Advances in Multiphasic Screening and Testing

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The multiphasic testing center of the future will probably be used both for periodic screening tests and for referrals by practicing physicians. Recent widespread interest of several branches of the Federal Government in multiphasic screening stems from the possibility that, through its use, the enormous cost of chronic illness to the country may be reduced.

Recent advances in automation and the storage, retrieval, and analysis of data by computers make it economically feasible to obtain much more information about the patient's health than ever before. New instrument developments include both screening and diagnostic analysis of electrocardiograms by computers, analysis of heart sounds by computer, and a wide variety of other physiological and biochemical instruments.

To allow for the inclusion and evaluation of these new procedures, a number of multiphasic testing centers will be needed which can do both research and routine testing. Close cooperation between the medical profession, the public health services and industry will be needed to best serve both the public and the medical profession.

Although it is generally agreed that screening tests, as they are looked upon at present, are not diagnostic tests, one reason for performing the tests is to select, out of a large number of apparently healthy persons, those who have a relatively high probability of having the disease or diseases being sought. Definitive diagnostic procedures then can be performed. Thus, while it may not be considered a diagnostic procedure in and of itself, screening is the preliminary step in a procedure which has as its end objective the establishment of a diagnosis. Furthermore, some of the tests being used in screening centers are the same tests that are performed by diagnostic clinical laboratories today. An example is the use of automated analyzers to run a battery of biochemical tests. New methods and tests will be developed, some of which will provide information more nearly diagnostic in nature, such as computer analysis of electrocardiograms.

Since tests of this kind are included in screening centers, it appears quite possible that such centers might also be useful as referral laboratories for individual physicians. Thus, instead of sending a patient to several different laboratories to obtain a
variety of tests such as x-ray studies, clinical chemical determinations, and electrocardiograms, the physician could send his patients to a screening center and have all the tests performed in one place. This should result in a reduction in cost to the patient and yet should give the physician the reliable information he needs—provided the screening centers use accepted test procedures and are organized to take advantage of automated equipment and data handling by computers. For example, a significant portion of the persons who go through the Permanente multiphasic screening unit are referred by private physicians. In fact, such centers should probably be referred to as multiphasic testing centers or multitest laboratories which could be used either for screening or diagnostic work.

Through multiphasic screening tests on the same persons over long periods, significant trends might be found which could lead to a prediction of impending onset of a chronic disease. The physician might then begin preventive measures based on the trends established by the screening procedure, without further definitive testing. In this way the screening program may assume somewhat more of a diagnostic nature.

The use of screening procedures in medicine is not new by any means. In a recent survey of the literature, it was found that almost 1,500 papers on this general subject have been published in the past 10 years alone. The papers deal with all aspects of screening, from philosophy and principles to detailed results of many programs. A recent United States Senate subcommittee investigating the use of multiphasic screening for the early detection and prevention of chronic disease produced a report containing more than 600 pages of testimony by a large number of experts in the field.

The present communication will be limited to a brief review of the subject, a discussion of recent advances in instrumentation and procedures which may have a strong influence on the future of medical screening and testing, and a view of future possibilities.

The Role of Screening in Medicine

Screening is the application of a methodical process to a large group of persons in order to separate that group into smaller individual groups having certain characteristics. As used in medicine, screening is usually thought of as the examination of a large number of apparently healthy persons in order to find out who among them has a high probability of having some specified abnormal condition. The winnowed group is then examined with definitive procedures to aid in arriving at a diagnosis. In this sense there is a distinction between screening tests and diagnostic tests, but it should be noted that even with tests that are generally looked upon as “diagnostic,” the actual diagnosis is made by a physician from information obtained from the physical examination and history as well as from tests.

In general, the abnormal conditions discovered by the screening procedure are of two types. In some cases, the person being tested may have a disease at a stage where there are overt clinical symptoms and signs; in others the findings may be only indicative of a pre-clinical stage. For persons of the latter group, preventive or therapeutic measures may prevent the actual disease or, more frequently, may keep serious complications from developing. At least in part the present wide interest in multiphasic screening is attributable to the preventive possibilities. At a recent United States Senate subcommittee hearing the total economic cost of illness to the country was estimated to be between 50 and 90 billion dollars annually. It was further estimated that if nothing were done to reduce the incidence of chronic disease in the next 10 years, the cost would increase until by 1975 the annual cost could be as high as 180 billion dollars. The possibility that this tremendous financial burden may be reduced by early detection of chronic illnesses and subsequent prevention of the debilitating aspects of such diseases is partly responsible for the interest of the Federal Government in multiphasic screening.

At one of the subcommittee’s hearings, Robert H. Ebert, M.D., dean of Harvard Medical School, discussing the problem of assigning priorities in programs contributing to the nation’s health, said that “no one would argue that disease prevention is the most valuable contribution.” Dean Ebert then pointed out the great advances that have been made in the prevention of contagious diseases and their sequelae through the development of vaccines for poliomyelitis and a host of other diseases. Turning to the problem of the detection of disease, Dean Ebert said that “multiphasic screening is a more efficient and economical method of case finding than the categorical approach.”

An extension of multiphasic testing involves the use of examinations performed periodically to es-
tablish trends. Decisions to begin some form of treatment may be based on changes in the many factors being measured rather than on a single deviation from a normal range. This has been referred to as “predictive medicine” or “predictive health,” and the process is in early stages of evaluation in several centers. George James, M.D., dean of Mount Sinai School of Medicine, in giving testimony at the previously mentioned Senate subcommittee hearings, said that “many of these same tests can also detect changes so early that they are more nearly indicators of a possible risk factor than a developing disease.”

Another form of screening in medicine is used to identify groups of persons who have a high probability of having no disease or defect, as in the case in screening people for certain occupations or as life insurance risks. In this case, the screened group is usually not subjected to further definitive testing unless the initial results are questionable.

Still another form of screening may be used in epidemiological studies where the primary goal is to obtain information. Each of these applications of screening may have certain requirements which could influence selection of the type of test to be used and the screening level.

It is to be strongly emphasized that when tests which are aimed at the early detection of disease are used in the screening program, these tests are only one phase of a two-phase plan. The second phase consists of performing whatever further tests and examinations may be necessary for the physician to arrive at a diagnosis. To perform only the screening phase is useless and may be harmful.

Review of Screening Programs

As the principles, procedures and philosophy of screening for health and disease have been thoroughly discussed and widely published, this communication will only briefly review types of screening programs and consider recent advances and their bearing on the present and future practice of medicine.

Single Test Screening

Single test screening in which a single test is used to screen for a specific disease has been in use for many years. Chest x-ray films for tuberculosis and drives for the detection of diabetes, glaucoma, cervical cancer, syphilis and other diseases are all well known and have been shown to be of definite value. It soon became evident that it would be more economical to perform more than one test at a time and multiple tests to screen for a number of diseases came into being. While most of the screening of the future will probably be of the multiple or multiphasic type, some single test screening will no doubt still be used in special cases.

Multiple Test (Multiphasic) Screening

In the strictest sense of the word, any program that uses more than one test screening for more than one disease is a multiphasic program. Thus, it is difficult to tell when multiphasic screening came into being. The first person to combine two tests probably started multiphasic screening. In one sense, though, multiphasic screening in medicine far antedates any of the programs that have been referred to here. In fact, the practicing physician himself performs a limited multiphasic screening procedure on each of his patients. For example, suppose a patient sees his physician because of a cough. Does the physician limit his examination to the patient’s chest—not if he follows the training he received in medical school. A medical history is obtained, including past illnesses and family history as well as a history relating to the chief complaint. In the physical examination the physician has been trained to check all medical systems, not just the one pertaining to the complaint. In many cases it is the practice of the physician to get some sort of blood and urine evaluation.

All these procedures serve to alert the physician to possible disease in the patient, whether related to the present complaint or not. This is, in essence, screening. Why have we been trained to make this kind of examination? Certainly one of the reasons is that it is in the patient’s best interest provided there is no undue economical burden placed on him or on the physician. This is one of the prime reasons why multiphasic screening or testing is beginning to occupy a more prominent place in medicine. New methods of making measurements and processing the resultant data are beginning to make it economically feasible to obtain much more information about our patients’ health, or lack of it, than ever before.

The first overt multiphasic screening program reported in California was performed in 1949 by Canelo, Bissell, Abrams and Breslow. In this program 945 persons were screened and the screening procedures were two blood tests, two urine tests, an x-ray film of the chest and a brief history. In
1955, Breslow\(^2\) reported on 16 additional programs which had been carried out in California since the first one in 1949. These 16 programs used as few as two and as many as 12 multiple tests. In 1951 a multiphasic screening program was initiated by the Kaiser Foundation Health Plan and was reported by Collen and Linden in 1955.\(^4\) This program utilized seven routine tests, a medical questionnaire and several special tests for persons over 40 years of age. Since 1951 the program at Kaiser Permanente under the direction of Dr. Morris Collen has expanded to become one of the most sophisticated programs in the United States today. In 1964 Collen, Rubin and Davis\(^5\) reported on the advantages of automation and computer analysis in screening. Nine advantages of this approach were delineated, with economy heading the list. A detailed description of the present Permanente testing procedure was given by Collen in 1966.\(^6\)

Many other multiphasic programs have been carried out by various agencies in many other states. Screening programs in at least 11 states, as well as some programs for private groups such as labor unions, were discussed in the previously mentioned Senate subcommittee hearings.\(^13\)

Three years ago the U.S. Public Health Service initiated a 10-year study at the Permanente Multiphasic Screening Clinic to determine the effect of periodic multiphasic screening on the mortality and morbidity of the persons screened. A similar program has been under way at the University of Pennsylvania for some time. In some areas screening clinics are being considered for the poverty programs. The City of Hope National Medical Center recently submitted a proposal to the U.S. Public Health Service for a $650,000 grant to establish a three-year program using multiple trailer-laboratories to carry out multiphasic screening at the work-site of three trade unions in the Philadelphia-Camden area.

It is fairly evident that in the immediate future there will be an increasing emphasis on utilization of multiphasic screening programs, not only for several programs of the Federal Government but also for use by private groups such as labor unions, insurance companies and industrial employers. Many of these programs will have been established and put in operation long before the answer as to their effect on morbidity and mortality has been established.

### New Procedures

#### Impact of Automation and Computers

It is only by the use of automated methods and data storage, analysis and retrieval by computers that the more ambitious multiphasic programs can be feasible economically. One of the large economic gains comes about through reduction in the amount of labor needed. Furthermore, much of the labor that is required can be done by non-professional and non-technical personnel.

The use of automated systems and computer handling of data has already been mentioned in respect to the Permanente program.\(^5,7,8\) The group at the Instrumentation Field Station, Heart Disease Control Branch, U.S. Public Health Service in Washington, D.C., has investigated the role of computers in diagnostic centers.\(^12,13\)

A published description of the present program at Permanente\(^6\) gives details as to how computers and automated or semi-automated procedures aid in that program. The person screened receives a packet of IBM cards, one for each station he visits. At these stations data is either punched into the card directly (autoanalyzer results) or the card is sense-marked for punch card operations. For tests which still require manual handling or verbal report of visual observations—for example retinal photographs, x-ray films and electrocardiograms—the results are sense-marked by the persons reading the data and are subsequently punched on IBM cards. By the time the person being screened finishes the testing procedure, much of the data have already been processed by the computer and, where indicated, subsequent more definitive diagnostic procedures are scheduled while he is still in the center. The ultimate goal, of course, is to have all the results “on line” so that immediately after the screening is completed, all subsequent procedures can be scheduled. Some of the obstacles to this goal will be discussed later.

Another potential use of computers in multiphasic screening or testing is in the analysis of all the data that are obtained in repeated examinations. These data can be subjected to complex multivariate analytical procedures to search for significant factors which can be used to establish “health profiles” for each person. Changes in these factors or profiles might serve as earlier indicators of impending diseases than we now have. At this stage in the development of multiphasic testing, that potential has not actually been demonstrated. It will be necessary to accumulate such data over a period of
several years before it can be determined if a “predictive” potential can be realized.

New Tests

New test procedures which can contribute to the ultimate success of multiphasic screening and testing are at present in various stages of research, development and evaluation. For the most part these new procedures are based on the use of electronic instrumentation. It is not possible to discuss all of the new tests or testing procedures that are in the process of development. I will mention some of those of which I am aware.

Perhaps more is being done along these lines in the cardiovascular than in other fields. Computer analysis of electrocardiograms has been under intensive study by several groups. One of the best known of these studies is that by Cacerec9,10 of the Heart Disease Control Branch of the U.S. Public Health Service. He has developed computer programs for the detailed analysis of the conventional 12-lead electrocardiogram. Data acquisition systems are being developed so that the electrocardiogram can be put on magnetic tape in either analog or digital form and the tapes played into computers through the proper conversion systems for analysis. In cases where the analysis is needed on a “stat” basis the electrocardiogram signals can be fed directly to a computer for “on-line” analysis.

An intermediate type of electrocardiogram analysis is also under evaluation. An instrument now being tested consists of a self-contained computer which analyzes a five-lead electrocardiogram and gives an answer as to “within normal limits” or “outside normal limits.” This is truly a screening instrument and if the answer were “outside normal,” the person screened would then be subjected to a diagnostic electrocardiogram procedure, probably computerized. Such an intermediate system has the advantage that the more complex and detailed analysis is performed only on “positives” (in one screening center this amounts to about 20 per cent of the total number screened).

Another instrument analyzes heart sounds and, through the use of a self-contained computer, presents the results as “within” or “outside” normal limits. The sounds which are outside normal limits are categorized as to whether the abnormality occurs in systole, diastole or as a split second sound. This instrument has been tested on more than 15,000 children and found to be useful. Its application to adults is currently under investigation.

Other new automated procedures are being developed which will give measurements of respiratory function, pulse wave velocity, pulse wave contour and peripheral blood flow, as well as new biochemical measurements such as the amounts of trace metal elements in the blood. Advances in measurement methods in the fields of biochemistry and physiology are under intense investigation and many new procedures will be forthcoming in these fields. More and more emphasis is being placed on obtaining “real time”* data and in certain cases this may involve the use of in vivo tests. It may then be possible to utilize more “dynamic” tests rather than tests of single static type. By dynamic tests, I am referring to a “tolerance” test, one which measures the ability of the body to respond to a displacement from the normal level. The glucose tolerance test is an example of dynamic testing in which a measure of the body’s ability to handle a glucose load gives much more information than a single measure of a fasting blood sugar. Tolerance tests when the response time is one of minutes may also show promise but would require more nearly real time testing than that for a glucose tolerance test. It soon may be possible to perform hydrogen ion tolerance tests or electrolyte tolerance tests where the response to a small amount of ammonium chloride or to a sodium or potassium load may be determined. Such data may give more information on a person’s fluid and electrolyte status than a single test of blood pH, sodium or potassium. Further downstream in time, tests of tolerance to intermediary metabolic components such as lactic acid may be possible.

The new tests discussed above all involve relatively simple types of measurements such as a chemical concentration or analysis of an electrical analog signal.

Other types of tests, some of which are very important and which are used today, have a type of readout that will be difficult to automate. Tests of these types usually require some sort of judgment based on the recognition of complex morphological properties. Examples are x-ray films and stained smears for morphologic study of cells (Papanicolaou stain). While efforts are being made to automate these readouts, it is doubtful that satisfactory methods will be forthcoming in the near future. This means that it will still be some time before it will be possible to have a complete anal-

*“Real time” data—Data that are obtained either continuously or intermittently in such a manner that the results are available with virtually no delay.
analysis of screening tests before the person being screened leaves the screening center.

Multiphasic Screening Research

If the full potentials of multiphasic screening and testing are to be realized, a continuing research program will be needed. As new tests, techniques and data handling systems are developed to the point where they could be economically included in a multiphasic program, some arrangement should be made for their evaluation. Certainly no new procedure should be routinely included in multiphasic programs until such an evaluation is made. One could visualize a limited number of regional centers where such research could be carried out as part of their total program. When these centers show that a new technique is useful, it could then be turned over to other screening or testing centers which are providing a routine service.

The Permanente center evaluates new procedures. For example, a study is under way to investigate the usefulness of performing trace metal concentrations in serum. Such studies may need fairly long periods before a conclusion about their significance can be reached. In addition, it appears advisable that more than one center should be evaluating the same new procedures, as there may be significant differences in the type of populations served by various centers.

It seems reasonable to assume that multiphasic screening or testing will become a standard procedure in certain areas in the field of medicine. In order that these programs can best serve both the public and the medical profession, close cooperative effort between the medical profession, the various public health services and industry will be needed.

REFERENCES