INTRODUCTION

The 1954 Field Trial of the poliomyelitis vaccine, developed by Dr. Salk, was initiated and organized by the National Foundation for Infantile Paralysis, and conducted by the medical and health authorities in conjunction with many volunteering agencies and the American public. It was guided and evaluated by the Poliomyelitis Vaccine Evaluation Center which was established at the request of the National Foundation as an impartial, independent organization at the University of Michigan.

The Field Trial must be viewed in the perspective of an unprecedentedly large biological experiment conducted in a human population. This was implicit in a news release by the Foundation on November 17, 1954, which called the intended trial "a nationwide study to determine the effectiveness of a vaccine in preventing poliomyelitis." In the planning of an epidemiological study of that scale, strict mathematical desirabilities must be tempered with feasibility and practicability but only to the extent that scientific principles can be maintained in the collection, analysis and interpretation of the data. Consideration must be given not only to the theory and the ideal, but also to the alternatives. Biological precision at its best has wide parameters and rarely, if ever, matches the concrete orderliness of the mathematical concept. Poliomyelitis presents, in addition, the problems of variation in distribution, in incidence, and in diagnosis. Consequently, any pre-arranged study dependent upon limited numbers inevitably requires selection. The Field Trial was planned, therefore, to be carried out in selected areas of high incidence in an age group selected because it usually experienced the highest incidence; also the population to be inoculated was selected, necessarily, by voluntary participation.

It may be worth while to visualize the circumstances which prompted the undertaking. Just think: After years of theoretical consideration, of investigating and speculating, here was a vaccine which was a natural development of accumulated technical advances and experimental demonstrations that antibody is directly correlated with protection against poliomyelitis. Here was substantial evidence that children receiving the material developed significant levels of antibody without harmful effect. Here was an agency, headed by a forceful imaginative administrator, possessing the financial resources, the staff, the nationwide organization, the public support, and the desire to subject the material to a critical test of effectiveness. Moreover, it was highly desirable to determine for the guidance of future research whether or not the currently accepted hypotheses of pathogenesis and immunity to poliomyelitis were sound. It has been repeatedly emphasized that time would be gained no matter what the outcome. The size and scope of an adequate test was appreciated. A plan for the test had been developed and accepted by authorities in many of the areas which would be involved. Large scale production of vaccine under specified conditions had been organized. This was the situation in December, 1953, when the proposal was made that the evaluation be conducted at the University of Michigan.

Obviously, if the test were to be carried out, every effort should be made to collect proper data from which unbiased quantitative appraisal of the results could be obtained. It was apparent that the evaluating agency would have to develop a record system and a plan of procedure to be used uniformly in an extended network of operation. It would have to assume direct authority for the collection and adequacy of information. Collation, analysis and interpretation would have to be made uninfluenced by partisan interests and carefully guarded against the circulation of splintered, premature impressions. Finally, it was recognized that acceptance of this scientific and public responsibility meant also acceptance of uncertain features in the design of the study that had been agreed upon, which might not permit accurate measurements of vaccine effect. Criticism would then revert to the evaluating agency for having proceeded under those conditions.

The next month was spent in reviewing the numerous, complex problems, technical and sociological, as to feasibility and dependability. The available information was considered and consultations were held with specialists in epidemiological, clinical, virological, sociological, and statistical investigations. The amount of vaccine which would be available was uncertain. The time schedule, consequently, was also uncertain. The probable delays might well reduce the size of the experimental population which could be serviced before the closing of schools or the beginning of the poliomyelitis season. Nevertheless, it seemed likely that these situations would be resolved. The conditions required for safety testing of vaccine appeared satisfactory and further tests of antigenic potency were assured. There remained, however, significant reservations regarding the proposed plan of study. This, the observed control plan, was administratively simple but it possessed theoretical and practical disadvantages in that the group to be observed for comparison with the vaccinated was not really comparable; intentional or unintentional bias could not be controlled and results except of extreme differences might lead more to argument than conclusion. This plan contained one important asset, however, in that acute harmful effects of vaccine would be promptly demonstrable.

Introduction of a strictly controlled procedure, the placebo plan of study, was recommended and although it required more work and detailed supervision, epidemiological consultants from certain of the most populous states believed it feasible and supported the recommendation. With this design, variations in the volunteering population are randomized between vaccinated and control subjects so as to make them completely comparable. Distinction between test and control subjects is eliminated by concealing the nature of the inoculum given. The procedures of investigation would thus apply without bias to the vaccinated and control populations. The placebo plan then became a requisite of the Field Trial with the understanding that if supply of vaccine were limited, the placebo study would be given preference because of its greater efficiency, accuracy, and dependability.

The possibility of staffing the Center appeared promising. Under these conditions the decision was made to undertake the program. But it must be emphasized that this large responsibility could not and would not have been undertaken without the strong endorsement and support offered by numerous outstanding investigators who would be actively involved in the vaccination program. Approval of the administrative officers of the University of Michigan had been given provided that there was a reasonable probability an adequate study could be made and that the independent character of the Evaluation Center was assured. Parentheti-

cally, this understanding was honored completely by all parties throughout the entire period of operation. All efforts then concentrated on the rapid development of the Evaluation Program.

The results of the vaccine Evaluation Program involving 1,829,916 children in 211 areas of 44 states were reported on April 12, 1955, at the University of Michigan. It was not a preliminary report, but, as stated at that time, was a summary of objective analyses of valid data from records which were essentially complete. It permitted reliable conclusions as to the effectiveness and deficiencies of the vaccine which was used.

This, the Final Report, is somewhat anticlimactic because results observed in the last two years have added new information and because the extended analyses it contains have not altered the basic data or the conclusions presented in the Summary Report. Certain inconsequential mistakes in the latter have been corrected; they were almost entirely limited to typographical errors in ancillary charts or tables. It was planned to complete the Final Report by the fall of 1955. The excessive demands created by the untoward events of that spring, the necessary return of the limited professional staff to their normal positions and the time required for new personnel to deal effectively with material of such complex nature have caused delays.

Because of the varied interests represented in the medical features of the study, a constant succession of panning expeditions has been carried out, requiring new machine runs of the punch cards, retabulations, careful study and more time. Some flecks and a few nuggets of importance to specific technical fields have been disclosed. Additional methods of analysis and presentation have also been employed.

There is no end to checking and rechecking, appraising and reappraising, writing and rewriting. Extended explorations of the data in response to questions raised by reviewers of the Summary Report have been painstaking and time consuming.

Prominent among the questions raised was the suggestion that since the incidence of poliomyelitis was greater in subjects receiving placebo injections than in those who refused to participate, the difference resulted from a provocation of paralysis by the placebo. The collected material has been examined almost continuously from all conceivable angles which bear on this possibility, without revealing evidence in support of it. The difference in characteristics and behavior of the nonparticipants appears to explain the variation adequately. The data on this subject are presented in almost excessive detail.

Similarly, the data have been searched carefully for evidence of deleterious effects of the vaccine itself without disclosing any such influence. This has been associated with minute consideration of the cases occurring in vaccinated subjects; they are associated primarily with material of poor potency rather than the reverse.

Explanation has been sought for the reported lack of significant protection from paralytic poliomyelitis of six-year-old children in placebo areas by reviewing the various possibilities. This subject is thoroughly discussed but no

single explanation for the aberrant finding is obvious although several reasonable suggestions present themselves. The failure relates primarily to Type I infections.

The laboratory studies of response to vaccination have been extensively analyzed and have yielded important generalizations concerning the study population, the antigenic potency of vaccine, the occurrence of subclinical infection and the behavior of patients undergoing infection. Important contributions to the evaluation of technical performance are included. The nature of the illnesses associated with non-poliomyelitis virus infections and their complicating role in the Field Trial have been analyzed.

Intricate presentations are made of the muscular impairment noted by the physical therapists in their careful, specialized examinations of the patients.

The account of the development of diagnostic criteria from complex data may be almost too detailed, but the intent was to present the manner in which they were derived as well as the final criteria.

The core of the evaluation program, which is often forgotten in the consideration of results, consists of the procedures for collection of data, the handling of the records, their verification, coding and preparation for use. They are carefully described together with the precautions employed to avoid disclosure of information. The information may be helpful to the management of other studies of similar nature.

The essential features of most of these activities were outlined in the Summary Report. They are again presented in summary form in the first chapter and then extensively in the succeeding chapters of this Final Report. The number of tables is so great that in places they are widely separated from the related text. It is likely that few except those with special interests will be concerned with much of the minute detail, but it is presented for their information. These expanded presentations contain information regarding a number of subjects subsidiary to the primary objective and are of themselves major contributions to the study of poliomyelitis and to epidemiological research generally. For example, the information compiled from work in the Field Trial concerning the practical laboratory diagnosis of poliomyelitis and the careful appraisal of the technical procedures are important contributions.

A few terms which have special meanings as used in this report and a brief definition of each are listed in the Glossary. A Bibliography is provided and, in lieu of an index, the Table of Contents lists topics in detail. The Appendices contain copies of forms, outlines of procedures, letters and instructions to the field, and comprehensive tables of data for individual Field Trial areas.

This volume is presented with a certain pride of accomplishment. There is satisfaction in the performance of the Vaccine Evaluation Center and some surprise that the evaluation of such a large experiment could be done so efficiently in the presence of so many imponderables and potential pitfalls. There is confidence in the quality of the data, in the unbiased character of the extensive analyses and their presentations, in the dependability of the conclusions even though some questions remain to which the data did not provide clear-cut answers. There is

great assurance that the study, both in design and performance, is a contribution of major value to the field of medical research, generally. It is gratifying that the undertaking provided knowledge which unequivocally established the product developed by Dr. Salk as an effective vaccine for the prevention of poliomyelitis.

There is also a sense of relief that despite the numerous interruptions and obstacles, the work is completed. The report reflects inadequately the atmosphere and the spirit of its making; time has moved on as usual but the Field Trial and the data in the report remain a milestone in the advance of preventive medicine.

And so, with both pride and relief, this Final Report on the Evaluation of the 1954 Field Trial of Poliomyelitis Vaccine represents the relinquishing of a trust which has been borne to the best of our ability.

April, 1957 — Thomas Francis, Jr.