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—Editorial—

Research in Mass Radiography

The discovery of the X-ray by Roentgen in 1895 provided a greatly improved way of identifying the silent, insidious process of tuberculosis before it had developed into open and often intractable disease. The photofluorograph, when it came into use some 40 years later, made possible the application of X-ray to mass case finding and opened the way to a new and aggressive campaign against tuberculosis.

Because we have had this diagnostic tool, countless lives have been saved, but our use of X-ray to find tuberculosis admittedly has limitations, some of which are not yet fully understood. Some of these arise from the variability of interpretation, others from the variable patterns of the disease itself and from our lack of fully definitive knowledge of the disease process.

Having been convinced by the experiences of industrial and segmental surveys that the value of photofluorography in detecting tuberculosis far outweighed the shortcomings, the Public Health Service launched its program of community-wide mass chest X-ray surveys 5 years ago. At the same time, however, the Service undertook an extensive research program seeking fuller knowledge of both the advantages and the limitations of mass radiography. In Columbus, Ga., a study was organized to assay the effects of the community-wide chest X-ray survey on the control of tuberculosis. Concurrently, at the Central Cooperative Clinic in Philadelphia, another investigation was undertaken to follow the health history of tuberculosis suspects discovered in mass surveys. These research facilities have had the common purpose of providing the knowledge which will sharpen and refine mass X-ray survey operations.

This kind of research is of necessity a long-term undertaking, but the work is now producing results. In last month's Tuberculosis Control Issue of PUBLIC HEALTH REPORTS, the third of a series of reports from the Columbus, Ga., study was presented. The current issue carries a description of the Philadelphia Central Cooperative Clinic study which forms the first of a series of reports from that installation. In the Columbus study, tuberculin-test data, resurvey

X-ray films, and physical examination findings are now available which, in combination with detailed information about the development of tuberculosis in the area, should help to clarify the "endogenous-exogenous" controversy over the nature of tuberculosis. In the Philadelphia study, careful observation and detailed physical findings over a prolonged period of follow-up will be correlated with initial X-ray findings to give a clear understanding of the latter's significance. Such results should provide a more precise basis for the intensive follow-up of those persons whose continued medical supervision following their discovery in X-ray surveys would appear to be most profitable and necessary, both for the individual and for the public health.

Such problems demand painstaking work, careful observation, and detailed analysis. It is hoped that these studies will provide scientific knowledge which will enable us to retain the advantages of the mass chest X-ray survey and to minimize its limitations.

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Central Cooperative Clinic Study of Follow-Up in Tuberculosis Control

I. Background, Objectives, and Methodology

By Donald Ottenberg, M.D., Katharine Boucot, M.D., W. Edward Chamberlain, M.D., Louis Cohen, M.D. and Sara E. Yelton, M.A.*

The intensified search for tuberculosis in the apparently healthy population is burdened with perplexing problems related to disposition of the survey-discovered case. Although physicians recognize the challenge of the "silent" lesion they have as yet few guides to help them meet it.

In 1949, over 14 million individuals were screened by photofluorographic surveys in the United States, and about 200,000 had lesions "suspicious" of tuberculosis. The size of the group requiring diagnosis and counsel in a single year of case-finding activities, emphasizes the need for refined criteria for selection and disposition of persons found. The problem is an old one but seems somehow to take on new proportions when large numbers are surveyed and when one attempts to arrive at reasonably objective criteria for their management.

The problem of assessing the significance of many of the lesions encountered in surveys is present from the beginning of the survey until final disposition of the discovered patients. The uncertainty first appears with the initial question: "Who among the individuals surveyed should be referred to a physician for further study?" Since the shadows visible on X-ray films may range from the barely perceptible to the very obvious, it is necessary to select from a relatively large number those that are thought to require further investigation. At present, this selection is a somewhat arbitrary activity. Readers can separate the survey population into positives and negatives only imperfectly because of the difficulty in defining a lesion, and yet there is no thoroughly documented follow-up experience from which to formulate this definition. Furthermore, not only is the basis of selection likely to be different from one reader to another, but each reader has a limited ability to select patients consistently on the basis of

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his own criteria. Errors of omission and commission are therefore inevitable. Persons who should be referred for clinical study may be advised that they are free of disease, while others may be needlessly subjected to psychological trauma and wasted effort.

The physician to whom the survey-discovered patient is referred may find himself in an even more disturbing position than the interpreter of the survey film. He is confronted by a patient, not a film, and the patient's question, "What does the shadow on my X-ray mean?" The answer may influence the entire life of the patient and his family, and it must be given with conviction. Yet the physician has meager information on which to proceed. The results of his examination, no matter how thorough, will be essentially negative in the majority of patients, and his accumulated knowledge of the probable course of clinically manifest disease provides but a hypothetical basis for his advice to the patient with unsuspected disease. The physician knows that nothing will reassure the anxious patient better than prompt dismissal, but the possible consequences of such a decision are all too clear. Most physicians resolve this dilemma by advising periodic observation, a choice much more difficult for the patient to accept and for the physician to enforce. Although this course satisfies the desire of the physican to serve the interests of both the patient and the community, he frequently is faced with further difficult decisions concerning the kind of observation required as well as the frequency and duration of observation.

The preponderance of lesions of minimal extent, so encouraging in many ways, is at the same time a source of difficulty in the diagnosis and prognosis of patients referred from surveys. Since about three-fourths of the lesions uncovered by surveys are minimal, the clinician must deal primarily with the stage of the disease about which knowledge is least secure. Minimal tuberculosis is notoriously covert and the problems associated with it have received less scrutiny than those of more advanced disease. The frequency with which shadows visible on X-rays are associated with a positive tuberculin reaction but not with a history of tuberculosis suggests that a large proportion of minimal lesions must heal spontaneously. Clinical axioms and prognostic criteria established largely through experience with more advanced disease, then, may not be wholly applicable to the diagnosis and management of patients with minimal disease.

There is today much controversy about the desirability of hospitalizing the patient with minimal involvement. Some take what would appear to be the more cautious course and hospitalize every patient with active minimal disease for whom a bed can be found, while others hospitalize such patients only rarely. Since it may be just as hazardous to hospitalize a patient who would be better off at home as to fail to send to the hospital one who would benefit greatly by such

a move, the question is not academic. Furthermore, in view of the serious shortage of beds in many parts of the country, a conclusive answer to this question, although difficult to achieve, is greatly to be desired.

These problems are familiar to all who conduct surveys and to many practitioners throughout the country to whom the discovered patients are referred. Re-emphasis seems justified, however, as a first step in attempting to obtain maximal effectiveness of survey procedures. While it would be naive to suggest that foolproof criteria for selection and disposition of patients will ever be attained, the magnitude and complexity of the problems brought forth by surveys demand a search for any common denominators that might be used with confidence. It seems likely that a rational basis for dealing with any patients with previously unsuspected disease—in this instance survey-discovered patients—can be provided only by careful study of the natural course of the disease in such patients themselves.

For this reason, the Division of Chronic Disease and Tuberculosis, Public Health Service, early in the development of its case-finding efforts, established a clinical research facility for long-term observation of survey-discovered patients. This project, which is the subject of this report, was considered to be one phase of a broad research program for the evaluation of mass surveys as an instrument of tuberculosis control. Another phase of the program is the facility for epidemiological studies established in Muscogee County, Ga., where the significance of survey-discovered cases is being evaluated in relation to all tuberculous patients in an entire community. The third phase of study focuses on the problems of X-ray interpretation, in an attempt to improve the usefulness of this basic tool in the discovery, diagnosis, and management of individuals with pulmonary tuberculosis.

The program for systematic investigation of the course of the disease in survey-discovered patients was established at the Temple University School of Medicine in 1946 as the "Central Cooperative Clinic for study of follow-up methods in the control of tuberculosis." The study was developed and has been conducted with the active participation of five agencies: The Tuberculosis Divisions of the U. S. Public Health Service, the Pennsylvania Department of Health, and the Philadelphia Department of Health; the Temple University School of Medicine; and the Philadelphia Tuberculosis and Health Association.

This paper presents a description of the clinic's organization and methods. In addition it seems appropriate to discuss the special problems related to surveys which form the background to the establishment of the project. Future publications will present the findings for the group of patients at the time of initial examination and the results of follow-up observations.

Investigative Approaches

It is of interest to inquire how, in a disease as ancient as tuberculosis, we can still be faced with fundamental problems of recognition and clinical understanding of the disease. Part of the answer may lie in the difficulty of achieving a systematic observation of the entire cycle of any chronic disease. Most follow-up studies in tuberculosis have been conducted on special groups of patients. When the evaluation of therapy is the objective, only patients who warrant the therapy are observed; and when incipient disease is the central interest, only patients who were previously negative by certain criteria are included. Similarly, sanatorium and post-sanatorium groups are restricted samples. Few studies, if any, have been conducted on samples truly representative of the tuberculous population. And yet, mass surveys conducted in the general population turn up a group which might be considered representative of the nonhospitalized tuberculous population. We are now exposing unfamiliar elements of the total problem which have previously escaped attention. Consequently, it is impossible, with the scanty evidence presented by many of these patients, to interpret their disease in the light of previous experience.

Like other chronic diseases, tuberculosis is a continuous process progressing by infinitesimal degrees, from the first moment of infection through the various stages leading to recovery, chronicity, or death. The population of individuals afflicted may be visualized as occupants of a continuum, with varying numbers at each of the many stages through which the paths of the continuum progress. Understanding of the natural history of the disease depends upon knowledge of its entire span. Until now, systematic observations have been concentrated at the extremes of the continuum, where the disease is either considerably advanced or just begun. The great gap in knowledge of the nature of the disease is in the large middle range between the two extremes. Here are the latent and asymptomatic lesions and the apparently stable scars. This is the part of the continuum of tuberculosis which is newly brought into the open by mass X-ray surveys, and many of the problems related to surveys can be traced to our meager understanding of this large segment.

Ideally, a comprehensive study of the entire cycle of tuberculosis would be longitudinal in approach. It would require the systematic observation and periodic tuberculin testing of a very large sample of normal individuals to identify infected persons promptly. These individuals would then be followed intensively from incipience through the entire course of the disease to full recovery or death. However, for a disease with the incidence of tuberculosis, the size of the sample required makes this approach extremely complicated and prohibitively expensive.

A second approach is cross-sectional, whereby an apparently healthy population is examined to detect all persons in it who have evidence of the disease at a single point in time. This provides a profile of the disease in all stages of development. It is a very useful picture of the range of the disease, but for elucidation of the natural history is limited in providing only a static instead of a dynamic portrayal. The patterns of movement of patients (in the continuum) from one phase of disease to another are not revealed by this approach.

The program of the Central Cooperative Clinic combines the two approaches in an attempt to realize the advantages of each. As a short cut to the more elaborate longitudinal study, initial screening by mass X-ray survey provides a starting point from which a longitudinal study of a more restricted population may proceed. Intensive follow-up of all the individuals identified in the survey supplies a dynamic portrayal of the disease. This applies primarily to the middle range of the continuum, however, since the two end-points are largely missed. Part of the cycle is not far enough advanced to show evidence on the X-ray and another portion is so advanced that the individuals in it cannot be expected to be found in true proportion among apparently healthy people. This limitation is not considered serious, since our knowledge of the two extremes is better documented than is our knowledge of the middle portion of the continuum.

In many respects these considerations may not be limited to tuberculosis but might apply to other chronic illnesses as well. The public health and clinical problems of defining what constitutes significant deviations from normal may be similar in tuberculosis and other diseases. It seems logical to assume that, as in tuberculosis, solution of these problems will require an understanding of the nature and course of the entire spectrum of the disease. It appears likely that this understanding will be achieved no more easily for other diseases, but only through long-range systematic observations of representative groups of individuals. Investigative approaches used in the study of tuberculosis may be a valuable guide.

The Central Cooperative Clinic

The fundamental problems posed by mass survey activities may be expected to yield only to a multiple attack from many angles. The Central Cooperative Clinic is an attempt to perform one essential part of the research required. Its purpose is the systematic, long-range, and continuous observation of a complete yield of patients from a number of routine surveys to determine the ultimate clinical outcome for such patients.

Ideally, such observations should be detached, without interference by the observer with the natural course of the disease. This, however, can never be fully realized in observations on human beings; for not

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only does the observation itself affect the course, but active interference is necessary when indications for treatment become evident. Nevertheless, a fairly reliable portrayal of the course of the disease may be obtained if the investigation embraces as many persons with X-ray evidence of disease in a given survey population as possible, and if almost all such persons are followed with equal intensity. These basic principles guide the conduct of the Central Cooperative Clinic study.

The group of patients is unselected in the sense that no lesion that could conceivably be tuberculous was presumed to be unworthy of further observation. All of the survey films were interpreted independently by at least two readers, and any individual whose film was considered by either of the readers, to show evidence characteristic or suspicious of tuberculosis, was included for further study. The patients admitted to the clinic were all given the same type of intensive initial examination and then carried on a schedule of periodic observation.

The special efforts that are required to retain cooperation of the group are reflected in the composition of the clinic staff. Permanent full-time members include two physicians, three public health nurses, two medical social workers, two laboratory technicians, a radiology technician, a biostatistician, three statistical clerks, and four stenographers. In addition, there is a weekly medical conference with three permanent consultants: a radiologist and two specialists in chest diseases, one of whom is Director of Surveys.

The 643 patients who comprise the case load were identified from among 15,245 persons X-rayed in 17 surveys conducted in Philadelphia during the years 1946 and 1947. Three government agencies, 1 neighborhood community, and 13 private industrial establishments were included. All of the surveys were conducted by the Philadelphia Tuberculosis and Health Association as part of its routine case-finding program.

Persons whose 70-mm. films were classified as "T" (tuberculosis) by one or both readers were called in for a consultation with the Director of Surveys at the Philadelphia Tuberculosis and Health Association who discussed the need for further evaluation with each individual. The director called the family physician by telephone in the presence of the patient and made known the nature of the findings and the purposes of the suggested follow-up at the clinic. A large majority of individuals interviewed in this way accepted appointments for visits to the clinic, and only rarely did a physician fail to consent to the proposed observation. At the end of each interview, a 14″ x 17″ X-ray of the chest was obtained.

When the 70-mm. film was called "S" (suspicious) by one or both readers, the individual was recalled for 14″ x 17″ reexamination. If this film was read as "T," the individual was admitted by the pro-

cedure described above. It was the policy to have films designated "N" (negative), "S," or "O" (nontuberculous disease) reviewed by the three members of the consultant conference. In practice, when all three consultants could not review a film, it was reviewed by at least one of them. If the film showed evidence of tuberculosis, the individual was admitted to the clinic after an orienting interview as described above.

Persons who failed to keep appointments were sent two form letters 1 month apart urging them to report. When these measures failed, the social workers and nurses made intensive efforts to obtain cooperation. In certain instances, patients with known disease already under supervision in other clinics chose not to transfer to the Central Cooperative Clinic for follow-up. Attempts were made to obtain periodic medical reports and films on these patients. When patients moved out of town after admission to the study, the follow-up was continued through the cooperation of official and voluntary health agencies in the new place of residence.

During the initial visit to the clinic each patient was given a complete physical examination and medical, social, occupational, and contact histories were elicited. Specimens were obtained for complete blood count, sedimentation rate, serologic tests for syphilis, and urinalysis. Each patient was skin-tested with tuberculin and histoplasmin, by the intradermal method using 0.0001 mg. PPD and 0.1 cc. 1:1000 histoplasmin. Routine roentgenographic studies on 14" x 17" film consisted of a single posterior-anterior projection and a posterior-anterior stereoscopic pair taken after repositioning of the patient. Specimen bottles were given to each patient with instructions for collection of sputum, and an appointment was made for a return visit in 48 hours to allow reading of the skin test reactions and for obtaining gastric washing specimens for bacteriological study.

Early in the study an attempt was made to obtain gastric washings examinations on all of the patients. It soon became obvious, however, that a considerable number would fail to return if this type of examination were required without exception. For this reason, the policy was modified and "gastrics" were reserved for the more amenable patients, unless a suspicion of activity warranted special efforts to obtain the examination in any particular case.

At the time of the 48-hour visit, the patient was again interviewed by the physician who demonstrated the films and interpreted the results of examinations carried out on the previous visit. After the skin test reactions were inspected, special radiographic studies were performed (apical lordotics, laterals, planigrams, etc.) if they were indicated from the review of the routine films. Sputum specimens were examined by smear and by inoculation of two tubes each of Petragnani's and Loewenstein's media. Positive cultures were

routinely confirmed by differential subculture at room temperature and at 37° C., and, in addition, by intraperitoneal inoculation of guinea pigs.

At the end of the 48-hour visit the patient was instructed to call the clinic physician at an appropriate time for a report of the conference diagnosis and recommendations. Specimen bottles were again given to the patient with instructions for their use at the time of the next visit, for which an appointment was made by mail.

At the first weekly meeting of the consultant conference following these visits, the clinical data and films of each case were reviewed. A working diagnosis was reached, and decisions were made as to interval of reexamination, special studies, and referral for treatment when indicated.

The usual interval for reexamination was 3 months, with a 6-week schedule for patients with more dubious status. At each follow-up visit an interval history was elicited by the physician, and roentgenographic and bacteriological examinations similar to those of the initial visit were performed. In many cases, additional sputum specimens were mailed in by the patients between visits.

In the beginning, the conference reviewed each set of additional films and other data on all of the patients, but as the case load and the number of serial films increased, it became necessary for the clinic physicians to screen the films and other data in order to select the more questionable cases for conference consideration. Although it was not feasible for the conference to review each case following each visit, an attempt was made to have a conference review of all cases periodically.

Patients were informed of their negative status only when the conference had unanimously agreed on two successive examinations that no tuberculosis was present. These patients were not discharged from the study, but were asked to return for annual "checkup" films. Appointment letters were sent for the annual follow-up.

It was clearly understood that the success of a long-range follow-up program would hinge upon the ability of the clinic to keep its case load; and in the day-to-day conduct of the clinic much attention was given to maintaining personal and enduring relationships with the patients. The clinic started at a disadvantage because of the unpleasant connotations of a "free clinic" in the minds of some patients. Much effort was expended to eliminate this prejudice, and every known source of inconvenience to the patient was avoided. Patients were seen at their convenience by appointment. This obviated any prolonged "bench-sitting" and loss of time, but was achieved at the cost of a very elaborate scheduling procedure. The patient's working hours and place of employment, his stated preference for visiting hours, the type of examination to be performed, and the advantages of hav-

ing certain favored personnel present were only some of the factors to be considered in fixing an appointment for each visit. And even then, a return postcard was enclosed in each appointment letter to allow the patient to suggest a more convenient hour. Although arrangements were made whenever possible through the medical departments of industrial plants to allow compensated time off for workers to visit the clinic, some sessions in the evenings, on Saturdays, and on holidays had to be arranged. The case of each ex-serviceman was investigated thoroughly by the medical social workers to determine possible service-connection and compensable disability. For those patients requiring treatment, local resources of all official and voluntary agencies were thoroughly exploited.

Throughout the period of study, each family physician was kept acquainted with the findings by periodic reports, and no major decisions were made without prior consultation. The clinic limited its activities to diagnostic examinations, and patients requiring therapy were referred to their physicians or appropriate agencies.

The extensive discussion of these details is warranted by the fact that these measures and attitudes became an essential part of the endeavor. It became evident that patients respond best in an informal atmosphere, provided dignity is preserved and no confidence is breached. The attainment of rapport and such an atmosphere in a follow-up clinic cannot be accomplished with ease. Indeed, success seems unlikely in any extended follow-up program on individuals with free choice unless continuous attention is given to this fact. Despite all of our best efforts, the problem of delinquency has not been negligible. Future reports will give further discussion to this problem, which also has implications for many diseases besides tuberculosis.

Of course, there remains the problem of patients who failed to appear initially. And yet, to preserve the validity of the results, it is essential to know what happened to those who should have been but were not observed. Although major emphasis to date has been placed upon the case load, further information will be sought for those read positive in the survey but never studied. A careful record of all those individuals has been preserved to make such studies possible. It is not expected that detailed information will be accessible on individuals who were uncooperative from the outset, but, at the very least, knowledge of the incidence of reported tuberculosis morbidity and mortality in this group can be ascertained, and it should be possible to learn what members of the group are alive and working. Information on disease and death will be gathered by checking the vital statistics files of the Philadelphia Department of Health. Knowledge of the current status of the living will require canvassing by letter, telephone, and home visit. Useful data on this group are also

to be expected from the resurvey of the original 17 establishments which is under way.

Summary

With increasing frequency, physicians throughout the country are being confronted with the problems presented by individuals found in surveys to have lesions. The proper disposition of these patients is important to the success of the survey program, but it is frequently difficult to achieve. The lack of reliable criteria for prognosis, the paucity of documented follow-up experience with such patients, the differences in the characteristics of survey-discovered and manifest tuberculosis and the limitations of roentgenographic interpretation all contribute to the problem.

The advantages and disadvantages of longitudinal and cross-sectional approaches have been discussed in relation to investigations for the elucidation of problems posed by patients identified in surveys. A plan of study which combines both approaches has been formulated with the establishment of the Central Cooperative Clinic for the systematic and prolonged observation of survey-identified patients. The project is a cooperative research enterprise initiated and conducted by the U. S. Public Health Service, the Pennsylvania Department of Health, the Philadelphia Department of Health, the Temple University School of Medicine, and the Philadelphia Tuberculosis and Health Association. The objectives of the study have been stated and the methodology has been discussed in detail.

It has been suggested that the problems encountered in other chronic diseases may be amenable to a similar approach.

Effect of PAS on the Emergence of Tubercle Bacilli Resistant to Streptomycin

A Public Health Service Cooperative Investigation*

The effectiveness of streptomycin in the treatment of tuberculosis has one serious limitation: the ability of the tubercle bacillus to adapt itself to the presence of the antibiotic. The most promising approach to the problem of streptomycin-resistant organisms was suggested by *in vitro* studies, which showed that bacterial populations readily developed mutants in the presence of one drug or another but no doubly-resistant mutants that could grow out in the presence of two independently acting drugs. In this way a second drug might be expected to delay the emergence of organisms resistant to streptomycin.

The present paper reports the effect of para-aminosalicylic acid (PAS) on the emergence of tubercle bacilli resistant to streptomycin in cases of pulmonary tuberculosis. The results of *in vitro* streptomycin sensitivity tests on cultures of tubercle bacilli isolated from sputum specimens obtained from 103 patients who received dihydrostreptomycin and PAS therapy are compared with results from a concurrent series of 114 patients who received dihydrostreptomycin alone.

The data were obtained in a cooperative study which was a part of the program of clinical trials of streptomycin therapy in the treatment of tuberculosis initiated by the Tuberculosis Study Section of the Division of Research Grants and Fellowships of the National Institutes of Health. In this present inquiry, clinicians in 10 centers managed their patients under a common protocol, made observations in a uniform manner, and pooled them for combined analysis and presentation. Sensitivity testing was centralized in two laboratories in an effort to attain homogeneity of data by limiting the variation in testing technique. The design of the investigation provided for the chance allocation of cases selected for study to three regimens: dihydrostreptomycin alone, dihydrostreptomycin and PAS, and streptomycin and PAS. More comprehensive results of the investigation will be presented later.

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*Presented at the 47th Annual Meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1951, by Dr. Frederick Beck. Previous papers in the series on the evaluation of streptomycin in treatment of tuberculosis are: (1) A controlled investigation of streptomycin treatment in pulmonary tuberculosis. Pub. Health Rep. **65**; 1421 (1950), and (2) Resistance to streptomycin of tubercle bacilli isolated from patients treated with streptomycin. Pub. Health Rep. **66**: 277 (1951).

The study was coordinated by the Field Research Branch of the Division of Chronic Disease and Tuberculosis, Public Health Service. Statistical analysis was performed and the report prepared for the group by Miss Nancy J. Brombacher of that office. The opinions expressed in this report represent the consensus of the investigators.

The clinicians who, with their staffs, participated in the study were:

INVESTIGATOR	LOCATION
Dr. Theodore L. Badger	The Channing Home for the Tuberculous, Boston, Mass.
Dr. Frederick Beck	Ray Brook State Tuberculosis Hospital, Ray Brook, N. Y.
Dr. Francis P. Dawson	Middlesex County Sanatorium, Waltham, Mass.
Dr. Alfred Goldman	Robert Koch Memorial Hospital, Koch, Mo.
Dr. Ralph Horton	Homer Folks Tuberculosis Hospital, Oneonta, N. Y.
Dr. N. Stanley Lincoln	Hermann M. Biggs Memorial Hospital, Ithaca, N. Y.
Dr. Howard M. Payne	Freedmen's Hospital, Washington, D. C.
Dr. Rufus F. Payne	Battey State Hospital, Rome, Ga.
Dr. H. McLeod Riggins	New York, N. Y.
Dr. Arthur M. Stokes	Mount Morris Tuberculosis Hospital, Mount Morris, N. Y.
Dr. H. Stuart Willis and Dr. Lynn Johnsen.	The North Carolina Santorium, McCain, N. C.

The participating bacteriologists in the central laboratories were:

Mr. William Steenken, Jr	The Trudeau Laboratory, Trudeau, N. Y.
Dr. Guy P. Youmans	Northwestern University Medical School, Chicago, Ill.

Materials and Methods

Patient Population

Originally 157 patients were designated to receive dihydrostreptomycin alone, and 158 to receive dihydrostreptomycin and PAS. The present analysis has been limited to observations on 114 patients who completed a 13-week course of 1 gram per day of dihydrostreptomycin, and 103 who received a similar course of dihydrostreptomycin plus 10 grams per day of PAS. Prior to treatment, positive cultures which were sensitive to streptomycin were obtained from all of these patients. None of the patients had received more than 10 grams of streptomycin or dihydrostreptomycin prior to admission to the study.

Observations

Observations were made at 10 points during a 27-week period. Specimens for culture were obtained during the week preceding the start of treatment, during treatment (in the 4th, 6th, 8th, 10th, and 12th weeks), and after treatment (in the 14th, 18th, 22d, and 27th weeks).

Isolation and Cultivation of Tubercle Bacilli. The plan of the study called for a uniform and reasonably thorough test for the presence of tubercle bacilli in sputum, to be used by all the participating sanatoria. The test was based on two specimens of sputum taken on different days of the observation week. When expectoration was copious, a morning collection of sputum was recommended; otherwise, a 24-hour sputum specimen was obtained. In the relatively rare cases where expectoration was absent, gastric washings were obtained.

In each hospital, the two specimens were planted in duplicate on tubes of whatever egg-yolk medium had been found most satisfactory. When growth in one of the four tubes was well developed, the culture was sent to a central laboratory for sensitivity testing. In general, all tubes were held at least 6 weeks before being discarded as having "no growth."

For the present analysis, a positive test was defined as any test in which growth occurred in one or more tubes, and a negative test, as one in which at least three tubes were read and all showed no growth. Since some tubes were missing or contaminated, tests in which less than three tubes were available, with no growth present in the available tubes, were classified as unknown. In these tests there was too little evidence to justify a "negative" classification and no evidence of a "positive."

Sensitivity Determinations. A standard procedure was established by the laboratory investigators for the uniform performance of sensitivity tests. From the primary cultures received from the sanatoria, subcultures were made in Tween-albumin liquid medium. When the Tween-albumin subcultures were 7–10 days old and had reached a fairly heavy and uniform density, the flasks were shaken vigorously to produce an even suspension for use as a source of inocula.

In view of the chemical similarity between streptomycin and dihydrostreptomycin, the laboratories used streptomycin in the test media to assay dihydrostreptomycin resistance. Streptomycin in final concentrations of 100, 10, and 3 micrograms per milliliter was added to 3 tubes of Herrold's egg-yolk agar; a fourth tube containing no streptomycin was used as a control. Tests were read at 14, 21, 28, and 35 days after inoculation from the Tween-albumin subculture. The amount of growth in each culture tube was estimated on a 1+ to 4+ scale.

Specimens from patients who received the two-drug regimen were

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also tested for PAS sensitivity. The concentrations of PAS in the three drug-containing tubes were 0.1, 1 and 10 mg. percent. In the present study, resistance to PAS occurred in only one culture.

The level of sensitivity to streptomycin has been defined as the highest concentration of streptomycin (mcg./ml.) in which growth of 20 colonies or more occurred at any of the four reading times. The definition is subject to two conditions: (1) that growth in the control tube was 3+ or 4+, and (2) that growth in streptomycin did not exceed growth in the control. If those conditions were not met, the result was considered "unknown." Three levels of sensitivity were distinguished: resistant to 100 mcg., resistant to 10 mcg., and sensitive.

Completeness of Observations. Since 9 tests for bacteriological status after the initiation of therapy were specified, a total of 1,953 tests would be expected on the 217 patients forming the case material for the study. However, a complete series of observations could not be obtained on every patient. Where status was clearly indicated by tests given before and after a missing observation in a series, estimates were made. A total of 104 observations, or 5 percent, were neither obtained nor estimated.

Missing observations appeared to have a random distribution. Concentrations of four or more missing tests in the series for a single patient occurred in only 3 percent of the dihydrostreptomycin group, and 2 percent of the dihydrostreptomycin-PAS group. Since these percentages were relatively low, no cases were excluded on the basis of missing information on bacteriologic status, and the data have been included at the observation points at which they are available.

Results

In the course of the pretreatment tests, an unexpected result, which requires further study before its significance can be properly evaluated, was obtained. For 46 patients (20 in the dihydrostreptomycin group, and 26 in the dihydrostreptomycin-PAS group) streptomycin-resistant organisms were identified in cultures of pretreatment specimens. None of these 46 patients was reported to have received either streptomycin or dihydrostreptomycin previously.

Examination of subsequent tests, however, casts doubt on the validity of the pretreatment observation for seven patients. The nine subsequent observations for these patients showed no further indication of resistance. For the remaining 39 patients, subsequent test results can neither confirm nor refute the initial finding, since any resistance appearing in tests after the initiation of treatment may have been due to the effect of the prescribed course of dihydrostreptomycin.

Only a moderate level of bacterial resistance to the drug was reported for the majority of these patients. Forty yielded cultures resistant to 10 micrograms of drug and only 6 to 100 micrograms. The rate of growth was not rapid for a number of the pretreatment cultures. Resistance was first reported on the 14th day for 16 of these pretreatment cultures, on the 21st day for 16, on the 28th day for 11, and on the 35th day for 3.

The possibility exists that information on previous drug therapy was incompletely or incorrectly reported to the hospitals and that a substantial proportion of this group actually had streptomycin or dihydrostreptomycin prior to the study. A careful investigation of all the factors involved is now under way. Results on these cases have been excluded from the major analysis.

Course During Observation

The most elementary basis for evaluating the effect of PAS in the emergence of streptomycin resistance is to compare the status of the patients in the dihydrostreptomycin group with that of the patients in the dihydrostreptomycin-PAS group at each of the 10 observation points. The second paper in this series emphasized that the significance of bacterial resistance depends not only on the frequency of its occurrence in positive cultures, but also upon the frequency with which the positive cultures themselves occur in a population. This is particularly true in a comparison of two regimens in which the differential effect of chemotherapy may not be limited to the development of resistance. The interrelationship between the bacteriological and resistance findings was taken into account in establishing the axis of classification of the groups. The distributions of the groups by categories at each of the observation points afford a basis for comparison of the course of the dihydrostreptomycin group over the 27 weeks with the similar course of the dihydrostreptomycin-PAS group. The actual distributions, which include the numbers of "unknowns" as well as the numbers in the five known categories, are given in the appendix table. Percentage distributions based on the total known observations are given in table 1 and figure 1.

It is apparent that, for both drug groups, the major movements occurred almost entirely during the 13-week period of drug administration. By the 14th week of observation, both groups were distributed by categories into proportions which remained fairly stable throughout the remainder of the 27 weeks.

While the nature of the changes for the two groups was similar in that they occurred for the most part during the treatment period, distinct differences in the composition of the two groups throughout the 27 weeks are apparent. Tubercle bacilli were not cultured from the sputa of a higher proportion of patients in the dihydrostreptomycin-

Table 1. *Percentage distributions of groups of 114 dihydrostreptomycin and 103 dihydrostreptomycin-PAS patients by bacteriological status and streptomycin resistance status at 10 points of time*

Status	Observation week from beginning of therapy									
	Pre-treatment	4	6	8	10	12	14	18	22	27
DHSM Group										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Negative cultures	0	8.0	18.7	24.3	32.7	33.3	37.3	37.9	38.5	36.3
Positive culture	100.0	92.0	81.3	74.8	66.4	65.8	61.8	59.3	57.7	57.8
Sensitive	100.0	71.4	47.7	34.6	23.4	16.2	10.9	15.7	10.6	14.7
Resistant to 10 mcg.	0	18.8	23.3	24.3	26.2	28.0	30.9	26.9	24.0	23.5
Resistant to 100 mcg.	0	1.8	10.3	15.9	16.8	21.6	20.0	16.7	23.1	19.6
Patient dead	0	0	0	.9	.9	.9	.9	2.8	3.8	5.9
DHSM-PAS Group										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Negative cultures	0	11.0	30.3	37.5	47.5	55.6	52.4	54.1	48.9	46.3
Positive culture	100.0	88.0	67.7	60.4	50.5	42.4	45.6	43.9	48.9	51.6
Sensitive	100.0	82.0	60.6	57.3	43.4	36.4	36.6	36.7	37.2	40.0
Resistant to 10 mcg.	0	3.0	6.1	2.1	4.1	2.0	5.0	4.1	8.5	8.4
Resistant to 100 mcg.	0	3.0	1.0	1.0	3.0	4.0	4.0	3.1	3.2	3.2
Patient dead	0	1.0	2.0	2.1	2.0	2.0	2.0	2.0	2.2	2.1

PAS group. Markedly lower proportions of patients with positive cultures resistant to streptomycin are noted for the combined-drug group than for the single-drug group. For the former the proportion of those with sensitive cultures was higher than for the latter. In the two groups, however, the proportion of deaths does not differ appreciably.

At 14 weeks, 52 percent of the combined-drug group had negative cultures as against 37 percent in the single-drug group. The frequency of occurrence of resistant cultures shows an even greater contrast. The total proportion of patients whose cultures were resistant to at least 10 mcg. was 9 percent for the dihydrostreptomycin-PAS group (less than one-fifth of the 51 percent reported for the dihydrostreptomycin group). The proportions with sensitive bacilli were 37 percent for the combined-drug group and 11 percent for the single-drug group. Deaths were 2 and 1 percent, respectively.

Highest Level of Resistance During Treatment

The two groups may also be compared in a somewhat different way. Since the proportion of patients with negative cultures increased rapidly during the period of drug therapy in both groups, but more rapidly in the two-drug group, the proportions with negative cultures at 14 weeks include patients who may have developed resistance earlier. A truer picture of the incidence of resistance may be obtained by comparing the proportions of the groups in whose cultures resistance appeared at any time during the treatment period.

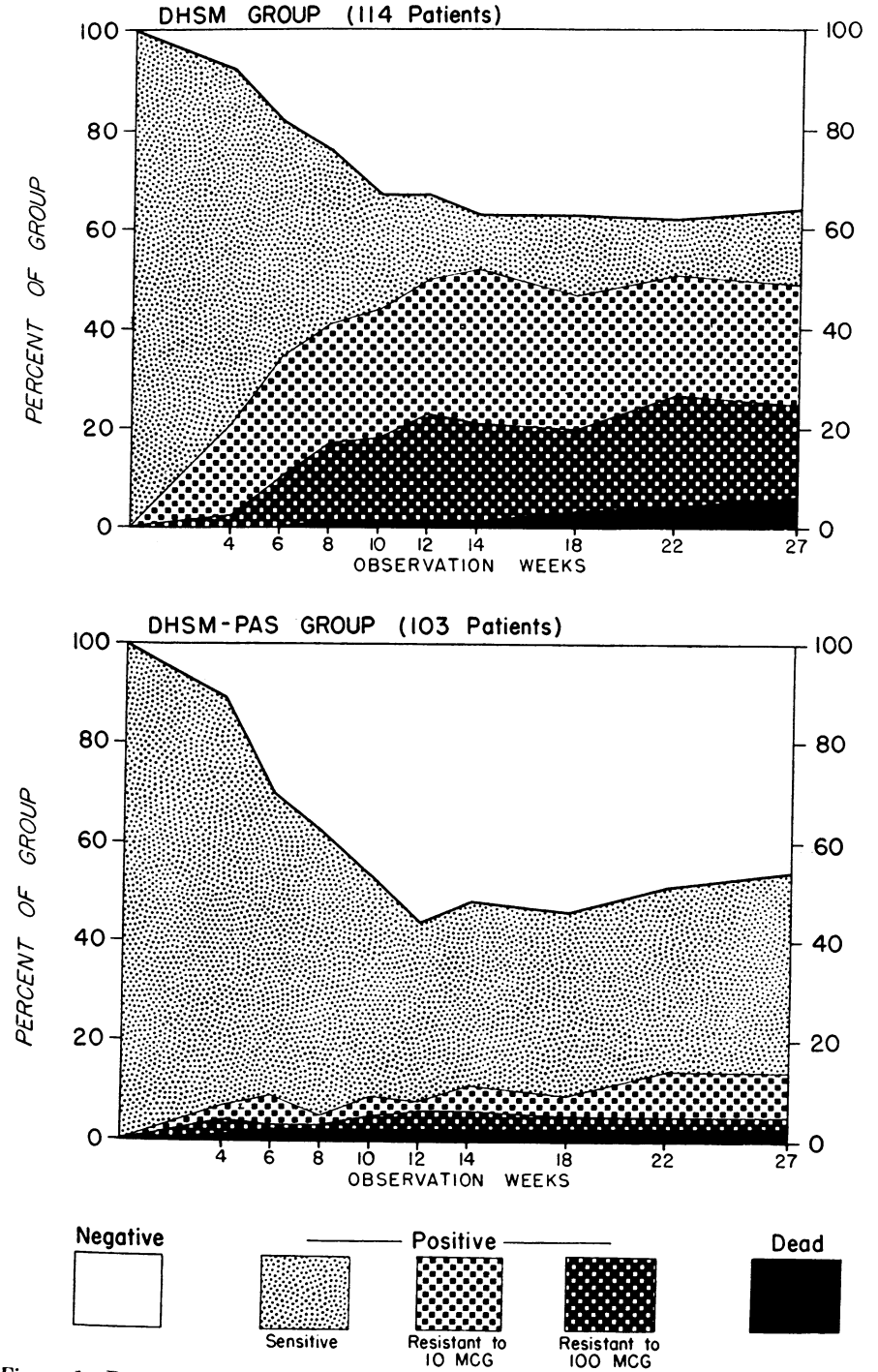


Figure 1. Percentage distribution of dihydrostreptomycin and dihydrostreptomycin-PAS groups by bacteriological status and streptomycin resistance status, at 10 points of time.

Table 2. *Distributions of dihydrostreptomycin and dihydrostreptomycin-PAS groups by highest level of resistance found in cultures from specimens obtained between the 4th and 14th weeks of observation*

Highest level of resistance reported	DHSM Group		DHSM-PAS Group	
	Number	Percent	Number	Percent
Total	114	100.0	103	100.0
100 mcg	34	29.8	8	7.8
10 mcg	41	36.0	13	12.6
None	39	34.2	82	79.6

In table 2 and figure 2, the categories "resistant to 10 mcg." and "resistant to 100 mcg." represent the highest level of resistance found for patients for whom at least one resistant culture was reported for any of the six observation points between the 4th and 14th weeks, inclusive. On this basis, cultures resistant to 100 mcg. were reported for 30 percent of the dihydrostreptomycin group and only 8 percent of the dihydrostreptomycin-PAS group. The total proportions of the groups whose cultures were resistant to at least 10 mcg. (the sum of the two categories) were 66 percent and 21 percent, respectively. Thus, resistance was noted at some time during drug administration in the cultures of about one-third as many combined-drug patients as for single-drug patients.

Relation to Type of Case

An attempt has been made to determine whether the capacity of PAS to decrease the frequency of streptomycin-resistant cultures is associated with a particular type of case. For this purpose, sensitivity test results of this investigation have been correlated with certain X-ray and clinical observations which reflect the status of the patients at the beginning of observation. The method of X-ray evaluation and of analysis of the X-ray data differed only in detail from that fully described in the first paper of this series.

The patients in the two groups were classified on the basis of their initial characteristics with respect to stage and course of disease, predominant morphology, dynamics of the tuberculous process, presence of cavitation, and body temperature. The frequency with which resistant cultures appeared during the period of drug therapy in each of the subgroups thus obtained was compared.

Since the size of the individual groups is, in some instances, so small that chance variations may be very large, detailed results are not presented here. However, while resistance consistently appeared less frequently in the cultures of patients in the combined-drug group, the characteristics of those patients in each group whose cultures did develop resistance were similar. Thus, it may be that the action of PAS in the suppression of bacilli resistant to streptomycin is not selective as to type of case.

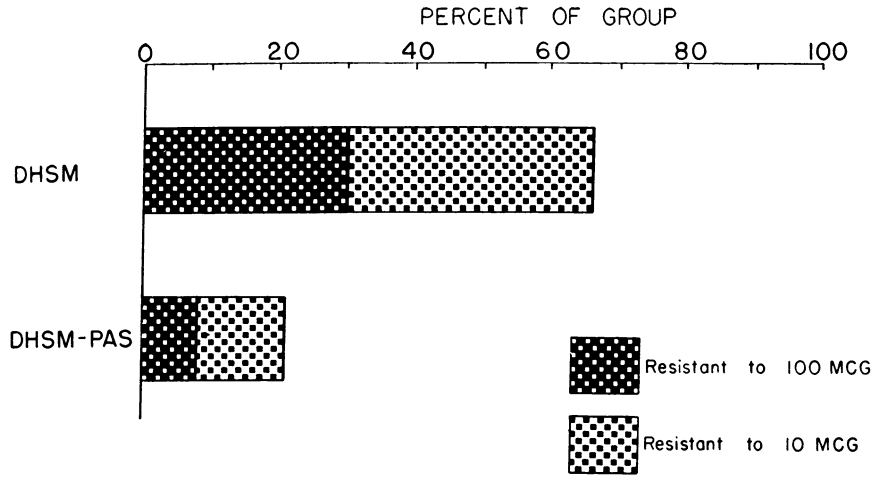


Figure 2. Percentages of dihydrostreptomycin and dihydrostreptomycin-PAS groups producing cultures resistant to 100 mcg. of streptomycin and to 10 mcg. at least once between the 4th and 14th week of observation.

Certain interesting patterns common to both groups appeared. Resistance was more often associated with far advanced disease than with moderately advanced disease; with cavitary disease more frequently than with non-cavitary; with progressive rather than stationary or retrogressive processes; and among the febrile more often than among the afebrile. When the cases were classified by predominant morphology (exudative, caseous, fibrotic) or by dynamics (acute, subacute, chronic), no meaningful differences in the incidence of resistant cultures were apparent. This failure to discern differences may well reflect the limitations of classification, rather than the absence of relationship. The greater frequency of resistant bacilli in the cultures derived from febrile patients, or those with far advanced, with cavitary, or with progressive disease may be simply a reflection of the greater frequency with which bacilli, resistant or sensitive, are found in these subgroups. Further investigation of these relationships is planned through the combination of several studies in this series.

Summary

The design of a cooperative investigation sponsored by the Public Health Service provided for the chance allocation of pulmonary tuberculosis patients to three regimens: dihydrostreptomycin alone, dihydrostreptomycin and PAS, and streptomycin and PAS. As a part of the study, sputum specimens were obtained at 10 points in a 27-week period from patients located in 10 participating institutions. Tests for the presence of tubercle bacilli were performed by the institutions. Resulting positive cultures were tested by central laboratories for sensitivity of the bacilli to the chemotherapeutic agents.

The effect of PAS on the emergence of tubercle bacilli resistant to streptomycin has been studied in 114 patients receiving dihydrostreptomycin and 103 patients receiving dihydrostreptomycin and PAS. The patients received drug therapy for 13 weeks, and were observed for a total of 27 weeks. All of the patients received 1 gram of dihydrostreptomycin daily, while one group received, in addition, 10 grams of PAS daily.

The results show that:

1. In both groups, the major changes in bacteriological status occurred during the period of drug administration, with only minor shifts thereafter.

2. At the 14th week, the first observation point after the end of drug therapy: (a) Tubercle bacilli were not cultured from the sputa of 37 percent of the dihydrostreptomycin group and from 52 percent of the dihydrostreptomycin-PAS group. (b) Streptomycin-resistant organisms were found in the cultures from 51 percent of the dihydrostreptomycin patients and only 9 percent of the dihydrostreptomycin-PAS patients.

3. The action of PAS in suppressing the emergence of streptomycin-resistant bacilli does not appear to be confined to any particular type of case.

4. The significance of the identification of resistant organisms in pretreatment cultures from 46 patients is obscure and poses a problem for further investigation.

Appendix table. ***Distributions of groups of 114 dihydrostreptomycin and 103 dihydrostreptomycin-PAS patients by bacteriological status and streptomycin resistance status at 10 points of time***

Status	Observation week from beginning of therapy									
	Pre-treatment	4	6	8	10	12	14	18	22	27
DIISM Group										
Total	114	114	114	114	114	114	114	114	114	114
Negative cultures	0	9	20	26	35	37	41	41	40	37
Positive culture	114	103	87	80	71	73	68	64	60	59
Sensitive	114	80	51	37	25	18	12	17	11	15
Resistant to 10 mcg	0	21	25	26	28	31	34	29	25	24
Resistant to 100 mcg	0	2	11	17	18	24	22	18	24	20
Patient dead	0	0	0	1	1	1	1	3	4	6
Unknown	0	2	7	7	7	3	4	6	10	12
DIISM-PAS Group										
Total	103	103	10	103	103	103	103	103	103	103
Negative cultures	0	11	30	36	47	55	53	53	46	44
Positive culture	103	88	67	58	50	42	46	43	46	49
Sensitive	103	82	60	55	43	36	37	36	35	38
Resistant to 10 mcg	0	3	6	2	4	2	5	4	8	8
Resistant to 100 mcg	0	3	1	1	3	4	4	3	3	3
Patient dead	0	1	2	2	2	2	2	2	2	2
Unknown	0	3	4	7	4	4	2	5	9	8

BCG Vaccination in Poland

This second [1] in the series of Tuberculosis Research Office publications concerned with BCG vaccination programs throughout the world appears to be as valuable a report as its predecessor.[2] Excellently illustrated by charts and maps, it documents the immense amount of material gathered in Poland during the largest single campaign in any individual country that has yet participated in the international BCG campaign. It is based on statistical data collected by Polish and Scandinavian teams in the course of their field work and follows closely the pattern set by TRO's first report on the Czechoslovakian campaign.

Like the latter, it is divided into four main sections, dealing first with the organization and performance of the campaign, second with the variability, completeness, and reliability of the material, third with results of statistical tabulation and analysis, and last with charts giving basic statistics on tuberculin testing and BCG vaccination. This mass testing and vaccination was accomplished in war-devastated Poland in 1948–49 through the collaboration of the Polish Ministry of Health and Joint Enterprise, the organization created by the United Nations International Children's Emergency Fund, and three Scandinavian voluntary groups (later known as the International Tuberculosis Campaign).

The program proper was preceded by work performed from May 1947 to June 1948 under the auspices of the Danish Red Cross which indicated an unusually high prevalence of tuberculosis infection and disease in Poland and confirmed the seriousness of tuberculosis as a national health problem. Material forming the basis of statistical reports includes data on the testing of 4,703,561 and the vaccination of 2,263,952 persons. Over 93 percent of the individuals tuberculin tested completed their tests. Of these, 52 percent were tuberculin negative, and 99.5 percent of the negative reactors were vaccinated.

Details of organization and administration will be of interest wherever similar programs are contemplated. Field work, directed from headquarters in Warsaw, was conducted through each of 14 provincial and 2 municipal stations under the leadership of first a

[1] A review of Mass BCG Vaccination in Poland, 1948–1949, with Special Reference to Statistics on Tuberculin Testing and BCG Vaccination, prepared by the Tuberculosis Research Office, World Health Organization, Copenhagen and published by the International Tuberculosis Campaign, December, 1950. Copies may be obtained from International Tuberculosis Campaign, Svanemollevej 25, Copenhagen, Denmark.

[2] Mass BCG Vaccination in Czechoslovakia 1948–1949, prepared by the Tuberculosis Research Office, World Health Organization, Copenhagen and published by the International Tuberculosis Campaign, August 1950. Reviewed in PUBLIC HEALTH REPORTS 66: 444 (1951).

Scandinavian physician and later his Polish colleague. This station leader, aided by a secretary, supervised the work of three vaccination teams, each consisting of two to four vaccinators, two clerks, and a driver with a car. In each locality, actual work was preceded by wide publicity as well as meetings with health, welfare, school and political leaders, designed to promote popular understanding and support. At the height of the campaign, more than 400,000 persons were tested in a month, and half as many vaccinated. On the average each team could visit between four and five places and examine between 2,000 and 3,000 children daily.

The report states that "Information from responsible observers gave the impression that the statistical work in the field was good and records and statistics were reasonably accurate and complete . . . There were very few significant errors and defects." There are a great number of statistics, presenting all the essential information on the campaign, including tabulations of participation, tuberculin sensitivity and vaccinations, by age, sex, and detailed geographic subdivision. The Moro patch and Mantoux tests were employed for selection of individuals to be vaccinated and tuberculin sensitivity was found to be on the average unusually high in the Polish population. Positive reactors totaled 8 percent at age 1; 21 percent at age 5; 42 percent at age 10; 67 percent at age 15, and about 90 percent at age 20. The prevalence of positive tuberculin reactions among females was slightly higher than among males, and, as might be expected, considerably higher in urban than in rural areas, particularly among young adult groups. Tuberculin sensitivity, then, was on the whole higher than that reported from Czechoslovakia, where it was 3.8 percent at 1 year; 11 percent at 5 years; 26 percent at 10 years; 48 percent at 15 years, and 75.2 percent in the 20–24 year age group. In Czechoslovakia, also, there was little difference in sensitivity for urban and rural groups.

The lack of detailed population statistics for Poland made it impossible to determine the extent and completeness of testing and vaccination. TRO estimates, however, that 60 percent of the children and young adults from 1 to 18 years of age and between 80 and 90 percent of the school age groups of 6 to 14 years were actually reached. In any event, Mass Vaccination in Poland constitutes another useful permanent record from either a national or international point of view. For those who, in contemplated future studies, attempt to assay the protective value of BCG vaccination in Poland, it will be an indispensable guide.

Incidence of Disease

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

Reports From States for Week Ended June 16, 1951

Poliomyelitis

For the current week 162 cases of poliomyelitis were reported, which is about 12 percent more than the 143 cases reported for the previous week. There is a correction in last week's total from 171 to 143, since only 3 instead of 31 cases were reported in Oklahoma. For the current week the States reporting 5 or more cases were as follows, the figures for last week being shown in parentheses: Texas 41 (34), California 20 (19), New York 12 (15), Oklahoma 9 (3), Louisiana 9 (7), Alabama 7 (5), Florida 7 (4), Colorado 6 (2), Georgia 6 (1), Oregon 5 (2), Iowa 5 (0), and Wisconsin 5 (1).

In Texas nearly two-thirds of the cases in the past month have been concentrated in two counties—Harris and Nueces—which have a combined population of about 1 million. Available reports do not indicate any concentration of cases in California. More than half of the cases in New York State have been reported in New York City.

The total number of cases for the United States for the current week (162) compares favorably with that for the same week last year (236). The cumulative total since the seasonal low week is 1,069 as compared with 1,323 for the same period last year.

Hansen's Disease

The San Francisco Health Department has reported a case of Hansen's disease in a 12-year-old girl who came from the Philippines with her parents 2 years ago.

Epidemiological Reports

Gastroenteritis

Dr. R. H. Hutcheson, Tennessee Commissioner of Health, has reported an outbreak of food poisoning in a family of 10 persons residing in McNairy County. All members of the family except a nursing infant became ill suddenly with headache, nausea, vomiting, and

diarrhea from 2 to 5 hours after a noonday meal on June 3. Food consisted of fried canned mackerel, home-made biscuits, hot cocoa, and a drink made from powdered fruit mixture. The canned mackerel, which was opened, cooked, and eaten within 30 minutes, was suspected of being the vehicle of infection, but this has not been proved.

Dr. J. C. Hart, Connecticut Department of Health, has reported two outbreaks of gastroenteritis in a private school, occurring 6 days apart. Both followed turkey dinners. In the first outbreak, about 65 in a population of 135 were known to be ill, and 70 were affected in the second. The incubation periods varied from 10 to 24 hours, with the majority between 10 and 16 hours. In both instances abdominal pain and diarrhea were the main symptoms, with recovery in 24 to 48 hours. Specimens of turkey and stool cultures of food handlers are undergoing bacteriological examination.

Comparative Data for Cases of Specified Reportable Diseases: United States

[Numbers after diseases are International List numbers, 1948 revision]

Disease	Total for week ended—		5-year median 1946–50	Seasonal low week	Cumulative total since seasonal low week		5-year median 1945–46 through 1949–50	Cumulative total for calendar year—		5-year median 1946–50
	June 16, 1951	June 17, 1950			1950–51	1949–50		1951	1950	
Anthrax (062)	1			[1]	[1]	[1]	[1]	39	19	25
Diphtheria (055)	51	80	118	27th	4,778	7,237	10,687	1,871	2,966	4,330
Encephalitis, acute infectious (082)	8	22	11	[1]	[1]	[1]	[1]	402	317	212
Influenza (480–483)	509	326	326	30th	128,706	147,888	147,888	114,164	137,304	127,040
Measles (085)	14,312	12,802	14,073	35th	444,772	266,501	524,160	416,071	247,372	489,214
Meningitis, meningococcal (057.0)	63	75	61	37th	3,290	3,048	2,975	2,329	2,134	2,003
Pneumonia (490–493)	701	975	[2]	[1]	[1]	[1]	[1]	[3]40,895	53,220	[2]
Poliomyelitis, acute (080)	162	236	236	11th	[4]1,069	[4]1,323	1,323	[4]2,282	2,454	1,697
Rocky Mountain spotted fever (104)	14	28	27	[1]	[1]	[1]	[1]	94	127	132
Scarlet fever (050) [5]	1,048	729	1,263	32d	65,084	53,638	77,499	49,393	37,199	54,955
Smallpox (084)		1		35th	14	44	66	6	23	45
Tularemia (059)	8	30	28	[1]	[1]	[1]	[1]	322	476	476
Typhoid and paratyphoid fever (040, 041) [6]	43	61	82	11th	[7]557	730	761	[7]992	1,240	1,246
Whooping cough (056)	1,385	2,763	2,106	39th	58,314	85,779	79,018	36,732	64,263	47,752

[1] Not computed.
[2] Data not available.
[3] Additions: week ended June 9—Indiana 12 cases, West Virginia 5, Florida 7, Utah 6; week ended June 2, Tennessee 36.
[4] Deductions: Georgia, 1 case each for weeks ended June 2 and June 9. Addition: West Virginia, 1 case for week ended June 9.
[5] Including cases reported as streptococcal sore throat.
[6] Including cases reported as salmonellosis.
[7] Deductions: Arkansas, week ended March 31, 2 cases; week ended March 3, 1 case.

NOTE.—Oklahoma reported only 3 cases of poliomyelitis instead of 31 for the week ended June 9.

Reported Cases of Selected Communicable Diseases: United States, Week Ended June 16, 1951

[Numbers under diseases are International List numbers, 1948 revision]

Area	Diphtheria (055)	Encephalitis, infectious (082)	Influenza (480–483)	Measles (085)	Meningitis, meningococcal (057.0)	Pneumonia (490–493)	Poliomyelitis (080)
United States	**51**	**8**	**509**	**14,312**	**63**	**701**	**162**
New England	**10**		**4**	**1,225**	**5**	**22**	**1**
Maine	7		1	13		1	
New Hampshire				78		2	
Vermont				262			
Massachusetts	3			612	1		
Rhode Island				47		3	
Connecticut				213	1	16	1
Middle Atlantic	**4**	**4**	**2**	**3,511**	**8**	**117**	**15**
New York	3	2	[1] 1	1,667	4	28	12
New Jersey		2	1	1,076	1	49	1
Pennsylvania	1			768	3	40	2
East North Central	**4**		**8**	**2,909**	**11**	**82**	**11**
Ohio	2			388	4		1
Indiana	2		6	135		14	2
Illinois			1	364	4	30	2
Michigan			1	324	1	38	1
Wisconsin				1,698	2		5
West North Central	**3**	**1**	**11**	**645**	**4**	**63**	**6**
Minnesota	3		1	49	1	11	
Iowa				38		2	5
Missouri		1		308	2	1	
North Dakota			8	76		32	
South Dakota				9			
Nebraska				8			
Kansas			2	157	1	17	1
South Atlantic	**10**	**2**	**188**	**1,380**	**12**	**94**	**18**
Delaware				46			
Maryland			3	362		19	1
District of Columbia				51		4	
Virginia		1	178	500	5	48	1
West Virginia	2			196			1
North Carolina	7	1		43	4		2
South Carolina	1			17	1	1	
Georgia			7	83	1	22	6
Florida				82	1		7
East South Central	**4**	**1**	**2**	**379**	**12**	**48**	**12**
Kentucky	2			81	4	6	3
Tennessee	1	1		55	2		
Alabama	1			233	4	29	7
Mississippi			2	10	2	13	2
West South Central	**9**		**94**	**1,165**	**3**	**172**	**61**
Arkansas			76	173		30	2
Louisiana	1		1	13		22	9
Oklahoma			17	32	1	5	9
Texas	8			947	2	115	41
Mountain			**182**	**648**		**58**	**12**
Montana			27	71			1
Idaho				82			
Wyoming				53		3	
Colorado			86	97		27	6
New Mexico				76		4	1
Arizona			69	171		24	3
Utah				98			1
Nevada							
Pacific	**7**		**18**	**2,450**	**8**	**45**	**26**
Washington			4	302	3	2	1
Oregon	3		12	494	3	27	5
California	4		2	1,654	2	16	20
Alaska			27				
Hawaii				11			

[1] New York City only.

Anthrax: Pennsylvania, 1 case.

Reported Cases of Selected Communicable Diseases: United States, Week Ended June 16, 1951—Continued

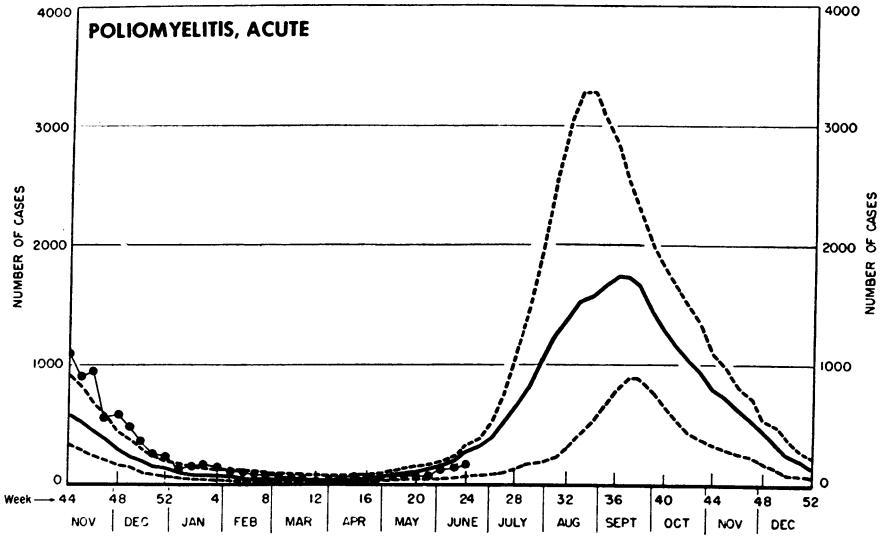
[Numbers under diseases are International List numbers, 1948 revision]

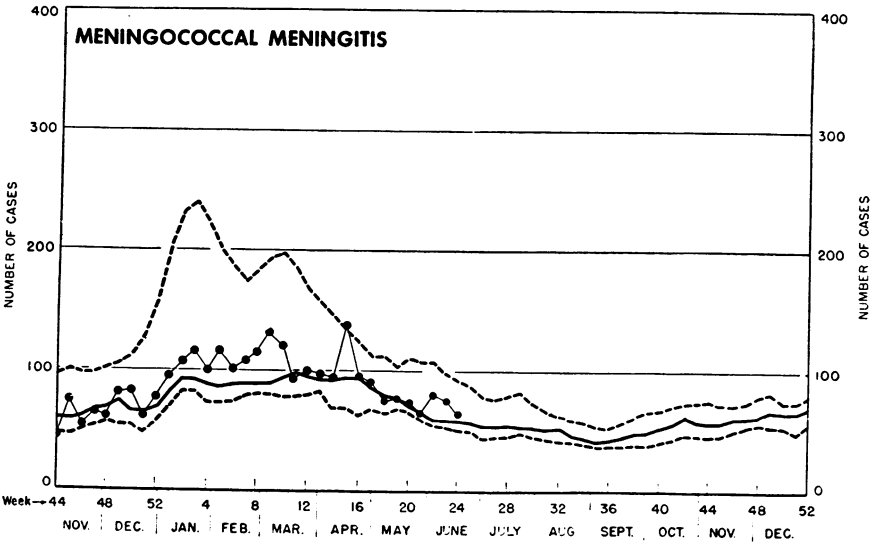
Area	Rocky Mountain spotted fever (104)	Scarlet fever (050)	Smallpox (084)	Tularemia (059)	Typhoid and paratyphoid fever [1] (040, 041)	Whooping cough (056)	Rabies in animals
United States	**14**	**1,048**		**8**	**43**	**1,385**	**136**
New England		**107**			**3**	**42**	**1**
Maine		16				6	1
New Hampshire		[2] 2				3	
Vermont						3	
Massachusetts		74			2	20	
Rhode Island		1				1	
Connecticut		14			1	9	
Middle Atlantic		**272**			**6**	**164**	**6**
New York		[2] 181			2	65	4
New Jersey		38			1	60	
Pennsylvania		53			3	39	2
East North Central		**331**			**3**	**167**	**24**
Ohio		88				24	5
Indiana		5			1	20	17
Illinois		33			2	19	1
Michigan		164				51	1
Wisconsin		41				53	
West North Central		**39**			**1**	**69**	**23**
Minnesota		9				6	1
Iowa		4				21	4
Missouri		15			1	9	18
North Dakota		1				3	
South Dakota		5				2	
Nebraska		1				2	
Kansas		4				26	
South Atlantic	**7**	**77**		**1**	**3**	**209**	**18**
Delaware	1						
Maryland	2	21				2	
District of Columbia		9				6	
Virginia	1	8				73	7
West Virginia		6			2		
North Carolina	2	24		1		64	
South Carolina	1	3				2	9
Georgia		2			1	13	2
Florida		[2] 4				49	
East South Central	**1**	**28**			**8**	**94**	**30**
Kentucky		13			4	16	7
Tennessee	1	11			2	21	11
Alabama		2			1	45	8
Mississippi		2			1	12	4
West South Central		**25**		**5**	**10**	**473**	**34**
Arkansas		2		4	3	76	3
Louisiana		1			3		
Oklahoma		3			1	10	3
Texas		19		1	3	387	28
Mountain	**5**	**61**		**2**	**5**	**117**	
Montana		5				12	
Idaho	2	25			1	14	
Wyoming				2		9	
Colorado	2	8				26	
New Mexico		1			1	12	
Arizona		5				36	
Utah	1	[2] 17				8	
Nevada							
Pacific	**1**	**108**			**4**	**50**	
Washington		13				6	
Oregon	1	3				3	
California		[2] 92			4	41	
Alaska							
Hawaii					1		

[1] Including cases reported as salmonellosis. [2] Including cases reported as streptococcal sore throat.

Communicable Disease Charts

All reporting States, November 1950 through June 16, 1951





The upper and lower broken lines represent the highest and lowest figures recorded for the corresponding weeks in the preceding 5 years. The solid line is a median figure for the preceding 5 years. All three lines have been smoothed by a 3-week moving average. The dots represent numbers of cases reported weekly, 1950–51.

FOREIGN REPORTS

CANADA

Reported Cases of Certain Diseases

Week ended May 26, 1951

Disease	Total	Newfoundland	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia
Brucellosis	1									1	
Chickenpox	989	12		27		106	556	52	17	75	144
Diphtheria	1								1		
Dysentery:											
Amebic	1						1				
Bacillary	4						3				1
Encephalitis, infectious	2						1	1			
German measles	358			4		18	205		7	45	79
Influenza	44			31	5		5	2			1
Measles	1,339	5		101	4	247	484	56	13	267	162
Meningitis, meningococcal	1						1				
Mumps	616	1		49		139	275	22	19	55	56
Poliomyelitis	1						1				
Scarlet fever	384				1	74	28	53	12	66	150
Tuberculosis (all forms)	196	18		5	5	79	40	12	7	3	27
Typhoid and paratyphoid fever	13					5			1	2	5
Venereal diseases:											
Gonorrhea	263	9		2	6	86	50	18	18	24	50
Syphilis	93	5		4	3	38	16	5	3	2	17
Primary	6					2	2			1	1
Secondary	4					1	3				
Other	83	5		4	3	35	11	5	3	1	16
Whooping cough	110	1		5	1	23	45	7	6	15	7

Week ended June 2, 1951

Disease	Total	Newfoundland	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia
Brucellosis	4					2	1			1	
Chickenpox	1,134	3		32		199	512	64	22	117	185
Diphtheria	4					3			1		
Dysentery, bacillary	10					1	7	2			
German measles	388	1		1		50	228		13	37	58
Influenza	41			22	1		4	9			5
Measles	1,694	4		106	1	607	453	44	5	331	143
Meningitis, meningococcal	4					1	3				
Mumps	652	1		17		170	233	50	40	53	88
Scarlet fever	347	3		4		92	34	42	20	55	97
Tuberculosis (all forms)	207	17			2	82	29	20	6	32	19
Typhoid and paratyphoid fever	12					10	1			1	
Venereal diseases:											
Gonorrhea	251	8		10	6	56	56	28	18	27	42
Syphilis	70	1		7	2	25	13	3	5	4	10
Primary	5					2	1		1	1	
Secondary	6					4	1				1
Other	59	1		7	2	19	11	3	4	3	9
Whooping cough	147					63	30	6	6	18	24

CUBA

Reported Cases of Certain Diseases—4 Weeks Ended May 26, 1951

Disease	Total	Pinar del Rio	Habana		Matanzas	Santa Clara	Camaguey	Oriente
			Habana City	Total				
Brucellosis	1		1	1				
Cancer	82	3		11	11	30	2	25
Chickenpox	54	1	27	29	1	1	12	10
Diphtheria	17		4	10	4	2		1
Hookworm disease	16			16				
Leprosy	3			2				1
Malaria	6	1		1				4
Measles	56	10	25	29	9	1	1	6
Tuberculosis	66	2		14	13	17	10	10
Typhoid fever	52	8	10	22	1	13	3	5
Whooping cough	42					12	30	

JAMAICA

Reported Cases of Certain Diseases—4 Weeks Ended May 26, 1951

Disease	Total	Kingston	Other localities
Chickenpox	70	15	55
Diphtheria	5	5	
Leprosy	2	1	1
Ophthalmia neonatorum	3	1	2
Tuberculosis, pulmonary	52	14	38
Typhoid fever	62	7	55
Typhus fever (murine)	4	3	1

MADAGASCAR

Reported Cases of Certain Diseases and Deaths—March 1951

Disease	Aliens		Natives	
	Cases	Deaths	Cases	Deaths
Bilharziasis			20	
Diphtheria	1		7	5
Dysentery:				
Amebic	2		137	
Bacillary			20	1
Erysipelas			14	1
Influenza	229		4,832	35
Leprosy			19	
Malaria	274	8	37,232	114
Measles	12		231	5
Meningitis, meningococcal			2	
Mumps	7		330	
Paratyphoid fever	1		1	
Plague			23	17
Pneumonia (all forms)	6	3	561	53
Puerperal infection			4	
Tuberculosis, respiratory	4	1	102	19
Typhoid fever	5		13	
Whooping cough	62		335	2

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

The following reports include only items of unusual incidence or of special interest and the occurrence of these diseases, except yellow fever, in localities which had not recently reported cases. All reports of yellow fever are published currently. A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday in each month.

Plague

Indochina. For the week ended June 2, 1951, 2 cases of plague were reported in Cambodia as compared with 12 for the previous week.

Smallpox

India (French). During the week ended June 2, 1951, 27 cases of smallpox were reported in Karikal as compared with 17 for the previous week.

Indochina. During the week ended June 9, 1951, smallpox was reported in ports of Viet Nam as follows: Hanoi 44 cases, Haiphong 30, and Nam-Dinh 11.

Iraq. For the week ended June 9, 1951, 16 cases of smallpox were reported in Iraq.

Yellow Fever

Gold Coast. During the period May 30–June 3, 1951, one fatal suspected case of yellow fever was reported in Nsaba which is about 25 miles north of Winneba.

Nigeria. The fatal suspected case of yellow fever reported June 6, 1951, in Eziachi, Okigwi area, was not confirmed.

Peru. One death from yellow fever was reported Feburary 16, 1951, in San Jose de Sisa, San Martin Department.