ways, the organization and equipment indicate new trends, but are safely grounded on long experience. The project is expensive, but many details are of interest even to those whose resources are limited. Moreover, if its clinical worth is proved, the benefits in medical care could offset the capital and running costs.

The examination programme includes the following:

(1) ECG with 6 leads, combined with phonocardiogram. Results are recorded by mark-sense cards, but the intention is to evaluate the ECG by computer analysis.

(2) Glucose load test: 75 g of glucose in 240 ml of water; blood-sugar level determined after 1 hour (if slightly elevated also after 2 hours).

(3) Chest X-ray with 70-mm film, postero-anterior projection, read by a radiologist.

(4) X-ray mammography on women over 45 years of age. Cephalocaudal and lateral views of each breast are taken; mammographs are read by a radiologist.

(5) Supine pulse rate and blood pressure. Recorded manually on mark-sense cards.

(6) Visual acuity by reading a wall chart, as well as pupillary escape test. Mark-sense card recording.

(7) Tonometry. The intra-ocular pressure is noted on mark-sense cards. (At the same time the left pupil is dilated for later retinal photography.)

(8) Vital capacity and one-second forced expiratory rate, recorded manually on mark-sense cards.

(9) Hearing test by automated audiometer, with the graphed readings transferred to a mark-sense card.

(10) Questionaries. (1) One medical, self-administered, in the form of 207 pre-punched cards, each with a single question. The patients drop the cards in boxes with "yes" or "no", and a card-reading machine records the results. (2) A psychological questionary, also self-administered.

(11) Blood tests: haemoglobin, white-cell count, Venereal Disease Research Laboratories' test for syphilis (VDRL), rheumatoid factor (latex fixation slide test), blood groups and eight chemical tests (serum glucose, creatinine, albumin, total protein, cholesterol, uric acid, calcium and transaminase) carried out by AutoAnalyzer and the results directly punched on cards.

(12) Urine tests: for bacteriuria (chemically) and for pH, blood, glucose, and protein by paper-strip tests.

(13) Retinal photograph, read by an ophthalmologist.

(14) Weight and skinfold thickness are measured manually. Height and transverse body measurements are automatically recorded on punch cards.

Routinely, all patients above 40 years of age are recommended sigmoidoscopy, and for women a gynaecological examination with cervical smear is also recommended.

The automated multitest laboratory has its own data centre. The computer plays an important role as an integrating part of the laboratory. Automatically, the computer prints out the summary report for the physician. The capacity is exceedingly high, and routine examinations of 4000 people a month are reported. For details, the reader is referred to the reports in the literature.

Generally speaking, this is an indication of a possible evolution, at any rate in countries with good resources. One difficulty may be satis-

factory co-operation with the physicians. In California such co-operation has been achieved, but in other parts of the world the conditions may differ.

It is interesting to note that such a laboratory centre can utilize equipment and methods that elsewhere might be impracticable or too costly. Thus it can help to develop and test methods specially suited to screening. Such possibilities for research are certainly most welcome.

CHAPTER 6

CONCLUSIONS

Reviewing the subject of early disease detection, it is clear to us that, although for a number of years there has been an increasing interest in screening among both the medical profession and the public, we are still at a very early and comparatively primitive stage in the systematic detection and treatment of early disease. For some conditions we have powerful methods of detection, but we do not yet know the effect of early treatment (e.g., diabetes mellitus); for others we are still experimenting to find satisfactory tests (e.g., chronic simple glaucoma); for only a relatively few conditions are there at present well-tested and successful means of pre-symptomatic detection and treatment (e.g., cancer of the cervix), and even here there are certain qualifications.

It is therefore important to ask ourselves in what particular respects is further investigation, promotion, or education needed. These are big problems, affecting whole populations and carrying the implications of radical changes in emphasis in the practice of medicine towards prevention, and it may be helpful to consider some of the possible ways in which these aims may be realized, point by point.

NEED FOR FURTHER EPIDEMIOLOGICAL INVESTIGATIONS AND THE ALLIED NEED TO ACHIEVE STANDARDIZATION

Too often in the past people have undertaken work in different countries on the same disease condition, only to find at a late stage that each group has been using differing definitions and therefore getting different results. This has happened, for instance, with carcinoma-in-situ of the cervix uteri and with glaucoma simplex. At the same time there is so much work to be done in areas where it is necessary to examine large populations at a low risk for the condition under study that great advantage would be gained if results could be pooled or at least intelligently compared.

WHO has already played a large part in fostering co-operative international studies. As we have seen, WHO expert committees or seminars have considered many of the chronic diseases, notably tuberculosis, non-specific respiratory disease, anaemia, malnutrition, high blood pressure, ischaemic heart disease, diabetes mellitus, mental illness and the cancers. In some instances (e.g., with anaemia, cardiovascular disease and diabetes) special attention has been paid to reaching internationnaly acceptable definitions.

Two conditions that we believe still need internationally accepted definitions are carcinoma-in-situ of the cervix and glaucoma simplex. Of course, reaching acceptable definitions, diagnosing, and then discovering the effect of treatment are lengthy processes entailing much painstaking work by teams of investigators. The need to establish the sensitivity and specificity of screening tests and the effect of early treatment are the reasons for the epidemiological surveys to which we have paid such attention in this report. Surveys are, however, undertaken for a number of reasons, and the object of investigating the feasibility of presymptomatic diagnosis and treatment may not always be one of those reasons. There is a need for a clearing-house for information about epidemiological studies directed towards the development of screening techniques and for reminding those contemplating the initiation of studies that future screening possibilities might be borne in mind during the planning stages. While there is, in our opinion, everything to be said for the value of developing screening by *ad hoc* studies of individual conditions, so broad is the field of early disease detection that the whole field needs to be kept under continuous review.

Conditions for which, in our view, more organized epidemiological work is urgently needed are dealt with in the following paragraphs.

Carcinoma of the uterus

More well-planned trials of the effect of cervical cytology on mortality are badly needed. At present we are largely relying on studies carried out in British Columbia, in some United States cities, such as Memphis, San Diego and Louisville, in Norway and in Great Britain, all of which have drawbacks as regards either population size or epidemiological acceptability.

Glaucoma simplex

Two or three small studies have suggested that previously accepted screening criteria are inadequate. There is need for more studies of this kind, conducted in such a way that results would be comparable.

Mental illness

This is quantitatively a vast world problem yet little can at present be done about its early detection and treatment. Surveys which are aimed at defining early mental disease and at establishing acceptable diagnostic techniques, and which incorporate controlled trials of treatment, are badly needed.

Asymptomatic bacteriuria

There is more than a suggestion that undetected urinary infections early in life may lie at the root of much crippling arterial hypertension in later life. Early diagnosis and prompt treatment could potentially have a very important impact. Surveys are being carried out but, in view of the importance of the ultimate condition, the problems of the significance of bacteriuria might be attacked on a larger scale, as well as by longitudinal studies starting in infancy.

Cancer of the breast

We are still ignorant of the effect of diagnosing breast cancer before symptoms are reported. At present, advances in clinical treatment have had disappointing results and mortality remains little affected. At least one large-scale mammography survey is in progress[217]. In view of the long time that must elapse before an effect on the death rate can be seen, it may perhaps be wise to ensure that valid results will be obtained in as short a time as possible by at least duplicating the work elsewhere. The preventive value of breast self-examination has never been adequately assessed, so far as we are aware, and, since this is much cheaper, safer and generally more practicable than X-ray mammography, it seems most important that its value (or otherwise) should be known for certain. The value of self-examination might be tested by comparing two populations, trial and control. If the technique were shown to be truly beneficial it should become much easier to propagate it more widely.

Lung cancer

The appalling prognosis for lung cancer, even when detected radiologically at the earliest possible stage, calls for more work directed towards better screening methods and, if possible, prevention. Is seems likely that cytological examination can show abnormal cells in the sputum at

a pre-cancerous stage, which could lead to localization of cancer in a bronchus before it appears radiologically. There is need for more work on these lines, with agreed standards of cytological nomenclature, diagnostic procedures and follow-up arrangements.

High blood pressure.

Trials have been carried out which demonstrate the value of hypotensive drugs in improving the outlook for people with an advanced degree of essential hypertension. So far, however, there is a lack of published work on the effects of treating minor degrees of essential hypertension, although it is clear that even small sustained rises in blood pressure are associated with a reduced life expectation. We know of two such randomized controlled trials but, with new drugs now becoming available, more trials might profitably be carried out. The unpleasant effects of some of these drugs are a real drawback, but the newer preparations are reported as having fewer side-effects.

RECORDS

For the selective screening of high-risk groups of the population a *sine qua non* is the ability to know who constitutes these groups. It may, of course, be enough to issue a general invitation to a particular group (e.g., adult women for cervical cytology); but there is always a strong possibility that those persons at highest risk may opt out. It is therefore often more successful (as well as better public relations) to issue individual invitations to attend by appointment. In the type of surveillance from a health centre or group general practice to which we have referred, individual invitations are essential. In order to draw particular groups in large numbers from the population, records capable of being dealt with by automatic data-handling methods are needed. In practice this may be difficult, both from the point of view of the design of a suitable record and what should be put on it and from the point of view of keeping the information confidential. In general practice, for example, the patient's medical record is likely only to be handled by physicians or those in his close confidence. But in the future, it seems likely that we must expect general practitioners' records to be handled at data-processing centres. How is this to be done without a breach of confidence? It appears to us, therefore, that the design and handling of records is an important and urgent problem.

ECONOMICS

Considering its importance, surprisingly little is known about the economics of early disease detection. Most probably this is because screening has so far been largely experimental and the question of its economic cost has not arisen. Certainly, in the case of screening for tuberculosis, a good deal is known about the cost, since this was introduced as a service long ago. It would be valuable to study the cost of screening for different conditions, either alone or in combination, under different systems of medical care. Undoubtedly the arrangements for medical care in some countries are at present more suited to early disease detection than those in other countries. Comparative, and comparable, economic studies of this sort would be useful.

EDUCATION

Practicable techniques for screening for early disease are now available, but still, as a profession, medical practitioners continue to see clinical conditions for the first time at a late stage of development, when treatment is less likely to be successful. Also, clinicians in general are too oriented towards conventional diagnosis and treatment to think readily in preventive terms. Thus there is much room for improving both the attitude of the public and the attitude of the profession to the early detection of disease, as we have pointed out in Chapter 3 (page 75). Hitherto diagnosis has been the province of the clinician, who has been concerned mainly with the individual patient. It has been possible to have a high standard of clinical practice co-existing with poor over-all medical care, owing to an unequal distribution of resources. Implicit in early disease detection (cervical cancer screening, for example) is the idea of extending preventive clinical medical services to a whole community, and this in turn postulates a new way of thinking about the medical and auxiliary professions. The medical profession itself, and the public, may therefore be on the verge of a revolution in their attitude to clinical (as opposed to traditional) preventive medicine, and there should be good opportunities to influence the course of medical and public education so as to further, to the best advantage, this changing approach. New departments of general practice, post-graduate institutes, departments of social medicine and the like are growing up. These should promote the training of physicians and the dissemination of new ideas through attachments and fellowships and by facilitating interchanges.

REFERENCES

1. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 45
2. World Health Organization, Regional Committee for Europe (1964) *The pre-symptomatic diagnosis of diseases by organized screening procedures* (Fourteenth session, Prague), EUR/RC14/Tech. Disc./6 (mimeographed)
3. Dawber, T. R., Moore, F. E. & Mann, G. V. (1957) Coronary heart diseases in the Framingham study. *Amer. J. publ. Hlth*, **47**, Suppl., 4
4. American Medical Association, Council on Medical Service (1955) *A study of multiple screening: descriptive data on thirty-three screening surveys* (revised), Chicago
5. Commission on Chronic Illness (1956-59) *Chronic illness in the United States, Volumes I-IV.* Cambridge, Mass., Harvard University Press
6. Breslow, L. (1955) Multiphasic screening in California. *J. chron. Dis.*, **2**, 375
7. American Public Health Association (1960) *Chronic disease and rehabilitation: a program guide for state and local health authorities*, New York
8. Kurlander, A. B. & Carroll, B. E. (1953) Case-finding through multiple screening. *Publ. Hlth Rep. (Wash.)*, **68**, 1035
9. Wilson, J. M. G. (1962) *Report on multiphasic screening* (Report on WHO Travelling Fellowship to the USA), 62 R/UK-13 (mimeographed)
10. California, State Department of Public Health, Bureau of Chronic Diseases. Chronic Illness and Aging Unit (1963) *Bibliography on disease detection: health maintenance, periodic health examination and multiphasic screening*, Berkeley, Calif. (mimeographed)
11. Chapman, A. L. (1949) The concept of multiphasic screening. *Publ. Hlth Rep. (Wash.)*, **64**, 1311
12. Mountin, J. W. (1950) Multiple screening and specialized programmes. *Publ. Hlth Rep. (Wash.)*, **65**, 1359
13. Smillie, W. G. (1952) Multiple screening. *Amer. J. publ. Hlth*, **42**, 255
14. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 48
15. Remein, Q. R. & Wilkerson, H. L. C. (1961) The efficiency of screening tests for diabetes. *J. chron. Dis.*, **13**, 6
16. Holland, W. W. & Humerfelt, S. (1964) Comparison of blood pressure: comparison of intra-arterial and cuff values. *Brit. med. J.*, **2**, 1241
17. *Lancet* (1966) Measuring blood pressure, **1**, 414

18. Elwood, P. C. & Jacobs, A. (1966) Haemoglobin estimation: a comparison of different techniques. *Brit. med. J.*, **1**, 20
19. Thorner, R. M. & Remein, Q. R. (1961) *Principles and procedures in the evaluation of screening for disease. Publ. Hlth Monogr.*, No. 67 (*Public Health Service Publication*, No. 846)
20. Hollows, F. C. & Graham, P. A. (1966) *The Ferndale glaucoma survey.* In: *Glaucoma, epidemiology, early diagnosis and some aspects of treatment: proceedings of a symposium held at the Royal College of Surgeons of England*, Edinburgh, Livingstone, p. 24
21. Graham, P.A. & Hollows, F.C. (1966) *A critical review of methods in detecting glaucoma.* In: *Glaucoma, epidemiology, early diagnosis and some aspects of treatment: proceedings of a symposium held at the Royal College of Surgeons of England*, Edinburgh, Livingstone, p. 103
22. Hollows, F. C., Graham, P. A. (1966) Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. *Brit. J. Ophthal.*, **50**, 570
23. Davis, H. J. & Jones, H. W., jr (1966) Population screening for cancer of the cervix with irrigation smears. *Amer. J. Obstet. Gynec.*, **96**, 605
24. Davis, H. J. (1962) The irrigation smear: a cytologic method for mass population screening by mail. *Amer. J. Obstet. Gynec.*, **84**, 1017
25. Butterfield, W. J. H., Keen, H. & Sharp, C. L. E. H. (1964) Diabetes survey in Bedford, 1962. *Proc. roy. Soc. Med.*, **57**, 193
26. United States of America, Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics (1964) *Glucose tolerance of adults, United States, 1960-1962, diabetes prevalence and results of a glucose tolerance test, by age and sex*, Washington, D. C. (*Public Health Service Publication*, No. 1000, Series 11, No. 2)
27. Stamler, J., Berkson, D. M., Young, Q. D., Hall, Y. & Miller, W. (1963) Approaches to the primary prevention of clinical coronary heart disease in high-risk, middle-aged men. *Ann. N.Y. Acad. Sci.*, **97**, 932
28. Jolliffe, N., Rinzler, S. H. & Archer M. (1959) The Anti-Coronary Club: including a discussion of the effects of a prudent diet on the serum cholesterol level of middle-aged men. *Amer. J. clin. Nutr.*, **7**, 451
29. Christakis, G., Rinzler, S. H., Archer, M., Winslow, G., Jampel, S., Stephenson, J., Friedman, G., Fein, H., Kraus, A. & James, G. (1966) The Anti-Coronary Club: a dietary approach to the prevention of coronary heart disease. A seven-year report. *Amer. J. publ. Hlth*, **56**, 299
30. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 65
31. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume IV. Chronic illness in a large city: the Baltimore study*, Cambridge, Mass., Harvard University Press, pp. 262, 448
32. Weinerman, E. R., Breslow, L., Belloc, N. B., Waybur, A. & Milmore, B. K. (1952) Multiple screening of longshoremen with organized medical follow-up. *Amer. J. publ. Hlth*, **42**, 1552
33. New York, State Department of Health, Bureau of Chronic Disease and Geriatrics (1960) *Report on Cortland County screening demonstration* (unpublished)
34. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume IV. Chronic illness in a large city: the Baltimore study*, Cambridge, Mass., Harvard University Press

35. Commission on Chronic Illness (1959) *Chronic illness in the United States: Volume III. Chronic illness in a rural area: the Hunterdon study*, Cambridge, Mass., Harvard University Press, pp. 273, 304
36. Beuchley, R. W., Robert, M. A., Drake, M. & Breslow, L. (1958) Height, weight and mortality in a population of longshoremen. *J. chron. Dis.*, **7**, 363
37. Borhani, O. N., Hechter, H. H. & Breslow, L. (1963) Report of a ten-year follow-up study of the San Francisco longshoremen. *J. chron. Dis.*, **16**, 1251
38. Wylie, C. M. (1961) Participation in a multiple screening clinic with five-year follow-up. *Publ. Hlth Rep. (Wash.)*, **76**, 596
39. Wylie, C. M. (1961) Use of death rates in evaluating multiple screening. *Publ. Hlth Rep. (Wash.)*, **76**, 1111
40. Stamler, J. (1962) *Annual report [of the] Chronic Disease Control Division, Chicago Board of Health*, p. 12 (mimeographed)
41. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 29
42. Franco, S. C., Gerl, A. J. & Murphy, G. T. (1961) Periodic health examinations: a long term study, 1949-1959. *J. occup. Med.*, **3**, 13
43. United States of America, Department of Health, Education, and Welfare, Public Health Service, Division of Occupational Health (1963) *Periodic health examinations - abstracts from the literature*, Washington, D. C. *(Public Health Service Publication*, No. 1010)
44. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 28
45. Williamson, J., Stokoe, I. H., Gray, S., Fisher, M., Smith, A., McGhee, A. & Stephenson, E. (1964) Old people at home. *Lancet*, **1**, 1117
46. *Calif. Hlth* (1961) **19**, No. 11 (Biennial Report Edition)
47. Wilson, J. M. G. (1965) Some aspects of the epidemiology of cervical cancer. *Mth. Bull. Minist. Hlth Lab. Serv.*, **24**, 72
48. Grundy, F. & Mackintosh, J. M. (1957) *The teaching of hygiene and public health in Europe*, Geneva, p. 109 (*Wld Hlth Org. Monogr. Ser.*, No. 34)
49. WHO Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel (1964) *Promotion of medical practitioners' interest in preventive medicine. Twelfth report of the . . .*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 269)
50. Brockington, F., Silver, G. & Vuletic, A. (1964) *Teaching of the medical student for comprehensive medical practice (with emphasis on extramural institutions)*, Geneva, WHO/Educ/126 (mimeographed)
51. College of General Practitioners (1965) *Present state and future needs of general practice*, London, Council of the College
52. Breslow, L. & Hochstim, J. R. (1964) Sociocultural aspects of cervical cytology in Alameda County, Calif. *Publ. Hlth Rep. (Wash.)*, **79**, 107
53. Kegeles, S. S., Kirscht, J. P., Haefner D. P. & Rosenstock, I. M. (1965) Survey of beliefs about cancer detection and taking Papanicolaou tests. *Publ. Hlth Rep. (Wash.)*, **80**, 815
54. Wakefield, J. & Baric, L. (1965) Public and professional attitudes to a screening programme for the prevention of cancer of the uterine cervix. *Brit. J. prev. soc. Med.*, **19**, 151
55. Central Health Services Council (1964) *Health education: report of a joint committee of the Central and Scottish Health Services Councils*, London, H. M. Stationery Office, p. 10

56. Joslin, E. P., Root, H. F., White, P. & Marble, A. (1959) *The treatment of diabetes mellitus*, 10th ed., Philadelphia, Lea & Febiger, p. 19
57. Wilkerson, H. L. C. & Krall, L. P. (1947) Diabetes in a New England town. *J. Amer. med. Ass.*, **135**, 209
58. Walker, J. B. & Kerridge, D. (1961) *Diabetes in an English community: a study of its incidence and natural history*, Leicester, University Press
59. McDonald, G. W., Fisher, G. F. & Pentz, P. C. (1965) Diabetes screening activities, July 1958 to June 1963. *Publ. Hlth Rep. (Wash.)*, **80**, 163
60. United States of America, Department of Health, Education, and Welfare, Public Health Service (1961) *Diabetes fact book*, Washington, D. C. (*Public Health Service Publication*, No. 890)
61. United States of America, Department of Health, Education, and Welfare, Public Health Service (1960) *Diabetes program guide*, Washington, D. C. (*Public Health Service Publication*, No. 506), p. 30
62. Commission on Chronic Illness (1957) *Chronic illness in the United States:* Vol. IV, Appendix D, *Chronic illness in a large city*, Cambridge, Mass., Harvard University Press, p. 460
63. Reid, J. J. R. (1962) *Diabetes mellitus: certain aspects of prevention, detection and treatment* (Report on WHO Travelling Fellowship to the USA), 62 R/UK-13 (mimeographed)
64. Reid, J. J. A. (1960) Public knowledge of diabetes. *Med. Offr.*, **103**, 325
65. Redhead, I. H. (1960) Incidence of glycosuria and diabetes mellitus in a general practice. *Brit. med. J.*, **1**, 695
66. College of General Practitioners (1962) A diabetes survey. *Brit. med. J.*, **1**, 1497
67. Kirkland, J. A. & Morgan, H. G. (1961) An assessment of routine hospital urine testing for protein and glucose. *Scot. med. J.*, **6**, 513
68. Rundles, R. W. (1945) Diabetic neuropathy: general review with report of 125 cases. *Medicine (Baltimore)*, **24**, 111
69. Garland, H. (1960) The neurological complications of diabetes mellitus: clinical aspects. *Proc. roy. Soc. Med.*, **53**, 137
70. Ashton, N. (1959) Diabetic retinopathy: a new approach. *Lancet*, **2**, 625
71. Dunlop, D. M. (1954) Are diabetic degenerative complications preventable? *Brit. med. J.*, **2**, 383
72. Marble, A. (1955) Coronary artery disease in the diabetic. *Diabetes*, **4**, 290
73. Johnsson, S. (1960) Retinopathy and neuropathy in diabetes mellitus: comparison of the effects of two forms of treatment. *Diabetes*, **9**, 1
74. Wolff, O. H. & Salt, H. B. (1958) Serum-lipids and blood sugar levels in childhood diabetes. *Lancet*, **1**, 707
75. Keen, H. (1959) Paper read to Medical and Scientific Section, British Diabetic Association, Annual Clinical Meeting at Guy's Hospital, London (unpublished)
76. Newburgh, L. H. & Conn, J. W. (1939) A new interpretation of hyperglycemia in obese, middle-aged persons. *J. Amer. med. Ass.*, **112**, 7
77. *Lancet* (1965) Obesity and diabetes. **1**, 1260
78. Root, H. F., Mirsky, S. & Ditzel, J. (1959) Proliferative retinopathy in diabetes mellitus: review of eight hundred and forty-seven cases. *J. Amer. med. Ass.*, **169**, 903
79. Beckett, A. G. (1962) Harmful effects of delay in diagnosis of diabetes mellitus. *Practitioner*, **189**, 57
80. Brown, I. K. & Jones, A. T. (1964) Retinopathy and diabetic control. *Brit. J. Ophthal.*, **48**, 148

81. Collyer, R. T. & Hazlett, B. E. (1961) Retinopathy and neuropathy in one hundred growth-onset diabetic patients. *Canad. med. Ass. J.*, **85**, 1328
82. Daysog, A., jr, Dobson, H. L. & Brennan, J. C. (1961) Renal glomerular and vascular lesions in pre-diabetes and in diabetes mellitus: a study based on renal biopsies. *Ann. intern. Med.*, **54**, 672
83. Hoet, J. P. (1954) Carbohydrate metabolism during pregnancy. *Diabetes*, **3**, 1
84. Wilkerson, H. L. C. (1959) Pregnancy and the prediabetic state. *Ann. N. Y. Acad. Sci.*, **82**, 219
85. Fajans, S. S. & Conn, J. W. (1954) An approach to the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisone. *Diabetes*, **3**, 296
86. Joslin, E. P,, Root, H. F., White, P. & Marble, A. (1959) *The treatment of diabetes mellitus*, 10th ed., Philadelphia, Lea & Febiger, p. 48
87. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 166
88. Ford, M. J. & Glenn, B. (1951) Undetected diabetes among the relatives of diabetics. *Sth. Med. J. (Bgham, Ala.)*, **44**, 239
89. Harris, H. (1949) The incidence of parental consanguinity in diabetes mellitus. *Ann. Eugen. (Lond.)*, **14**, 293
90. Harris, H. (1950) The familial distribution of diabetes mellitus: study of relatives of 1241 diabetic propositi. *Ann. Eugen. (Lond.)*, **15**, 95
91. United States of America, Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics (1964) *Glucose tolerance of adults, United States, 1960-1962: diabetes prevalence and results of a glucose tolerance test, by age and sex*, Washington, D. C. (*Public Health Service Publication*, No. 1000, Series 11, No. 2)
92. *Brit. med. J.* (1965) Inheritance of diabetes mellitus. **1**, 940
93. WHO Expert Committee on Diabetes Mellitus (1965) *Report of a . . .*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 310)
94. Keen, H., Rose, G., Pyke, D. A., Boyns, D., Chlouverakis, C. & Mistry, S. (1965) Blood sugar and arterial disease. *Lancet*, **2**, 505
95. Ostrander, L. D., Francis, T., Hayner, N. S., Kjelsberg, M. O. & Epstein, F. H. (1965) The relationship of cardiovascular disease to hyperglycemia. *Ann. intern. Med.*, **62**, 1188
96. England and Wales, Registrar General (1962) *The Registrar General's statistical review of England and Wales for the year 1960: Part I. Tables, Medical*, London, H. M. Stationery Office
97. England and Wales, Registrar General (1966) *The Registrar General's statistical review of England and Wales for the year 1964: Part I. Tables, Medical*, London, H. M. Stationery Office
98. Logan, W. P. D. & Cushion, A. A. (1958) *Morbidity statistics from general practice: Volume I (General)*, London, H. M. Stationery Office (General Register Office, *Studies on Medical and Population Subjects*, No. 14)
99. United States of America, Department of Health, Education, and Welfare, Public Health Service (1964) *Heart disease in adults, United States, 1960-1962*, Washington. D. C. (*Public Health Service Publication*, No. 6, Series 11)
100. World Health Organization (1965) *The work of the World Health Organization in cardiovascular diseases, 1959-1964*, Geneva, PA/24.65 (mimeographed)
101. WHO Expert Committee on the Prevention of Rheumatic Fever (1966) *Report of a . . .*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 342)

102. Miller, R. A., Smith, J., Stamler, J., Hahneman, B., Paul, M. H., Abrams, J., Hait, G., Edelman, J., Willard, J. & Stevens, W. (1962) The detecting of heart disease in children: results of a mass field trial with use of tape-recorded heart sounds. *Circulation*, **25**, 85

103. Wilson, J. M. G. & Heasman, M. A. (1959) Coronary artery disease: an epidemiological review. *Mth. Bull. Minist. Hlth Lab. Serv.*, **18**, 94

104. Kennedy, A. C. (1957) Observations on the incidence of coronary heart disease in a rural area in S. W. Scotland. *Scot. med. J.*, **2**, 420

105. Epstein, F. H., Ostrander, L. D., Johnson, B. C., Payne, M. W., Hayner, N. S. Keller, J. B. & Francis, T. (1965) Epidemiological studies of cardiovascular disease in a total community, Tecumseh, Michigan. *Ann. intern. Med.*, **62**, 1170

106. Epstein, F. H. (1965) The epidemiology of coronary heart disease. *J. chron. Dis.*, **18**, 735

107. World Health Organization, Regional Office for Europe (1963) *Survey of the prevalence of ischaemic heart diseases in certain European countries: report on a technical meeting*, Copenhagen, EURO, 179.3 (Pr) (mimeographed)

108. Rose, G. A. (1962) The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull. Wld Hlth Org.*, **27**, 645

109. WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease (1962) *Arterial hypertension and ischaemic heart disease: preventive aspects. Report of an Expert Committee*, Geneva, p. 19 (*Wld Hlth Org. techn. Rep. Ser.*, No. 231)

110. Burgess, A. M., Fejfar, Z. & Kagan, A. (1963) *Arterial hypertension and ischaemic heart disease: comparison in epidemiological studies*, Geneva, World Health Organization

111. Kagan, A. (1965) Interpretation of electrocardiograms. *Milbank mem. Fd Quart.*, **43**, (Part 2), 40

112. Rose, G. A., personal communication

113. Stokes, J. & Dawber, T. R. (1959) The silent coronary: the frequency and clinical characteristics of unrecognized myocardial infarction in the Framingham study. *Ann. intern. Med.*, **50**, 1359

114. Acheson, R. M. & Acheson, E. D. (1958) Coronary and other heart disease in a group of males aged 65-85. *Brit. J. prev. soc. Med.*, **12**, 147

115. Hinkle, L. E., Carver, S., Benjamin, B., Christenson, W. & Strone, B. (1964) Studies in ecology of coronary heart disease. I. Variations in the human electrocardiogram under conditions of daily life. *Arch. environm. Hlth*, **9**, 14

116. Paul, O., Lepper, M. H., Phelan, W. H., Dupertnis, G. W., MacMillan, A., McKean, H. & Park, H. (1963) A longitudinal study of coronary heart disease. *Circulation*, **28**, 20

117. Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, W. & Stokes, J. (1961) Factors of risk in the development of coronary heart disease: six year follow-up experience of the Framingham study. *Ann. intern. Med.*, **55**, 33

118. Dawber, T. R., Kannel, W. B., Love, D. E. & Streeper, R. B. (1952) The electrocardiogram in heart disease detection: a comparison of the multiple and single lead procedures. *Circulation*, **5**, 559

119. Thomas, A. J., Cochrane, A. L. & Higgins, I. T. T. (1958) The measurement of the prevalence of ischaemic heart disease. *Lancet*, **2**, 540

120. Blackburn, H., Keys, A., Simonson, E., Rantakarju, P. & Punsar, S. (1960) The electrocardiogram in population studies. *Circulation*, **21**, 1160

121. Thompson, W. B., Hudmet, H. B., jr, Russo, P. E., Brown, F. R. & Mostley, K. T. (1961) A review and study of cardiovascular disease screening with the miniature chest X-ray. *J. chron. Dis.*, **13**, 148
122. Cooper, G. R. (1965) Blood lipids. *Milbank mem. Fd Quart.*, **43**, (Part 2), 49
123. Rose, G. A. & Blackburn, H. (1968) *Cardiovascular survey methods*, Geneva, (*Wld Hlth Org. Monogr. Ser.*, in press)
124. Oliver, M. F. & Stuart-Harris, C. H. (1965) Present position concerning prevention of heart disease. *Brit. med. J.*, **2**, 1203
125. Oliver, M. F. & Boyd, G. S. (1959) Effect of bilateral ovariectomy on coronary-artery disease and serum-lipid levels. *Lancet*, **2**, 690
126. Morris, J. N. & Heady, J. A. (1953) Coronary heart disease and physical activity of work. *Brit. med. J.*, **2**, 1053, 1111
127. Morris, J. N. & Crawford, M. D. (1958) Coronary heart disease and physical activity of work. *Brit. med. J.*, **2**, 1485
128. England and Wales, Registrar General (1958) *The Registrar General's statistical review. Decennial supplement on occupational mortality 1949-53. Part II*, London, H. M. Stationery Office
129. Doyle, J. T., Heslin, A. S., Hillebal, H. E. & Formel, P. F. (1959) Early diagnosis of ischaemic heart disease. *New Engl. J. Med.*, **261**, 1096
130. Gertler, M. M. & White, P. D. (1954) *Coronary heart disease in young adults*, Cambridge, Mass., Harvard University Press
131. Spain, D. M., Nathan, D. J. & Gellis, M. (1963) Weight, body type and the prevalence of coronary atherosclerotic heart disease in males. *Amer. J. med. Sci.*, **245**, 63
132. Doll, W. R. & Hill, A. B. (1956) Lung cancer and other causes of death in relation to smoking. *Brit. med. J.*, **2**, 1071
133. Hammond, E. C. & Horn, D. (1958) Smoking and death rates: report on forty-four months of follow-up of 187, 783 men. *J. Amer. med. Ass.*, **166**, 1159, 1294
134. Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., Kagan, A. & Gordon, T. (1959) Some factors associated with the development of coronary heart disease (six years follow-up experience in the Framingham study). *Amer. J. publ. Hlth*, **49**, 1349
135. Doyle, J. T., Dawber, T. R., Kannel, W. B., Kinch, S. H. & Kahn, H. A. (1964) The relationship of cigarette smoking to coronary heart disease. *J. Amer. med. Ass.*, **190**, 886
136. Kannel, W. B. (1964) Cigarette smoking and coronary heart disease. *Ann. intern. Med.*, **60**, 1103
137. World Health Organization Regional Office for Europe (1965) *Working group on studies of preventive measures in ischaemic heart disease: summary of discussion*, Copenhagen EURO-179.3 (mimeographed)
138. Groom, D. (1961) Population studies of atherosclerosis. *Ann. intern. Med.*, **55**, 51
139. Smirk, F. H. (1957) *High arterial pressure*, Oxford, Blackwell, p. 687
140. Hodge, J. V. & Dollery, C. T. (1964) Retinal soft exudates. *Quart. J. Med.*, **33**, 117
141. Pickering, G. W. (1965) Hyperpiesis: high blood pressure without evident cause: essential hypertension. *Brit. med. J.*, **2**, 959, 1021
142. Kain, H. K., Hinman, A. T. & Sokolow, M. (1964) Arterial blood pressure measurement with a portable recorder in hypertensive patients: I. Variability and correlation with "casual" pressures. *Circulation*, **30**, 882
143. Rose, G. A., Holland, W. W. & Crowley, E. A. (1964) A sphygmomanometer for epidemiologists. *Lancet*, **1**, 296

144. Boe, J., Humerfelt, S. & Wedervang, F. (1957) The blood pressure in a population. *Acta med. scand.*, Suppl., No. 321
145. Miall, W. E. & Oldham, P. D. (1958) The inheritance of arterial blood pressure. *Clin. Sci.*, **17**, 404
146. Hamilton, M., Pickering, G. W., Roberts, J. A. F. & Sowry, G. S. C. (1954) The aetiology of essential hypertension: I. The arterial pressure in the general population. *Clin. Sci.*, **13**, 11
147. Kagan, A., Gordon, T., Kannel, W. B. & Dawber, T. R. (1959) *Blood pressure and its relation to coronary heart disease in the Framingham population: hypertension*, Vol. III, American Heart Association
148. United States of America, Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics (1964) *Blood pressure of adults by age and sex, United States, 1960-1962*, Washington, D. C. (*Public Health Service Publication*, No. 1000, Series 11, No. 4)
149. Pickering, G. W. (1955) *High blood pressure*, London, Churchill, p. 299
150. Bechgaard, P. (1946) Arterial hypertension: a follow-up study of one thousand hypertonics. *Acta med. scand.*, Suppl., No. 172
151. Society of Actuaries (1959) *Build and blood pressure study*, Chicago
152. Ungerleider, H. E. & Gubner, R. S. (1958) *Life assurance and medicine*, Springfield, Ill., Thomas
153. Kemsley, W. F. F., Billewicz, W. Z. & Thomson, A. M. (1962) A new weight-for-height standard based on British anthropometric data. *Brit. J. prev. soc. Med.*, **16**, 189
154. Edwards, D. A. W., Hammond, W. H., Healy, M. J. R., Tanner, J. M. & Whitehouse, R. H. (1955) Design and accuracy of calipers for measuring subcutaneous tissue thickness. *Brit. J. Nutr.*, **9**, 133
155. United States of America, Department of Agriculture, Agricultural Research Service, Human Nutrition Research Division (1960) *Heights and weights of adults in the United States*, Washington, D. C. (*Home Economics Research Report*, No. 10)
156. Commission on Chronic Illness (1957) *Chronic illness in the United States: Volume I. Prevention of chronic illness*, Cambridge, Mass., Harvard University Press, p. 267
157. *Brit. med. J.* (1964) Disposition to obesity. **2**, 1543
158. England and Wales, General Register Office (1957) *Tuberculosis statistics for England and Wales 1938-1955*, London, H. M. Stationery Office (*Studies on Medical and Population Subjects*, No. 10)
159. WHO Expert Committee on Tuberculosis (1964) *Eighth report*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 290)
160. Springett, V. H. (1956) *Minimal pulmonary tuberculosis found by mass radiography*, London, Lewis
161. Yerushalmy, J. (1953) The reliability of chest roentgenography and its clinical implications. *Dis. Chest*, **24**, 133
162. Horwitz, O. & Palmer, C. E. (1964) Epidemiological basis of tuberculosis eradication: 2. Dynamics of tuberculosis morbidity and mortality. *Bull. Wld Hlth Org.*, **30**, 609
163. Styblo, K. (1964) Identification of high tuberculosis risk groups in connection with the epidemiological and clinical study of tuberculosis in Czechoslovakia, in collaboration with WHO. *Bull. int. Un. Tuberc.*, **35**, 363
164. Erin, L. (1960) Detection of pulmonary tuberculosis by sputum survey. *Tubercle* (Lond.), **41**, 363

165. Scottish Health Services Council (1963) *Bronchitis: report by a sub-committee of the Standing Medical Advisory Committee*, Edinburgh
166. Mork, T. (1962) A comparative study of respiratory disease in England, Wales and Norway. *Acta med. scand.*, Suppl., No. 384
167. Holland, W. W. (1965) Respiratory disease in England and the United States. *Arch. environm. Hlth.*, **10**, 338
168. College of General Practitioners (1961) Chronic bronchitis in Great Britain. *Brit. med. J.*, **2**, 973
169. Holland, W. W., personal communication
170. World Health Organization, Regional Office for Europe (1962) *Symposium on chronic non-specific lung diseases, Moscow, 10-15 December 1962*, EURO-212 (mimeographed)
171. England and Wales, Registrar General (1966) *The Registrar General's statistical review of England and Wales for the year 1964: Part I. Tables, medical*, London, H. M. Stationery Office
172. England and Wales, Registrar General (1957) *The Registrar General's statistical review of England and Wales for the year 1952. Supplement on cancer*, London, H. M. Stationery Office, p. 114
173. Posner, E., McDowell, L. A. & Cross, K. W. (1959) Mass radiography and cancer of the lung. *Brit. med. J.*, **1**, 1213
174. Cuthbert, J. (1959) Bronchogenic carcinoma: a mass radiography group compared with a practitioners group. *Brit. J. Dis. Chest*, **53**, 217
175. Gifford, J. H. & Waddington, J. K. B. (1957) Review of 464 cases of carcinoma of the lung treated by resection. *Brit. med. J.*, **1**, 723
176. Waddington, J. K. B. (1960) Surgical aspects of the mass X-ray campaign, Liverpool, 1959. *Med. Offr.*, **104**, 293
177. Boucot, K. R., Cooper, D. A. & Weiss, W. (1961) The Philadelphia Pulmonary Neoplasm Research project: an interim report. *Ann. intern. Med.*, **54**, 363
178. Frost, J. K. (Cytology Laboratory, Department of Pathology, Johns Hopkins Hospital, Baltimore, Md, USA), personal communication
179. Canti, G. (1964) "Analysis of 100 cases of bronchial carcinoma", Paper presented at Annual Meeting, British Society for Clinical Cytology, London (unpublished)
180. Lilienfeld, A. (1963) American Cancer Society-Veterans' Administration co-operative study for evaluation of radiologic and cytologic screening in the early detection of lung cancer: progress report. *Acta Un. int. Cancr.*, **19**, 1330
181. Knox, E. G. (1966) *Cervical cytology: a scrutiny of the evidence.* In: McLachlan, G., ed., *Problems and progress in medical care; Essays on current research*, 2nd Series, London, Oxford University Press, p. 277.
182. Jones, H. (1952) In a discussion of a paper by Hertig, A. T., Younge, P. A. & McKelvey, J. L., entitled "A debate: What is cancer in situ of the cervix? Is it the pre-invasive form of true carcinoma?" *Amer. J. Obstet. Gynecol.*, **64**, 807, 816
183. Petersen, O. (1955) *Precancerous changes of the cervical epithelium in relation to manifest cervical carcinoma*, Copenhagen, Danish Scientific Press
184. Lange, P. (1960) Clinical and histological studies on cervical carcinoma, precancerosis, early metastases, and tubular structures in the lymph-nodes. *Acta path. microbiol. scand.*, Suppl., No. 143
185. Clemmesen, J. (1962) *On the prognosis of precancerous conditions of the uterine cervix.* In: *Proceedings of International Conference: the morphological precursors of cancer*, Perugia, University of Perugia, p. 463

186. Koss, L. G. et al. (1961) "A Long-Term Cyto-histologic Study of Untreated Carcinoma-in-Situ and Related Abnormalities of the Uterine Cervix." Paper presented at First International Congress of Exfoliative Cytology, Vienna (unpublished)
187. Younge, P. A., Hertig, A. T. & Armstrong, D. (1949) A study of 135 cases of carcinoma in situ of the cervix at the Free Hospital for Women. *Amer. J. Obstet. Gynecol.*, **58**, 867
188. Boyes, D. A., Fidler, H. K. & Lock, D. R. (1962) Significance of in situ carcinoma of the uterine cervix. *Brit. med. J.*, **1**, 203
189. Dunn, J. E. (1962) The use of incidence and prevalence in the study of disease development in a population. *Amer. J. publ. Hlth*, **52**, 1107
190. Dunn, J. E. (1958) Preliminary findings of the Memphis-Shelby County uterine cancer study and their interpretation. *Amer. J. publ. Hlth*, **48**, 861
191. Kashgarian, M., Dunn, J. E., Erickson, C. C. & Sprunt, D. H., unpublished observations
192. Terris, M. & Oalmann, M. C. (1960) Carcinoma of the cervix: an epidemiologic study. *J. Amer. med. Ass.*, **174**, 1847
193. Boyd, J. T. & Doll, R. (1964) A study of the aetiology of carcinoma of the cervix uteri. *Brit. J. Cancer*, **17**, 419
194. Aitken-Swan, J. & Baird, D. (1966) Cancer of the uterine cervix in Aberdeenshire: epidemiological aspects. *Brit. J. Cancer*, **20**, 624
195. Koch, F. (1966) *The population screening for cervical carcinoma in the Borough of Frederiksberg 1962-1963; application of the irrigation smear technique in a mass screening*, Copenhagen, Munksgaard
196. McGregor, J. E., Fraser, M. E. & Mann, E. M. F. (1966) The cytopipette in the diagnosis of early cervical carcinoma. *Lancet*, **1**, 252
197. Cameron, C. B. & Hussain, O. A. N. (1965) 6-Phosphogluconate dehydrogenase activity in vaginal fluid: limitations as a screening test for genital cancer. *Brit. med. J.*, **1**, 1529
198. Labrum, A. H. & Gibbs, D. F. (1964) "Clinical Significance of Levels of 6-Phosphogluconate Dehydrogenase in Vaginal Fluid." Paper presented at "Technicon" Conference: "Automation in Analytical Chemistry", London (unpublished)
199. Ladinsky, J. L., Sarto, G. E. & Peckham, B. M. (1964) Cell size distribution patterns as a means of uterine cancer detection. *J. Lab. clin. Med.*, **64**, 970
200. England and Wales, Registrar General (1966) *The Registrar General's statistical review of England and Wales for the year 1964: Part I. Tables, medical*, London, H. M. Stationery Office
201. England and Wales, Registrar General (1957) *Cancer statistics for England and Wales, 1901-55*, London, H. M. Stationery Office (*Studies on medical and Population Subjects*, No. 13)
202. England and Wales, Registrar General (1957) *The Registrar General's statistical review of England and Wales for the year 1952. Supplement on cancer*, London, H. M. Stationery Office, p. 11
203. Lilienfeld, A. M. (1963) The epidemiology of breast cancer. *Cancer Res.*, **23**, 1503
204. England and Wales, Registrar General (1957) *The Registrar General's statistical review of England and Wales for the year 1952. Supplement on Cancer*, London, H. M. Stationery Office, p. 74
205. Park, W. W. & Lees, J. C. (1951) The absolute curability of cancer of the breast. *Surg. Gynec. Obstetr.*, **93**, 129

206. Lewison, E. F. (1963) An appraisal of long-term results in the treatment of breast cancer. *Acta Un. int. Cancr.*, **19**, 1547
207. Berg, J. W. & Robbins, G. F. (1963) Twenty year follow-up of breast cancer. *Acta Un. int. Cancr.*, **19**, 1575
208. England and Wales, Registrar General (1957) *The Registrar General's statistical review of England and Wales for the year 1952. Supplement on Cancer*, London, H. M. Stationery Office, p. 12
209. England and Wales, Registrar General (1957) *The Registrar General's statistical review of England and Wales for the year 1952. Supplement on Cancer*, London, H. M. Stationery Office, p. 17 (diagram B 4 and B 5)
210. Bloom, H. J. G. (1965) The influence of delay on the natural history and prognosis of breast cancer. *Brit. J. Cancer*, **19**, 228
211. Sutherland, R. (1960) *Cancer, the significance of delay*, London, Butterworth
212. Hawkins, J. W. (1944) Evaluation of breast cancer as a guide to control programmes. *J. nat. Cancer Inst.*, **4**, 445
213. Taylor, G. W. & Wallace, R. H. (1947) Carcinoma of the breast: end result, Massachusetts General Hospital, 1933-1935. *New Engl. J. Med.*, **237**, 475
214. Kreyberg, L. & Christiansen, T. (1953) The prognostic significance of small size in breast cancer. *Brit. J. Cancer*, **7**, 37
215. Gershon-Cohen, J. & Borden, A. G. B. (1964) Detection of unsuspected breast cancer by mammography. *Ann. N. Y. Acad. Sci.*, **144**, 782
216. Egan, R. L. (1962) Mammography, an aid to diagnosis of breast cancer. *J. Amer. med. Ass.*, **182**, 839
217. Stapiso, S., Strax, P. & Venet, L. (1966) Evaluation of periodic breast cancer screening with mammography: methodology and early observation. *J. Amer. med. Ass.*, **195**, 111
218. Eger, S. A. (1965) Early diagnosis in colon and rectal cancer. *CA (N. Y.)*, **15**, 275
219. Clark, T. W., Schor, S. S., Elsom, K. O., Hubbard, G. B. & Elsom, K. A. (1961) Value of periodic examinations in detecting cancer of the rectum and colon. *Postgrad. Med.*, **27**, 290
220. Hertz, R. E., Deddish, M. R. & Day, E. (1960) The periodic examination: evaluation of routine tests and procedures. *Ann. intern. Med.*, **54**, 1209
221. Sorsby, A. (1956) *Blindness in England, 1951-1954*, London, H. M. Stationery Office (Ministry of Health)
222. New York State, Department of Health (1966) *Glaucoma, a screening program guide*, Albany, p. 14
223. Strömberg, U. (1962) Ocular hypertension: frequency, course and relation to other disorders occurring in glaucoma, as seen from mass survey of all inhabitants over forty years of age in a Swedish town. *Acta ophthal. (Kbh.)*, Suppl., No. 69
224. Goldmann, H. (1959) Some basic problems of simple glaucoma, *Amer. J. Ophthal.*, **48**, 213
225. Duke-Elder, S. (1957) The Bowman Lecture: the aetiology of simple glaucoma. *Trans. ophthal. Soc. U. K.*, **77**, 205
226. Friedmann, A. I. (1966) Serial analysis of changes in visual field defects employing a new instrument to determine the activity of diseases involving the visual pathway. *Ophthalmologica (Basel)*, **152**, 1
227. Gloster, J. & Buchanan, W. M. (1965) Automatic device for rapid assessment of the central visual field. *Brit. J. Ophthal.*, **49**, 57
228. Perkins, E. S. (1965) Glaucoma screening from a public health clinic. *Brit. med. J.*, **1**, 417

229. Paterson, G. D. (1966) *The value of family studies in the detection of glaucoma simplex.* In: *Glaucoma: epidemiology, early diagnosis and some aspects of treatment. Proceedings of a Symposium held at the Royal College of Surgeons of England, London,* Edinburgh, Livingstone, p. 51
230. Kaitz, A. L. & Hodder, E. W. (1961) Bacteriuria and pyelonephritis of pregnancy (prospective study of 616 pregnant women). *New Engl. J. Med.*, **265**, 667
231. Miall, W. E., Kass, E. H., Ling, J. & Stuart, K. L. (1962) Factors influencing arterial pressures in the general population in Jamaica. *Brit. med. J.*, **2**, 497
232. Kincaid-Smith, P. & Bullen, M. (1965) Bacteriuria in pregnancy. *Lancet*, **1**, 395
233. Little, P. J. (1965) Prevention of pyelonephritis of pregnancy. *Lancet*, **1**, 567
234. Kass, E. H. (1962) Pyelonephritis and bacteriuria. *Ann. intern. Med.*, **56**, 46
235. Simmons, N. A. & Williams, J. D. (1962) A simple test for significant bacteriuria. *Lancet*, **1**, 1377
236. Brumfitt, W., Davies, B. I. & Rosser, E. ap I. (1961) Urethral catheter as a cause of urinary-tract infection in pregnancy and puerperium. *Lancet*, **2**, 1059
237. Kellgren, J. H., ed. (1963) *The epidemiology of chronic rheumatism: a symposium arranged by the CIOMS*, Blackwell, Oxford, Vol. I
238. Mikkelsen, W. M., Dodge, H. J., Duff, I. F., Epstein, F. H. & Naiper, J. A. (1963) *Clinical and serological estimates of the prevalence of rheumatoid arthritis in the population of Tecumseh, Michigan, 1959-60.* In: Kellgren, J. H., ed., *The epidemiology of chronic rheumatism: a symposium arranged by the CIOMS*, Blackwell, Oxford, Vol. I, p. 239
239. Epstein, F. H., Francis, T., Hayner, N., Johnson, B. C., Kjelsberg, M. O., Naiper, J. A., Ostrander, L. D., Payne, M. W. & Dodge, H. J. (1965) Prevalence of chronic diseases and distribution of selected physiologic variables in a total community, Tecumseh, Michigan. *J. chron. Dis.*, **81**, 307
240. Kellgren, J. H. (1964) Heberden Oration, 1963: the epidemiology of rheumatic diseases. *Ann. rheum. Dis.*, **23**, 109
241. Lawrence, J. S., Hewitt, J. V. & Popert, A. J. (1963) *Gout and hyperuricaemia in the United Kingdom.* In: Kellgren, J. H., ed., *The epidemiology of chronic rheumatism: a symposium arranged by the CIOMS*, Blackwell, Oxford, Vol. I, p. 176
242. Shepherd, M. (1964) Minor mental illness in London: some aspects of a general survey. *Brit. med. J.*, **2**, 1359
243. Great Britain, Medical Research Council (1965) Clinical trial of treatment of depressive illness. *Brit. med. J.*, **1**, 881
244. Gruenberg, E. M. (1964) *Epidemiology.* In: Stevens, H. A. & Heber, R., ed., *Mental retardation: a review of research*, Chicago, University of Chicago Press, p. 259
245. Jaeggi, A. & Jaeggi, F. (1965) Renseignements des enfants et adolescents réputés arriérés dans le canton de Genève. *Psychiat. Enf.*, **8**, 453
246. Weinberg, A. N. (1961) Detection of congenital galactosemia and the carrier state using galactose-C14 and blood cells. *Metabolism*, **10**, 728
247. WHO Study Group on Iron Deficiency Anaemia (1959) *Report . . .*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 182)
248. Berry, W. T. C., Cowin, P. J. & Magee, H. E. (1952) Haemoglobin levels in adults and children. *Brit. med. J.*, **1**, 410
249. Kilpatrick, G. B. & Hardistry, R. M. (1961) The prevalence of anaemia in the community: a survey of a random sample of the population. *Brit. med. J.*, **1**, 773
250. Berry, W. T. C. (1954) Symptoms as a guide to anaemia. *Brit. med. J.*, **1**, 918.

251. Wood, M. M. & Elwood, P. C. (1966) Symptoms of iron deficiency in a community. *Brit. J. prev. soc. Med.*, **20**, 117
252. Elwood, P. C. & Wood, M. M. (1966) Effect of oral iron on symptoms of anaemia. *Brit. J. prev. soc. Med.*, **20**, 172
253. Spooner, R. D. (1960) The incidence of anaemia in general practice in New South Wales. *Med. J. Aust.*, **2**, 727
254. Elwood, P. C. & Jacobs, A. (1966) Haemoglobin estimation: a comparison of different techniques. *Brit. med. J.*, **1**, 20
255. Jungner, G. & Jungner, I. (1966) *The health screening in Värmland.* In: *Surveillance and early diagnosis in general practice*, London, Office of Health Economics
256. Fry, J. (1962) Minor maladies. *Practitioner*, **189**, 633
257. WHO Expert Committee on Medical Assessment of Nutritional Status (1963) *Report...*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 258)
258. Day, E. (1960) What is an adequate "cancer checkup"? *Postgrad. Med.*, **27**, 274
259. WHO Expert Committee on the Prevention of Cancer (1964) *Report...*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 276)
260. Collen, M. F., Rubin, L., Neyman, J., Dantzig, G. B., Baer, R. M. & Siegelaub, A. B. (1964) Automated multiphasic screening and diagnosis. *Amer. J. publ. Hlth*, **54**, 741
261. Collen, M. F. (1966) Periodic health examinations using an automated multitest laboratory. *J. Amer. med. Ass.*, **195**, 830
262. Suchet, A. S. (1963) Méthode active de surveillance de la santé des grandes collectivités agricoles et industrielles. *Acta med. sociol.*, **2**, 237
263. Jungner, G. (1966) *Data processing in the clinical laboratory.* In: *Proceedings on Automated Data Processing in Hospitals: International Conference in Elsinore, 1966*, Stockholm, Swedish Council of Hospital Operation Rationalization, p. 235
264. Hayatawa, J., Bissell, D.M. & Nelson, M.F. (1961) *Calif. Hlth*, **19**, 57

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