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# POLIO VACCINES

## HEARINGS

BEFORE A

## SUBCOMMITTEE OF THE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE HOUSE OF REPRESENTATIVES

EIGHTY-SEVENTH CONGRESS

FIRST SESSION

ON

DEVELOPMENTS WITH RESPECT TO THE MANUFACTURE OF LIVE VIRUS POLIO VACCINE AND RESULTS OF UTILIZATION OF KILLED VIRUS POLIO VACCINE

MARCH 16 AND 17, 1961

Printed for the use of the Committee on Interstate and Foreign Commerce

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# POLIO VACCINES

THURSDAY, MARCH 16, 1961

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND SAFETY OF THE
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
*Washington, D.C.*

The subcommittee met, pursuant to notice, at 10 a.m., in room 1334, New House Office Building, Hon. Kenneth A. Roberts presiding.

Present: Representatives Roberts, Rhodes of Pennsylvania, Rogers of Florida, Schenck, Nelson and Thomson.

Also present: Representative Harris (chairman of the full committee), and Kurt Borchardt, legal counsel.

Mr. ROBERTS. The subcommittee will please be in order.

The Subcommittee on Health and Safety of the Committee on Interstate and Foreign Commerce is holding hearings this morning on the present status of the oral polio vaccine.

On March 14, President Kennedy requested the Congress to appropriate $1 million for approximately 3 million doses of the vaccine to be stockpiled in case of polio outbreaks in the United States. The press and radio gave a good deal of play to this request but some of the stories may have left the impression that the new vaccine will be available for emergency use at an early date.

The subcommittee has called this hearing in order to give the Department of Health, Education, and Welfare and persons representing organizations knowledgeable in the field an opportunity to state for the benefit of the committee and the American people what the present status is of production of oral polio vaccine in the United States, and when that vaccine is expected to become generally available to the public, and what the Department expects to be its course of action during the interim period.

Under the provisions of the Public Health Service Act relating to biological products, no person may sell a vaccine unless such product has been manufactured in an establishment licensed by the Department of Health, Education, and Welfare. The subcommittee has been informed that as of March 14, 1961, no applications for licenses have been filed by pharmaceutical manufacturers.

Unless the American people have a complete understanding of the present status of the oral polio vaccine in the United States, great harm may come from premature reliance on early availability of the new vaccine either for emergency use or for general public use.

Therefore, the subcommittee felt it best to call this hearing on short notice in order to lay the complete facts with regard to the present status of the oral vaccine before the American people.

The chair regrets if the call for hearings on such short notice has caused any inconvience to Government officials and other witnesses. However, the Chair felt that no time should be lost in attempting to clarify the situation, especially since only a short while ago widespread attention was given by the news media to an article which appeared in the Journal of the American Medical Association in which the author of the article cast doubt on the effectiveness of the Salk vaccine which at the present time is the only polio vaccine available in the United States.

Since then the American Medical Association and the Public Health Service have expressed their complete confidence in the effectiveness of the Salk vaccine and have urged its continued use during the current year. President Kennedy, in making his request for funds for the purchase of the oral vaccine, likewise stressed the need for continued use at the present time of the Salk vaccine.

The subcommittee feels that in the interest of the welfare of the American people the record should be completely clear on the status of the oral vaccine in the United States: where we stand at this juncture, when the American people might expect to have available an ample supply of the new vaccine, and what the wise course is to follow during the interim period.

It is a personal pleasure this morning to introduce our first witness. He is the newly appointed Surgeon General of the U.S. Public Health Service. Dr. Terry comes from my beloved State of Alabama. He was born at Red Level down in Covington County, and he has distinguished himself in the Public Health Service. He is a graduate of the Agricultural College and later attended the University in New Orleans.

Dr. Terry, it is, certainly, a pleasure to have you with us today, and I am sure that we will see a lot of each other in the months to come. My very best wishes to you in your new position.

You may proceed as you wish with your statement.

**STATEMENT OF DR. LUTHER L. TERRY, SURGEON GENERAL, PUBLIC HEALTH SERVICE; ACCOMPANIED BY DR. ARNOLD B. KURLANDER, ASSISTANT SURGEON GENERAL; DR. ALEXANDER D. LANGMUIR, CHIEF, EPIDEMIOLOGY BRANCH, COMMUNICABLE DISEASE CENTER; DR. RODERICK MURRAY, DIRECTOR, DIVISION OF BIOLOGIC STANDARDS, NATIONAL INSTITUES OF HEALTH; DR. C. A. SMITH, CHIEF, COMMUNICABLE DISEASE CENTER; AND EDWARD J. ROURKE, ASSISTANT GENERAL COUNSEL, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE**

Dr. TERRY. Thank you, Mr. Chairman. I certainly appreciate your good wishes and I am sure that I shall need them with the great responsibility of this position that I am in.

I have recently assumed the position of Surgeon General in the Public Health Service. I am not new to the Public Health Service, having been in our Service for 18½ years, and during the past 10 years having been associated with the National Heart Institute.

Consequently, Mr. Chairman, I am not unaware of the importance of this committee, nor of the tremendous support and assistance that we have received from this committee in the past.

At the outset I would like to say that we are appreciative and that I shall do everything in my power to assist the committee in any of its actions. I shall look forward to your continued support.

I have a brief prepared statement which I would like to read into the record, if I may, sir. At the end of that time I should like to introduce my colleagues, whom I have with me here. I should, also, at that time, like to submit additional material to the committee for your use as you see fit, either to go into the record or however you would like to handle it, sir.

Mr. ROBERTS. Very well.

Dr. TERRY. Your immediate concern is with the current status of the oral vaccine. When may it be expected and what are its potential advantages?

With your permission, however, I should like first to make a few comments on the status of poliomyelitis control in the United States, the overall role of the Public Health Service in the polio picture, and something of our present and future plans for continuing and vigorous action to help bring this cruel and crippling disease under final control.

There has been much emphasis—and rightful emphasis—on the numbers of persons who remain unvaccinated in our population. The Public Health Service, with the aid of the medical profession, the National Foundation, dozens of organizations, and thousands of individuals, has been engaged in the active promotion of wider vaccinations.

You will have noted, I am sure, President Kennedy's statement earlier this week giving strong endorsement to present national efforts to push vaccinations with the highly effective vaccine we now have on hand.

It is of the highest importance, as the President has pointed out, that our present consideration of the oral vaccine should not deflect attention from the goal of maximum vaccinations with Salk vaccine before next summer.

The President's comment accompanied the announcement, as you know, that he was requesting a $1 million appropriation for the purchase of oral vaccine when it becomes available, for an epidemic reserve and for necessary investigations and more precise study of its effects. It does not mean that the oral vaccine is any more imminent than it was last week or the week before.

The purpose is to place the Service in a state of readiness for the day when such a vaccine is licensed and on the market.

At the present time no completed applications have been made to the Public Health Service for licensing. Although we confidently anticipate that one or more applications may be forthcoming within the next 6 months, or possibly sooner, it is impossible to set any more precise time than that.

The licensing function is, as you know, one of the five major functions which the Service presently performs with respect to the Salk vaccine and other biological products. They are—or will be—equally applicable, of course, to the oral vaccine. A brief review of these functions may serve, I believe, as useful background for your questions and will help, as well, in placing the present and future status of the oral vaccine in proper perspective.

## LICENSING

The responsibility for licensing, as you are aware, rests with the Secretary of Health, Education, and Welfare who acts upon the recommendation of the Surgeon General. As Surgeon General I am, in turn, advised by the Director of the National Institutes of Health and the Director of the Division of Biologics Standards.

The Division has the responsibility under the law for protecting the public by administering standards designed to insure the safety and potency of medical biological products used in the United States and for seeing that these standards are maintained.

The standards which the Division applies to these products are rigorous. It is their policy—and one with which, I am sure, we are all in accord—that biological products used for the prevention or the treatment of illness must be of the highest quality which our scientific knowledge and testing can produce.

It has been the application of these high standards to the oral vaccine which has occasioned the criticism from some quarters that the Public Health Service has been slow in licensing the oral vaccine.

It has been pointed out that approximately 236 million doses of various strains of the oral vaccine have been used in the U.S.S.R., and in other countries abroad. There is evidence that the vaccine has been effective—in fact, highly effective. The manufacturing and testing requirements under which this vaccine was produced were less rigid than those now proposed for American manufacture.

The staff of the Service and our scientific advisers have recognized the obvious advantages in ease of administration of an oral vaccine and such other potential advantages as quicker, possibly longer lasting immunity. They have remained insistent that certain technical problems be resolved. Among them is the exclusion of simian viruses. Though the disease potential of these agents is not fully known, our advisers and staff have consistently advised that they be excluded from vaccine produced in this country.

I am sure you would agree with me that this is in the public interest. I would simply point out further that with an effective vaccine already on hand, this wise caution could be exercised without hampering the fight against polio.

## SURVEILLANCE

One of the continuing and important responsibilities of the Service, in association with the States and local communities, is to keep a constant and watchful check on illnesses of all kind.

For the specific purpose of providing a doublecheck on the safety and potency of the Salk vaccine, the Service set up a national poliomyelitis surveillance program at the Communicable Disease Center in Atlanta in April 1955.

Through this program we have been able to maintain a constant tally of polio and poliolike diseases, to compile necessary data on incidence, safety, effectiveness, and other aspects of polio control. This mechanism, of proved usefulness, will be of equal usefulness when the oral vaccine is licensed and in wide use.

RESEARCH

The relationship of research to the extension of control over polio or other illnesses is, of course, obvious. Without the brilliant investigative work of scientific investigators over a long period of years, millions of parents everywhere would be facing the coming summer season with a crawling sense of dread. So short is human memory that we forget it was only 5 years ago when every American parent shared this familiar apprehension.

The Public Health Service's responsibilities in the wide field of research are well known to you. In polio, our role in recent years has been less associated with the development of preventives than with their testing and application. Since 1953, the Service, however, has called time and again upon the talents of the Nation's scientists in helping to resolve the many, various and continuing problems which have been associated with the poliomyelitis program.

The Service is immeasurably grateful to these expert advisers. As Surgeon General, Mr. Chairman, I propose to continue to call upon them, and others, to provide us with the most expert advice possible on the use and application of the oral vaccine as well as on other health measures.

PROMOTION

I mentioned earlier the role which the Service has played in helping to promote the Salk vaccine and our present intention to press for wider use of the Salk vaccine before this summer. I suggested that we rightfully emphasized the numbers of unvaccinated.

On the other hand, we should take note of the fact that as a result of this promotional effort—which has, by no means, been of our doing altogether—well over 80 million have been vaccinated. This is a triumph of preventive medicine without parallel in our history. This triumph has been achieved through the efforts of the many; and in it the communications media have played a vital and indispensable part.

I am happy to report, Mr. Chairman, that we have been assured of the support of the Advertising Council, for the fifth successive year, in our present vaccination drive. Their campaign, conducted with the generous assistance of American newspapers, radio, television, billboards, car cards and other media, has been of tremendous assistance to us in the past.

I have every confidence that when the oral vaccine becomes available, we will have their help and the help of the medical and public health professions in putting it to rapid use.

STIMULATION

The Public Health Service, as the principal Federal health agency, has responsibilities not only in its own right but in stimulating others to action. This stimulatory role takes many forms: the encouragement of research, demonstration, scientific publication, and consultation with professional groups and individuals on a wide variety of programs.

During the past 3 years, the Service has exercised this function with respect to the oral vaccine in continuous consultation with industry at all levels, in the review of data by our own staff and our consultants

and in many other ways. I can assure you, Mr. Chairman, that we will continue to do our best, within those areas which are appropriate for Federal action, to help speed the early production of the oral vaccine.

It was with these fivefold responsibilities in mind that my predecessor, Dr. Leroy E. Burney, on June 30, 1958, appointed a Public Health Service Committee on Live Poliovirus Vaccine. Made up of experts in the field of virology and vaccines, the Committee's job has been to keep abreast of developments in the oral polio field and to keep the Surgeon General and his staff continuously advised on developments in the whole field.

I should like to submit, for the record, a list of major actions undertaken since that date by the Service to insure that we would remain continuously informed on the oral vaccine and be in a position to take appropriate action at the appropriate time.

The chronology begins with the formation of this expert committee. The last item in it is the submission by the President last Tuesday, March 14, of the request for a supplemental appropriation for $1 million to set up a reserve supply of oral vaccine for epidemic use when it becomes available.

You will note, Mr. Chairman, that the chronology includes two international conferences on the subject of the oral vaccine, an on-the-spot survey of the Russian experience by Public Health Service personnel in May 1960, a number of public announcements by the Service on the progress of the oral vaccine, a symposium conducted at the midwinter sessions of the American Medical Association—copies of which I should like also to submit for the record—and the recommendations of the Surgeon General's Committee on Poliomyelitis Control which met in Atlanta, Ga., on January 23 and 24 of this year.

This Committee, made up of representatives of 29 national organizations, representing both the medical and health professions and the general public, in sessions freely open to and reported by the press, were provided with a thorough review of the whole polio picture. I should like to submit for the record, Mr. Chairman, their very thoughtful recommendations as well as a copy of my response to them.

I would point out that this Committee had the advice and counsel of a number of leading experts in virology, including the major developers of the oral vaccine, as well as of experts in public health administration.

Among their major recommendations was the establishment of the oral polio reserve for which President Kennedy earlier this week requested an appropriation of $1 million.

This chronology will show, I believe, that the Service has not only sought to keep abreast of developments but has sought, by every means appropriate to a Federal agency, to encourage early production of an oral vaccine which will be safe and effective.

The culmination of this 3-year effort, which grew in intensity during the past year, was the publication on November 23, 1960, in the Federal Register, of a Notice of Proposed Rule Making for Poliovirus Vaccine.

Since that date our scientists have been in continuous touch with their scientific conferees in industry. As a result, industry is thoroughly familiar with the manner in which the requirements were developed and with the requirements themselves.

I have every confidence that as soon as they have completed their testing procedures and taken the necessary—and highly complicated—steps that are required for mass production of the vaccine, we shall begin receiving requests for licensing. I am advised by Dr. Murray that the final, formal requirements will be sent forward for publication in the Federal Register by the end of this month.

In summary, Mr. Chairman, may I express once more my appreciation for this opportunity to review for you these recent developments with respect to the oral vaccine and the Public Health Service's 6-year association with the polio vaccination program.

With only 2,265 paralytic cases last year as against many thousands annually in the pre-Salk vaccine days, we can, as a Nation, take great satisfaction in how far we have come in the control of polio. None of us will be satisfied until the day comes when we have stamped out polio once and for all in the United States and, in the longer run, helped play our part in its elimination from the world.

We may take perhaps justifiable pride that these two weapons—the Salk and the Sabin vaccines—are the product of the creative genius of American scientists. Building, as scientists must, on the work of their predecessors, they have furnished the world with the means for preventing incalculable suffering to the world's children.

It remains for all of us now to turn our continuing best efforts to the long but infinitely rewarding job of putting both of these weapons to work in the service of mankind.

Mr. Chairman, this completes my formal statement.

At this point, sir, I would like to submit to the committee the material which I mentioned in my presentation.

The first is a brief chronology of activities related to the live poliovirus vaccine which I believe members of the committee already have.

The second is a group of papers which constituted a symposium presented at the midwinter meeting of the American Medical Association in November 1960.

The third is a group of the subcommittee reports of the Surgeon General's Advisory Committee on Poliomyelitis Control.

The fourth is the report of the committee itself on the basis of the subcommittee's reports.

The fifth is a release which was issued on February 28, 1961, and constitutes our latest effort from the Public Health Service toward informing the public, the medical profession, and all of those interested and involved in the problem of poliomyelitis control of the situation and of the recommendations that the Service makes at the present time.

The sixth is a brief review of the promotional effort exerted over the past 5 years by the Service and others.

Also, Mr. Chairman, at this time, if I may, I would like to take the opportunity of introducing my colleagues to the committee. And after I have introduced them, we would all like to make ourselves freely available to questions from the committee.

Mr. ROBERTS. Without objection, those documents may be inserted in the record.

(The documents follow:)

## BRIEF CHRONOLOGY OF ACTIVITIES RELATED TO LIVE POLIOVIRUS VACCINE

June 30, 1958 — PHS Committee on Live Poliovirus Vaccine established by the Surgeon General. Since that time, the committee has met on 15 occasions as a committee and has, in addition, participated in conferences organized by the Pan American Health Organization and by the Public Health Service in relation to the Surgeon General's Advisory Committee on Poliomyelitis Control.

Nov. 13, 1958 — The Committee had its first formal meeting and conferred with members of industry having an interest in virus vaccines and with scientists active in live poliovirus research. This was mainly an orientation meeting designed to determine the stage of evolution of live poliovirus vaccine.

May 1959 — Public statement by Surgeon General on progress in developing and testing of oral polio vaccine published in Public Health Reports, journal of the Public Health Service.

June 1, 1959 — First report of the PHS Committee on Live Poliovirus Vaccine to the Surgeon General of the Public Health Service.

June 22-26, 1959 — First International Conference on Poliovirus Vaccines held in Washington under the joint auspices of the World Health Organization and the Pan American Health Organization. At this week-long conference reports were presented on all significant aspects of work on live poliovirus vaccine. The conference was attended by invited scientists from all over the world, including the USSR.

Aug. 12, 1959 — Second report of the PHS Committee on Live Poliovirus Vaccine to the Surgeon General of the Public Health Service. This included a set of suggestions relating to important aspects which would have to be covered in the development of standards for a safe and effective live poliovirus vaccine.

Aug. 14, 1959 — Committee's report sent to vaccine producers.

Aug. 28, 1959 — Public statement on current status of oral polio vaccine issued by the Surgeon General. This was published in full in the November 1959, issue of Public Health Reports.

Oct. 9, 1959 — Joint meeting between the PHS Committee on Live Poliovirus Vaccine, interested scientists, and members of industry to discuss the points raised by the committee relative to safety and effectiveness.

Oct. 29, 1959 — Transcript of Oct. 9 meeting sent to vaccine producers.

Nov. 16, 1959 — Recommendations Relating to the Manufacture of Live Poliovirus Vaccine issued by the PHS Committee on Live Poliovirus Vaccine. This document, which was prepared following the October 9th meeting, sets forth the essential features of any future standards which would be applicable to a safe and potent live poliovirus vaccine to be distributed for general sale and unrestricted use. The recommendations were sent on this date to the vaccine producers.

Dec. 19, 1959 — Special article in The Journal of the American Medical Association by Dr. Leroy E. Burney, Surgeon General of the U. S. Public Health Service, entitled "Current Status of Live Poliovirus Vaccine."

Mar. 22, 1960 — The PHS financed publication and sent to all medical school libraries and to vaccine producers the report on use of live polio vaccine in Russia made by Dr. Dorothy Horstmann of the Yale University School of Medicine for the World Health Organization.

Apr. 20, 1960 — Symposium on Polio Vaccine held by The Academy of Medicine of New Jersey.

May 12-16, 1960 — Soviet-American meeting on poliomyelitis, Moscow, USSR.

June 6-10, 1960 — Second International Conference on Poliovirus Vaccines held in Washington. This conference made available the latest information on the investigations of live poliovirus vaccines which had been going on all over the world. The published proceedings of this conference as well as those of the first conference on June 22-26, 1959 represent valuable sources of information and documentation.

June 13-16, 1960 — Meeting of World Health Organization Expert Committee on Poliomyelitis. A report of this Committee has appeared as WHO Technical Report Series, No. 203, 1960.

July 26-28, 1960 — Fifth International Poliomyelitis Conference, Copenhagen. This represented a roundup of up-to-date information concerning both live poliovirus vaccine and inactivated (Salk) vaccine.

Following this conference it was possible to evaluate the status of live poliovirus vaccine and look forward to its availability as a licensed product if production difficulties could be solved. Steps were initiated toward the adoption of regulations relating to the manufacture and testing of live poliovirus vaccine.

July 28, 1960 — The PHS sent "Recommendations Relating to the Manufacture of Live Poliovirus Vaccine" - revised July 27, 1960 to vaccine producers.

Aug. 24, 1960 — Public announcement by the Surgeon General, at a press conference, that live poliovirus vaccine is considered suitable for use in the U. S. At this conference, a report of the recommendations of the PHS Committee on Live Poliovirus Vaccine was also released.

Aug. 25, 1960 — Recommendations relating to the manufacture of oral poliovirus vaccine issued by Public Health Service Committee on Live Poliovirus Vaccine and sent to manufacturers. This document was a further elaboration of the earlier document of Nove. 16, 1959.

Sept. 20, 1960 — Public announcement of a Surgeon General's Advisory Committee on Poliomyelitis Control to advise on plans for wider use of Salk vaccine and for use of oral vaccine when it becomes available.

Oct. 11 & 12, 1960 — Agenda planning committee of the Surgeon General's Advisory Committee on Poliomyelitis Control met at the Service's Communicable Disease Center in Atlanta, Georgia.

Nov. 9, 1960 — Formal letter sent to vaccine manufacturers requesting information on their plans for production of oral vaccine.

Nov. 18, 1960 — Advance copy of standards to be published in the Federal Register (see below) sent to vaccine manufacturers.

Nov. 23, 1960 — Publication of a Notice of Proposed Rule Making for Poliovirus Vaccine, Live, Oral. This appeared in the Federal Register on said date page 11111. Public comment was invited.

Nov. 30, 1960 — Synposium on Present Poliomyelitis Immunizatio, American Medical Association Mid-Winter Clinical Session, Washington, D.C. Papers presented by Dr. Leroy E. Burney, Dr. E. Russell Alexander, Dr. Roderick Murray, and Dr. Alexander Langmuir. This group of papers constituted a rather concise presentation of the current status of both live and inactivated poliovirus vaccines, indicating the success with the latter and the problems anticipated with the former. Following this meeting, the Surgeon General held a press conference to answer questions relating to the data presented at the symposium.

Jan. 23 & 24, 1961 — Meeting of the Surgeon General's Advisory Committee on Poliomyelitis Control at the Communicable Disease Center in Atlanta, Georgia. General sessions were open to the press and a press release was issued summarizing committee actions.

Feb. 13, 1961 — Request for $1 million for purchase of oral polio vaccine for study and evaluation of its use as an epidemic control measure submitted to the Bureau of the Budget by the Public Health Service. Public announcement had been made previous day by President Kennedy of his intent to request the funds for establishment of an epidemic reserve

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| Feb. 16, 1960 | Distribution of Recommendations of the Surgeon General's Advisory Committee on Poliomyelitis Control to the press and to health, medical and civic organizations. |
| Mar. 14, 1961 | Senate Hearings held on request for $1 million to purchase oral vaccine. |
| Mar. 15, 1961 | No applications have as yet been filed for license for live poliovirus vaccine. The Public Health Service is keeping close contact with the technical representatives of those manufacturers who are interested in producing live poliovirus vaccine. Public comment to the Nov. 23 Notice of Proposed Rule Making has been received and considered. Document being prepared for publication the Federal Register. |

# SYMPOSIUM
# ON
# PRESENT STATUS OF POLIOMYELITIS AND POLIOMYELITIS IMMUNIZATION

Papers presented at the
American Medical Association Mid-Winter Clinical Sessions
Washington, D. C. - November 30, 1960

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U. S. DEPARTMENT OF
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FOR RELEASE ON DELIVERY
WEDNESDAY, NOVEMBER 30, 1960

Introductory Remarks*
by
Dr. Leroy E. Burney
Surgeon General

All of us can agree that in the U. S. we have come a long way toward controlling paralytic poliomyelitis. Within the past five years, some 93 million persons have used the Salk vaccine and 78 million of them are now fully immunized. This is a monumental achievement in preventive medicine. I know of no parallel in medical history.

For this the medical and public health professions, the National Foundation, dozens of other organizations and thousands of individuals deserve great and enduring credit.

During these five years, there have not only been many improvements in the inactivated vaccine, but a marked increase in potency has been achieved. Steady progress has also been made in the development of oral vaccines. Dr. Hilary Koprowski of the Wistar Institute in Philadelphia, Dr. Herald Cox of the Lederle Laboratories, and Dr. Sabin of the University of Cincinnati have been world leaders in this work.

It is now evident that an oral live, attenuated vaccine will take its place along with Salk vaccine as an additional weapon for the control of polio.

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This, therefore, seems an appropriate period to assess our past experience in the use of polio vaccine, to review the current status of the development of new polio vaccine, to review the current status of the development of new polio vaccines, and to consider the problems that will confront us as we move toward our ultimate goal of complete protection against paralytic polio in the U. S.

To do this, I have asked the three men in the Public Health Service who have been most closely associated with our polio activities to give you progress reports.

Dr. Russell Alexander, Chief, Surveillance Section, Communicable Disease Center, will report to you on data provided by health departments throughout the nation and analyzed by the epidemiologists in our poliomyelitis surveillance unit. The incidence, the trends, and the shift in epidemic patterns will help to point up the dimensions and the nature of our unfinished business in the control of this disease.

Dr. Roderick Murray, Director, Division of Biologics Standards, will then report on improvements in the inactivated vaccines and, more particularly, will discuss the technical problems, the licensure requirements, and the prospects for production of oral vaccine. Dr. Murray has participated in the international conferences held this year and has studied the results of the oral vaccine in this country and in several foreign countries. He has served as Chairman of the Technical Advisory Committee on Live Vaccine, men well qualified to give us expert judgment on the extraordinarily complex problems of choice of strains, and methods of testing for safety and effectiveness.

Finally, I will ask Dr. Alexander Langmuir, Chief, Epidemiology Branch, Communicable Disease Center, to discuss some of the epidemiological considerations inherent to the effective use of both the inactivated and the oral vaccines.

At the conclusion of these reports, I will outline to you some of the plans we have made to date to work with you and with the various professional and public groups who have an important role to play in the further advancement of poliomyelitis control.

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Symposium on Present Poliomyelitis Immunization.

A. Extent of the Problem - E. Russell Alexander, M. D.
Chief, Surveillance Section
Communicable Disease Center, Atlanta

The pattern of occurrence of poliomyelitis in the United States has changed. In each succeeding year this change has become better defined. The disease is now concentrated among the unimmunized population, which we have failed to reach while we have all shared in the most intensive campaign of vaccination on the history of this country. The residual pattern of disease representa a measure of our failures to apply vaccine completely enough. The following remarks will attempt to summarize briefly our present status. The data to be presented are largely those collected by the Poliomyelitis Surveillance Unit of the Communicable Disease Center.

Morbidity Trends

In the first figure, annual poliomyelitis incidence rates are shown for the period 1935-1960. After the peak period of 1950-54, a downward trend began in 1955, and was continued through 1957, associated with increasing Salk vaccine utilization. Although this trend was halted and reversed in 1958 and 1959, a preliminary estimate for 1960 yields a lower total than for either of those years. Through the week ending November 19, 1960, 3033 cases were reported to the National Office of Vital Statistics,

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For presentation at the A.M.A. Mid-winter Clinical Sessions, Washington, D. C., November 30, 1960.

of which 2089 were paralytic. From this we would estimate the total cases for 1960 to be about 3600. Although this would represent an even lower annual total than in 1957, a comparison of paralytic cases reported shows them to be nearly equal in number. Due to some changes in the diagnostic criteria, and decreased prevalence of other enterovirus diseases in 1960 as compared with 1957, paralytic poliomyelitis gives the more valid comparison. By all measures we are at a low point in morbidity for recent years.

Geographic Distribution

In the second figure is depicted paralytic poliomyelitis occurrence in the United States during 1960. Three major epidemics are shown. In Providence and Rhode Island, an early onset of paralytic cases signalled a large epidemic, resulting in 86 paralytic cases caused by Type I poliovirus. In Baltimore, the epidemic started late in the year, and through November 4, 91 paralytic cases had been reported. In this instance Type III poliovirus was the cause. In Puerto Rico, from March to October, Type I poliomyelitis spread throughout the island, in both rural and urban populations, and totalled 475 paralytic cases to this date.

Other concentrations of the disease are listed, and it is worthy of note that they include many rural or county-wide outbreaks. Examples are the adjoining counties of Somerset in southern Pennsylvania and Garrett and Allegheny Counties in northern Maryland, where Type III poliovirus was prevalent. Border counties of North and South Carolina provided a focus of 42 paralytic cases due to Type I poliovirus. Three rural counties of central Kentucky accounted for 30 more paralytic cases, predominantly Type I poliovirus.

Epidemiologic Pattern

In all this occurrence, there is striking repetition of a basic epidemiologic pattern. Fundamentally, there is a concentration among pre-school, lower socioeconomic children in crowded urban areas and selected rural localizations. This pattern was first seen in 1956, after widespread use of vaccine. It is illustrated in the following two figures on pre- and post-vaccine epidemics. The first figure contrasts a rather general distribution in Chicago in 1952, compared with a well demarcated concentration among lower socioeconomic groups in crowded slums in 1956, predominantly Negro in this instance. In the next figure, of Kansas City, Mo., the discrete pattern of 1959 is distinctly different from that of 1952, and once more defines the characteristics of the susceptible population--the unimmunized.

This year in Providence, R. I. poliomyelitis was concentrated in children in lower socioeconomic housing developments, where failure to utilize the available vaccine, completely, had resulted in islands of susceptibles in an otherwise well protected community. In Baltimore, the localization in crowded slums was even more evident; the attack rate in negroes was approximately twice that in the white population, and large suburban areas remained free of disease.

When the occurrence is in other than urban areas the pattern persists. Beside the concentrations among negroes and Puerto Ricans in cities, we find concentrations in poor farming areas, among Indians, and isolated religious sects. In all instances the pattern of polio is the pattern of the unvaccinated.

Vaccine Utilization

Since 1955, more than 350 million ccs. of formalin-inactivated vaccine have been applied to the United States population. Within the last year, from September 1959 to September 1960, 54 million ccs. were distributed. Each fall, for the last three years, a national survey of immunization status has been conducted, under the direction of the National Office of Vital Statistics. Examination of these data yields some valuable measures of the residual unvaccinated population. In the last figure are shown the percents of the population by age that have received a full course of four or more poliomyelitis inoculations, as measured by surveys in September 1959 and 1960. It may be seen that in this year the percent of the 5-9 age group with four or more doses increased from 32 to 50%, and of the 10-14 age group from 28 to 47%, but the level in the pre-school child (ages 1 to 4) was increased only from 22 to 35%. More important to note is that approximately one-half of school age children (5 to 15 years) have not received four inoculations, and approximately two-thirds of children age 1-4 are similarly inadequately protected. This latter age group is the most important, accounting for the greatest proportion of polio cases in recent years. Although only 13% of this age group have had no inoculations, this is a decrease in the uninoculated of only about three percentage points from the previous year. It is apparent from more extensive studies of these survey results that during the last year the majority of vaccine distributed has been used in further inoculation of those already partially immunized. Very little has been used to further reduce the number of persons who have not yet received a single injection.

Vaccine Effectiveness

Using these annual surveys of immunization status, and the reports of paralytic poliomyelitis which you, the physicians of the country, have

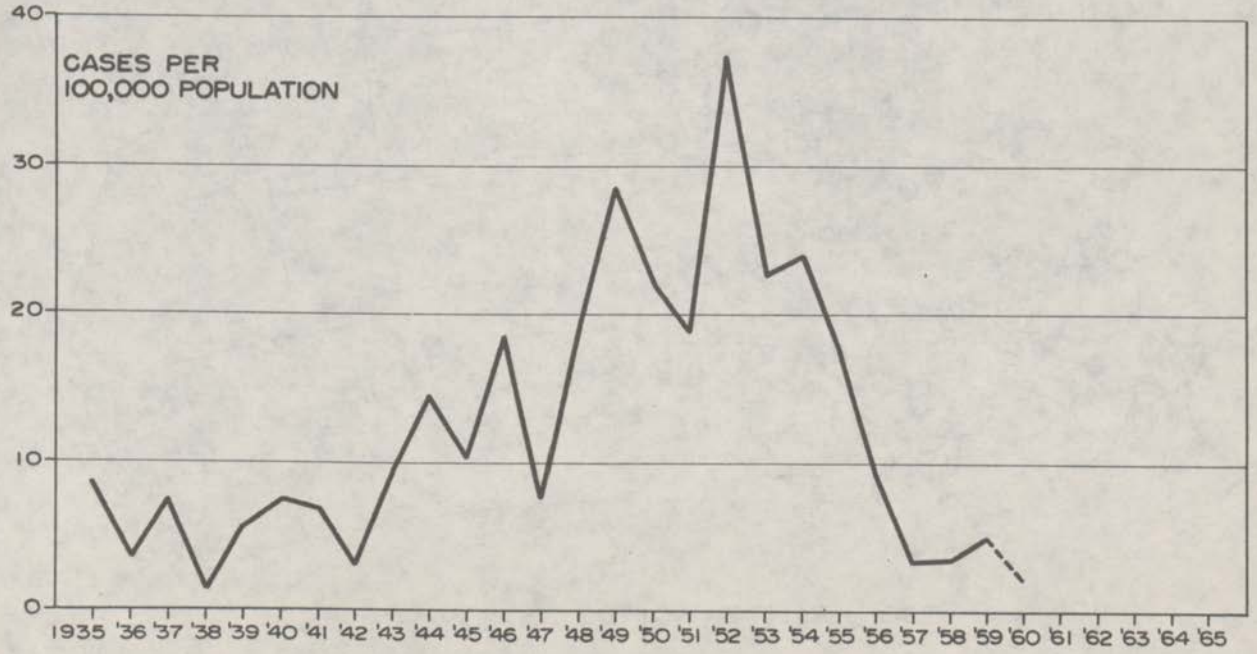
carefully reported through your local health departments, we have made broad, crude estimates of the efficacy of the formalin-inactivated vaccines, as they have been used in the field. These crude estimates yield an efficacy of vaccines in prevention of paralytic poliomyelitis above 90%. In such broad national estimates, however, there are factors of upward bias, which we may recognize and correct for in the more accurate measurements of efficacy which have been made around local epidemics. Such estimates have been made in Des Moines, Iowa, and Kansas City, Mo. in 1959, and in Providence, R. I. in 1960. In each instance we find the efficacy of the vaccine to be greater than 80% for three or more doses, and significantly greater for four or more doses.

Summary

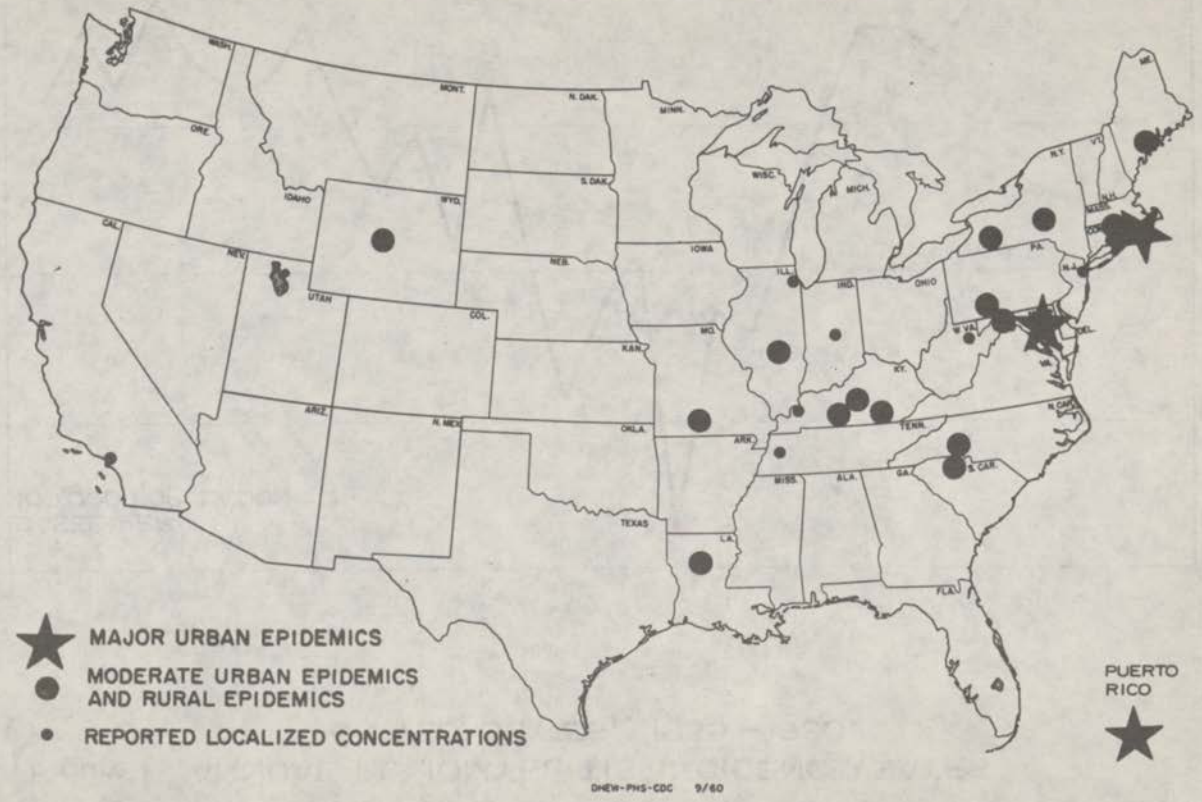
In 1960, although the annual total of poliomyelitis cases will be lower than in any recent years, and paralytic cases will be closely comparable to the low of 1957, the disease continues to occur in a repetitive pattern. This pattern is predominantly of lower socioeconomic preschool children, often in crowded urban centers, but in all cases reflecting the distribution of the residual unimmunized population. Surveys of immunization status continue to reveal significant proportions of the population inadequately protected. Comparative surveys in successive years show that although great proportions of the population have attained adequate levels of immunization, we have been less successful in reducing the number of completely unvaccinated persons.

Figure I ANNUAL POLIOMYELITIS INCIDENCE RATES
UNITED STATES, 1935 – 1960

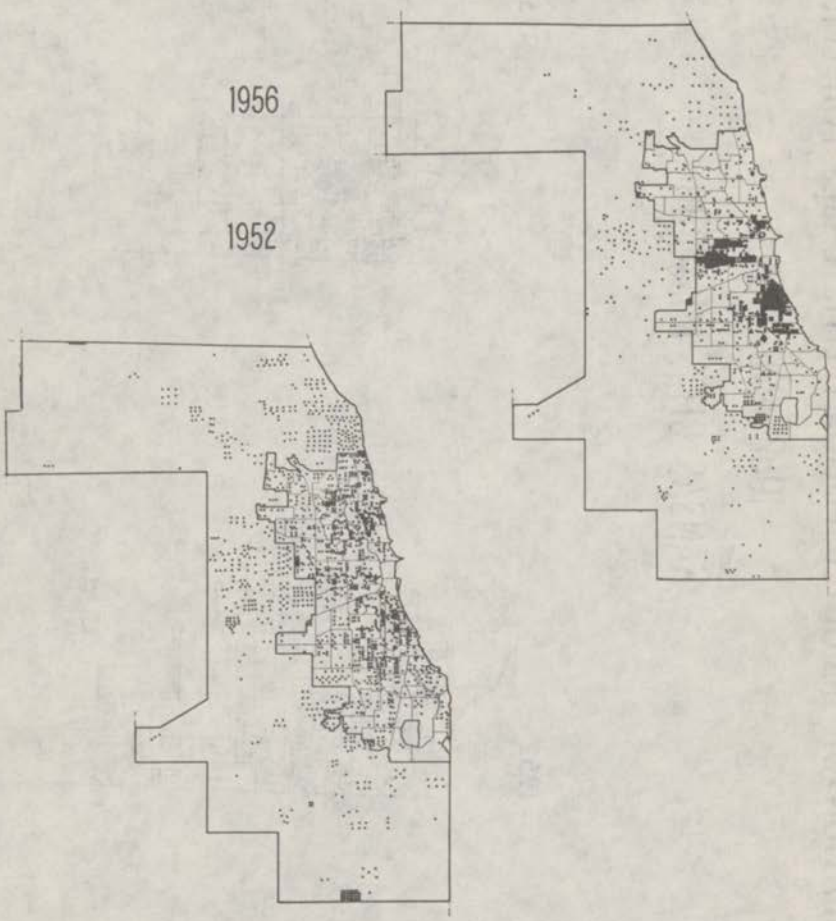
SOURCE: NOVS



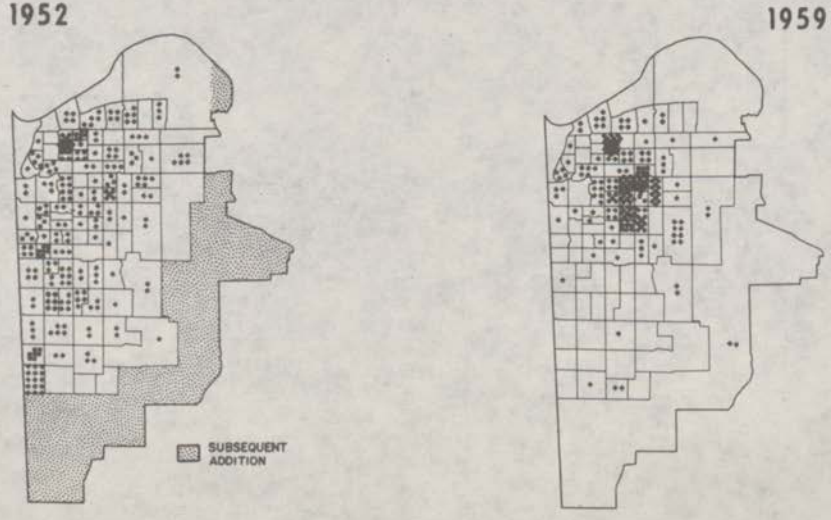
## PARALYTIC POLIOMYELITIS - 1960



# LOCATION OF REPORTED POLIOMYELITIS CASES FOR EPIDEMIC YEARS 1952 AND 1956 CHICAGO and COOK COUNTY, ILLINOIS

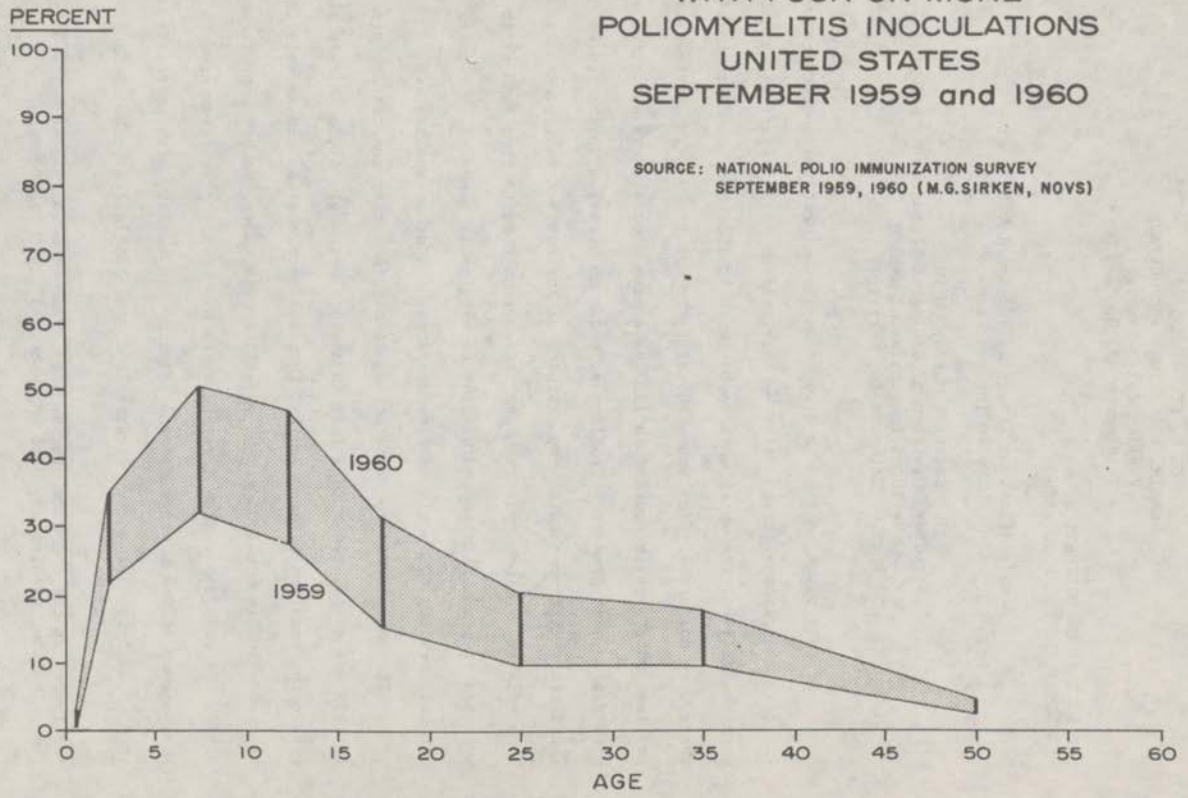


# LOCATION OF REPORTED POLIOMYELITIS CASES FOR EPIDEMIC YEARS 1952 AND 1959 KANSAS CITY, MISSOURI



## PERCENT, BY AGE, OF THE POPULATION WITH FOUR OR MORE POLIOMYELITIS INOCULATIONS UNITED STATES SEPTEMBER 1959 and 1960

SOURCE: NATIONAL POLIO IMMUNIZATION SURVEY
SEPTEMBER 1959, 1960 (M.G.SIRKEN, NOVS)



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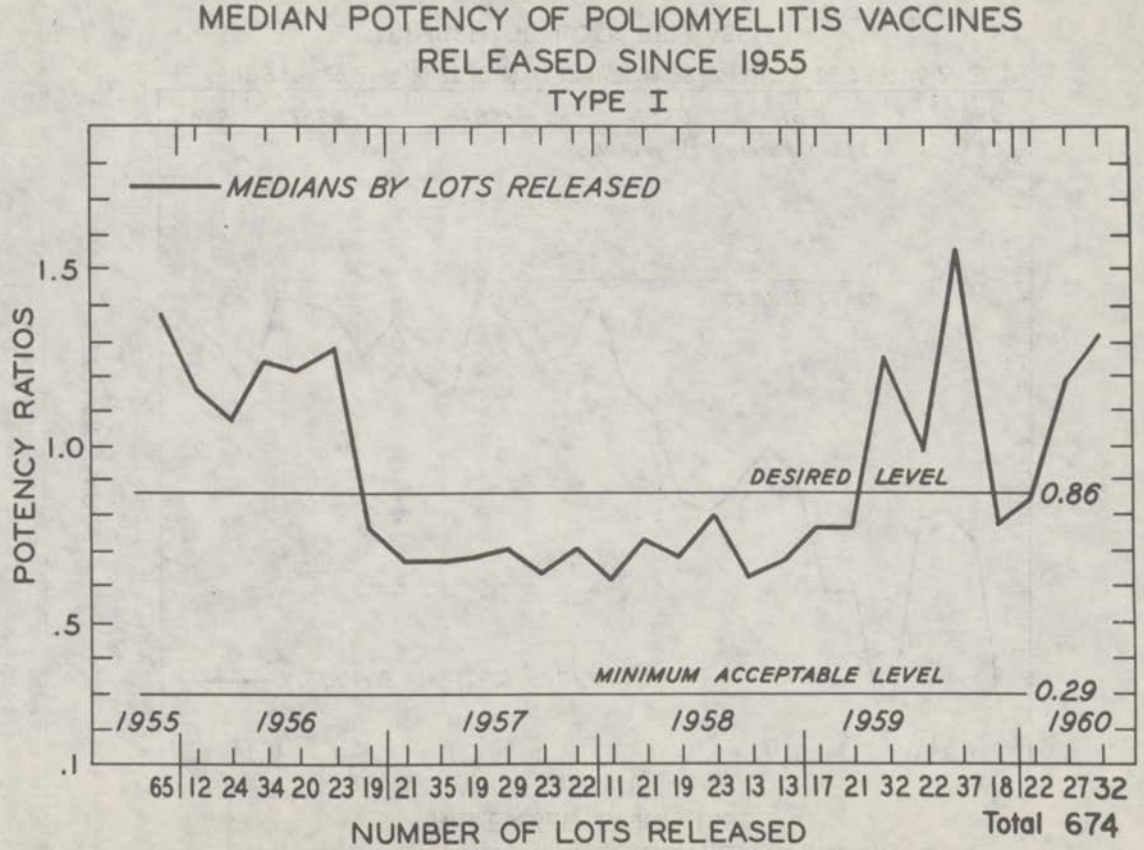
# Standardization, Licensing and Availability of Live Poliovirus Vaccine*

by
Roderick Murray, M. D.
Director, Division of Biologics Standards
National Institutes of Health
Bethesda 14, Maryland

At this point in time, a discussion of the problems encountered with inactivated poliomyelitis vaccine -- Salk vaccine -- is relatively simple. Once the difficulties which were encountered in 1955 had been surmounted, there were no further problems with safety in the field. The revised safety testing procedures introduced in 1955 have been consistently effective in providing a safe product. Problems do occur on occasion in the course of manufacture which emphasize the validity of the revised test procedures. Some relatively minor problems have arisen from time to time such as the presence of penicillin in the vaccine as originally produced, but it is now possible readily to obtain vaccine prepared with other antibiotics.

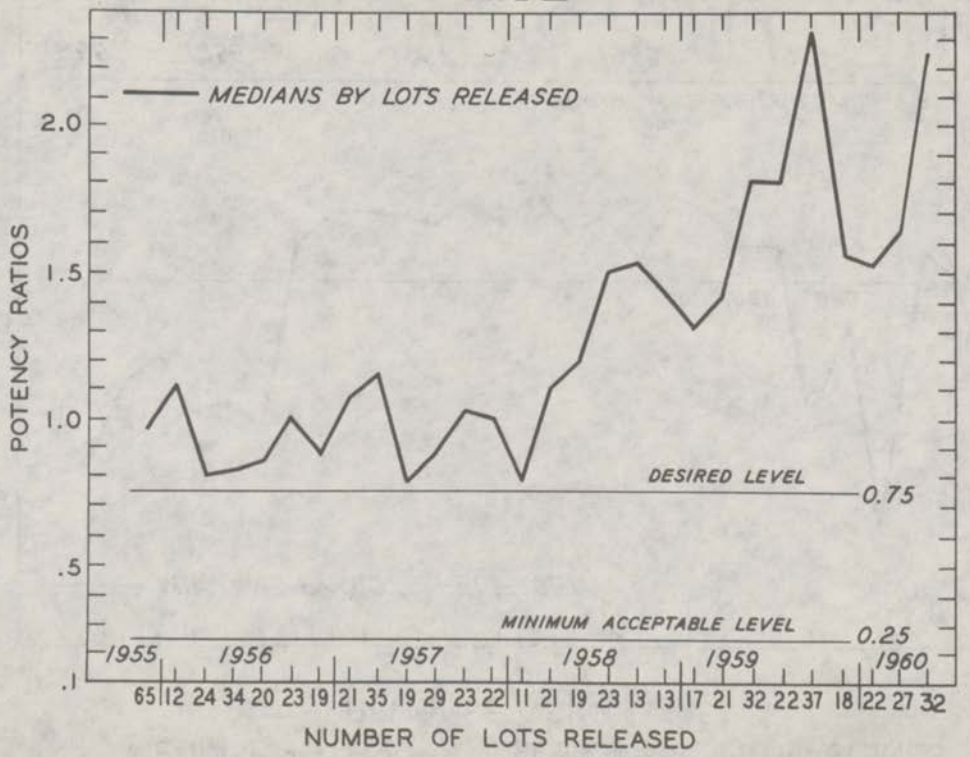
The introduction of more stringent manufacturing and testing procedures in 1955 was associated with a fall in average potency. Although remaining within the required potency limits, this was nevertheless undesirable in a vaccine which is not 100 percent effective even under the best conditions. During the past two years, however, there has been a gratifying rise in the potency of the average vaccine reaching the market, with increases of as much as 5-fold or more. Figures 1, 2, and 3 illustrate the trend of

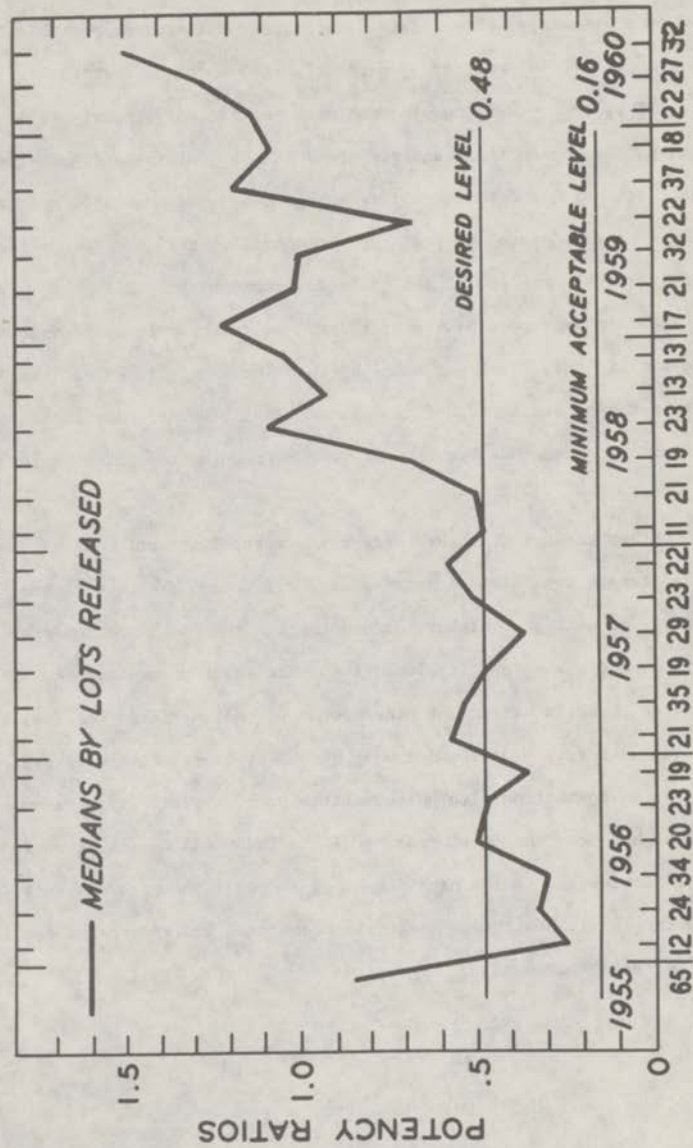
*Delivered at the AMA Midwinter Session, Symposium on Present Poliomyelitis Immunization, Washington, D. C. November 30, 1960, 12:00 Noon.


MEDIAN POTENCY OF POLIOMYELITIS VACCINES
RELEASED SINCE 1955
TYPE I
MEDIANS BY LOTS RELEASED
POTENCY RATIOS
1.5
1.0
.5
.1
DESIRED LEVEL
0.86
MINIMUM ACCEPTABLE LEVEL
0.29
1955
1956
1957
1958
1959
1960
65 12 24 34 20 23 19 21 35 19 29 23 22 11 21 19 23 13 13 17 21 32 22 37 18 22 27 32
NUMBER OF LOTS RELEASED
Total 674

MEDIAN POTENCY OF POLIOMYELITIS VACCINES
RELEASED SINCE 1955

TYPE II




MEDIAN POTENCY OF POLIOMYELITIS VACCINES
RELEASED SINCE 1955
TYPE III
MEDIANS BY LOTS RELEASED
DESIRED LEVEL 0.48
MINIMUM ACCEPTABLE LEVEL 0.16
POTENCY RATIOS
1.5
1.0
.5
0
1955
1956
1957
1958
1959
1960
65 12 24 34 20 23 19 21 35 19 29 23 22 11 21 19 23 13 13 17 21 32 22 37 18 22 27 32
NUMBER OF LOTS RELEASED

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the median potency of all lots of vaccine released up to July 1, 1960, plotted on a bimonthly basis. This upward trend has made it possible to call for a general increase of 50 percent in the level of acceptable potency. This new potency requirement will go into effect early in 1961.

A variety of multiple antigen preparations containing diphtheria, tetanus, pertussis, and poliomyelitis antigens are now available and can be readilly integrated into the pediatric immunization regime. Such products meet requirements for each of the individual components. However, a recent report indicated the possibility of lowered pertussis potency in some lots, despite satisfactory tests performed by both the manufacturer and the NIH. This has not been confirmed and the matter is at present under laboratory investigation. There has been no question concerning the potency of the poliomyelitis components.

Another product which has recently attracted attention is a purified preparation. The advantages of purification are obvious and the possibility of achieving higher potency through the concentration step used for such preparations is attractive. The potency requirements are the same as those in effect for other forms of poliomyelitis vaccine.

The successful solution of many of the problems which have presented themselves in connection with poliomyelitis vaccine since it appeared on the market has been due to the advice of the Technical Committee on Poliomyelitis Vaccine and to the high degree of cooperation which has existed between the Public Health Service, this Committee, and the pharmaceutical manufacturers involved.

Live Poliovirus Vaccine:

Live poliomyelitis vaccine has been one of the most exhaustively discussed products ever to enter into the realm of specific prophylaxis. A number of international and other meetings have been convened to consider the data as they have developed.* The proceedings of many of these meetings have now been published (1,2, 3) and form the definitive information on which our present views of this product can be based. Regretably, copies of many of these documents are scarce.

The Public Health Service early anticipated the delay in general availability of the vaccine which would occur if regulations relating to manufacture and testing were not in existence by the time manufacturers might apply for licenses under the provisions of the Public Health Service Act. Consequently, those of us who are responsible for licensure have tried to keep current on all available laboratory and field information. This has been done through the activities of the Public Health Service Committee on Live Poliovirus Vaccine. Numerous meetings have been held with interested parties and, thanks to the excellent cooperation of investigators and potential manufacturers, all have been kept informed of the result of important studies even before they were published.

The Committee has prepared a number of reports. The latest one (4), released on August 24, is a summary of recommendations based upon the field and laboratory experience with the Koprowski, Lederle, and Sabin

*1. First International Conference on Live Poliovirus Vaccine, Washington, D.C. June 1959
2. 1960 Symposium on Polio Vaccines, Newark, N.J., April 20, 1960
3. Soviet-American Meeting, Moscow, May 1960
4. Soviet 4th International Scientific Conference on Poliomyelitis, Moscow, May 1960
5. Second International Conference on Live Poliovirus Vaccines, Washington, D. C., June 1960
6. 5th International Poliomyelitis Conference, Copenhagen, July 1960

sets of strains. The Committee recommended the use of the Sabin Type 1, 2 and 3 strains but noted that the Type 3 strain had some unfavorable features and that a search for a superior Type 3 strain should be continued.* It also recommended that the Sabin Type 1 strain be used as a reference in the conduct of the neurovirulence tests. In addition, the Committee expressed the view that the use of live poliovirus vaccine was more appropriate on a community than on an individual basis. This, of course, alludes to some special features of live poliovirus vaccine: the fact that it is an oral vaccine; the ease of use on a large scale, that there is the possibility of interference by other enteroviruses and even by vaccine strains used in other persons; that immunologic and epidemiologic surveillance needs to be maintained; and that the vaccine must be used quickly once it is thawed. The proposal for community-wide use also reflects the manner in which the vaccine had been most successfully used in the field. The Committee did not mean to imply that they considered it dangerous to use the vaccine on an individual basis.**

Concurrently with the August 24 report and looking forward to the eventual licensing of oral vaccine, a set of recommendations was prepared to guide prospective manufacturers. These recommendations became available on August 26 and set forth the necessary procedures, tests, etc. to be applied in the manufacture of live poliovirus vaccine. The recommendations have

*In its recommendations the Public Health Committee went a little further than the World Health Organization Expert Committee on Poliomyelitis which met in Washington on June 13 through 16, 1960. The report of the WHO Committee (5) noted that a majority considered that the Sabin Type 1 and Type 2 strains approached more closely to the optimum than did the other strains, but refrained from expressing a preference for any of the Type 3 strains available.

** This concept is also expressed in the World Health Organization Expert Committee report (5) with the words, "....All programs both within the country and even outside the borders of a particular country should be carried out on a coordinated basis."

now been incorporated into a Notice of Proposed Rule Making which appeared on page 11111 of the Federal Register of November 23, 1950, leading the way to the eventual adoption of regulations under which live poliovirus vaccine can be manufactured as a licensed product.

The problems to be faced in the production and use of a safe and effective live poliovirus vaccine cannot be covered in detail within the scope of this presentation. They fall into three general areas: (a) strain selection; (b) manufacturing problems; (c) utilization problems.

(a) STRAIN SELECTION. This is probably the most important single problem and most of the initial research was focussed upon it. Information on the following is considered to be necessary in arriving at a decision on strain selection:

(1) Low neurovirulence for monkeys.

(2) Genetic stability (or stability on human passage).

(3) Capacity to spread from vaccinated to non-vaccinated persons.

(4) Occurrence and degree of viremia.

(5) Genetic markers.

(6) Experience gained from field studies relative to safety and effectiveness of the vaccine.

Apart from their basic immunologic differences the types of poliovirus differ in other ways and play different roles in the epidemiologic and other features of poliomyelitis. This means that rigid generalizations concerning the properties listed above cannot be made on an inter-typic basis.

Low Neurovirulence. Neurovirulence for monkeys is a property which can be tested for in the laboratory and which has some correlation

with safety in man. This property formed the original basis for selection of candidate strains for initial testing. It is well recognized, with certain exceptions, that neurovirulence in man is related to neurovirulence findings in monkeys. For instance, strains which cause paralysis in man also cause paralysis in monkeys, strains which cause lesser degrees of paralysis in man are similarly less virulent for monkeys, and we now know that many strains exist which, while causing evidence of infection in monkeys, apparently cause no discernible disease in man. Thus, there is a gross correlation between neurovirulence in monkeys and neurovirulence for man. The exact relationship would be difficult to determine and, because of the danger to human beings inherent in an experimental approach to this problem, it would be an improper line of investigation. It is considered, therefore, that other things being equal, we give preference to the use of strains having the lowest degree of neurovirulence for monkeys.

Genetic stability. It is theoretically desirable for all strains to be genetically stable. However, all the strains which have been studied have shown lack of stability of varying degree. But there has been no indication in the field experience that this degree of genetic instability has been of significance to recipients of the vaccine and to their contacts.

Capacity to spread. All of the strains studied exhibited this property to some degree; however, capacity to spread appears to be less than that of wild strains of poliovirus and, except for some reports of institutional spread, all of the vaccine strains were limited in their capacity to spread.

Occurrence and degree of viremia. This property was inadequately studied prior to the conduct of the large scale field trials. The information

now available, while still incomplete, indicates that some viremia is encountered in the case of the Lederle Type 1 and Type 3 strains as well as with the Sabin Type 2 strain. It has not been encountered with the Sabin Type 1 or Type 3 strains. It should be remembered that our ability to detect viremia depends to some extent on the sensitivity of the tests used. In the case of the Sabin Type 1 and Type 3 strains, where this property would be the most critical, viremia has not been encountered and the neurovirulence characteristics of these strains are also low. The Sabin Type 2 strain, although it does result in some viremia, has a low neurovirulence and other properties which leads us to conclude that this strain is suitable for use and does not present any hazard.

Genetic markers. The so-called genetic markers are of importance in assuring that the virus in the vaccine has not undergone any otherwise undetectable changes during the course of manufacture and that wild strains have not been inadvertently introduced.

Field experience. The ultimate assessment of the vaccine is in the field and this experience provides the information which makes it possible to accept the general use of oral vaccines with confidence. Since it is not possible to select strains which all show equally favorable properties there must be clear cut evidence of safety and effectiveness as demonstrated in man. Satisfactory experience with 100,000 susceptibles has been recommended as evidence of safety and a high level of antibody conversion (90 percent or better) as evidence of effectiveness.

Live poliovirus vaccine has been little used in the United States. The degree of use of killed vaccine presented a situation that was not

ideal for studying the live vaccine, which in one form or another has been widely studied in some areas of the world and widely used in others. The report of the World Health Organization Expert Committee on Poliomyelitis indicates that approximately 50,000,000 persons have received Sabin strains, 6,000,000 to 7,000,000 Koprowski strains, and approximately 2,000,000 the Lederle strains. Recent information indicates that as of November 1 a total of 236,000,000 doses prepared from Sabin strains have been given to some 74,000,000 persons in the U.S.S.R. with reported success even though the testing and manufacturing requirements are less rigid than those proposed for vaccine to be manufactured in the U.S.A.

I have dwelt on the problems of strain selection because of their great importance. Now let me mention briefly the other two general types of problems that must be solved:

(b) MANUFACTURING PROBLEMS. These relate to the preparation of a safe and effective vaccine from the selected strains. Involved here are the difficulties encountered with adventitious agents derived from the monkey kidney cell cultures. These agents can multiply in the tissue culture cells during the growth phase of the live poliovirus. Most of these agents are viruses, many of which are unidentified and whose properties are not known. Detecting such agents, preventing accidental contamination with other viruses including wild poliovirus strains, and retaining strain properties are only a few of the difficult tasks that confront the manufacturers. To prevent changes in the strain properties they must use a rigid seed virus system and study virus markers; and finally, they must demonstrate that they can consistently produce a series of satisfactory lots of vaccine.

(c) UTILIZATION PROBLEMS. This includes such matters as dosage of the vaccine and the conditions encountered in local and regional situations, epidemic use, etc. which Dr. Langmuir will discuss in greater detail.

## Conclusions

It would be fair to say that the results of laboratory and field studies to date have now established the validity of live poliovirus vaccine as a principle. Actually this was predictable because of the similarity between live poliovirus vaccine and the mode of natural acquisition of immunity against poliomyelitis. The main difference being, of course, that with live poliovirus vaccine the process can be kept under control and carried out with strains possessing known properties. Requirements for such vaccines have now been developed but at the present time there are no license applications pending, nor are we in a position to predict the availability of vaccine beyond the general statement on the subject being made here today by Dr. Burney.

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# Epidemiological Considerations*

by
Dr. A. D. Langmuir
Chief, Epidemiology Branch
Communicable Disease Center
Atlanta, Georgia

Five and one-half years ago, when the Salk vaccine first became available, some epidemiologists, including the present speaker, were hopeful that the disease could rapidly be eradicated. Since that time, its incidence has declined due in large measure to the use of this vaccine. But polio seems far from being eradicated. The dreamed-for goal has not been achieved. In fact many students of the problem question that eradication of poliomyelitis infection with inactivated vaccine is a scientifically tenable concept.

Soon a basically new type of poliovirus immunization, the oral vaccine, will be entering the picture. Dr. Albert B. Sabin, one of the developers of an oral vaccine, is now calling for the eradication of poliomyelitis, arguing that the oral vaccine makes this scientifically possible. It is pertinent, therefore, at this symposium to review the experience of the past five and one-half years, both from the practical and the scientific points of view. It may be worthwhile to examine the

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reason for the failure of the first prediction and to accept the possibility of achieving the ideal goal that has been set for us.

Is it possible to eradicate poliomyelitis through the use of either Salk-type or oral vaccine or of some appropriate combination of both? Can we define the conditions that must be met to achieve this goal?

From the practical point of view, it is obvious that the optimists for eradication in 1955 made a basic miscalculation. They overestimated the degree of popular acceptance of the killed vaccine. In the first place, they certainly did not anticipate the tragic episode in which a number of children contracted polio after vaccination. There followed long delays in production and distribution while the problems of safety and availability were worked out. While these problems have now been solved with new and improved products, it is probable that some of the disturbing effects of this episode are still being felt in some parts of the country among some population groups. The most serious of these effects, of course, is the reluctance to accept immunization.

Whatever the reasons, it is evident that an overestimate of potential vaccine acceptance was made. Large parts of the population still remain unimmunized or only partially protected in spite of unprecedented national publicity and large Federal subsidies at the initiation of the program. As Dr. Alexander has emphasized, less than 32% of the population under 40 years of age has yet received the recommended full course of three doses plus the booster. More

significant is the fact that immunization acceptance has been far from uniform. Large "islands" of poorly vaccinated population groups exist--in our city slums, in isolated and ethnically distinct communities, and in many rural areas. To an increasing degree, as Dr. Alexander has shown, epidemics and outbreaks of poliomyelitis are becoming limited to these groups.

Whatever the reasons for non-acceptance of the present vaccine we, in the medical and health professions, have failed to reach these groups with an effective educational appeal supported by the necessary community-wide organization.

From the theoretical point of view, those who hoped for eradication of poliomyelitis with the Salk vaccine were not aware of its limited capacity to prevent infection of the alimentary tract. While the scientific evidence remains controversial, there is a substantial amount of data to show that this vaccine produces only serological immunity. Thus, although it prevents paralysis, it may not influence the capacity to spread the infection.

The epidemiological evidence, on the other hand, leads to a different conclusion. The increasing trend for poliomyelitis outbreaks to be confined to selective and isolated groups of poorly vaccinated persons without spreading to contiguous areas where vaccination levels are higher is believed by some epidemiologists to indicate a rather marked effect of Salk-type vaccinations on limiting community spread of wild virus.

Thus some scientists believe that the Salk vaccine cannot achieve eradication and that to eliminate the paralytic form of the disease essentially 100% of the population must be fully immunized. Other scientists believe that a somewhat lower immunization level would be sufficient to break the chain of infection. Whichever group is correct, it is certain that the present levels of immunization are too low and too nonuniform to expect the elimination of the disease.

When a new oral vaccine becomes available, both scientific and practical administrative considerations will clearly enter into their effective use. These oral vaccines have several obvious advantages over the inactivated vaccine. They can be given by mouth in a sweet syrup or candy form thus obviating the unpleasant and awkward hypodermic syringe. They can bring substantial alimentary tract immunity as well as circulating antibodies and thus should prevent natural reinfection and spread and the vaccine viruses may spread to siblings, parents and others in close association with the vaccinated person, thus conferring additional immunity within the group.

Oral vaccines, however, have the same basic limitations of the present Salk-type vaccine; namely the need for repeated doses. According to Dr. Sabin's recommendations, supported by many others, the oral vaccine must be fed as a monovalent antigen at intervals of at least six weeks. It also seems best to start at about three months of age. It may be desirable, moreover, to feed a final dose of triple vaccine at about one year of age, or about six months after the three monovalent feedings,

in order to correct any failures of one of the preceding doses to take. The much hoped-for single dose of trivalent vaccine, in brief, has not materialized.

Thus, regardless of the many advantages of the oral vaccine, a systematic series of immunizations according to an orderly schedule remains a basic requirement.

Four general methods have been proposed for use of the oral vaccine which are under study. These are: (1) community-wide immunization; (2) selected area immunization; (3) infant immunization; (4) epidemic control. The relative merits and some of the problems which can be anticipated with each of these uses will be discussed.

Community-wide immunization suggests a popular and glamorous form of use. Community immunization with vaccines has been used in the Soviet Union and in neighboring countries in probably 100 million persons. It has been reported to be highly successful. This form of use has also been applied in certain countries and selected areas of other countries in Central and South America. Reports from these countries reveal varying success.

In this country, oral vaccines have been used on a community-wide basis in Miami and with certain age groups in Cincinnati, Rochester and Ithaca. Placebo control field trials have also been undertaken in Several communities in Minnesota. The success of these American trials has still to be evaluated.

The application of this method of use in the Soviet Union is understandable. Russia has in recent years been experiencing increasing

incidence of poliomyelitis in an essentially unimmunized population and the mass use had the obvious advantage of being the easiest way to immunize these populations. An essential feature of the Russian plan includes a comprehensive program for the immunization of all infants beginning at three months of age. This plan involves a course of six feedings, first of monovalent vaccine, followed later by multivalent combination of types.

In Nicaragua in 1958, oral vaccines were used during and after an epidemic of Type II poliomyelitis. While a systematic plan for the continuing immunization of infants was developed, it was not fully successful in execution. In the late months of 1959 and early months of 1960, only 1 and 1/2 years later, a moderately severe epidemic of Type I poliomyelitis occurred. The cases appeared largely in children who had not received the oral vaccine at the time of the previous epidemic or who had been born subsequent to it and had not been vaccinated. Thus, while the vaccine undoubtedly conferred immunity on the recipient, the program as carried out equally clearly failed to eradicate the disease from the country. In other countries where mass programs have been conducted, such as Costa Rica, a continuing incidence of cases is still being reported.

In the United States, the community-wide programs that have been conducted have met with varying community responses. In Miami, it is estimated that approximately 80% of the population from infancy to 40 years of age responded. In this program only a single doses of triple vaccine was tried. The proponents of the program admit that it would be extremely difficult to achieve equally great responses to a second or third course of feeding. Further study is needed of the residual groups

that failed to respond in the community-wide program. It may be confidently expected that many of the nonresponders consist of those who had not accepted the Salk-type vaccine; whereas the most response will likely be found among those with the highest levels of past immunization.

Thus, the indications for community-wide use need the most careful consideration. Such programs would be of value only when it would be possible to assure essentially complete response for three properly spaced doses from the population age group designated in the program. Furthermore, no such program should be contemplated, in my opinion, until an adequate plan to insure the complete immunization of all newborn infants within their first year of life has been organized on a continuing basis. Few, if any communities in the United States, have such an organization now. To undertake a community-wide program without a continuing infancy program is to invite a repetition of the Nicaragua experience.

Selected area immunization as distinct from community-wide immunization would seem to have many applications in this country. It should be possible by simple advanced planning, including prior sample surveys and analysis of past poliomyelitis incidence, to delineate the areas needing special attention. Immunization campaigns with oral vaccine could be concentrated in select areas on a precinct, block, or even house-to-house basis. Each campaign could be adapted to the particular interests and special cultural pattern of the selected area. Each single campaign would provide useful experience in developing the program. While lacking in popular glamour, such campaigns should become eventual valuable adjuncts to the total community program of poliomyelitis control. I should make

I should make very clear in presenting these observations on community-wide or selected area immunization that no decision has been reached on any of these patterns. The Surgeon General's Committee on Poliomyelitis Control will consider these and other matters and make their recommendations to the Surgeon General.

Infant immunization should be recognized as the primary necessity of any program for the eradication or even for the effective control of poliomyelitis. With the peak incidence of paralytic poliomyelitis now falling within the 1-2 year age group, it is obvious that the immunization program must reach a high proportion of infants. Those newborns whose parents seek regular pediatric supervision will be adequately protected on schedule. So will many of the infants coming within the sphere of well-baby conferences and health department clinics. The children falling between these two types of services will suffer. To reach them will require well-planned community organization. From my experience I believe that an individual record based on the birth certificate, with appropriate follow-up, will be necessary.

Epidemic control also may become one of the valuable uses of the oral vaccines. They possess certain characteristics that are uniquely applicable to such use. Ease of administration, rapidity of the antibody response after feeding, and a potentially ready acceptance by the public--all favor the oral vaccines for epidemic control.

In this country in recent years the surveillance of epidemics has been intensified. Most of them have been promptly recognized at their outset. Typing of the causative strains of poliovirus, in particular, has usually been prompt.

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If a practical control measure with a prompt reaction, such as the oral vaccines were known to be available, future epidemics should be identified even more rapidly. Each first case of poliomyelitis disease in any community indicates that the virus is already quite widely spread. The first case should call for an alert. Subsequent cases should stimulate prompt action. To achieve full potential value of all vaccines for epidemic control will require an intensified surveillance of all cases of poliomyelitis and of the polio-like diseases throughout the country. Prompt and reliable virus diagnostic services mustbe generally available. An adequate epidemic reserve of all vaccine that could be made immediately available as soon as the indications were recognized would facilitate the most effective epidemic control.

In the immediate future, before the oral vaccines become available, what should the program be? The answer is obvious. Salk-type vaccines are now available. They are of proved potency. They should be used extensively. No one who has not yet been immunized should wait for the oral vaccine. Anyone who is only partially immunized should be urged to complete his series, including the fourth or booster dose. Most of the cases of poliomyelitis that will occur between now and the time that oral vaccines become available will arrive in this unimmunized or incompletely immunized group. There is no basis for delay.

Finally, in the period after oral vaccines become available will there be a sound basis for the use of the Salk-type vaccines? The answer, in my opinion, is "yes." The two types of vaccine will be in fair competition. Many physicians and health officers may choose to convert to the new product

because of its many apparent advantages. Others may continue to be satisfied with their experience with the Salk-type vaccine and with its incorporation in a systematic immunization schedule with the quadruple antigens. They may wish to watch and wait a little while for more experience to accumulate. It is difficult to predict how the two products will prosper. New developments in vaccine and as yet unanticipated events in the epidemiology of poliomyelitis may still occur. It is possible that the long hoped-for single dose of vaccine, whether it be inactivated or a live, attenuated virus, when it is developed and shown to confer solid immunity, will become the procedure of choice sometime in the future.

One thing is certain; namely that the availability of the oral vaccine in and of itself will not result in the eradication of poliomyelitis. Careful planning and sound community organization will be necessary to achieve the goal of eradication that Dr. Sabin has called for. This will call for a more comprehensive effort than has yet been applied to the use of the Salk-type vaccine during the past five and one-half years.

U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
Washington 25, D.C.

FOR RELEASE ON DELIVERY
WEDNESDAY, NOVEMBER 30, 1960

Summary Statement*
by
Dr. Leroy E. Burney
Surgeon General

It is clear from the evidence presented in the papers by Drs. Alexander, Murray and Langmuir that, with improved methods of potency, we have in the Salk vaccine a preventive for poliomyelitis with an established efficacy of between 90 and 95 percent when the full course is administered.

It is equally clear that large numbers of the U. S. population have not taken advantage of the vaccine. With almost one-half of the children under five not yet fully vaccinated, it is apparent that ways and means must be found to carry forward the fight against polio with the means that we already have at hand. The prospect of an oral vaccine, however promising, should not in any way deflect us from this course.

In reviewing for you the field trials with the oral vaccine, both in the United States and abroad, our purpose has been to bring you as fully up to date as possible. As Dr. Murray and Dr. Langmuir have indicated, the Service has exerted every effort to keep abreast of this wealth of information on the new vaccine as it has developed.

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For presentation at the A.M.A. Mid-Winter Clinical Sessions, Washington, D.C., November 30, 1960

Last August, our Advisory Committee on Live Poliomyelitis Vaccine reached the conclusion that the information thus far developed demonstrated that a live, attenuated, orally administered vaccine was suitable for use in the United States and recommended the Sabin strain.

The Committee recognized at that time that there are still many problems to be worked out in taking production out of the laboratory and into mass production. This was true of the Salk vaccine and is certainly no less true of the oral vaccine. These problems have been by no means resolved. In fact, based on the latest information provided informally by prospective manufacturers, it is our judgment at the present time that we cannot expect to have an oral vaccine for use by this summer.

With large quantities of the Salk vaccine available, it is evident that if we are to pursue our common goal of stamping out poliomyelitis in America, we must exert an even greater effort than in the past. For the possibility of a new vaccine will further encourage procrastination, either by individuals or by communities. I would urge that your association and you as individuals begin planning now for mid-winter campaigns with the Salk vaccine. In this you will have the active support, through the Advertising Council and other means, of the Public Health Service.

In the meantime, the Public Health Service proposes to continue in the effort, already launched, to be in as complete a state of readiness as possible when the oral vaccine becomes available for use.

Toward the end of last September I announced the formation of a Committee on Poliomyelitis Control, made up of members of the medical and

health professions and of representatives of the general public. Its function is to aid the Service and me in reaching decisions on how best to carry forward the fight against polio with both the Salk vaccine and the oral vaccine when it becomes available.

The problems of integrating this potential new agent into the present pattern of immunization against polio are many and complex. They are, as you have seen, both technical and administrative.

In preparation for the first meeting of this Committee, scheduled for mid-January, four subcommittees are now at work. They are:

1. A subcommittee on primary immunization with oral vaccines, with responsibility for considering primary immunization, the choice of type for initial dose, number, spacing, season limitations, contraindications, and other safeguards.
2. A subcommittee on the use of formalin-inactivated vaccines to consider, the most desirable age to start immunization, the number and spacing of subsequent doses and boosters, the use of purified and quadruple antigens, contraindications, and possible combined use with oral vaccines.
3. A subcommittee on epidemic measures and possible community-wide use of the oral vaccine to study its possible intensive use in selected population groups, the duration of time for which such programs might continue, seasonal limitations, and so on.

4. A subcommittee on community organization for control to study and recommend steps which might be taken, through the use of both a live and a killed vaccine, to finish the job of eliminating polio from the country. Reporting, surveillance, laboratory diagnosis, long term care, and other, similar questions are also being considered by this group.

The task of these subcommittees is a difficult one. We have every confidence, however, that they will develop sound staff papers upon which the Committee on Poliomyelitis Control can base its own recommendations to the Public Health Service.

To sum up then: only the future can tell whether control of poliomyelitis will be accomplished through a live, orally administered vaccine, the killed vaccine, or a combination of both. The Salk vaccine has proved to be an effective prophylactic in our fight against polio. It is now available either as a polio vaccine or incorporated in multiple antigens.

Even the advent of an effective oral vaccine--which now seems indicated in the months ahead--will not remove the necessity for persistent and painstaking efforts in the years ahead to raise the immune status of our population. In fact, the need may be even greater since the possible wide-spread use of an oral vaccine will tend to suppress circulating viruses. If the immune status of the population is not maintained at a high level, large numbers of persons will become vulnerable. The introduction of wild viruses into the community or the exposure of susceptible persons to poliomyelitis while travelling in areas of the world where the disease is endemic could defeat our best efforts.

Our present position as physicians and health officers can be easily summed up. It is, in my opinion, our clear and unmistakable duty:

1. To press for regular, routine immunization of infants and the very young against polio.

2. To search out those groups and individuals in the community, particularly in the lower socio-economic groups, who have not been vaccinated and bring the protection of the vaccine to them.

3. To plan now for the advent of the new vaccine and be ready to use it when it appears.

Cooperation in the fight against polio has been generously evident in the past. I am sure that it will be generously offered once more.

Subcommittee Reports prepared by The Agenda Committee

for the meeting of the

COMMITTEE ON POLIOMYELITIS CONTROL

January 23-24, 1961
Atlanta, Georgia

I. Subcommittee One - Primary Immunization with Oral Vaccines
-Dr. John R. Paul, Chairman-

II. Subcommittee Two - Use of Formalin-Inactivated Vaccines
-Dr. David Bodian, Chairman-

III. Subcommittee Three - Mass Use and Epidemic Measures
-Dr. John P. Fox, Chairman-

IV. Subcommittee Four - Community Organization for Poliomyelitis Control
-Dr. C. A. Smith, Chairman-

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Communicable Disease Center
Atlanta, Georgia

## I. SUBCOMMITTEE ONE: Primary Immunization with Oral Vaccines

General Considerations - The Committee believes that the oral poliovirus vaccine will be used in the immediately ensuing years either on a simultaneous community-wide basis and/or according to other schedules. Until such time as sufficient live poliovirus vaccine is available for general use, however, every effort should be made to utilize the presently available Salk-type vaccine.

It is recommended that the oral poliovirus vaccine shall not be administered without adequate medical supervision. Both medical and public health supervision and surveillance are essential.

### 1. Procedures for the Administration of the Oral Vaccine*

Oral vaccine is recommended for all individuals six weeks of age and over (special recommendations for the newborn are given in a separate section - see below). Those who have had previous inoculations of the Salk-type vaccine should also receive the oral preparation. Not only will this fortify their own immunity, but also it will enhance intestinal resistance to infection, which is of value in limiting the dissemination of wild polioviruses and hence in the ultimate protection of unvaccinated susceptible persons in the community.

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* This refers to the vaccine containing the attenuated strains of poliovirus developed by Dr. A. B. Sabin.

Immunization with oral poliovirus vaccine should be carried out in the United States preferably between the months of November and June. The three types of virus are to be administered separately, in monovalent form, in the sequential order of: Types I, III and II, given at intervals of not less than six weeks. The recommended dose is 500,000 plaque forming units (p.f.u.) of each type.

Schedule:

| | Vaccine Type | Interval | Dose |
|---|---|---|---|
| 1st Dose | Monovalent Type I | | 500,000 p.f.u. |
| 2nd Dose | Monovalent Type III | 6 weeks | 500,000 p.f.u. |
| 3rd Dose | Monovalent Type II | 6 weeks | 500,000 p.f.u. |

There is no indication that further immunization with either the oral vaccine or Salk-type vaccine will be necessary, although experience in the duration of immunity produced by this oral vaccine alone is at present limited to 2 years. However, with other attenuated strains antibodies have been found to persist for at least 7 to 10 years.

2. Special Program for the Newborn*

It is recommended that all newborn children be given monovalent Type I oral poliovirus vaccine within the first three days of life regardless of the season of the year; and it is proposed that a record of this neonatal immunization be entered on the birth certificate. The presently available data indicate that a dose containing five million p.f.u. is desirable at this early age.

The first three days of life are not optimum for immunization, but by using an increased dosage it is possible to obtain approximately 85% effectiveness. The recommendation for neonatal vaccination is made because the maximum number of children can be reached in this manner. If after discharge from the hospital they are lost to follow-up, at least they will have been immunized against Type I which is the type of poliovirus causing by far the greatest number of cases of paralytic poliomyelitis.

The proposed neonatal dose of Type I vaccine is not intended to replace the regular vaccination schedule which should begin six weeks later

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* This section applies to all infants born either after or in the absence of a simultaneous, community-wide oral vaccination campaign. The community-wide program should include all recently born infants not still in the hospital. Those newborn infants in the hospital as the program begins and those born subsequently should be immunized according to the schedule in Section 2 without regard to the current stage of the community-wide program. This conforms with recommendations made by Committee Three.

(see schedule below). Thus it is imperative that the neonatal dose should be followed by the administration of all three types of oral poliovirus vaccine, given in monovalent form, starting again with Type I at six weeks of age and following with Types III and II at intervals of not less than six weeks. Each dose of this series should contain 500,000 p.f.u. Finally at the age of 10 to 12 months, trivalent oral vaccine, in a dose containing 500,000 p.f.u. of each of the three types should be given to cover some of the failures that might occur, particularly when the monovalent vaccine has been given during the summer period of high frequency of infection with interfering intestinal viruses.

The following is a schedule which has been selected to fit in with usual current practices in the immunization of infants with a number of other antigens with which the oral vaccine may be coincidently administered.

Schedule for the Newborn:

| | Age | | Dose |
|---|---|---|---|
| Monovalent Type I | 0 - 3 | days | 5,000,000 p.f.u. |
| Monovalent Type I | 6 | weeks | 500,000 p.f.u. |
| Monovalent Type III | 3 | months | 500,000 p.f.u. |
| Monovalent Type II | 4 1/2 | months | 500,000 p.f.u. |
| Trivalent Type I, II & III | 10 - 12 | months | 500,000 p.f.u. of each type |

This schedule is designed to facilitate the replacing of Salk-type vaccine by oral vaccine along with the usual program of infant immunization. It is anticipated that an infant thus vaccinated would not require the Salk-type vaccine against poliomyelitis.

3. Consideration of the Stability of the Vaccine and Vehicles Recommended for Administration

A. Stability. The undiluted vaccine is stable at -20°C. for three years or longer. Repeated freezing and thawing is not deleterious. Vaccine diluted 1:10 in buffered salt solution for addition to the vehicle can be kept in an ordinary refrigerator (+4°C.) for at least a week and need not be refrigerated during the period of actual administration. Stability of the vaccine in candy form (prepared according to a process to be published shortly) is very good.

B. Vehicles. Vehicles whose effect on the vaccine viruses is unknown should not be used. Pure sugar in many forms has no deleterious effect; simple syrup U.S.P., or ordinary granulated or lump sugar, to which a measured amount of the diluted vaccine is added in the form of drops immediately before administration, can be used. For all persons, except infants, vaccine incorporated in candy provides the simplest method of administration.

4. Possible Contraindications to Oral Vaccination

A. Tonsillectomy. There is no evidence to date that removal of

tonsils at about the time of oral vaccination has had any deleterious effect. However, it is recommended that the oral vaccine be withheld (i.e., postponed) in persons who have undergone tonsillectomy within a two-week period, and in those on whom tonsillectomy will be performed in the two weeks following oral vaccination. There is evidence that tooth extractions and other oral surgery are not contraindications to oral vaccination.

B. Pregnancy. Live poliovirus vaccine has been given to several hundred pregnant women, and thousands of others have been exposed to orally vaccinated children. Harmful effects to mother or fetus have not been observed so far.

C. Penicillin hypersensitivity. The amount of penicillin in a dose of oral vaccine is so small that penicillin hypersensitivity is not a contraindication.

D. Therapy with steroids. There is no evidence from large field trials that oral vaccine, given to persons receiving steroids or to those on chemotherapy for malignant disease, is followed by any ill effects. In the light of present evidence, therapy with such agents is therefore not a contraindication to oral vaccination.

E. Acute illness. Oral vaccination should be delayed in persons with obvious acute illness except for those with minor respiratory infections. The purpose of this recommendation is to minimize the possibility of erroneously attributing naturally occurring poliomyelitis to oral vaccine.

F. The following were considered and classified as not being contraindications to oral vaccination:

Prematurity

Agammaglobulinemia

DPT inoculation

Smallpox vaccination

Chronic illness

5. Seasonal Limitations and Geographic Considerations

Mention has been made that in the United States the optimal time for the administration of the oral vaccine is from November 1 until May 31. For the southern tier of States, in which the poliomyelitis season as well as the season for other enterovirus infections has been recognized as starting prior to June 1, a shorter period is preferable, i.e., November 1 to March 31.

## ADDENDUM

a) Legal implications: Matters of this nature were not listed in the assignment for this Subcommittee. However, it is proposed that legal opinions be sought from appropriate sources. Such opinions should consider: the liability of the manufacturer of the vaccine, of the public health agency or agencies promoting its use, and of the physician supervising the actual administration of the oral vaccine for incidents attributed properly or by implication to the vaccine.

This suggestion is made not for the purpose of anticipating any special trouble but rather as a safeguard to indicate that such matters have not been completely overlooked.

b) Special fields for study: It is recommended that during those field trials with oral vaccines currently (1960-1961) being conducted in this country, special observations be made which bear on any possible or theoretical contraindication to the use of the oral vaccines. Particular attention might be directed to problems relative to tonsillectomy, to steroid therapy, and to pregnancy in the vaccinees or their contacts.

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## II. SUBCOMMITTEE TWO: Use of Formalin-Inactivated Vaccines

The evidence at hand has confirmed a high degree of efficacy of killed virus vaccine, exceeding 90 percent in individuals receiving four doses, under various conditions analyzed as part of the National Poliomyelitis Surveillance Program. There is no doubt that adequate utilization of killed virus vaccine in the recommended dosage would of itself eliminate local epidemics in the United States by the summer of 1961. Since this vaccine is the only one that is likely to be available in 1961 for this purpose in amounts which will permit programs having any probability of fulfillment, there is an urgent need to improve its utilization beginning immediately. Although the incidence of paralytic poliomyelitis in 1960 will approximate the lowest ever recorded, it is known that large "islands" of inadequately immunized population groups still remain in many communities. It is, therefore, likely that several local epidemics, perhaps of major proportions, will occur in 1961 unless more adequate immunization is achieved.

### Recognition of Population Segments Under Risk

Summarizing the present evidence of the occurrence of paralytic poliomyelitis and the immunization status in the country, the population group which is now at greatest risk from paralytic poliomyelitis is the age group under five.

In any one community, the level of immunization for poliomyelitis in this age group will vary from neighborhood to neighborhood according to socioeconomic level. Hence, the immunization level with three or more doses in the age group under five may be 70 percent in a large community, but the level may vary from 10 percent to 90 percent within that community.

It follows, then, that a good index of the risk of an epidemic of paralytic poliomyelitis, in a given community, is the level of immunization in the group under five years of age in the lower socioeconomic neighborhoods of that community.

The Need for Local Surveys of Immune Status

Since experience in recent years has indicated that epidemics have occurred in communities where the level of immunization of the population one to five years of age has been below 85 percent, no community can feel secure with respect to the occurrence of epidemics unless it knows that its own immunization status exceeds this figure. It is recommended, therefore, that all communities conduct surveys of vaccine utilization or otherwise determine the level of immunization in this age group. A useful index for this purpose may be obtained by a survey limited to the lower socioeconomic neighborhoods. Communities which arrive at figures which indicate less than this level of immunization should take immediate and energetic steps to raise this figure first in the children below five years of age and then in

higher age groups in the entire community. Experience has further shown that special groups such as young adults, and groups recently moving into urban centers from rural areas, may not be safely ignored. Certain rural areas and crowded urban centers have been the major foci of poliomyelitis incidence since 1956, due to inadequate immunization.

Recommended Goal for Immunization Level

Vaccination programs for this age group should aim at an immunization level with three or more doses which exceeds 85 percent in the lower socioeconomic neighborhoods. This goal is essential to prevent epidemics of paralytic poliomyelitis.

Initiation and Maintenance of Immunity

The basic immunization series should consist of four doses, a second given one month after the first, the third approximately seven months later, and the fourth one year after the third. At least three doses should be administered prior to the onset of the season of epidemic prevalence; the period between the second and third dose may be shortened to one month if necessary. If immunization is to be begun before six months of age, poliomyelitis vaccine should be given either as a part of a multiple antigen or as a separate injection. In either case three initial doses shall be given one month apart followed by a fourth after seven months and a fifth one year later. In the case

of children who have completed the recommended series and received the first dose of poliomyelitis vaccine four or more years ago, an additional dose will provide supplementary protection; this is advisable especially for children on entry to school and for individuals at high risk of infection in epidemics, or preparing to travel to highly endemic areas.

Strengthening Local Immunization Programs

Each community has the responsibility for the full utilization of its own medical, public health, and lay resources to protect its people from a formerly dreaded but now preventable disease. There is, however, a need for exploration of additional sources of aid in implementing local programs for the prevention of poliomyelitis epidemics in 1961. In a country which takes pride in the voluntary approach to public health problems, there is still need for mobilization of the full resources of local medical and public health groups, the National Foundation chapters, service organizations, and Federal resources where necessary. The challenge is the elimination of all epidemics in 1961, a goal which is known to be attainable with existing tools.

Because of the unpredictability of poliomyelitis incidence in 1961 and the availability of only the killed virus vaccine as a tool for the

prevention of epidemics, the Subcommittee wishes to urge the recommendation by the Agenda Committee that the fullest publicity of the foregoing statement be permitted.

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Dr. David Bodian, Chairman
Dr. Justin M. Andrews
Dr. U. Pentti Kokko
Dr. Roderick Murray
Dr. Jonas E. Salk
Dr. Alex J. Steigman
Dr. William H. Stewart
Dr. Cecil B. Tucker

## III. SUBCOMMITTEE THREE: Mass Application and Epidemic Measures

### Preamble

Our overall goal is maximum protection of the population against poliomyelitis. Although available in adequate supply and effective, killed-virus vaccine so far has not reached substantial nonimmune segments of the U. S. population nor has it demonstrably influenced the spread of wild polioviruses.

To achieve the high level of protection that is desired, some new approach seems necessary. Such an approach may be offered by the impending availability of live virus vaccine which can be taken by mouth rather than parenterally. Evidence indicates that this new vaccine has at least two additional possible advantages over that now available. First, many of those who fail to present themselves for vaccination may develop contact-acquired infections with the progeny of the vaccine strains. While the immunity that may result is clearly advantageous, it should be recognized that the infecting progeny strains may possess greater neurovirulence than the parent vaccine strains. Second, and of greater importance, the new vaccine is expected to induce not only protection against paralytic poliomyelitis but also relative protection of the alimentary tract against infection with wild strains of poliovirus. This latter protection is similar to that afforded by naturally acquired immunity and is not furnished by killed-virus

vaccine. The individual immunized with oral vaccine should no longer serve as an effective link in the natural chain of poliovirus transmission. If enough individuals are so immunized, wild virus strains may not be able to invade the community and spread. In this manner, some protection not now conferred by the killed-virus vaccine, would be afforded to remaining nonimmunes in the population.

The necessary first phase of the inauguration of the oral vaccine is an intensive effort to vaccinate all possibly susceptible persons in the population. However, success in this phase will not constitute a permanent solution to the problem. As a second phase, obviously, the initial community-wide vaccination must be followed by a systematic program of immunization of newborn infants and revaccination of those groups which surveillance, both serologic and epidemiologic, may indicate as having lowered immunity.

The key to the successful large scale use of oral polio vaccine is the active participation of the practitioners of medicine in both the planning and conducting of the program. The exact mechanisms of such a campaign would be the responsibilities not only of national authorities but also of the local communities. For guidance in planning and organizing the inaugural phase of the use of the live virus vaccine the following recommendations based on current knowledge are offered:

Maximum Immunization Defined

Paralytic polio, obviously, would no longer occur if vaccine-induced immunity could be effectively maintained in all persons lacking naturally acquired immunity. Since most persons in the U. S. older than 40 years of age possess naturally acquired immunity, maximum immunization would be achieved in essence by a program of effective vaccination that reached all persons younger than 40.

Considerations Governing Maximum Immunization with Oral Live Virus Vaccine

The currently recommended method of utilizing the new vaccine is to feed consecutively the three monovalent vaccines in approved doses at 6 week intervals in the order Type I, III and II with a concluding dose of trivalent vaccine to immunize those persons (possibly 5 percent) who fail to respond to one or another of the monovalent vaccines. Administratively, mass application would be greatly facilitated if the vaccine were made available in single dose units and in generally palatable form such as a candy ball for older children and adults, or flavored syrup for infants. Even more important for a maximum rate of community acceptance would be a reduction in number of doses which might become possible after further study of the efficacy of single or multiple doses of trivalent vaccine. Indeed, such regimens with trivalent vaccine may be advised now for the 20 to 40 year age group in which immunity to one or two types can be

presumed, or when a program must be begun shortly before or during the summer season. Whatever the regimen employed, the proportion of takes to each virus type should be determined by careful serologic sampling in order that the possible need for supplemental revaccination may be recognized.

Introduction of the oral vaccine into the community would not be best accomplished on the basis of uncoordinated and possibly sporadic vaccination of individuals by private physicians and health agencies. Such use of the vaccine would do little more for the vaccinated individual than would the killed-virus vaccine and might well fail to achieve the full community protection which constitutes the peculiar potential advantage of the live virus vaccine. To insure maximum benefit to the community with the greatest safety, oral vaccines should be used on a community-wide basis in a coordinated manner. Each stage of the vaccination program, e.g., feeding of a monovalent type or the final trivalent dose, should be accomplished within a 2-3 week period. Even the make-up clinics, which may be established to care for individuals missed in the systematic vaccination program because of absence from school, etc., should be scheduled within this period, although near the end. Such application not only would achieve more rapidly the desired results of individual immunization and interruption of circulation of wild poliovirus but also would minimize immunization failures due to interference by contact-acquired infections with heterologous strains of vaccine virus. A rapid, intense program also may reasonably be expected

to reach a greater proportion of the population than a less intense, prolonged effort. This also would tend to minimize the absolute occurrence of contact-transmitted infection which some consider to constitute a potential hazard because of the possibly increased neurovirulence of the progeny virus strains.

It should be noted that, as part of the second or maintenance phase of the vaccination program, a schedule is being proposed for the immunization of infants which includes an initial feeding of the Type I vaccine in the hospital shortly after birth.* The community-wide program recommended in the foregoing should include all recently born infants not still in the hospital. Those infants in the hospital as the program begins and those born subsequently should be vaccinated according to the schedule recommended for infant immunization and without regard to the current stage of the community-wide program.

The rapid community saturation desired necessitates intensive pre-planning and organization by State and local health departments working with the medical profession and other community agencies. To insure effective penetration of the population segments which heretofore have not accepted killed-virus vaccine, the assistance of social scientists should

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* Strong dissent noted by Dr. Hammon on the grounds that the newborn infant may have much greater susceptibility than older children and that there have been too few observations to assure safety with respect both to the vaccine virus strains and possible adventitious monkey viruses.

be sought in the planning stage, and the experiences in the several community programs already conducted in this country and others should be reviewed.

To insure proper evaluation of the results and to facilitate the subsequent maintenance program, preparations should include: 1) provision of appropriate forms for recording name, age, sex, and residence of each person vaccinated, the time and place of vaccination, and the vaccine type and lot number; 2) provision for recording vaccine distribution to clinics, physicians, pharmacies, schools, industries, etc., by amount, type, lot number, and date of distribution; 3) provisions for careful surveillance to include the discovery of all cases of suspected infectious disease involving the central nervous system, their clinical evaluation, and collection of appropriate specimens for their virologic laboratory evaluation.

The nation-wide inaugural program should be conducted and completed, if possible, in the period November through May. This is because of the greater prevalence during the summer months of infections with naturally occurring enteroviruses which may, by their interfering effect, block immunizing infection with the vaccine strains. Whenever begun, it would be desirable when possible that the vaccination program be shortly preceded by a sampling of the enterovirus flora of the community (perhaps by collecting sewage samples) to determine the relative abundance of potentially interfering viruses and to characterize by type any wild polioviruses present.

Finally, during the community program the few recognized contra-indications to vaccination of individuals should be observed. In addition, it would seem wise to desist from community programs during serious outbreaks of significant disease, e.g., influenza, the occurrence of which might complicate the problem of post-vaccination surveillance.

Use of Oral Vaccine in 1961

Current estimates suggest that no more than limited amounts of vaccine will be available before the fall of 1961. In this event, the vaccine initially available should be reserved for one or both of the following purposes.

If only very small amounts become available by summer, the vaccine should be used only in special studies and for experimental purposes. Although basic safety and efficacy of the oral vaccine have been established, some important questions remain unanswered. In particular, there should be studies of the stimulation of intestinal resistance in persons of various ages following different regimens of vaccine administration (monovalent, bivalent, and single or multiple trivalent doses) in an effort to discover a satisfactory schedule which involves fewer doses than that now recommended for community-wide programs. To this end, it is recommended that health authorities be encouraged to undertake carefully controlled community studies. Further, to assist interested communities, the consultative

services of the CDC in designing records and planning epidemiologic and laboratory surveillance should be made available.

If larger but still limited amounts of vaccine become available, these should be reserved for use in areas threatened by outbreaks (see Epidemic Measures) and, possibly, for communities known to have been poorly immunized with killed-virus vaccine.

As a general principle, to exploit to the maximum the peak public receptiveness developed in preparing for a community-wide program, it is strongly recommended that no community program be initiated until a fully adequate supply of vaccine is assured. Indeed, it may be wise to defer all community programs except those directed against threatening outbreaks until the supply is adequate to permit a nation-wide effort, since much of the necessary publicity program may be more effectively and economically conducted on a national basis.

Epidemic Measures

In the event of a community outbreak which offers a serious threat, it is recommended that the serotype of the responsible poliovirus be determined promptly and that the corresponding monovalent oral vaccine be administered immediately irrespective of the previous polio immunization status of individuals. If delay in virus typing is unavoidable, the trivalent oral vaccine should be given. To take maximum advantage of such episodes,

plans should include provisions to complete the full immunization program in the community as promptly as possible.

In anticipation of possible outbreaks, the necessary record forms (see above) should be developed and kept available. Provisions also should be made to maintain close clinical and laboratory surveillance with special attention to obtaining appropriate specimens from and clinically evaluating all patients with suspected infectious CNS disease.

Finances

It is recognized that the overall program recommended herein on a nation-wide basis would be expensive. Since success in the inaugural community-wide program requires that the vaccines be freely available, this phase must derive its basic support from public funds.* Such funds also might well be utilized to support special studies that may be initiated in certain communities in 1961.

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* Dissenting opinions:
1. Dr. Bond believes this should be fully considered before inforporating it as a recommendation.
2. Dr. Youmans feels that the concept of a category of medically indigent should be retained.

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Dr. James O. Bond
Dr. Victor J. Cabasso
Dr. William McD. Hammon
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Dr. Huntington Williams
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## IV. SUBCOMMITTEE FOUR: Community Organization for Poliomyelitis Control

To achieve the goal of the permanent elimination of paralytic poliomyelitis from the United States will require the attainment of high levels of immunity in all population segments of all communities in the country. These high levels of immunity must be maintained indefinitely. Such a goal is both worthwhile and realistic but it will require sound leadership, the full support of both official and voluntary agencies and effective continuing community organizations at all levels of government - Federal, State, and local.

Extensive programs of immunization with poliomyelitis vaccines must be organized to reach those who have not yet been adequately protected and to insure that all newborns are immunized during infancy. A regular surveillance of poliomyelitis and polio-like diseases is essential. Periodic checks on the adequacy of the immunity levels in all population groups are needed. These should consist of representative sample surveys conducted both by interview and by serological testing. Adequate provisions must also be maintained for the long term care and rehabilitation of those victims of the disease that already have developed.

### Community Organization

Responsibility for achieving and maintaining high levels of immunity

to poliomyelitis rests with each local community. State and Federal agencies can provide consultative assistance, surveillance, epidemiological, statistical, and laboratory diagnostic services and epidemic aid, but they cannot perform the actual immunizations. These must be accomplished locally.

Every local community should be encouraged to organize for this purpose. To be effective a community organization will require the full support of:

1. Official Government Agencies

   The health department should lead in the organization, but other official bodies such as the school system, welfare department, the police, etc., will be needed.

2. Professional Organizations

   The county medical society must play a leading role, but other professional groups such as the pediatricians, obstetricians, hospital administrators, nurses, and social workers will also be needed.

3. Voluntary Agencies

   The National Foundation has a logical primary interest, but the active support of many other citizen groups and lay organizations will be essential to success.

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Choice of Vaccines

Each community organization must decide the broad outlines of the immunization program most suitable to its population. Either or both the formalin-inactivated, and orally administered live attenuated, virus vaccines may be used.

At present only the formalin-inactivated vaccines are available. These are of proved effectiveness and should be used more extensively in the immediate future than they have been in the recent past. The quadruple antigen vaccines are specially suitable for use in regular pediatric immunization schedules.

The oral vaccines soon to become available offer several advantages, particularly for organized community use and for epidemic control. Both types of vaccine suffer from the practical administrative disadvantage in that multiple doses at 4 to 6 week intervals or longer are necessary to achieve adequate immunization.

It can be anticipated that honest professional judgments regarding the relative merits of the two kinds of vaccines will differ. Either or both vaccines can and undoubtedly will be used in varying preference for a number of years. Each local community organization will have to decide its own choice of vaccines and set its own program priorities.

Program Priorities

In planning its immunization programs each community will adapt its activities to its own needs, traditions, and cultural patterns. Certain general principles, however, can be outlined to assist in the decisions:

1. Infant immunization should receive first priority in all communities. A continuing program for the adequate immunization of infants is crucial to the long term elimination of paralytic poliomyelitis. All other poliomyelitis immunization programs should be coordinated with and be made subordinate to the infant immunization program.
2. Selected area immunization should be employed to achieve high levels of immunity in those "hard to reach" population groups that have responded least well to previous programs. The methods to be used in such programs should be carefully adapted to the particular circumstances and peculiar needs of each area. Taking the service to the people on a school district, precinct, block, or even door to door basis may be desirable and even necessary.
3. Community-wide immunization should be employed only when an adequate community organization has been created that will assure a high level of response from all segments of

the population for the prescribed number of doses of vaccine, and when a continuing program for effective infant immunization exists. Community-wide programs may include individuals in all age groups or an age limitation may be set such as under 40 years or under 20 or any other appropriate limit. Each community must set its own age level based upon an analysis of the age distribution of recent poliomyelitis cases in the area, knowledge of immunity and immunization status based upon appropriate surveys and many other local administrative considerations. In essentially all communities the individuals deserving higher priority, next to the infants, are the preschool children.

Epidemic Control

To achieve success epidemic control measures must be initiated promptly and be conducted on a thoroughly comprehensive scale. The prior existence of a community organization for poliomyelitis control with its continuing program of immunization is the best insurance against the occurrence of an epidemic. If an outbreak does occur, however, the community organization should facilitate the rapid action necessary to contain it.

The occurrence of even a single case of poliomyelitis in any community in the country should now be the cause for concern. A second case

calls for immediate investigation and an alert for action. Additional cases warrant institution of epidemic control measures at once.

The epidemic area or population group or groups at risk should be broadly delineated by epidemiological means. Intensive immunization should be conducted within and surrounding these groups at risk. Special efforts should be made to reach all of the individuals at risk in the epidemic areas as nearly simultaneously as possible within a few days or at least within one week.

If oral vaccine is available the monovalent type corresponding to the epidemic strain should be used. If for special reasons the epidemic type is unknown or multiple types are found to be spreading then trivalent oral vaccine should be used. If oral vaccine is not available, formalin-inactivated vaccine should be used. The recently developed "hypo-spray" or "jet-gun" has proved most popular in mass vaccine programs and its use is recommended whenever large numbers of persons are to be immunized parenterally.

Each case of poliomyelitis and polio-like neurological illness that occurs in an outbreak should be immediately and carefully investigated for evidence of source of infection and to determine the population group at risk. The extension of cases to new areas or the occurrence of new types of poliovirus calls for immediate modification of the mass immunization

program. The occurrence of several separate foci of infection in a community calls for full community-wide immunization if necessary even including whole metropolitan areas.

Surveillance

The orderly progress of poliomyelitis control demands a continuous national surveillance based upon the full reporting and investigation of all cases of poliomyelitis, the aseptic meningitis syndrome, and other conditions simulating either paralytic or non-paralytic poliomyelitis. Each case should be subject to epidemiological investigation including discriminating clinical evaluation, history of poliomyelitis immunization both with inactivated and oral vaccines, history of contact with others who have received oral vaccine within the preceding two months, and follow-up for residual paralysis. Manufacturers, lot numbers, and dates of administration should be recorded.

By whatever means are necessary and practical, a records system of State and local health services must be able to furnish accurate data concerning the following:

1. Percentage of population vaccinated with emphasis on that group 0 through 5 years of age.
2. Types of vaccine used including the name of manufacturer and lot number.

3. Efficiency of distribution to and within local units of administration.

Periodic sampling and surveys should be conducted to determine adequacy of immunization levels and to delineate areas and population groups in which intensification of the immunization program is required. The CDC Quota Sample Survey technique has proved practical and effective for these purposes. The Indiana system of requiring all boards of education to report each year on the immunization status of all newly registered children in the schools has been tested and found valuable. Both of these systems are recommended.

Laboratory Services

Essential to national surveillance and the guidance of effective control of poliomyelitis is the availability of high quality laboratory diagnostic services including the isolation and identification of viruses from cases and the determination of antibodies. Each sporadic case and a reasonable sampling of epidemic cases, should receive virological study. Each State health officer should provide these necessary services or arrange for them to be provided.

A systematic and continuing survey of antibodies to the three types of poliovirus should be conducted among well selected and representative population groups throughout the country to determine the levels of serological

response actually being achieved by the immunization program, to measure the duration and titers of circulating antibodies, and thus to provide a sound basis for guiding the national immunization program. This program should be the joint responsibility of the Public Health Service and collaborating State and private laboratories.

Laboratories of special competence should be established to provide the highly technical services needed to discriminate between wild strains and attenuated vaccine strains of polioviruses, and to determine genetic markers. The Public Health Service should designate and support such laboratories and establish proper channels for submission of specimens and set priorities for use of these important but highly specialized services.

Long Term Care and Rehabilitation

Patients with severe residual paralysis acquired in past epidemics and those, fortunately relatively small in number, who are still becoming victims of the disease, constitute a serious and continuing problem requiring community organization to solve. While clinical research conducted at Poliomyelitis Clinical Study Centers has greatly improved degrees of recovery and the development of mechanical devices has greatly improved the return of useable function, nevertheless a large residue of patients with seriously debilitating disease continues to exist. Continuation of

support for the adequate long term care and rehabilitation of these patients is an essential phase of the total poliomyelitis control program.

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# RECOMMENDATIONS

of the

# SURGEON GENERAL'S COMMITTEE ON POLIOMYELITIS CONTROL

Meeting at Communicable Disease Center

Atlanta, Georgia

January 23-24, 1961

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

There are four goals in the control of poliomyelitis:

1. Prevention of epidemics
2. Control of epidemics
3. Prevention of endemic poliomyelitis
4. Eradication of paralytic strains of polio virus from the population of the United States

The following suggestions are intended to bring the U. S. closer to these goals.

--Surgeon General's Committee on Poliomyelitis Control

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## THE IMMEDIATE PROGRAM

### 1. Intensify Immunization Program Now

Immediate steps should be taken by all interested groups to intensify drives for vaccination with the formalin-inactivated vaccine. Each State and local health department should accept responsibility for seeing that there is effective organization of the medical, public health, educational, and citizen resources within its jurisdiction to achieve this.

The plan proposed by the Public Health Service to encourage local community drives designed to reach the lower socioeconomic and younger age groups through neighborhood organization -- the "Babies and Breadwinners" campaign -- is endorsed. It is recommended that the plan be widely distributed by the Service, by the organizations represented on the Committee and other interested agencies.

The community organization pattern achieved through this effort can be readily extended or modified to other, similar health measures.

### 2. Priorities for Achieving Immunization Goals

The following goals and priorities for vaccination efforts are recommended:

A. Every unvaccinated person should be fully immunized against polio for his own protection.

B. Immunization campaigns should be especially intensive in neighborhoods with less than 85% vaccination in groups under age 6, where epidemics are most likely to occur.

C. First priority should be directed to attaining complete and early coverage of the infant and pre-school group under 6 years of age.

D. Other children under 10 years of age and parents of young children are the next most important groups.

To achieve and maintain these goals requires a highly effective and continuing program of infant immunization.

3. Vaccination Schedules - Formalin-inactivated Vaccines

The schedules for use of formalin-inactivated vaccines presently are:

A. Initial Immunization - all ages except infants under 6 months of age

| Order of Doses | Interval from Last Dose |
|---|---|
| 1st | - |
| 2nd | one month |
| 3rd* | 7 months or before the next poliomyelitis season* |
| 4th | one year |

*At least 3 doses should be administered prior to the beginning of the poliomyelitis season.

B. Immunization of Infants Under 6 Months of Age**

| Order of Doses** | Interval from Last Dose |
|---|---|
| 1st | 1-1/2 - 2 months of age |
| 2nd | one month |
| 3rd | one month |
| 4th | 7 months |
| 5th | 1 year |

**Including use of combined antigens for other communicable diseases.

C. Additional Doses

After the completion of either of the above schedules supplementary booster doses are indicated for children on entry to school and for persons with unusual exposure to infection.

## THE CONTINUING PROGRAM

### 4. Immunization is a Medical Procedure

All types of poliomyelitis vaccine should be used only under the direction of licensed physicians or official health departments.

All community sponsored immunization programs for the control of poliomyelitis should be planned and carried out in closest cooperation with private physicians and local medical societies.

### 5. Surveys of Immunization Status

All communities should conduct periodic evaluations of their poliomyelitis status. The quota sample survey technique is practical and widely applicable. The Indiana system of requiring school boards to report on the immunization status of each newly registered child in schools has been tested and is recommended. It is particularly important to maintain up-to-date estimates of the vaccination status of preschool children in neighborhoods of suspected low immunization levels.

### 6. Epidemic Use

The use of any available vaccine should be intensified in the face of an epidemic. When oral vaccines become available, every effort should be made to achieve total community participation in the immunization program on a single day or in a few consecutive days.

7. Surveillance

The National Poliomyelitis Surveillance Program should be continued and expanded. The essential features include:

A. Case investigation consisting of clinical evaluation, history of contact with others who have received polio vaccines within the preceding two months, and follow-up for residual paralysis at 60 days. Manufacturers, lot numbers, and dates of administration of polio vaccines should be recorded.

B. Laboratory diagnostic service for each sporadic case of poliomyelitis and a reasonable sampling of epidemic cases.

C. Evaluation of the poliomyelitis immunization status of the country annually by a random sample survey procedure.

D. Serological surveillance consisting of periodic systematic surveys of antibodiesto the three types of poliovirus among representative population groups throughout the country to ascertain the levels of serological response being achieved and to measure the duration and titers of circulating antibodies.

E. Virologic surveillance of circulating enteroviruses including polioviruses in communities should be carried out.

F. Characterization of poliovi ruses in specially designated laboratories with particular competence to discriminate between "wild" poliovirus strains and the attenuated vaccine strains used as oral vaccine.

G. Constant surveillance of the prevalence of polio-like disease through the systematic reporting and laboratory study of cases and outbreaks of ECHO, Coxsackie, and other virus infections simulating poliomyelitis.

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8. Behavioral Studies

Repeated observations have shown that there are easily delineated groups who have not been immunized in spite of ready availability of vaccine. Despite these observations of fact, the underlying cause has not been studied sufficiently.

Investigations (possibly correlated with immunization surveys) should be conducted to identify the barriers that keep people from obtaining the health care they need, and to show how these barriers can be eliminated. The information gathered should be pooled and energetic programs should be undertaken, with adequate resources, to determine how non-acceptance can be overcome.

9. Research

Further research in the field of inactivated and living virus vaccines is strongly endorsed. Collaboration of scientists, public health officers, and individuals representing various organizations throughout the country who are interested in this problem is encouraged in order to fill in many gaps in our information and knowledge. Examples of such research are:

A. Development of markers that are more specific, in order to facilitate strain differentiation.

B. Continued efforts to develop more satisfactory strains for vaccine.

C. Efforts to provide and evaluate a more potent inactivated vaccine to permit adequate immunization with fewer injections.

D. Research seeking the advantages of various immunization schedules, especially for the newborn.

E. The control of epidemics through various applications of available vaccines and programs.

10. Assistance to Other Countries

The Surgeon General should encourage the development of programs to furnish immunizing agents to other countries for the control of poliomyelitis.

## THE ORAL VACCINE PROGRAM

11. Production of Oral Vaccine

The Public Health Service should continue to make every effort to encourage the early production and ready availability of an oral polio vaccine.

12. Priorities for First Available Supplies of Oral Vaccine

If the first available supplies of oral poliovirus vaccine should be limited in amount, then they should be utilized in the following priority order:

First: Epidemic control, investigations and community studies.

Second: Immunization of infants and pre-school children.

Third: Selected area immunization of those segments of the population that are least well immunized.

13. Reserves of Oral Poliomyelitis Vaccine for Epidemic Use

The Public Health Service should maintain reserves of oral poliovirus vaccine for use in epidemics.

14. Vaccination Schedules - Oral Vaccines

When oral vaccines become available, the Public Health Service should recommend dosage schedules based on the report of Subcommittee I, with whatever changes may be indicated at the time.

LAUDER--WO 3-5742

U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
Washington 25, D. C.

FOR IMMEDIATE RELEASE
Tuesday, February 28, 1961 HEW-P23

Surgeon General Designate Luther L. Terry of the Public Health Service announced today that he has accepted and is putting into immediate operation recommendations made by the Service's Advisory Committee on Poliomyelitis Control for a stepped-up program to prevent polio epidemics in 1961.

The recommendations which concern current use of the Salk polio vaccine and future use of oral polio vaccines were made following a two-day meeting of the Advisory Committee, held late last month at the Service's Communicable Disease Center in Atlanta, Ga.

Dr. Terry has notified members of the Advisory Committee of his acceptance of their recommendations and has forwarded copies to all State and Territorial Health Officers urging their cooperation in encouraging communities to start vaccination drives early.

"I share the sense of urgency expressed by many Committee members on the need for intensive efforts to immunize as many people as possible before this year's polio season," Dr. Terry said. "I call particular attention to the Committee's findings that the recommended dosage schedules may be modified to permit the administration of three shots of Salk vaccine before summer to persons who have not as yet had any vaccine."

In carrying out the program recommended by the Advisory Committee, the Public Health Service has offered assistance in identifying neighborhood groups needing protection against polio and in bringing the attention of medical agencies concerned with polio control, to these non-immune groups.

(More)

The Service will also support State and local health departments in alerting the public to the need for polio vaccinations through continued cooperation with the Advertising Council's polio vaccination campaign.

A "Babies and Breadwinners" plan to promote vaccination of infants and fathers, particularly in low income areas where the need for vaccination is greatest, has been developed by the Service and endorsed by the Committee. It will be widely circulated to medical societies, health agencies, PTA's, and other civic groups.

In addition, Dr. Terry said, CDC will emphasize the need for immunizing infants and will encourage behavioral studies in identifying reasons why some people refuse immunization and in methods for overcoming this refusal. The Service will also continue its active liaison with industry to hasten the availability of oral vaccine.

Submitted to House of Representatives Subcommittee on Health and Safety of the Committee on Interstate and Foreign Commerce for the record of Hearings conducted on polio vaccine March 16, 1961.

## PUBLIC HEALTH SERVICE ACTIONS (1955-1961) IN PROMOTING USE OF POLIOMYELITIS VACCINE

The promotional efforts exerted by the Public Health Service during the past five years have been sustained and intensive. Although precise measurements of promotional efforts are difficult to measure, it is no exaggeration to say that the polio vaccination program has commanded more time and attention than any other single health program within the Public Health Service's responsibility.

The following brief summary includes only the bare highlights of this effort. It will provide, however, a quick overview of the leadership provided by the Service in this national effort to bring the protection of the Salk vaccine to as many persons as possible in the shortest possible time--an effort which has occupied the time and energies of hundreds of organizations and thousands of individuals. This effort, as Surgeon General Luther L. Terry has pointed out, has resulted in the greatest single achievement in preventive medicine in our history.

1. Financial Support

Under the authorization of the Poliomyelitis Vaccine Assistance Act, which was first approved on August 12, 1955 and later extended on February 15, 1956 through June 30, 1957, the Public Health Service administered $53.6 million in grants in aid to States for the purchase of vaccine and the administration of poliomyelitis prevention programs.

2. Removal of Controls

When it became apparent that the initial vaccine supply shortage was ending, on August 1, 1956, the system of voluntary allocation of supplies was discontinued. This enabled areas which had aggressive vaccination programs underway to increase their supplies and averted the danger that other areas, though needing vaccine, would hold up supplies while their programs were being organized.

3. Public Statements, Press Conferences, and Press Releases

Beginning with the announcement of the lifting of allocation controls, virtually all statements by Federal officials have continuously urged prompt and extensive use of the vaccine. The first Presidential statement, urging vaccination, was issued on November 28, 1956. Since then, several Presidential statements have been issued, the most recent being President Kennedy's statement on March 13, 1961.

At the end of the polio season each fall, beginning in 1957, a summary of the polio situation has been a featured item of a press conference by the Secretary of Health, Education, and Welfare. The importance of fall and winter vaccinations has been stressed. The Surgeon General has also continuously issued statements urging vaccinations and reporting on the progress of nation-wide vaccination programs.

Almost all of the 33 Public Health Service press releases on polio issued since August, 1956, when the acute supply shortage ended, have stressed vaccination in addition to reporting specific news developments. Assistance has been given by the Public Health Service over a four year period in the development of dozens of popular magazine articles. CIO-AFL and other trade union periodicals, the foreign language press, house

organs and other specialized publications have all carried the vaccination message. Dozens of radio and TV shows have also dealt with the vaccination program.

4. Advertising Council

Beginning in 1957, the Public Health Service has financed and sponsored annual nationwide advertising campaigns in association with the American Medical Association and the National Foundation, urging vaccinations. Materials have been prepared for the Council by a top flight task force of the Young and Rubicam advertising agency. Television spots, featuring famous TV, sports, theatrical and other personalities, have appeared on network shows and have been supplied to local television stations. Radio announcements, newspaper and magazine advertisements, car cards and billboards have been used in these campaigns; and each has been accompanied by parallel public information campaigns conducted by the Service, the National Foundation, the National Health Council and many other organizations. The campaign for 1961 is already under way and within a month materials will begin appearing in the communications media.

5. State Health Departments

A how-to-do-it manual of "Suggestions for Developing a Comprehensive Poliomyelitis Vaccination Program", developed in cooperation with a committee of health educators from the States, was sent to all State health departments in early 1957. Copies were made available to them by the Public Health Service for local agencies. A revised and more elaborate "packet" was issued to States in 1959. In addition, samples of Advertising Council materials, special pamphlets, examples of successful local

campaigns and other promotional aids have been issued in 20 separate mailings to State health officers and State health educators over the past three years. The most recent effort has been a detailed plan-for-local action, entitled, "Babies and Breadwinners" which is receiving similar wide distribution by the Service and interested professional and voluntary agencies. This campaign, developed by the Public Health Service, was endorsed by the Advisory Committee on Poliomyelitis Control in late January.

The Service's Communicable Disease Center has assisted State and local leaders in surveys in 50 cities to help them identify areas where the unvaccinated live so that special drives can be conducted in those areas. This survey system, created by the Communicable Disease Center, has also been used by a number of other communities.

c. Voluntary Agencies

Voluntary health agencies, PTA's, labor and other citizen groups, beginning in 1955, have been represented at a series of advisory committee meetings called by the Surgeon General. Public Health Service assistance has been given to them in developing materials for their publications and for issuance to their local affiliates. Through a special arrangement with the National Health Council, an appeal for voluntary agency support of local drives has gone to the hundreds of agency members during the past two years. The Council has also placed special editorials in more than a thousand daily and weekly papers. Articles, prepared by or stimulated by Public Health Service information officers and others, have appeared in the magazines of women's clubs, labor organizations and other groups.

Cooperation with the Metropolitan Life Insurance Company and the Equitable Life Assurance Society has resulted in full page ads in the Saturday Evening Post and other leading magazines, posters in schools, etc. Polio vaccination exhibits have been shown at conventions of PTA's and other groups.

7. Professional Organizations

Representatives of the major health and medical organizations have attended all advisory meetings called by the Public Health Service and assistance has been offered them in developing material for their memberships. The Service has also participated in special efforts made by the American Medical Association, the most notable being a special meeting, called by the AMA and attended by the heads of all State medical societies in January 1957. Plans made at this meeting were so successful in stimulating local drives that a temporary vaccine supply shortage occurred in the spring of 1957. Public Health Service officials have participated in numerous meetings of the American Medical Association on the subject of polio, the most recent being the November 30, 1960, special symposium on poliomyelitis at the mid-winter clinical sessions in Washington, D. C. The papers given by the Surgeon General and other Public Health Service officials at this meeting have been published in the Journal of the American Medical Association and are the most recent of numerous articles on polio which the Service has placed in that journal and in the journals of other medical and health organizations.

In 1959, the Surgeon General requested the presidents of the Academy of Pediatrics, and the Academy of General Practice to conduct special campaigns for the vaccination of infants and young children.

These campaigns were energetically pursued and were accompanied by a special appeal by the Chief of the Children's Bureau.

Public Health Service and American Medical Association efforts to promote private physician and health department leadership in polio drives throughout the U. S. have been closely coordinated. The American Medical Association has scheduled its mailings of Advertising Council and other materials to State and local medical societies to coincide with Public Health Service mailings to health departments. The American Medical Association's special materials have also included vaccination reminder cards for physicians to mail to their patients and letters from the AMA president to 174,000 practicing physicians.

Articles in pharmaceutical journals, counter cards supplied by vaccine producers, and special messages from the Surgeon General have enlisted the cooperation of the Nation's druggists in pushing polio vaccination drives. Nursing journals have also carried appeals regularly, as well as the publication of the American Osteopathic Association.

C. Industry

The Surgeon General has written vaccine producers each year to encourage production of adequate supplies of vaccine, and the industry has been kept continuously informed both on the technical and the promotional efforts being executed by the Service.

Conclusion

While it is clear, from this brief summary, that the wide use of the written and spoken word on the subject of polio vaccinations is by

no means the result of Public Health Service effort alone, much of it has been the direct result of Service action. In this sustained effort, the Service has had the full and enthusiastic cooperation of four successive Secretaries of Health, Education, and Welfare and their staff assistants as well as many other officials of the Executive Branch of the Federal Government, Members of the Congress, and many thousands of citizens throughout the nation.

It is the intention of the Service, with the present "killed" vaccine, and with the oral vaccine, when it becomes available, to continue to do its part in the job of stamping out polio in America and to help in the longer effort to bring it under control throughout the world.

Dr. TERRY. At my far right at the end of the table is Dr. C. A. Smith, who is the Chief of the Communicable Disease Center in Atlanta, Ga., which is a part of our Service.

Next is Dr. Arnold B. Kurlander, who is Assistant Surgeon General in the Office of the Surgeon General of the Public Health Service. Dr. Kurlander has been our staff person in the office responsible for central coordination of all activities in the polio field for the past year.

The next is Dr. Roderick Murray, who is Director of our Division of Biologics Standards at the National Institutes of Health.

Next to my left is Dr. Alexander D. Langmuir, who is the Chief of the Epidemiology Branch of our Communicable Disease Center in Atlanta.

And finally, on the end is Mr. Edward J. Rourke, who is Assistant General Counsel for the Department of Health, Education, and Welfare.

Thank you, Mr. Chairman and members of the committee.

Mr. ROBERTS. Thank you, Dr. Terry. We are glad to have the gentlemen with you here. I appreciate your making them available to the committee for questions.

I would like to thank you for your very fine statement and to say again that the Chair regrets that it was not possible to give you more notice of this hearing.

As I explained before, because of the various announcements it was felt this hearing was proper and that we ought to try to get into the matter as soon as possible.

When did you assume office as Surgeon General of the U.S. Public Health Service?

Dr. TERRY. I actually started functioning in the office as of January 30, sir. However, I was not confirmed by the Senate until March 2, 1961.

Mr. ROBERTS. And almost all of the work with respect to the oral vaccine has taken place under your predecessor, Dr. Burney?

Dr. TERRY. The more recent developments. Of course, it extends back into the term when Dr. Scheele was Surgeon General.

Mr. ROBERTS. You were with the Heart Institute most of the time, that is, prior to your assuming office as Surgeon General?

Dr. TERRY. That is right, sir. I have been associated with the Heart Institute for 10 years, largely as a clinical investigator, but during the past 2½ years I was Assistant Director of the National Heart Institute.

Mr. ROBERTS. As you see it, Dr. Terry, what are the responsibilities of the Public Health Service with respect to the availability of new medical developments?

Dr. TERRY. I think the responsibility of the Public Health Service, Mr. Chairman, has been generally outlined in the five points which I have presented in my formal statement. In other words, I feel that all of those points with regard to our responsibilities are of importance. Namely, in terms of keeping surveillance on disease conditions as they exist in the United States; in terms of stimulating and performing research related to disease conditions; in relation to promotion of additional work as may be necessary in the study of diseases; and, also, promotion in the use of therapeutic and preventive agents

as they become available; and the stimulation of all persons concerned at all levels in relation to the production and application of measures, techniques, and substances which may be used in the prevention or treatment of diseases of man.

Mr. ROBERTS. Now, would it be correct to say that the Public Health Service is in the position of a regulatory agency in so far as the licensing of biologic products is concerned?

Dr. TERRY. That is correct, sir.

Mr. ROBERTS. Have standards been established for the production of the oral vaccine?

Dr. TERRY. Mr. Chairman, these standards are developed in our Division of Biologics Standards. I would like to present at this time, if I may, Dr. Murray, who is Chief of that Division, and allow him to answer your question in more detail than I could answer it, sir.

Dr. MURRAY. Mr. Chairman, the question of standards is difficult to define in a scientific sense. They come in two categories.

One form is written standards which would appear in the form of regulations; and the other standards for preparations which are issued to those interested, for the purpose of standardizing their product.

At the moment we have gone through the prcoess of developing written standards after a very prolonged period of accumulating information in this developing area.

A notice of proposed rulemaking was issued on November 23, 1960. This actually set forth the regulations which would govern the manufacture and testing of live poliovirus vaccine. Public comment was called for. This has been received, and is being reconciled with the text.

As Dr. Terry noted in his opening statement, it is anticipated that these regulations will become final sometime before the end of this month.

Mr. ROBERTS. Now, just what are the responsibilities of the Public Health Service with respect to the tests of new medical products?

Dr. MURRAY. The responsibility of the Public Health Service, as seen through the Division of Biologics Standards—and this concerns biological products only—is for the development of standards which are designed to assure the safety, purity, and potency of these products.

The Division, also, carries on research which is designed to investigate the suitability of standards, to evaluate standards, and, also, to examine products with a view to determining if standards have been met, as well as to inspect establishments seeking licenses and establishments which already have licenses, at periodic intervals. Recommendations are made for the licensing of biological products to the Secretary of HEW, who has the authority to issue licenses.

Mr. ROBERTS. I saw a statement made by Dr. Terry on page 3, the third paragraph, where he points out the responsibility and that various strains of oral vaccine have been used, in the U.S.S.R. and other countries abroad.

Other than the Soviet Union, what are the countries to which you referred, Dr. Terry?

Dr. TERRY. I am not certain of the exact countries outside of the Soviet Union; may I ask Dr. Langmuir to answer that?

Mr. ROBERTS. Yes.

Dr. LANGMUIR. The countries adjoining the Soviet Union—Poland, Czechoslovakia, Hungary, and Yugoslavia. And I am not sure of the details, but I feel confident that Rumania and Bulgaria have been included in this program with support from Moscow.

Also, when we were in Moscow last May, we learned that programs were underway in the mainland of China. The full extent of these we never learned in detail.

Mr. ROBERTS. Do you know of any tests that we have conducted in any of the other parts of the free world or tests conducted by other governments in the free world?

Dr. LANGMUIR. Very extensive tests and programs through many countries in Central and South America. Also, a test several years ago in Ruandi Urundi in the middle of Africa and in Leopoldville.

A great many small studies have been undertaken in, I guess, a dozen or more countries. I am thinking of Sweden—small studies in, say, Britain, South Africa. I am not sure that I am fully informed.

The record of the Pan American Health Organization conferences, held here in Washington in June of 1959 and 1960, made a serious effort to consolidate all of this information. And this is available.

Mr. ROBERTS. These tests were done with the oral vaccine?

Dr. LANGMUIR. Yes; with oral vaccine as compared to the Salk type.

Mr. ROBERTS. Further reading from Dr. Terry's statement:

> There is evidence that the vaccine has been effective—in fact, highly effective. The manufacturing and testing requirements under which this vaccine was produced were less rigid than those now proposed for American manufacture.

This question: Following these tests that we are speaking about, what steps were taken by the Public Health Service to stimulate production in the United States?

Dr. TERRY. Dr. Kurlander, could you comment on that?

Dr. KURLANDER. As you know, Mr. Chairman, most of the field testing of the various strains of the vaccines was done in foreign countries. The reports of the tests and the reports of the effectiveness of the use of these materials began to be published in international journals. International conferences were held, and our people were participants in these conferences, so that they could secure the latets up-to-date information. This would include not only published material but personal and scientific communications from other scientists about the effectiveness and methods in which the materials were used.

Our chronology indicates that we established the Public Health Service Committee on Live Poliovirus Vaccine, composed of eminent experts in vaccines in this country, prior to the international conferences. We did this so that we could begin as early as possible to keep ourselves informed, to keep our scientific colleagues in the country informed, and also to keep industry informed.

Our chronology indicates that our committee was formed as early as June 1958. The first international conference on poliovirus vaccines, at which time these official reports were presented, occurred approximately 1 year later.

Mr. ROBERTS. I assume that these tests are going on all of the time.

Dr. KURLANDER. That is correct.

Mr. ROBERTS. What tests are you making at the present time?

Dr. KURLANDER. If I may, sir, I should like to make it very clear that the Public Health Service did not perform the testing of these oral vaccines in the foreign countries.

Mr. SCHENCK. Will you yield?

Mr. ROBERTS. Yes.

Mr. SCHENCK. Why were those tests done in foreign nations?

Dr. KURLANDER. I would like to, if I may——

Mr. SCHENCK. Was it because of their ability to evaluate these things—was that the reason—or are their viruses much better than ours?

Dr. KURLANDER. May I ask Dr. Murray to answer that qeustion. He attended the international conferences.

Dr. MURRAY. A couple of factors are involved here, one of which is the fact that, since 1955, the Salk vaccine has been so widely used in this country that the population in the United States did not provide a suitable group in which oral vaccine could be investigated. Populations with more favorable situations suitable for investigation existed abroad. These situations were identified and developed by the scientists involved—that is, the scientists who were developing the oral vaccines. They were identified on the basis of their suitability, not having had prior experience with Salk vaccine, a matter which would have beclouded the outcome of such study; and, furthermore, the vaccine was easily accepted by the people in some of those areas because they did not have vaccine of any sort available.

Dr. TERRY. May I ask Dr. Langmuir to comment on this, too?

Mr. ROBERTS. Yes.

Dr. LANGMUIR. Pertinent to this question, I think it is well established that each of the various proponents—there have been three in this country—have tested their products in this country in selected populations before they went anywhere else in the world.

So it is not as though they went elsewhere to test. They went to the place to test that would give the best tests, but all of the questions were started and worked on in this country before any oversea activity.

Mr. ROBERTS. At page 2, Dr. Terry, you said that you might anticipate licensing applications in the next 6 months. Now you say—I want to be correct in this:

> Although we confidently anticipate that one or more applications may be forthcoming within the next 6 months, or possibly sooner, it is impossible to set any more precise time than that.

Does this mean that the vaccine will immediately be available when licensed, or must we wait for an indefinite time for manufacturers to release the product after licensing?

Dr. TERRY. I do not think we can give you a complete answer to that in terms of the quantities that will be available. But we expect that at the time that a vaccine is licensed there will be considerable quantities of it available at that time. I do not know whether Dr. Murray can say anything more specific about that or not, sir.

Dr. MURRAY. The question of licensing would come up when the manufacturer had developed sufficient manufacturing experience. And I think that we should emphasize here that this is the actual feature of the program which, perhaps, is lacking—that is, consistent manufacturing experience over a period of time and covering a number of successive lots of vaccine.

Licensing will occur when the manufacturer applies for a license and has demonstrated the ability to produce a satisfactory product for general distribution—not for research purposes, but for general distribution—in the case of five consecutive lots. This means that at the time of licensing the material from those five lots would be available for distribution, plus any other lots which would be coming off at that time or subsequently.

The lots that would be available would depend entirely upon the manufacturing posture of the particular processing plant and scheduling of production.

Mr. ROBERTS. Now, would that manufacturing experience have to be accumulated all in the United States or could it be based on experience that the pharmaceutical people have had with the product outside of the country?

Dr. MURRAY. The licensing would be based upon the evaluation of the evidence of the five successive lots, produced in the manufacturing establishments applying for the license. Some of the testing, particularly the testing which we require for administration to human beings, and which involves validation of the product rather than the particular lot, might be done elsewhere.

Mr. ROBERTS. Thank you very much.

Does the Public Health Service itself have any authority to bring about production of a new product, a new medical product, which they determine is highly desirable to protect the public health?

Dr. TERRY. Mr. Rourke.

Mr. ROURKE. The Service has long had authority to manufacture a biological for its own use, its own purposes. It has had this authority since 1944—to manufacture biologicals for its own research and demonstration purposes.

Mr. ROBERTS. In other words, theoretically for research purposes, the Public Health Service could proceed to produce this vaccine. And has any consideration been given to this course of action?

Mr. ROURKE. Not that I know of, sir.

Dr. TERRY. Dr. Murray.

Dr. MURRAY. I am not sure that I understood the question that the gentleman presented.

Mr. ROBERTS. I asked the question if the Public Health Service is authorized, for the protection of the public health, to bring about production of a new medical product itself. The answer was, "Yes," that you had that authority.

And then I wanted to know whether or not there was any consideration given by the Public Health Service to producing the oral vaccine in this particular situation?

Dr. KURLANDER. Mr. Chairman, the answer to that is, "Yes." This matter was discussed with Surgeon General Burney, since we were aware of the authority for the Service to manufacture a biological under existing authority in quantities needed for research and demonstration.

We, also, sir, under our authority, can manufacture a biological for public or private agencies when the material is not available from establishments licensed to produce the biological.

Since there are no establishments licensed as yet to produce the biological, it was the essence of our opinion in the immediate office

of the Surgeon General at that time that we did not believe it advisable for the Public Health Service to become a manufacturer of biologicals.

Mr. ROBERTS. Now, in view of the fact that there is no application for a license at the present time, and if that situation persists, do you think that the Public Health Service might review this situation and consider producing some of the oral vaccine?

Dr. TERRY. I can assure you, sir, from my standpoint, that if this condition obtains, we would review the situation and seriously consider it. I think the crux of the thing would be whether by so participating we could get a product available any more rapidly for the American people.

In general, I believe it has been the attitude of the Service that all of the progress was being made that could be made, sir, in terms of the production of a safe and potent oral vaccine. But if we ever feel that it is necessary, it certainly would be the responsibility of the Public Health Service to go directly into this in order to determine what should be done.

Mr. ROBERTS. To go back to the experiment that you know something about—the largest one involving 70 million or more persons in Russia who received some 236 million doses there—Whose product was used, if you know, Dr. Terry, in that experiment?

Dr. TERRY. Dr. Murray knows, I believe.

Dr. MURRAY. This was manufactured by the Smorodensev Institute for Poliomyelitis Research in Moscow, for the most part, and, also, manufactured to a lesser extent in Dr. Smorodensev's laboratory in Leningrad.

A small amount of initial material was provided for those studies by Dr. Sabin himself, but the bulk of the material used in the U.S.S.R. was produced in the U.S.S.R., using the Sabin strain.

Mr. ROBERTS. Did Dr. Sabin conduct that experiment in Russia, or did he simply supply the strain and the information for its application?

Dr. MURRAY. These studies were carried out by the Russians themselves.

Mr. ROBERTS. By the Russians themselves?

Dr. MURRAY. Although Dr. Sabin, I understand, did visit the U.S.S.R. and offered advice at the time.

Mr. ROBERTS. Are you familiar with the type of product that was used in the British Isles?

By one of Pfizer's subsidiaries?

Dr. MURRAY. Any product—I have no personal knowledge of this, I am sorry.

Mr. ROBERTS. Do you know anything about the experiments that were conducted in West Germany?

Dr. MURRAY. We have information—and this was discussed at the International Poliomyelitis Conference in Copenhagen last summer—that this was a Lederle product.

Mr. ROBERTS. A Lederle product?

Dr. MURRAY. Yes.

Mr. ROBERTS. They are considered American manufacturers.

Dr. MURRAY. That is correct. Lederle is an American manufacturer.

Mr. ROBERTS. Do you know of any steps that are being taken by the Lederle people to ask for a license, and do you know of any other licenses that have been applied for?

Dr. MURRAY. We have had some information filed, but no completed license applications.

Mr. ROBERTS. In your opinion, would oral vaccine be a much more economical proposition for the American people than the injectible type?

Dr. MURRAY. Confining myself to remarking on the mode of administration, the oral vaccine could be much more economically administered.

Mr. ROBERTS. Do we not run into some groups of our population—the lower socioeconomic groups—who resist getting shots?

Dr. TERRY. Dr. Langmuir has been very interested in working in this field. I think he is the appropriate person to respond.

Dr. LANGMUIR. We have made extensive surveys, participating with State and local health officials, and we have arranged through the Census Bureau for a nationwide random survey to measure the level of polio vaccination or polio immunization response in various groups in the country. There is no question that there are large sections of our populations inadequately immunized. Particularly this is true among preschool children as compared to school children. Rather generally there is a sharp relationship to the socioeconomic status. Those who live in areas where incomes are lower have had less adequate immunization than those who live in better areas.

Mr. ROBERTS. Now, with reference to the President's request for $1 million for the 3 million doses—is that cost figure of 30 cents a dose, about correct?

Dr. TERRY. I would say that this is nothing more than an educated guess, and I am not even sure that it is to well educated, for that matter, because we do not have the experience at this time. This is a rough estimate based on the approximate price for the cost of the Salk vaccine. Many feel that it will be cheaper to produce the oral vaccine in large quantities. And it is entirely possible that it may be cheaper than that.

It is conceivable that because of the great deal of testing that is necessary to come up with a suitable product, that it might be more expensive.

The Public Health Service has not made any attempt to set a price. I suppose if we had realized the fact that the two were going to be associated, in terms of mentioning a specific price, we would have preferred not to have mentioned how many doses.

On the other hand, this was the best guess that we could make today. And the price that the Public Health Service and the public pays when the vaccine is available will be determined independently then on the basis of the cost of the products to the manufacturers.

Mr. ROBERTS. There was a statement in the Evening Star of March 15, where Dr. Sabin says that the administration would be paying a price 10 times too high for polio vaccine if the administration proposes to pay $1 million for 3 million doses.

Dr. Sabin has been the leading developer of this type of vaccine?

Dr. TERRY. Yes.

Mr. ROBERTS. How would you reconcile that statement.

Dr. TERRY. I would not reconcile it except that it is his opinion, obviously. We made a guess. From a material standpoint, it does not make any difference, sir, because what we are going to pay has not been determined yet and will not be determined until the material is available. And Dr. Sabin could be just as wrong as we could be wrong. I hope he is right.

Mr. ROBERTS. In other words, it will depend a great deal on whether or not licenses are applied for and granted, and, perhaps, the qualifications of those people who receive the licenses? It would be another story entirely if you had to go into it yourself?

Dr. TERRY. Yes.

Mr. ROBERTS. Is that not true?

Dr. TERRY. I think you are right, sir. Of course, it depends upon how successful these batches or these lots test out. If one goes through the testing straight, and they are completely satisfactory, and one does not have to discard material and start over again that makes a big difference.

It depends a lot, too, upon the quantity that can be produced, once a company gets into commercial production. We have some indications in this direction, but we do not know the answers to it any better than Dr. Sabin does.

There was no attempt on our part to peg a price on polio vaccine. I can assure you that the Public Health Service will not pay any more for the polio vaccine than the cost of production justifies when it becomes available.

Mr. ROBERTS. The gentleman from Ohio.

Mr. SCHENCK. I pass.

Mr. ROBERTS. The gentleman from Florida.

Mr. ROGERS of Florida. I do have some questions, Mr. Chairman, concerning this. I, too, am quite concerned. You indicated that we would pay 10 times the possible cost. I felt sure that the Public Health Service would not do that.

Dr. TERRY. Yes.

Mr. ROGERS of Florida. Since there is no commitment to pay any such price I am encouraged by your answer.

Dr. TERRY. That is absolutely correct, sir.

Mr. ROGERS of Florida. I can understand that you are putting in a figure. And then, of course, whatever comes out would be according to a justifiable price.

Dr. TERRY. Yes.

Mr. ROGERS of Florida. So it can be made clear to the public, that, certainly, there is no set price.

I am concerned with the fact that your letter put out to manufacturers in November of 1960, according to your schedule that you presented to the committee here—I believe November 23, 1960, actually before that, November 9—a formal letter which was sent to vaccine manufacturers, requesting information on their plans for production of oral vaccine, where you say you have already put out certain standards and yet we still have no production or even a request for a license.

I wonder what response you had received from manufacturers to that formal letter that was sent November 9, 1960, which is some number of months past?

Dr. TERRY. Dr. Kurlander.

Dr. KURLANDER. I will be happy to answer.

Mr. ROGERS of Florida. Thank you.

Dr. KURLANDER. Would you like to have read the letter to the manufacturers?

Mr. ROGERS of Florida. Well, you might put it into the record, I think, or in the files of the committee. It would be well for us to have that.

Mr. ROBERTS. Without objection, that will be made a part of the record.

Dr. KURLANDER. Thank you, sir. May I, also, state that before I begin that the answers from the manufacturers relate to a situation as of late November and Dr. Murray, when I finish, could bring you more up to date.

May I also request permission of the committee to deal with these answers in terms of the total rather than giving specific names, inasmuch as this information was asked for by the Surgeon General in confidence?

Mr. ROGERS of Florida. Yes. I do not care about that. You may do that.

Dr. KURLANDER. Four questions were posed in the letter from the Surgeon General. These were:

(1) Has your organization made a definite decision to manufacture live poliovirus vaccine?

(2) If you are already committed to such a program, when do you anticipate vaccine will be available?

(3) What factors do you consider should be clarified or resolved in order to assist you in arriving at a determination of production schedules at the earliest possible date, bearing in mind always that the product should meet established standards for safety and potency?

(4) What in your considered opinion could the Public Health Service do in a general or particular way to facilitate the general availability of this product at the earliest possible date?

Two manufacturers gave an affirmative answer to the first question, the first question being, "Has your organization made a definite decision to manufacture live poliovirus vaccine?"

One additional manufacturer indicated an active interest but no commitment to a manufacturing program.

The remaining four responded negatively, but one of these qualified his reply by indicating that the company maintained an active interest in the matter.

Each of the companies which had indicated commitment referred to some of the difficulties in production of this product. One estimated the availability of approximately 11 to 12 million doses of each type of vaccine by the fall of 1961.

The second made no estimate and felt that it would not be in a position to do so until actual manufacturing experience had been gained.

A third company estimated it would take from 10 to 12 months to produce vaccine after a decision had been made by the company to enter into production.

The answers and comments to the last two questions, which were, in general, "How can we help, what can we do to hasten it," were, in general, not separated, but the following points were covered: It was considered that early adoption of regulations for the product

would be helpful. Clarification of testing methods were called for. Information as to dosage form and dosage schedule were suggested as being desirable.

The following problems were cited by one or more of the manufacturers:

(*a*) The questions raised by simian agents in the vaccine and in production;

(*b*) The possibility of condoning the presence of simian agents;

(*c*) The question of the stability of the Sabin strains used in manufacture;

(*d*) The question of the passage of virus from vaccinated persons to nonvaccinated persons;

(*e*) The necessity to develop manufacturing experience;

(*f*) The need for clarification of the nature of the programs in which live vaccine would be used.

Two manufacturers raised the question of Government indemnification in the case of product liability.

Reference was made to the method of inactivating some simian agents which had been worked out by Dr. Hiatt of the Division of Biologics Standards. The need for more experience with this method was indicated and an evaluation of the effect the process might have on the vaccine strains themselves.

This is a screening and rescreening of the letters that we received in an attempt to get this kind of information.

(The documents referred to follow:)

NOVEMBER 9, 1960.

Mr. H. W. BLADES,
*President, Wyeth Laboratories, Inc., Division of American Home Products, Inc., Philadelphia, Pa.*

DEAR MR. BLADES. It is not necessary to bring to your attention the worldwide interest in the use of live poliovirus vaccine which has developed in recent times. The studies and programs which have been carried on in a number of countries and the interest of such health organizations as the Pan American Health Organization and the World Health Organization attest to this. I do feel, however, that I should bring to your attention the fact that interest is also rising in the United States.

We have been fortunate in the United States that our technology has been able to produce sufficient inactivated poliomyelitis vaccine to provide protection to a high proportion of our people. Since community protection is not as complete as it could be, however, it behooves all of us to consider active use of all methods available for the prophylaxis of poliomyelitis, including live poliovirus vaccine.

During recent years the Public Health Service has made every effort to keep abreast of developments in this field in order to anticipate the production of live poliovirus vaccine as a biological product. Requirements and standards have been developed through the activities of the Division of Biologics Standards and the Public Health Service Committee on Live Poliovirus Vaccine in consultation with the proponents of these vaccines and with the scientific and technical personnel of interested manufacturers. The adoption of regulations incorporating the concepts evolved should do much in establishing the control and testing criteria for this product, thereby clearing the way for orderly production.

In addition, the Public Health Service is at the moment exploring the future use of this product with a group of consultants representing a great many medical, public health, and other organizations. As Surgeon General of the U.S. Public Health Service I have appointed a committee which will meet later this winter to consider such matters at a public meeting. All this effort will undoubtedly stimulate medical and public interest and it would be unfortunate if

such interest should develop in the absence of adequate supplies of vaccine. In this regard we believe that the demand and market for the vaccine would not be limited largely to the United States as is the case with the inactivated vaccine, but that oversea demand should be considerable.

I would appreciate it very much if you would provide answers to the following questions:

(1) Has your organization made a definite decision to manufacture live poliovirus vaccine?

(2) If you are already committed to such a program, when do you anticipate vaccine will be available?

(3) What factors do you consider should be clarified or resolved in order to assist you in arriving at a determination of production schedules at the earliest possible date, bearing in mind always that the product should meet established standards for safety and potency?

(4) What in your considered opinion could the Public Health Service do in a general or particular way to facilitate the general availability of this product at the earliest possible date?

Some problems remain to be resolved and I would like to mention the method developed by Dr. Caspar W. Hiatt of the U.S. Public Health Service for differential inactivation of certain simian agents as one possible solution to some of these problems.

Any information which you feel you are in a position to provide will be kept confidential as to the identity of the organization although it will be combined with information from others to develop a summary picture.

Sincerely yours,

L. E. BURNEY, *Surgeon General.*

REPLIES FROM BIOLOGICAL MANUFACTURERS TO THE SURGEON GENERAL'S LETTER OF NOVEMBER 9, 1960

Four questions were posed in the letter from the Surgeon General. These were:

(1) Has your organization made a definite decision to manufacture live poliovirus vaccine?

(2) If you are already committed to such a program, when do you anticipate vaccine will be available?

(3) What factors do you consider should be clarified or resolved in order to assist you in arriving at a determination of production schedules at the earliest possible date, bearing in mind always that the product should meet established standards for safety and potency?

(4) What in your considered opinion could the Public Health Service do in a general or particular way to facilitate the general availability of this product at the earliest possible date?

Two manufacturers gave an affirmative answer to the first question. One additional manufacturer indicated an active interest, but no commitment to a manufacturing program. The remaining four responded negatively, but one of these qualified his reply by indicating the company maintained an active interest in the matter.

Each of the companies which had indicated commitment referred to some of the difficulties in production of this product. One estimated the availability of approximately 11 to 12 million doses of each type of vaccine by the fall of 1961. The second made no estimate and felt that it would not be in a position to do so until actual manufacturing experience had been gained. A third company estimated it would take from 10 to 12 months to produce vaccine after a decision had been made by the company to enter into production.

The answers and comments to the last two questions were in general not separated, but the following points were covered. It was considered that early adoption of regulations for the product would be helpful. Clarification of testing methods were called for. Information as to dosage form and dosage schedule were suggested as being desirable. The following problems were cited by one or more of the manufacturers (*a*) the questions raised by simian agents in the vaccine and in production; (*b*) the possibility of condoning the presence of simian agents; (*c*) the question of the stability of the Sabin strains used in manufacture; (*d*) the question of the passage of virus from vaccinated persons to nonvaccinated persons; (*e*) the necessity to develop manufacturing experience; (*f*) the need for clarification of the nature of the programs in which live vaccine would be used. Two manufacturers raised the question of Government indemnification in the case of product liability.

Reference was made to the method of inactivating some simian agents which had been worked out by Dr. Hiatt of the Division of Biologics Standards. The need for more experience with this method was indicated and an evaluation of the effect the process might have on the vaccine strains themselves.

Mr. ROGERS of Florida. Have you taken the necessary steps to clear any doubts that have been raised in the letters you received from the manufacturers so far as their production is concerned? Have we taken the necessary steps to give that information to them?

Dr. KURLANDER. Mr. Rogers, we have. And I would like Dr. Murray to give a fuller explanation.

Dr. MURRAY. The resolution of technical matters is a continuous process which goes on all the time. And I would say that this has been resolved insofar as it is possible to do so in the present state of our knowledge, even to the extent of incorporating some of this in the regulations which will become effective later this month.

Mr. ROGERS of Florida. In other words, this regulation which is to become effective at the end of this month should clear up all of these points?

Dr. MURRAY. It will establish the basic network of testing which must be performed. This is no more than a formulization of what has been known for some time. But many of the problems which come up in production are day-to-day problems, and these can only be handled on a day-to-day basis, and we are handling this as time goes on.

Mr. ROGERS of Florida. Let me ask this, Doctor. Is there any reason now why manufacturers should not go ahead with immediate production of oral polio vaccine?

Dr. MURRAY. There is no reason.

Mr. ROGERS of Florida. Everything has been done from the Public Health Service to clear all questions that are absolutely necessary for them to go ahead with production?

Dr. MURRAY. I would not make an absolute statement. I would say that all major questions have been resolved.

Mr. ROGERS of Florida. Thank you.

Now, just a question or two more.

As I understand you, you were thinking of maybe purchasing this vaccine to put in a reserve, is that it?

Dr. TERRY. May I remark on that, sir?

Mr. ROGERS of Florida. Yes.

Dr. TERRY. The actual intention of purchasing this quantity of vaccine when a proper product becomes available would be to have a reserve which would be used to study the use of such a material in containing an already existing epidemic. In other words, the primary intention is this—let me go back just a moment.

The information and experience which we have on hand indicates at the present time that the oral vaccine begins to offer some protection within a few days. Because of this, it would seem to be in contrast to the Salk vaccine which requires literally weeks for the development of protection on the part of the individual. It would seem that the oral vaccine would be a good product to move into a community and to use in terms of containing an epidemic at its then current size and protecting the rest of the population.

Now, whether this would be possible or not, sir, we do not know. But it seems logical to most of us who have discussed it in great detail and considered all of the information which we have available.

Therefore, the intention of this reserve supply is to carry out what are in effect field research studies. These would give us the most information the earliest that we could get it on how to use the vaccine in the face of an outbreak in a community.

This is the basic reason for wanting the material available.

Mr. ROGERS of Florida. Thank you.

Now, as I recall, they had a testing of the oral vaccine in Miami, Fla. I wonder if any of your staff is familiar with the program.

Dr. TERRY. Dr. Langmuir is familiar with this study, sir.

Dr. LANGMUIR. I was an informal consultant to the State health department throughout the period of this program. They began, as I remember, about the middle of February. They administered the Lederle type of triple vaccine. It was done by small groups with nurses and clerks going from school to school and opening up clinics at an appropriate hour, under the leadership of a joint program of the State department of health, the county health department, and the University of Miami School of Medicine. By this very carefully planned approach with the full support of the medical society and the newspapers, the reports that I have seen indicated that they reached over 80 percent of the population of Miami under 40 years of age. They went to the adult group, a very unusual program.

Thus the acceptance of this product and the speed with which the community responds in a carefully prepared program has been well tested.

Mr. ROGERS of Florida. So far, have the results been fairly good? I realize you have not had much time yet to see.

Dr. LANGMUIR. This is one of the real problems of testing oral vaccine in this country. There was no polio of consequence, maybe a scattered single case or two before this program got underway.

To my knowledge, there have been essentially none since completion of the program. There may have been a scattered single case, but there has been no polio of consequence in south Florida this year. So there is no real test of whether oral vaccine has conferred protection. Almost certainly it has, because the blood tests on a large sample indicate a good response, and we think these are a sound measure of protection.

Mr. ROGERS of Florida. What about any other diseases—what is this business of other viruses in the oral vaccine? Has there been any reaction there?

Dr. LANGMUIR. There was no indication that other viruses were important in producing disease, but we often have a problem in polio in that a good many other viruses are known to produce diseases simulating polio. These are what we call the echo viruses and the Coxsackie viruses. They produce a mild form of disease with involvement of the brain and spinal cord which has to be studied very carefully to distinguish it from polio. Highly competent laboratory study is necessary in order to be certain that such cases are polio.

Dr. TERRY. As a part of your question I would like to ask Dr. Murray to explain just a little more what we are talking about in terms of these simian agents and simian viruses so that the committee will understand what we are referring to.

Dr. MURRAY. In anticipation of such a question, I have a few notes here which I will put together, if that is agreeable.

The increased use of the technique of cell cultivation for the isolation, growth, and study of viruses has brought to light many heretofore unknown viruses apparently present in the monkey from which the tissue cells were obtained. A large number of such agents have been encountered, principally derived from rhesus and cynomolgus monkeys and over 40 such "simian viruses" have been reported. These viruses may appear during the incubation of the kidney cell cultures prepared from apparently healthy monkeys and make their presence known by their destructive effect on the cells (cytopathogenic effect).

Many simian viruses were found in kidney cell cultures used for the production and testing of the Salk poliomyelitis vaccine. They have been classified, their properties have been studied, and standardized procedures have been adopted for determining whether these viruses are actually present in Salk vaccine or not. Great care has been exercised to ascertain that none of the simian agents actually was present in the Salk vaccine. The problem presented by these viruses was simplified in the case of Salk vaccine because of all the simian viruses encountered were found to be inactivated by the formaldehyde which was used to prepare the Salk poliomyelitis vaccine.

When we come to live virus vaccine, we have another problem.

Where monkey kidney cell tissue cultures are used in the production of biological products, it has been necessary to devise procedures designed to exclude such agents from the vaccines and to develop tests capable of detecting their presence. With the development of live polio virus vaccines, problems with simian viruses received new attention. Since the inactivation step, which is used in the preparation of Salk vaccine, cannot be applied, the only way of assuring that such agents are not present in the final product is to exclude them by an elaborate system of testing. The safety of this vaccine for administration to large numbers of persons demands that adequate control procedures be applied to assure that simian viruses are excluded from the vaccine. A great deal of the complexity of manufacture of live polio virus vaccine arises from efforts to exclude such agents from the vaccine.

Two examples of simian agents will illustrate the problems which are faced for live polio virus vaccine production. One of these is the so-called B-virus. This virus was originally identified by Dr. Sabin in 1934. It is highly pathogenic for man, having caused fatal encephalitis in most every case known to have been affected. It is frequently encountered in monkeys without causing apparent harm to the monkey itself. Fortunately, it can be tested for in rabbits and can be identified and excluded on this basis. It is also extremely sensitive to the inactivation process used in the manufacture of Salk vaccine and has not been a problem as far as the safety of this vaccine is concerned.

The actual pathogenicity for man of many of these agents is unknown, and the only safe course is to absolutely exclude them.

The vacuolating agent is another agent which has been encountered recently, and I mention this because it has a certain topical interest, and is a complicating factor in the manufacture of live vaccine.

Approximately 10 months ago the presence of this new virus, not previously suspected, was reported with considerable frequency in kidney cell cultures prepared from rhesus and cynomolgus monkeys.

This virus grows in cell cultures derived from animals of these species without causing any identifiable damage to the growth cells themselves. However, it was detected by using kidney cell cultures prepared from cercopithecus monkeys, obtained from Africa. The presence of this virus in a high proportion of experimental lots of live polio virus vaccine has presented a serious production problem. The properties of this virus are little known. It does not appear to cause disease in man, but has been demonstrated to cause infection without apparent illness. This simian virus can only be identified in the course of live polio virus vaccine production by using kidney cell preparations derived from cercopithecus monkeys at the present time.

The only certain course to follow in order to assure a safe vaccine with respect to these viruses is to call for the absence of any adventitious viruses and, in fact, all viruses except the virus of the vaccine itself.

Mr. ROGERS of Florida. Thank you very much.

Mr. ROBERTS. The Chair would like to acknowledge the presence of our distinguished chairman. The committee is always complimented when he comes and joins us. And we would be happy to hear any questions or comment he has.

Mr. HARRIS. Thank you, Mr. Chairman.

First let me compliment the committee for going into this problem at this particular time. I am always glad to give my attention and cooperation to the subcommittee with these problems.

I would like, if I might be permitted, to ask three or four questions for my own information. Some of them may be purely academic, I do not know.

In the first place, Doctor, is there a definition of what is a "virus"?

Dr. TERRY. Dr. Murray?

Dr. MURRAY. A virus is a submicroscopic micro-organism which has the characteristics of being able to pass through certain filters—this is the way it was originally identified. It may cause disease in man or animals. Many viruses cause diseases of plants. It is incapable of living by itself, but lives within the cells of the animal it infects.

There may be other definitions, but I think this covers the main characteristics of viruses.

Mr. HARRIS. Would you say there were X number of viruses, then?

Dr. MURRAY. There are an unknown number of viruses, sir.

Mr. HARRIS. Then, what is the difference between the Salk and the Sabin vaccine?

Dr. MURRAY. Salk vaccine is a vaccine which is prepared by the growth of viruses which are subsequently killed. But the resulting——

Mr. HARRIS. Which are subsequently killed?

Dr. MURRAY. Which is subsequently killed. The viruses are killed by formaldehyde, and so-called antigen which results therefrom, on injection into human beings, has the ability to stimulate the production of antibodies to the virus, thereby providing the mechanisms of protection against infection.

In the case of a live vaccine, however, we infect the individual with a living organism——

Mr. HARRIS. That is the Sabin vaccine?

Dr. MURRAY. That is the Sabin vaccine and other live virus vaccines—which then multiply within the person so infected, building

up a mechanism against disease much as would occur in normal infection.

Other examples of living virus vaccines are smallpox vaccine, which is an excellent example, and yellow fever vaccine.

Mr. HARRIS. Then Salk vaccine is what you might say would be a killed type, and the Sabin would be live?

Dr. MURRAY. That is correct.

Mr. HARRIS. Is oral vaccine and live vaccine the same?

Dr. MURRAY. Yes. The oral vaccine is the live vaccine. It is taken by mouth, and thus the name oral is attached to it.

Mr. HARRIS. Is it made by the Sabin process?

Dr. MURRAY. It is made from the Sabin virus strains; yes, sir.

Mr. HARRIS. The Russian development is of the Sabin strains?

Dr. MURRAY. They used the Sabin strains received originally from Dr. Albert Sabin himself.

Mr. HARRIS. Obtained from Dr. Sabin himself. Is that the only kind that the Russians manufactured?

Dr. MURRAY. To the best of my knowledge, sir, that is the only vaccine which the Russians are manufacturing.

Mr. HARRIS. Are we manufacturing any vaccine other than the Salk vaccine in this country?

Dr. MURRAY. At the present time, as we have brought out earlier, a number of pharmaceutical companies have entered into the production of live or oral poliomyelitis vaccine, but this has not reached the stage yet at which it can be licensed and sent out for general distribution.

Mr. HARRIS. They have not entered into the production of it, then? That is, they are still engaged in research; is that it?

Dr. MURRAY. I didn't catch the question; I am sorry, sir.

Mr. HARRIS. You just said that several companies had entered into the production of it. Then you added the qualification that, although they have entered into the production of it, they are not as yet licensed to produce it.

Dr. MURRAY. They can only be licensed after they have demonstrated their ability to produce a safe and potent product.

Mr. HARRIS. I appreciate that, but they cannot produce it until they are licensed, can they?

Dr. MURRAY. Yes. They have to obtain the experience in production before they can be licensed.

Mr. HARRIS. What do they do with it?

Dr. MURRAY. They will keep it in reserve presumably and use some of it for research purposes until they have gotten all of the evidence together which will qualify for a license, and at that time everything which meets standards will be released.

Mr. HARRIS. They cannot produce it for distribution to the public until they get a license?

Dr. MURRAY. That is correct.

Mr. HARRIS. But for experimental purposes, research, and so forth, they can?

Dr. MURRAY. That is correct.

Mr. HARRIS. Which, I think, is a very good procedure.

But so far as the public is concerned, at present there is no kind of vaccine being produced in the United States other than the Salk vaccine?

Dr. MURRAY. For general distribution, that is correct.

Mr. HARRIS. For general use by the public rather than for research and experimental purposes?

Dr. MURRAY. That is correct.

Mr. HARRIS. Are you in a position to say what the relative advantages are of the Salk vaccine and the so-called oral or live vaccine type?

Dr. MURRAY. The Salk vaccine, of course, has been used very effectively over the past 5 to 6 years now, and has been demonstrated to produce protection against poliomyelitis when used in the recommended dosage in 90 percent, or better, of individuals so innoculated.

It does produce adequate levels of antibody in the persons who are given the vaccine. It does not—there are some things which it does not do—for instance, prevent a person from harboring a polio virus which he might take in by mouth incidentally, and having this multiply in his gastrointestinal tract, but without harm to himself.

The Sabin vaccine, on the other hand, has the apparent advantage of ease of administration. It can be taken by mouth as against being given by needle. It does produce "immunity" of the gastrointestinal tract—although I must say parenthetically here that there are differences of scientific opinion on this fact—and it has been demonstrated in adequately controlled trials to produce antibodies in a high percentage of cases.

Now, another difference between them is that when Salk vaccine is given (if the vaccine has adequate potency) it does produce antibodies in the individuals so injected, unless the individual happens to be one of the rare ones who is incapable of producing antibodies.

The Sabin vaccine, however, may be affected in its use by the fact that the individuals may be harboring other enteroviruses at the time the vaccine is administered. Under such circumstances—and this would be particularly applicable in the summertime—the vaccination might not take.

Mr. HARRIS. Now, back to the first advantage you have just described.

Can you take overdoses of either?

Dr. MURRAY. I think that I can answer that best by saying that we don't know what an overdose of the Salk vaccine would be. We know of instances where 10 times the dose has been administered without harm to the individual, and this dose does produce a very marked effect on the antibodies of the individual. In other words, it is the equivalent of an excellent vaccine.

With the Sabin-type vaccine, we do know that larger amounts of virus than that recommended for administration have been administered to children without any difficulty.

I might mention that Dr. Langmuir noted that we attended a meeting in Moscow last year. At one of these meetings Dr. Chumakov reported a number of children got containers of the vaccine containing candy which were used and consumed as high as 300 doses without apparent ill effect, other than a gastrointestinal upset afterward.

Mr. HARRIS. In other words, so far as you know, then, there would not be any apparent danger of someone accidentally or otherwise taking too much of it, if the oral vaccine was used?

Dr. MURRAY. No; not in the usual dosage. I could foresee certain circumstances where the administration of an astronomically large dose might lead to trouble. But the errors which would occur in administration we don't believe would cause any damage.

Mr. HARRIS. Then I assume that the major interest, then, in developing the oral vaccine is for the purpose of having a vaccine which is competitive with the Salk vaccine, primarily speaking?

Dr. MURRAY. We entertain the view that it is not competitive, but that it is complementary, in the sense that it can be used easily, and be used to round out the—I hate to use the word "inadequacies," but the fact is that the Salk vaccine does not produce gastrointestinal immunity in the doses in which it is administered.

Dr. TERRY. May I ask Mr. Langmuir to comment on this question, too, sir?

Mr. HARRIS. Yes.

Dr. LANGMUIR. There is a great difference of opinion among us who are working actively in this field. I wouldn't know how you might take a vote of this, but I suspect it would fall reasonably 50–50 among ardent advocates that the oral vaccine is better—and Dr. Sabin, of course, is the greatest of all the advocates, and he says it is best. There are others—Dr. Salk says his vaccine is quite adequate and quite good. I don't believe we will have a resolution of this—excuse me, sir?

Mr. HARRIS. It is understandable for both of them.

Dr. LANGMUIR. We, who are on the firing line, where the reports are coming in constantly are rather impressed with how well the Salk vaccine has worked. The real problem in polio control is how to reach those children who haven't yet had any vaccine. Almost certainly the oral vaccine by its simple administration—a teaspoonful of sirup—will be highly attractive. We know from the various studies in Miami, Cincinnati, Rochester, Ithaca, that it is well accepted. So undoubtedly it will be much easier to reach some of these families where the fear of the needle is a major concern.

Also, we have every reason to think that in an epidemic situation the ease of administration will be a great advantage. I look to a community being concerned about even a few cases of polio; by watching carefully, within a short time, maybe only a few days, they will know whether a problem exists or an epidemic threatens. Then everybody in the community will take a dose of the oral vaccine simultaneously.

With oral vaccine this will be quite easy to organize, whereas giving needles to everybody might be possible but would be much more difficult.

Also, the response from this vaccine is much more rapid; within a few days to a week, we think, there should be protection.

Mr. HARRIS. Are you saying you think that you may reach the point where everyone will take a teaspoonful every morning before breakfast?

Dr. LANGMUIR. Some people have argued that we might do this every year. I doubt if that is a worthwhile procedure. I think we should progress in an orderly way and avoid any suggestion of a mass stampede.

And on the other side, if I may present some of the arguments for the Salk vaccine, it can be combined with other normal antigens that are used for protection against whooping cough, diphtheria, and tetanus.

Mr. HARRIS. The Salk vaccine can?

Dr. LANGMUIR. It can be combined into what we called a quadruple antigen vaccine or agent so that one needle you are giving protection against four different diseases. Health authorities find this most attractive. Pediatricians like this, and mothers like this. So actually this procedure calls for no more needles than before polio vaccine became available.

I anticipate that when oral vaccine becomes available that there will still be ardent advocates of one or the other. Over a period of years we will gain experience, and we will find unanticipated things that we don't know about yet that will influence the final decision on which vaccine becomes most popular.

Mr. HARRIS. I notice in your statement something about the importance of excluding simian viruses. And you also state that these agents are not fully known to the advisers and the staff.

Now, I thought you said awhile ago in response to a question by Mr. Roberts that everything was all ready, and the research work was completed, and we ought to move forward to the production of the oral-type vaccine.

Dr. TERRY. May I answer that, sir?

Mr. HARRIS. Yes.

Dr. TERRY. The point is this, we are ready to move forward with production as we can produce vaccine with the exclusion of these simian agents.

Mr. HARRIS. Well, if you don't know about them, and their potential, how can you move forward?

Dr. TERRY. Some of them are known to produce diseases, sir. So we do not know. I think the point there is that we can't afford to take a chance on having any of them in if some of them produce disease.

Mr. HARRIS. Now, I am using entirely too much time, but there was an article in the American Medical Association Journal recently which I am sure did concern the Public Health Service, in which there seemed to be some criticism directed to the Salk vaccine.

Frankly, I think that was a pretty serious situation. I know that you moved immediately to try to meet some of the criticism. But have you had an opportunity to go into that further to determine whether or not the charge made had any basis whatsoever?

Dr. TERRY. Mr. Harris, I think that all of the evidence that we have now was on hand at that time.

The most unfortunate part about this statement is that it appeared in the Journal of the American Medical Association, and was interpreted by many to be an expression of the attitude of the American Medical Association.

This is far from the truth, sir. The American Medical Association as a body has gone on record as approving the Salk vaccine and urging that it be used for the prevention of paralytic poliomyelitis.

Mr. HARRIS. Yes; that is true, Doctor, but, as I understand, or as I recall from the article itself, it was not reflecting on the product but it was charging that in the production of some of the vaccine it

turned out to be weak and ineffective. In other words, it would seem to me that the charge there was that the manufacturers had not lived up to the Goverment standards, and that it was weak, and, therefore, did not accomplish what it was supposed to accomplish.

Dr. TERRY. Mr. Harris, you are well aware of the fact that such materials cannot be placed on the market without being in effect approved by our Division of Biologic Standards of the Public Health Service.

Mr. HARRIS. That is the reason it makes it an even more serious indictment.

Dr. TERRY. That is correct, sir, because it indicts us. We feel that we have adequate evidence to the contrary, and, therefore, believe that this was the opinion of one individual which does not represent the true facts of the case.

Mr. HARRIS. Immediately on the heels of that, this problem of developing the oral vaccine comes in. The President himself sends up a request for a million dollars to move forward with it. All of this might seem to give by inference or otherwise some substance to the charge.

Dr. TERRY. I can see how you might get that inference, sir. But I would hasten to inform you that the decision that the Public Health Service would request this appropriation for the obtaining of a live vaccine was made before this matter arose in the Journal.

Mr. HARRIS. Do you think that the time will come when you can stamp out the disease?

Dr. TERRY. Yes, sir.

Mr. HARRIS. Stamp out this disease almost completely, like, for example, malaria?

Dr. TERRY. Well, we hope we can do better than we have done throughout the world with malaria. We would hope that we can do as well as we have done with malaria in this country. We are hopeful. But I think at the time we must be realistic. With an effective vaccine such as we have available now, like the Salk vaccine, we are disappointed that we have still such a large percentage of our population that has not taken the vaccine, and is still susceptible to the disease.

We would hope that the ease of administration and other factors related to a safe oral vaccine would allow us to cover a much larger percentage of the population, sir.

Mr. HARRIS. I heartily concur in the position that you have taken. I think it is very important.

Thank you for the time, Mr. Chairman. I did not intend to use so much.

Mr. ROBERTS. I would like at this time to welcome one of our new members, a distinguished new member, Mr. Thomson, the former Governor of his State.

Do you have any questions at this time, Mr. Thomson?

Mr. THOMSON. I was wondering, Mr. Chairman, Dr. Terry said, as I remember his testimony, that up to now there seemed to be no necessity for Public Health Service going into the manufacture of this biological.

Dr. TERRY. That is right.

Mr. THOMSON. Is the cost of manufacture one of the problems in the Public Health Service?

Dr. TERRY. No, sir, it has nothing to do with our decision on that, sir.

Mr. THOMSON. Is it an expensive process?

Dr. TERRY. We don't know exactly yet, sir, how expensive it will be. All of the indications are that it probably will be no more expensive and, hopefully, less expensive than the production of the Salk vaccine.

Mr. THOMSON. What appropriations would your Service need in the event that you wanted to go into the manufacture?

Dr. TERRY. I am not aware, sir, with regard to the question of what we would need.

Dr. KURLANDER. May I answer that?

Dr. TERRY. Dr. Kurlander.

Dr. KURLANDER. Mr. Thomson, the discussions about the possibility of the Public Health Service engaging in the production of biologic products were held in the main before Dr. Terry assumed office.

There are many considerations that one must go through in arriving at a decision as to whether the Public Health Service as an operating arm of the executive branch of the Government should engage in the manufacture of biological products.

There are many things that must be considered. The cost to us or the difficulty of setting up a manufacturing process or manufacturing plant is a relatively minor thing, because if this is our job, as Dr. Terry has said, we would do it. But there are questions of public policy involved, relationships with the industry and responsibilities to the people of the United States. Also a consideration of the fact that most of all the biological production in this country has not been done by Government.

These are issues of great public policy, and ones that we would require considerable advice on from the executive, from the Congress, and from scientific advisers as to what is in the best interests of the Nation over the long range.

Therefore, sir, we never came to any decision whatsoever as to what it would have cost to set up a production plant.

Mr. SCHENCK. Will my colleague yield?

Mr. THOMSON. Certainly.

Mr. SCHENCK. Are you subscribing to the theory that we ought to have less government in business and more business in government?

Dr. KURLANDER. Mr. Schenck, I really don't know how to answer that. What I am trying to say is that government has a function in the biological business, and the Congress has given us the authority to administer controls to assure safety, purity, and potency. I never felt that the Congress had wanted us to be producers in the sense of manufacturers for sale, because in our legislation, sir, we could not give it away for use, we would have to sell it. The whole history of the biological business has been that we played a role as authorized by the Congress, and industry played a role in accordance with the economics of this country.

But, again, I am not qualified to get deeply into the question you asked. I am a physician basically, sir.

Mr. SCHENCK. Your position, I take it, is that the real function of the Public Health Service is to establish the controls that are necessary for the public health of the Nation and not in producing medicines or drugs or any other preparations for the use of the public?

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Dr. KURLANDER. With one qualification, sir, if I may. If I, as a Public Health Administrator and a physician, felt that a dire emergency was facing this Nation, and that the only solution to handling this emergency was by us getting into this kind of thing, because nobody else would do it, then I think that in terms of our responsibility to the people of this country, I would favorably consider it.

I do not think this kind of situation exists today.

Dr. TERRY. As Surgeon General, I would like to concur in that, sir. I think the only reason that we would have to go into the production of such materials is, if private industry could not or would not produce it, and it was necessary to protect the health of the American people.

Mr. SCHENCK. Thank you very much.

Mr. ROBERTS. One of the reasons why we are having to go into this proposition with you and ask you why the industry has not moved faster is that the pharmaceutical industry has chosen not to come here today to give us some of the answers to some of the questions we are asking of you, Dr. Terry, and your colleagues. We are compelled to pursue this method of trying to get this information. They were invited, but they did not appear.

Now, do you feel that the U.S. public at the present time is at a disadvantage as compared with the people in those foreign countries where the oral vaccine has been made available?

Dr. TERRY. May I ask Dr. Murray to answer this?

Mr. ROBERTS. Yes.

Dr. MURRAY. I think there may be differences of opinion on this point. But I think the basic fact is that in this country the Salk vaccine is freely available, and failure to be immunized against poliomyelitis has been demonstrated to be coupled with failure to accept vaccination. Other countries which do not have Salk vaccine available would be in a position where live vaccine might be more necessary at an earlier date than it is in this country.

I don't believe that the population at large is at any serious disadvantage by not having live vaccine available at this moment, except for the very special situations I think that Dr. Langmuir touched on, that is, the ability to immunize patients becaus of the fear of the needle, and the possibility of using it in epidemic situations.

Mr. ROBERTS. What I had in mind, was the fact that in several sections of the country the fear of the needle is probably not going to grow any less, and would we not be at a disadvantage if we didn't have such vaccine to attack any epidemic which might develop?

Dr. TERRY. I think that is a very difficult question to answer, Mr. Roberts. One could rationalize, sir, and say that since the Salk type poliomyelitis vaccine is available, that it is more or less a matter of individual choice, the exercise of which has prevented people from obtaining the vaccine and thus getting whatever protection is afforded by the vaccine.

Admittedly, we would like to have an effective and a safe oral vaccine available. We are pushing all we can to get such a thing available. But we do not feel that we are in a critical stage or state from the simple standpoint that we already have the protection of a known effective agent which is safe. And insofar as the Public Health Service is concerned, sir, we don't intend to let any oral vaccine go on shelves until we are convinced that it is potent and safe.

Mr. ROBERTS. Of course you are going to continue to be handicapped so long as you don't have applications for licenses from the manufacturers, is that not true?

Dr. TERRY. That is right, sir. I do not think that should be interpreted to mean that none of the manufacturers is working on it.

Mr. ROBERTS. Mr. Rogers?

Mr. ROGERS of Florida. As a matter of fact, I understand some manufacturers are, and even are producing in other countries where it has been accepted. Our standard here is probably higher than used in other countries, is it not, on our vaccine, since we are requiring all of the other viruses to be removed or dead before the application of an oral vaccine manufacturer is approved?

Dr. MURRAY. Certainly the testing that is required in the United States is much more extensive than that which is being pursued in the Soviet Union, for instance, according to the information we get from the people involved.

Mr. ROGERS of Florida. What about in England?

Dr. MURRAY. In England I don't believe that any product has been licensed as yet, but the British draft regulations, as I have seen them, are very similar to our own, in fact have been based upon the American concepts.

Mr. ROGERS of Florida. I believe they are carrying on experiments in Japan, are they not? Or are you familiar with those, sir?

Dr. MURRAY. I only know what I have read in the newspapers, sir. But I understand that some studies are contemplated.

Mr. ROGERS of Florida. Do you have any coordinating effort now to bring together tests that may be going on in other parts of the world to take advantage of it?

Dr. TERRY. Dr. Langmuir?

Dr. LANGMUIR. The World Health Organization, through the Pan American Health Organization located here in Washington, sponsored two large and very carefully prepared conferences, one in June of 1959 and one again last June, 1960. They were beautifully organized conferences. Essentially all of the active workers in this field throughout the world, including scientists from South Africa, several from the U.S.S.R., Poland, Czechoslovakia, Europe, this country, and South America participated, and the documents were published in final form only 6 weeks after the completion of the conference. This represents an enormous consolidation of knowledge. I would say in my experience I know of no similar program for the consolidation of current knowledge comparable to this in the history of public health. The two volumes published will speed the resolution of the many issues that remain.

Mr. ROGERS of Florida. What I was thinking of, for instance, if Pfizer, who is a company here, manufacturer here, I think they have a plant in England, maybe a subsidiary, at Sandwich, if they are carrying on tests there, is there any tying in of what they are doing there with our studies, other than in a world conference?

Dr. TERRY. Dr. Murray?

Dr. MURRAY. Of course if they were in the situation of being prospects for obtaining a license for material to be sold in the United States, we would naturally have direct access to that information. But apart from that mechanism, there exists among the scientists

involved an informal and very effective circulation of information almost as soon as it becomes available; in fact, this has been a very gratifying aspect of the entire research work that has gone on in live poliomyelitis vaccine development. Copies of such reports, even before they are printed, reach us, and sometimes we distribute these to interested persons according to the worth of the report. This includes keeping the manufacturers of this country informed.

Mr. ROGERS of Florida. I just thought it might be helpful to us, because I realize that you can't keep up with all of it, and your staff and the study.

For instance, the studies now being made in Japan, and if you have any recent studies it might be well for us to have the results for the committee file, and if necessary for the record, I think it would be interesting for us to go over some of those, if you have them.

I wanted to ask a question or two, and then I will conclude, Mr. Chairman.

How many manufacturers produce Salk vaccine?

Dr. Murray, would you say in our country there is a fairly significant production?

Dr. MURRAY. I would have to total them up in my mind but it is either six or seven. The answer is six at the present time.

Mr. ROGERS of Florida. Six or seven? Are these the same six or seven that you have sent letters to asking about the production of the Sabin oral vaccine?

Dr. MURRAY. I believe these are the manufacturers that have the necessary background of tissue culture experience, and it was on that basis that I believe that these letters were sent.

Mr. ROGERS of Florida. So they would be the same ones?

Dr. TERRY. Dr. Kurlander?

Dr. KURLANDER. One in addition. In general, yes.

Mr. ROGERS of Florida. Well, it seems to me—would there be any advantage—not that this is true—but would there be any advantage in a manufacturer who is producing Salk vaccine to prefer not to produce another vaccine so long as they have already perfected a particular vaccine that is not on the market?

Dr. MURRAY. That would be entirely at the choice of the manufacturers, sir.

Mr. ROGERS of Florida. I wondered if we should broaden or try to encourage other manufacturers who are not now in the Salk vaccine business by asking them to take a look into this, because it might speed us up a little bit if we could get someone who perhaps is not in the present business of supplying vaccine. I wondered what you thought of something like that.

Dr. TERRY. Mr. Rogers, I do not feel that this is any deterrent to any of the companies. They are always looking for new products. No one can predict exactly today what is going to be the relative weighted usefulness of the two in the future, though we believe that both will continue to have a usefulness. And certainly any company that felt that it could and was in a position to handle the oral vaccine even though they were producing the Salk vaccine, I believe it would be no deterrent at all.

Mr. ROGERS of Florida. I just wonder what encouragement there would be for it if they felt they were producing an effective vaccine. I do not think there are any improper motives about it.

Dr. TERRY. I think it is a question of the industry's competitiveness, sir.

Mr. ROGERS of Florida. Yes. And that is why I wonder if it is wise for us to try to broaden our base. Perhaps it is not practical to. But from the letters that you sent out I wonder if perhaps other industries would be even interested. I can see that they might not if they are not already in that field. But it also occurs to me that it might not be wise for us to perhaps broaden our base if possible in trying to encourage manufacturers to take an interest in this, if, after you have sent out a letter and still have no real encouragement, other than from one or two—I believe you have two that indicated they might, one not very definite, and one indicating maybe in the spring of 1961 they might be producing some—what would be your reaction to broadening the base by sending a letter of inquiry, as we did?

Dr. TERRY. I personally do not believe that it would have any effect to broaden it into companies that are not set up, do not have the professional personnel, unless some company had decided for that, or other reasons already, to go into production.

In other words, I do not believe we could stimulate them or prod them into doing this.

At the same time, sir, I do not think there is any question but that any company which is producing biologicals is going to be interested in producing a live, potent, and effective poliomyelitis vaccine as early as they possibly can.

Mr. ROGERS of Florida. I just wondered why it is taking so long, then, while they are actually producing it in England, even one of our own companies, and yet we are not producing it here in this country.

Dr. TERRY. Will you answer that, Dr. Murray?

Dr. MURRAY. I do not believe, sir, that from the information that I have—and admittedly this is not direct information—that the situation in Great Britain is any different from what it is in the United States. The manufacture of the live vaccine is in its initial phases, and one or two manufacturers may have gone ahead to the extent of acquiring a few lots further down the line and have more tests off than the other one, but virtually as far as the two countries are concerned, I would think—and I base this on my contacts with my corresponding professional associates in Great Britain—that there is no difference in the progress.

Mr. ROGERS of Florida. So the only place would be Russia, and their standards are not as high as ours?

Dr. MURRAY. In Russia they have a different problem, and they have been carrying out——

Mr. ROGERS of Florida. They do not have the Salk vaccine.

Dr. MURRAY. Yes; they do, but apparently this has been produced only in limited operations.

Mr. ROGERS of Florida. I think this is true, and I think we ought to make this clear for the record that the vaccine in Russia actually was not produced in Russia, bus was produced by Dr. Sabin, and it is his basic formula or discovery that they are using and have used.

Would that be a correct statement?

Dr. MURRAY. No; I think that would not be a correct statement, because the vaccine that they are using in Russia was actually manufac-

tured in Russia, according to standards which they themselves adopted. The vaccine was manufactured using as its mother seed in production material which they got from Dr. Sabin, and in the development of their standards they relied heavily on the advice of Dr. Sabin originally.

Mr. ROGERS of Florida. Was his original vaccine not that which developed that program for them?

Dr. MURRAY. Yes.

Mr. ROGERS of Florida. That is the point I was trying to make: the development of the entire Russian program came originally from Dr. Sabin.

Dr. MURRAY. The basic work was done in this country.

Mr. ROBERTS. Thank you, Mr. Rogers.

Any further questions?

Mr. SCHENCK. Mr. Chairman, I was quite interested in the testimony of Dr. Terry and others that you are attempting to set up standards but have not yet set standards for the Sabin-type oral vaccine.

Dr. TERRY. Dr. Murray.

Dr. MURRAY. I would like to clarify that, if I may. The mere publication of the standards in the form of regulations represents a date in time. But this also represents discussions, the results of experimental work, investigations that have gone on for a few years. It is merely the culmination of that, taking into account poblems which have recently been encountered in the attempts of the manufacturers to produce the vaccine. So, the standards themselves do not have to exist before the manufacturer can get started. He starts manufacturing based upon his knowledge of the art, as it is acquired from his own experience and from the experience that has come from the medical literature.

Mr. SCHENCK. Then you are not yet in a position to set the standard?

Dr. MURRAY. The regulations——

Mr. SCHENCK. Or final standards.

Dr. MURRAY. The regulations are written, and they have been circulated, and have been considered by the manufacturers in one form or another for the past year and a half. And the text which will be published in the Federal Register later this month is merely the culmination of this.

Mr. SCHENCK. As I recall in the Salk vaccine development, where they manufactured batches of Salk vaccine carefully labeled, preserved under proper temperatures, and all this and that, they then had to send samples of each batch, numbered batch, to your laboratory, which made a test, and if your test equaled their test, then the batches by number were released.

Is my recollection correct on that?

Dr. MURRAY. They would be released on the basis of the consideration of all of the evidence, including those tests, if they were done; yes.

Mr. SCHENCK. Now, how many batches of material of the Sabin oral type must be presented for consideration to your evaluating laboratories before you will grant a license, let us say?

Dr. MURRAY. Five for each type.

Mr. SCHENCK. Now, after you have granted a license to a manufacturer based upon your testing of these five batches, and you found them satisfactory, then is there any way of indemnifying the manufacturer against a lot of suits which might be filed as a result of somebody taking this oral vaccine and perhaps already having polio and then having it blossom out?

Dr. TERRY. Mr. Schenck, our assistant general counsel is here. This is a matter that we have discussed. This is a legal problem.

I would like for him to comment on it to the basis of our discussion and consideration thus far.

Mr. ROURKE. The only authority the Service has to indemnify is in the course of a research contract. It has special authority acquired through an appropriation provision to indemnify the research contractor against certain liability which might follow the research.

The Service does not have any other authority to indemnify—for example, we have no authority to indemnify a licensee for any risk he incurs and liability he might suffer because his product, when sold on the market, is considered defective and damages are assessed. We have no authority.

Mr. SCHENCK. Assuming the manufacturers has developed a preparation which has met all of the tests of your laboratory, and has then been licensed and continues to have his batches tested as they go along, what assurance does the manufacturer have, or what backing up are you in a position to give the manufacturer in the event someone is infected by some disease which they claim was caused by this vaccine?

Mr. ROURKE. The only backing up would lie in the quality and integrity of the scientific work that Dr. Murray's outfit put into this development of standards and this testing of batches. In other words, it is this quality of scientific support from this process that I would think would give a manufacturer some assurance.

Dr. TERRY. Mr. Schenck, there is one other aspect to this question which I would like brought out, if I may.

As was mentioned in my opening statement, we maintain a surveillance unit which watches with the local and State health departments, and so forth, the development or the occurrence of poliomyelitis cases as they occur throughout the country.

Of course this is a very important function, and has some relation to the point that you are making. If I may, I would like to ask Dr. Langmuir to comment about this, sir.

Dr. LANGMUIR. Since 1955, when there was a problem in the early days of the Salk vaccine, at the Communicable Disease Center in Atlanta I have had responsibility for maintaining the surveillance program in many diseases, but polio is the one in question now.

We receive from the States very accruate information. Currently we get a telegram about a total count of cases about a week later, an individual record which gives the name and the identifying data, the dosage of vaccine received, if any, age, and then 60 days later we receive another followup where they check on the verification of the diagnosis, it is corrected, duplicates are eliminated, and laboratory results, which may take 2 or 3 weeks to perform, are consolidated in this record.

And we in turn publish this information in a report that goes out to over a thousand persons who are interested and concerned. As a result, I would say that we are in an excellent position to provide a

manufacturer with a great deal of protection against a false suit, against a false claim. We will know the background, we will know the expectancy in an area.

So that to me this is a logical regulatory function that we have of making information available so that every one will clearly understand what has happened.

This, I believe, was very helpful in clarifying the situation in 1955, and it is to me a continuing responsibility that we should give very high priority to.

Mr. SCHENCK. So your surveillance control, or quality control, this system, you feel, would be helpful to the manufacturer who might be confronted with a libel suit?

Dr. LANGMUIR. Or to a physician or anyone who might be the subject of an unfounded complaint of liability.

Mr. SCHENCK. Would the counsel feel that that would be of significant help in such a case, and if counsel for the Public Health were the counsel of XYZ Co., would he rely upon that?

Mr. ROURKE. I would think he would. I would be very grateful for this kind of support. But obviously I do not represent XYZ Co., and I would rather have the company speak for that, or its attorneys.

Mr. ROBERTS. Summing up a little bit, is the Public Health Service informed as to the State and local programs to administer the Salk vaccine to children whose parents cannot afford to pay for administration by private physicians?

Dr. TERRY. Dr. Langmuir.

Mr. ROBERTS. Would you comment on that, Dr. Langmuir.

Dr. LANGMUIR. At the present time we have no direct program in the Public Health Service for this. We visualize the great problem of immunizations as a fundamental local control responsibility. Each State has its own rules and regulations with regard to these services, developed since Jenner and smallpox, really, and certainly in the last 30 years. Some States provide vaccinations and all kinds of vaccines and immunizing agents free; others provide them for certain particular groups of the population; some provide these locally for some selected groups, and so on.

It is as free as public school education. The funds from the Public Health Service, general funds in the support of health to the States, it is permissible, I understand, to have the States use some of these funds for the purchase of polio vaccine. But since 1957 there has been no Federal support directly for this.

Mr. ROBERTS. Do you care to give us, or could you give us, an estimate as to how many children will be inoculated before the onset of the 1961 season?

Dr. LANGMUIR. There were about 50, between 50 and 60 million doses of vaccine distributed in the 12-month period just ended. There are roughly 4 million babies born—this is very crude—if they received the full recommended dosage, this would be four doses, so this would be 16 million doses of vaccine as the necessary replacement to maintain Salk immunization.

Also, with 4 million babies, there would be more pregnant women, and somewhere from one booster to a full course of four doses for women pregnant for the first time, and somewhere around 25 or 30 million doses a year would be the maintenance level, maintaining our immunization level at the present point.

So we can say in the last year a very substantial improvement in the immunization level in the country took place.

We do know that most of these went to booster shots, giving fourth doses to those who already had had three.

So that our problem still lies in getting maybe up to 50 percent of our preschool children, and particularly those under 1, to get the immunization started in that group, at least 50 percent of these children do not receive this immunization soon enough to be really effective in the control of polio.

Mr. ROBERTS. One other question. How many children are expected to be inoculated under free public State and local programs this spring?

Dr. LANGMUIR. I have no source of figures. Each State will vary, and within each State a great variation in this. I know of no estimates of this.

Mr. ROBERTS. Mr. Rogers?

Mr. ROGERS of Florida. Just one question, Mr. Chairman.

Could you tell me now when the Salk vaccine was actually discovered and when the Sabin vaccine was discovered?

Dr. TERRY. Dr. Murray?

Dr. MURRAY. Well, without actually referring to the literature, I would say that the Salk vaccine came into use, it was proved out in 1953–54, in that period. I would not like to comment on the Sabin vaccine, because I am not familiar as to the exact dates on which Dr. Sabin did his work.

But the whole question of the use of a live vaccine has been under study for approximately 10 or more years. And the Sabin vaccine itself has gone through small field trials to larger field trials during the last 3 to 4 years.

Mr. ROGERS of Florida. If you could supply for the record, if it is not too difficult, when Sabin was also discovered——

Dr. MURRAY. I would be happy to.

Mr. ROGERS of Florida. And it is taken orally?

Would you describe it quickly, how it is taken, and in how many doses?

Dr. TERRY. Dr. Langmuir has something which might interest you, sir.

Dr. LANGMUIR. I have this little vial which is one of my mementos of a trip to Moscow. The group of Dr. Chumakov and Dr. Voroshilova announced that they conferred with the Institute of Research in Russia—they do things by institutes in that country—and they take the sugar syrup which contains the virus and deliver it to a candy manufacturer, who in some safe way converts it into clumps, granulated sugar candy balls. I understand that as soon as it gets moist with saliva it disintegrates like an aspirin tablet, quickly, in a matter of a few seconds and it is not easy to spit out, there is no reason to spit it out, it is a pleasant experience.

And so it is swallowed, and it goes over the tonsils and into the stomach and intestines.

The different colors represent type 1, type 2, and type 3, and then the gray one—they have faded unfortunately so—the gray one represents all three together.

Mr. ROGERS of Florida. So you can't take one dose for all three?

Dr. LANGMUIR. This is one of the administrative questions with this, it is necessary to give at least four doses. And from a public health administrator's point of view, this is one of the limitations we didn't bring out sooner, you have to get them back.

Mr. ROGERS of Florida. Now, at what period of time?

Dr. LANGMUIR. Recommended at 6-week intervals in order that the first one will have taken and been eliminated before you start the next one. Otherwise they might compete with each other.

Mr. ROGERS of Florida. And how does that compare with the Salk vaccine?

Dr. LANGMUIR. Well, it is a month to 6 weeks, rather similar intervals, actually. But then there is a booster effect 7 months later recommended for Salk, and the triple vaccine, all three together are recommended to sort of varnish down the surface, to fill in any crevices that are left behind again 6 months after the three had been completed.

Mr. ROGERS of Florida. And, as I understand it, you think the oral probably is more effective in the long run according to the statement?

Dr. LANGMUIR. There is considerable difference of opinion, but I would say the weighted opinion favors a longer duration of effectiveness for the Sabin. There is a greater rapidity of response, so immunity develops faster with the Sabin.

There is, however, this problem of interference. You don't know for certain when you give the Sabin sugar sirup or pill that it will take, because there may have been another virus there and no room for the Sabin to take.

So you have no assurance that it takes.

We do know in this country that the reports indicate better than 90 percent as a consistence. This is the reason for the last triple dose to cover up and take.

Mr. ROGERS of Florida. Thank you.

I appreciate it, Mr. Chairman. And I want to say that I certainly have been impressed today by the fact that our public health service is on top of this problem. I do hope we can push it a little faster. And I think we have taken too much time in encouraging the production of this oral vaccine, since you have made the determination that it is now safe, according to your announcements and the regulations issued.

Mr. ROBERTS. Thank you, Mr. Rogers.

Dr. Langmuir, if you could supply for the record any information that might be helpful to the committee as to the number of children that you expect to be inoculated under the public State and local programs in the spring, we would be very appreciative.

(The information requested follows:)

ESTIMATED NUMBER OF CHILDREN WHO MIGHT GET POLIO VACCINE THROUGH FREE CLINICS DURING SPRING AND SUMMER OF 1961

There are approximately 3.8 million children between the ages of 5 and 15 who have had no vaccine. In general, these are children in low income families who would be unlikely to pay for vaccination. There are also 4.6 million children aged 0 to 5 who have had no vaccine. Some of these are children whose parents plan to have them vaccinated by private physicians. A sample survey conducted a few years ago indicates that about a third of the children in this age group get vaccinated by private physicians. This would indicate that approximately 1.5 million children under 5 are unlikely to get vaccinated if a charge is made.

Assuming that all children who would not get vaccinated if a charge were made would get vaccinated if offered vaccine in free clinics—and there is no data to indicate whether or not this assumption is correct—we could expect a total of 5.3 million children to be vaccinated if all communities held free clinics.

Mr. ROBERTS. We certainly appreciate the help that Dr. Terry and his colleagues have given our committee. We have held you on the witness stand for a long, long time. But we felt that this was a very important matter, and we wanted to hear from you.

I would like to make this announcement. Earlier I stated that we had not heard from the pharmaceutical people. I am informed that the Charles Pfizer Co. will file a statement with the committee tomorrow.

I would also like to state that, because he has expressed an interest in being heard, and because of the work that he has done in this field, Dr. Sabin will be a witness before the committee tomorrow, and that the committee is attempting to get word to Dr. Salk, and we are hoping that he, too, will join us tomorrow.

Dr. Youmans, who was here today and stayed with us, representing the American Medical Association, we will hear from this afternoon.

So the committee will stand in recess——

Dr. TERRY. Mr. Chairman, before we recess, may I show a publication which is headed "Babies and Breadwinners," which is a description of our proposal which will help promote the use of Salk vaccine until we have a satisfactory oral vaccine.

If I may, I would like to submit this to the committee for their interest and for their use as they see fit.

Mr. ROBERTS. It will be put in the record.

(The document referred to is as follows:)

## BABIES AND BREADWINNERS[1]

### PROPOSAL FOR 1961 NEIGHBORHOOD POLIO VACCINATION CAMPAIGN

This plan for a 1961 polio vaccination campaign is based on the following premises:

I. No oral vaccine will be available before the 1961 summer poliomyelitis season.
II. The Salk vaccine is plentiful and has proved highly effective.
III. Paralytic polio will be a public health problem until most people who are vulnerable are fully vaccinated.
IV. Concentrating public health efforts where they count the most—in very young children and young parents—is the best way to prevent future polio epidemics.
V. Success in this year's vaccination program demands special efforts directed toward neighborhood groups not yet reached by general appeals.

#### THE NEED

Paralytic polio in the United States has declined from 6,289 cases in 1959 to 2,265 cases in 1960. In 1952 over 21,000 paralytic cases were reported.

This is great progress. But we cannot rest comfortably as long as 38 percent of children 5 years and under, 63 percent of men aged 20 to 40, 48 percent of women aged 20 to 40 are not fully vaccinated.

Study of paralytic polio cases in 1960 shows that almost half were babies and children 5 years and under; young adults who contracted the disease were among those most seriously paralyzed.

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[1] Surgeon General's Committee on Poliomyelitis Control, Communicable Disease Center, Atlanta, Ga., Jan. 23 and 24, 1961.

These facts underlie the theme for this year's campaign: "Babies and Breadwinners."

THE TARGET

Paralytic polio in 1960 was concentrated in low-income areas, both urban and rural.

Vaccination records show that such low-income areas contain a much higher proportion of unvaccinated persons than the country as a whole. This is especially true of preschool youngsters and adults.

These "islands" of unvaccinated persons exist, even within generally well vaccinated communities. And while they exist, the threat of polio epidemics remains.

For these reasons, the special target of the 1961 campaign is the low-income neighborhood.

THE PROBLEM

Experience in a variety of health activities shows that people living in low-income neighborhoods are difficult to reach with an action message, for several reasons:

Their lives are so full of problems (getting enough food, heat and clothing; hanging onto jobs, etc.) that the danger of polio seems to them relatively remote;

They generally have no family physician to advise them;

They tend to distrust officials and outsiders;

They do not fully understand the need for polio vaccination and other health measures;

They have neither means nor time to travel to vaccination centers outside the immediate neighborhood.

Methods which have been outstandingly successful with other segments of the population have left these groups largely untouched. A new approach is needed, designed to meet this specific problem.

THE PLAN

It is proposed that the 1961 polio vaccination campaign be designed primarily to meet the specific problems of these areas of special need.

The theme "Babies and Breadwinners" would have several advantages:

Involving the lower socioeconomic groups without naming them as such;

Aiming at the groups least well vaccinated and most severely attacked in recent years;

Providing a fresh approach after 5 years of general promotion;

Including everyone while permitting concentration on target areas.

Essentially, what is proposed is a series of activities making polio vaccinations convenient, inexpensive or free, and desirable by neighborhood standards.

This can be done by:

(1) Bringing the vaccine to low-income neighborhoods instead of exhorting families to travel for it;

(2) Obtaining neighborhood sponsorship and leadership for the drive.

This approach has already been tried in a number of communities, both large and small. Enough has been learned to indicate that it can be highly successful, if every effort is made to do it in a special way.

THE MEANS

The proposed campaign calls for public health methods regarded as inefficient because they require great effort for statistically low results. But the so-called efficient methods will not now meet the need.

These are the steps recommended:

(1) Locating the unvaccinated islands in the community. Many health departments have already mapped this out. Help is available from the Communicable Disease Center, Public Health Service, in doing this job.

(2) Finding neighborhood leaders and enlisting them in the compaign. Effort spent in locating the people to whom others listen, and then appointing such persons as vaccination leaders, will be richly repaid in the success of the campaign.

(3) Calling on families by vaccination leaders. This can best be done through doorbell ringing or sidewalk conversation. The word of mouth approach is essential.

(4) Bringing the vaccine to the neighborhoods on a series of days over a relatively prolonged period.

This can be done in three ways:

(*a*) Mobile units—trucks, trailers, or station wagons equipped for vaccinations—parked on busy corners or in front of housing developments, with loudspeakers and music to call attention.

(*b*) Nearby clinics—in the heart of the neighborhood, no more than 3 or 4 blocks from any resident—in church basements, union halls, settlement houses, fire stations, lobbies of housing developments or, in rural areas, in Grange halls and town houses.

(*c*) Teams of doctors and nurses ring doorbells, carrying with them syringes and needles and other supplies for on-the-spot vaccinations.

### GETTING UNDERWAY

The keystone of any successful vaccination program, large or small, is approval by the physicians of the community. Voluntary participation of doctors and nurses is vital, since few health departments have staffs large enough to conduct such a program.

It should be pointed out that the target group is one not normally reached by private physicians in their offices. They are the people, for the most part, to whom physicians give their services without compensation at hospitals and in emergencies.

Getting the plan into action means:

On the national level:

(*a*) Notification of all affiliates of medical, health, professional, and civic organizations of the approval and the nature of the plan.

(*b*) Publication of material on the plan in appropriate national professional journals, organization magazines, etc.

(*c*) National promotion, already promised by the Advertising Council through newspaper advertising, TV/radio spots and other means.

On the State level:

(*a*) Endorsement of the plan by State medical societies and State health departments.

(*b*) Assistance to communities by State health departments, where needed.

(*c*) Publication of material on the plan in State medical, civic, and other bulletins.

On the local level:

(*a*) Agreement between local medical society and local health department on nature of the plan and neighborhoods to be covered;

(*b*) Cooperation of medical and health personnel to provide manpower for vaccinations;

(*c*) Careful scheduling of visits and clinics;

(*d*) Suport by local press, TV, radio, voluntary associations.

The pay-off comes on the local scene where the actual work is done.

### FOR LOCAL COMMUNITIES

Suggested ways to carry out neighborhood programs.

*Suggestions for getting started locally*

1. Call a meeting of representatives of the local medical society and health department to agree on the plan.

2. Arrange another meeting of community leaders asking for volunteers to make the many arrangements.

(Include school authorities, PTA's, National Foundation Chapter and other voluntary health agencies, women's clubs, business, labor and civic organizations, press, TV and radio.)

3. Make plan known through coverage of community leaders' meeting by press, TV and radio, so that plan will begin to be talked about. Include rough dates as to its start.

4. Work out a time schedule for giving the shots in specified areas and solicit the services of physicians for specific days and hours. Keep an accurate record of services available from doctors and nurses as they volunteer; this may take full time of one person. Stress the hours for house calls, mobile unit or clinic attendance, remembering that 5 to 9 p.m. are the best hours for reaching fathers.

5. Set up work programs for lay volunteers, making arrangements for clinic sites, answering telephone calls at headquarters, keeping records and being on hand for vaccinations, too. It is advisable to have extra hands at clinics for recordkeeping, keeping order and answering questions.

6. Announce the sites for vaccinations well in advance. Prepare simple posters and flyers listing these. Clinic sites may include: High school gyms, armories, fire stations, church basements, neighborhood or settlement houses, lobbies of housing developments, local department stores, American Legion posts, union halls, shopping centers, Grange halls (in rural areas).

Mobile units should be parked at busy intersections, opposite movie theaters, bowling alleys and bars, near subway and bus stations, shopping centers and the like.

Visiting teams of doctors and nurses should have schedules for their calls in certain neighborhoods.

7. Arrange early for sufficient vaccine. Don't start until enough is on hand to do the job. Delays in shipments can wreck the plan. Line up syringes, etc., by borrowing from hospitals and doctors' offices to augment health department supplies, if needed.

8. Aim at starting by April 1. Your goal is to see that everyone has at least three shots before the summer polio season. For some, this may mean giving the course of shots 2 weeks to a month apart instead of following the usual schedule.

### SPECIAL CONSIDERATIONS IN ACTIVATING THE PLAN

*Finding the neighborhood vaccination leaders*

Locating the right people in each target neighborhood to act as vaccination leaders is important to success. Just picking the heads of neighborhood organizations or depending upon an intelligent religious leader is not enough, although clergymen are important influences especially in Negro communities.

One excellent method is to conduct a face-to-face survey by skilled investigators or interviewers, who know how to ask questions and to evaluate the answers. They must discover who are the people who really carry weight with their neighbors in each neighborhood.

It is suggested that, where possible, such persons be sent to visit storekeepers, druggists, PTA officers, school principals, laundromat operators, beauty parlor proprietors, settlement house workers and, of course, clergymen, as the first step in a neighborhood plan.

The professional interviewers may be health educators, public health nurses, social case workers, county agricultural agents or, in some instances, where a university exists in the community, graduate students working the fields of sociology and anthropology. Ideally, the team should be prepared to spend at least a week in each neighborhood before compiling a list of likely candidates for block or area vaccination leaders.

*Enlisting vaccination leaders*

When one name has been mentioned by neighbors two or more times, that person may be considered to have possibilities as a vaccination leader. Then the task is to see him (or her) and explain the importance of what is being asked of him.

Explain that the vaccination leader should call on every family in his building or block or limited rural area to urge that they obtain polio protection before the summer of 1961. No leader should be expected to go out of his bailiwick. Each should be free to appoint assistants, if he wishes.

Don't be put off by seemingly inappropriate individuals. What counts is how influential they are in their own neighborhoods. The corner druggist may be regarded as a sage. The union organizer may be the opinionmaker in his district. The bartender may be the "neighborhood psychiatrist." Any of these has the advantage of not being official.

NOTE.—A potential leader frequently may be found in the woman known to the neighborhood as a good mother, to whom other women turn for counsel. If these women can be persuaded to become block leaders for polio vaccination, they should be helped by the provision of babysitters for their own children, while they make their block calls.

*Scheduling vaccination times and sites*

It is important not only that the vaccinations be available in the heart of the neighborhood (or in the homes themselves) but also that activities of the

vaccination leaders be timed to accompany or immediately precede the actual vaccinations. Word should be passed to vaccination leaders that the teams, mobile units or clinics will be there on a specific day and at what hours; calls should be made on that day or the day before. If too much time elapses between a block leader's call and the beginning of the vaccination project, too many families will forget about it.

The point the vaccination leader needs to make is: "Get Johnny protected against polio right now, here (when the doctor comes to the door) or downstairs (at a mobile unit) or around the corner (at church, union hall, etc.)."

Leaflets telling about the vaccination visits or clinics may be distributed a few days in advance, but also should be widely available on the day itself. Those who have not heard in advance about the project will read brief, simple leaflets when they see activity on a street corner or lines forming at the firehouse.

*Creating neighborhood interest*

Aim at creating an atmosphere of "everybody's doing it." This means a certain amount of excitement must be engendered. Loudspeakers, music, floodlights should accompany mobile unit. In New Jersey last summer, men with portable microphones walked through the neighborhood where the vaccination trucks were parked, calling on everybody to "come and get it." Spanish-speaking announcers were used in Puerto Rican areas.

Dr. William Dougherty of the New Jersey Department of Health says that much depends on getting a good-sized line at the unit from the start. Where there is a crowd, more crowds develop. It must be a "well-managed mob," he cautions, kept in line through wooden-horse dividers provided by the police. A certain number of patrolmen also should be assigned to keep order at each vaccination station. But with signs of real activity, with music that will keep people singing and with the vaccinees themselves emerging smiling, many people who had not intended to get the shots will be drawn in.

Dr. Dougherty used a special device to create curiosity, speed up the operation and assuage the fears of people who dread the needle: the hypospray gun, which gives shots by means of high pressure, with no needle used. In Providence, R.I., last summer 11,108 shots also were painlessly given in this way in 1 day. The guns have been used for mass inoculations against cholera, yellow fever, and typhoid as well as polio. There have only been several hundred sold to date although mass production now is underway. Where one is available, it is useful. The Communicable Disease Center of the Public Health Service in Atlanta has such a "gun." If contacted, the Center may be able to offer assistance, and will have further information about it. (Fear of the needle, incidentally, is more often present in parents than in very young children. They pass it on to their children, according to Dr. Dougherty.)

Preceding the on-the-spot excitement, some advance buildup should be planned. Posters can be placed in neighborhood groceries, lunchrooms, clubhouses, apartment house lobbies, playgrounds. Neighborhood bus stops are good loactions, especially in rural areas where such stops often are roofed.

Announcements from the pulpits of all neighborhood churches will do much to create interest. The cooperation of clergymen in encouraging attendance at the clinics or other vaccination units is especially effective in Negro neighborhoods.

Similar announcements at neighborhood meetings of all kinds also are helpful.

PROMOTION FOR BABIES AND BREADWINNERS DRIVE

The last 5 years have shown that exhortation alone is not effective with the target group. But all the forces of promotion and publicity that can be mustered are desirable—at National, State, and local levels—to reinforce face-to-face efforts. They will also have a bonus effect on parents in other socioeconomic groups who have overlooked complete vaccination for themselves and their children up to now.

The Advertising Council and its task force agency, Young & Rubicam, once again have agreed to undertake a nationwide promotion of polio vaccination. In cooperation with the Public Health Service, the American Medical Association, and the National Foundation, the council will prepare newspaper ads, radio spot announcements, TV films and slides, plus a car card.

These materials will be mailed directly to local outlets in April. Therefore, early in April, leaders of local drives should get in touch with officials of daily and weekly papers, radio and TV stations, and transportation advertising com-

panies and ask them to time their use of the Advertising Council materials to coincide with the dates of the local drives. This is also a good time to talk to the editors of company magazines and local club and other organization magazines to let them know they can obtain mats of ads from the Advertising Council free upon request.

*Organizational publications.*—National, State, and local magazines and bulletins published by health, education, civic, fraternal, women's, labor, religious, and foreign language organizations will be asked to carry up-to-date information on the status of polio vaccination and the continuing need for vaccination of babies and breadwinners. Editorials supporting this campaign would be particularly helpful, since many of these publications (labor, religious, foreign language) do reach low-income readers.

Foreign language publications are particularly important in areas where there are foreign-speaking populations. In many isolated cases, these have been the only source of vaccination information. One father in New Jersey took his son to New York City three times for shots because his Spanish newspaper mentioned the shots were available there—he did not know they also were being given free in his hometown.

*Trade papers and house organs.*—Editorial and matted advertisements for free usage will be widely used, if editors are contacted well in advance by local leaders of the drive.

*Medical journals.*—Reports covering studies on the factors influencing use of the polio vaccine and the special characteristics of the hard-to-reach groups should be of interest to physicians.

*Other professional publications.*—Nursing, physical therapy, occupational therapy, social work, health education, pharmaceutical, hospital, and other journals of the medical and health professions should be supplied with appropriate material on the 1961 campaign.

*Local publicity*

What is said, printed, pictured on the local scene has the most effect. Each community should plan and execute a local publicity program, aimed at the target populations insofar as possible.

This becomes a "doing" rather than speaking or writing activity. For special local events are what make news. They should be planned with a view to obtaining news stories and photographs in local media.

Here are a few examples:

(1) Kicking off the campaign: Do something to attract attention when your first mobile unit goes out, of your first team of doctors, or you open your first clinic. A parade by Cub Scouts and Brownies. A neighborhood rally at which prominent leaders, such as the mayor, speak from the steps of a mobile truck parked in the target area. In Boston in 1959, where 65 percent of the white low-income group was inadequately vaccinated and 70 percent of the colored population, compared to 35 percent to 45 percent of the upper and middle white groups, a mass vaccination clinic was held on Boston Common. To call attention to it, footprints were stenciled in white on streets leading to the clinic from the busiest parts of town. People naturally were curious about what they meant.

(2) Holding vaccination clinics in unusual places:

(*a*) Vaccination leader arranges for a doctor to give shots at a Sunday school class attended by preschool children.

(*b*) Neighborhood baseball team—in uniform—brings younger brothers and sisters to clinic.

(*c*) Head of the biggest local union gets vaccinated with his preschool children (and wife) at the start of a regular union meeting.

(*d*) Mobile unit visits a church supper in rural or suburban communities and, parked near the lawn, dispenses shots before festivities begin.

NOTE.—All these will make good photographs.

(3) Competitions:

(*a*) Get some local merchant to donate a prize for the apartment house or the block that gets 100 percent vaccinated during each round of shots.

(*b*) Stage a Father-and-Son or Mother-and-Daughter competition to sign up other fathers, sons, mothers and daughters for vaccinations in each neighborhood or on each block.

(*c*) Get high school essay contest going on subject of "Why Children Too Young To Go to School Need Polio Shots."

(4) Demonstration: If there is a hypo-spray gun in your community, borrow it for at least one public performance. In Providence, in 1960 there were lines

two blocks long, on a rainy day, for vaccinations, when word got around that the "needleless method" was being employed.

*Special publicity hints*

(1) Avoid precise references to ages of those needing vaccinations. Too many adults still think there are age restrictions.

(2) Use only the simplest of literature. About two small pages of text, with an attention-getting cover and a list of vaccination sites on the back, will do. The New York City Health Department has such a leaflet, entitled "Are You and Your Family Protected From Crippling Polio?" Many other cities also have such pamphlets. Give supplies of these to neighborhood vaccination leaders. When personally delivered, such leaflets have most effect.

(3) Ask your local chain store managers to include vaccination "reminders" on their "daily special" flyers that go out in all wrapped packages. Supermarkets frequently use these.

(4) Get utility and insurance companies serving the target areas to include "stuffers" with their bills, statements, and receipts.

(5) Schedule speakers before neighborhood meetings of all kinds. Be sure the speakers can answer all questions simply. Even a small audience within the target area is well worth the time of a busy health worker or doctor. Remember, the big effort for relatively few but vital responses is necessary now.

OTHER VACCINATION ACTIVITIES

In addition to the neighborhood plan, other methods of vaccinating babies and breadwinners may be considered.

*Labor unions*

Where young fathers are inadequately covered, as in most places, active support of unions is a must. Some unions already have held vaccination clinics, supported with union funds, for members and their families. Obviously more are now needed. Men in general are harder to reach than women, who often get vaccinated during pregnancy or when they take the children to a health center.

A polio clinic held in connection with a regular union meeting would bring the vaccine to many hundreds of fathers. With advance buildup, they may be persuaded to bring their wives and small children along. Point out that breadwinners as well as babies are vulnerable, particularly when they have young children who can carry the virus home to them. Nothing is more tragic than the incapacitation of a wage earner with a dependent family. It is a risk no longer necessary to take.

*Business and industry*

Vaccination clinics in factories and business offices have been successfully held in a number of cities. In Pittsburgh in 5 months in 1957, some 237 industries instituted programs that covered about 55,000 individuals. Little such activity has taken place anywhere in 1960. It is worth reactivating.

Vaccinations given at plant or office not only are convenient for employees but have a decidedly good effect on employee relations with management.

*Welfare departments*

Families on relief are eligible in most places for free polio vaccinations. Those who have not availed themselves of this protection should be approached in 1961. When welfare officials make a special effort to induce parents to get their children vaccinated, it pays off. In Pittsburgh it was found that a letter enclosed with a relief check motivated quite a few people.

According to the Allegheny County Health Department, intensive publicity in the central health district (a low-income area of Pittsburgh) led only 15 percent of those needing protection to obtain it. There was no problem of cost nor availability of services. The problem, according to the Department's March 1960 Public Health Bulletin, has crystallized into one of motivation for the segment of the population that has not responded. For families dependent on public assistance, certainly the efforts of welfare officials will not fall on deaf ears.

*Fraternal and other organizations*

Community clinics organized by fraternal, social, and voluntary health associations should not be overlooked in 1961. Many already have conducted such clinics with amazing success.

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The most popular type has been the low-cost clinic to which families come and pay a nominal fee ($1 or even 50 cents), with their donations placed in baskets on the registration tables and with no charge at all for those who cannot pay. People who can afford it often contribute more than $1, which usually helps to meet the overall costs.

While most of these communitywide clinics have not been held in the heart of low-income neighborhoods, there is some evidence that residents of such neighborhoods sometimes turn out for them.

Outstanding has been the program in Albany, N.Y., where communitywide clinics have been held since April of 1955. There have been 60 since 1956. It is estimated by Thomas J. McEnaney, national foundation chapter chairman there, that 92 percent of youngsters to age 19 have been inoculated either at school or in doctors' offices, while half of all adults aged 20 to 40 have had at least two shots in doctors' offices and at the community clinics. Third-shot clinics are being held monthly. New clinics are scheduled for March 1961. It is worthy of note that in Albany County in 1958 there were no polio cases reported, only two in 1959 and one in 1960.

The junior chamber of commerce, AMVETS, the American Legion, General Federation of Women's Clubs, National Congress of Parents and Teachers and many other organizations have promoted community clinics, with active response by large numbers of their local affiliates. In Oregon in 1959 the Jaycess saw 70 out of their 85 clubs participating. In Portland, a Negro unit of the Elks conducted a special clinic for its members. The AMVET program included doorbell ringing by members to urge attendance at clinics. The American Legion opened its post headquarters in the evenings for community clinics in hundreds of places.

This kind of activity should be promoted again in 1961, with extra emphasis on those organizations having units in soft-spot areas. Face-to-face calls and provision of transportation where needed will bring polio protection to many families not formerly reached.

Mr. ROBERTS. Thank you very much.

We will adjourn until 2 o'clock.

(Whereupon, at 12:35 p.m., the committee recessed, to reconvene at 2 p.m. the same day.)

AFTERNOON SESSION

Mr. ROBERTS. The subcommittee will be in order.

I think we have some more questions we would like to direct to the panel.

Will the gentleman from the Public Health Service take your seats?

## STATEMENT OF DR. LUTHER TERRY, ACCOMPANIED BY DR. ARNOLD B. KURLANDER, DR. ALEXANDER D. LANGMUIR, DR. RODERICK MURRAY, DR. C. A. SMITH, AND EDWARD J. ROURKE—Resumed

Mr. ROBERTS. In order to keep the record clear, I would like for counsel to read into the record section 301 of the Public Health Service Act, just through the first sentence, and then also read into the record section 352 of the act, both parts A and B.

Mr. ROURKE. Section 352 of the Public Health Service Act (42 U.S.C. 263) provides—

That (a) The Service may prepare for its own use any product described in section 351 and any product necessary to carrying out any of the purposes of section 301.

Paragraph (b). The Service may prepare any product described in section 351 for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section.

Section 301 of the Public Health Service Act, being 42 U.S.C. 241, provides in part—

The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnoses, treatment, control and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, nd pollution of lakes and streams.

Mr. ROBERTS. I would like to know if in the past there has been any vaccine or product that has been developed by the Public Health Service under the authority of these two sections.

Mr. ROURKE. Whether a product has been developed under the authority of 301, I would rather turn to the doctors here, perhaps Dr. Murray.

Mr. ROBERTS. Dr. Murray?

Dr. MURRAY. I believe we have one example in the case of the yellow fever vaccine, which was manufactured for a period of years by the Rocky Mountain Laboratory, which is a component of the National Institutes of Health. This vaccine, however, is now manufactured by a commercial company, and when this occurred, the Rocky Mountain Laboratory ceased to manufacture yellow fever vaccine.

Mr. ROBERT. Do you remember, Dr. Murray, about how long the Public Health Service carried on its manufacture of that?

Dr. MURRAY. I do not know the exact dates without consulting the records.

But it was during the war that they started manufacturing out at Hamilton, and it was some 8 or 9 years ago that the activity was entered into by the National Drug Co., which is the one licensed manufacturer of yellow fever vaccine.

Mr. ROBERTS. And would you supply that information for the record?

Dr. MURRAY. Yes.

(The information requested follows:)

PRODUCTION OF VACCINES BY THE PUBLIC HEALTH SERVICE

The Public Health Service is responsible for carrying out the provisions of the Public Health Service Act contained in section 351. Section 352(b) provides the authority under which the Public Health Service has in the past produced yellow fever vaccine and Rocky Mountain spotted fever vaccine. This section states: "The Service may prepare any product described in section 351 for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section."

The production of yellow fever vaccine was started at the Service's Rocky Mountain Laboratory, Hamilton, Mont., in 1941 and was discontinued in 1953. On May 22, 1953, National Drug Co., Philadelphia, Pa., was licensed for the commercial production of this product. This license is still in effect. During the period of production by the Public Health Service, this vaccine was distributed on request to Federal agencies of whom the Military Establishments were the prime users. On occasions, relatively small quantities were distributed to nongovernmental agencies such as airlines. From 1940 to 1948 the production of yellow fever vaccine was financed by direct Public Health Service appropriations and no charges were made to governmental agencies. A charge of $1.75 per five-dose vial was made to nongovernmental users. From 1948 until 1953, when production was discontinued, a charge of $1.75 per five-dose vial was made to all users including governmental agencies. This charge was based upon estimated costs of material and personnel. The present commercial cost

to governmental agencies is $3.30 (direct wholesaler, $4.16). 20-dose vial Government direct, $4.50 (direct wholesaler, $5.14).

The production of Rocky Mountain spotted fever vaccine at Rocky Mountain Laboratory, Hamilton, Mont., where the vaccine was developed, started in 1926, with the "tick type" vaccine, continuing to be produced until 1949; some stock being distributed as late as 1951. Commercial manufacturers were licensed for "chick embryo type" vaccine only. Wyeth Laboratories, Inc., Marietta, Pa., was licensed for this product July 14, 1945, with the license being canceled April 18, 1951. E. R. Squibb & Sons, New Brunswick, N.J., was licensed February 28, 1947, with the license cancelled April 18, 1951. Merck Sharp & Dohme, Philadelphia, Pa., was licensed to produce this product October 18, 1944, with the license still being in effect. Lederle Laboratories, Pearl River, N.Y., was licensed April 13, 1942, with the license still in effect. The Rocky Mountain Laboratory of the Public Health Service, during the period in which it produced Rocky Mountain spotted fever vaccine, distributed it on request to physicians and health officers at no cost. Commercial manufacturers' current suggested retail price (fair trade minimum) is $2.02 per 3 cubic centimeter vial, $9.40 per 15-cubic centimeter vial and $11.25 per 20-cubic centimeter vial.

Mr. ROBERTS. Now, in connection with some other experiences we have had, are you familiar with the procedure which the Government followed in the case of the development of penicillin?

Dr. KURLANDER. Mr. Chairman, I am not familiar with that process. That was some time ago, and I was engaged in fighting the war.

Legal counsel?

Mr. ROURKE. No.

Mr. ROBERTS. I am under the impression that that was done under the Defense Production Act. If you would also supply that information for the record, we would like to have that.

Dr. KURLANDER. Yes, Mr. Chairman.

(The information requested follows:)

The Public Health Service has authority under continuing appropriation language to make grants of funds, services, and supplies for venereal disease control. During the period 1946 to 1954 a number of venereal disease control grants were made in the form of penicillin since the Public Health Service could purchase penicillin centrally and distribute it to a number of the States more economically than these States could purchase the drug for their own account. In some cases penicillin could be so furnished the States by the Public Health Service at a saving of more than 60 percent. During the period indicated, the Public Health Service made grants of penicillin in the amount of some $4.5 million. This central purchase and distribution mechanism was discontinued in 1954 when the penicillin suppliers agreed that they would send penicillin directly to the States at the Federal price when State purchase orders therefor were endorsed by the Public Health Service as being on behalf of the Federal-State venereal disease control program.

Mr. ROBERTS. Now, let's go to the development of the Salk vaccine. What was the procedure followed in that case, and what was the role of the National Foundation in that case?

Dr. MURRAY. In the case of the Salk vaccine, it is my understanding that the National Foundation entered into agreements with a number of companies to produce a certain quantity of poliomyelitis vaccine, in the first instance for use in field trials, for validation of the safety and effectiveness of the vaccine, and later in order to provide vaccine for administration in the Foundation programs.

Mr. ROBERTS. Do you recall whether that was under an arrangement of a loan or an outright gift, or just how was that handled?

Dr. MURRAY. I have no personal knowledge of the way it was handled.

Mr. ROBERTS. Would you like to supply that for the record?

Dr. MURRAY. We will attempt to supply it.

(The information requested, supplied by the National Foundation, follows:)

FACT SHEET ON SABIN LIVE-VIRUS POLIO VACCINE PREPARED BY THE NATIONAL FOUNDATION

GENERAL

On August 24, 1960, the Surgeon General of the United States announced that the live-virus polio vaccine, developed by Dr. Albert Sabin with March of Dimes funds, has been found "* * * suitable for use in the United States."

Immediately, thereafter, Dr. Thomas Rivers, Medical Director of the National Foundation, announced that Dr. Sabin, with the approval of the March of Dimes organization, would make his virus strains available to all who wished to manufacture the vaccine.

"The vaccine was developed with the dimes and dollars of the American people, and is, therefore, the property of all," said Dr. Rivers.

Subsequently, Surgeon General Burney announced that, because of "the many problems still to be worked out in taking production out of the laboratory and into mass production * * * we cannot expect to have the oral vaccine available for use by this summer (1961)."

At the same time, Dr. Burney announced formation of a committee on poliomyelitis control made up of representatives of the medical and health professions and the general public to advise the Public Health Service on how best to carry on the polio fight with both the Salk vaccine and the Sabin oral vaccine, when it becomes available.

The report of this committee was approved by the new Surgeon General, Dr. Luther Terry, on February 28, 1961.

HOW DOES THE SABIN VACCINE DIFFER FROM SALK VACCINE?

Salk vaccine uses killed viruses. All three types of poliovirus are treated chemically to deprive them of their power to cause paralytic polio, but they retain their power to provoke the body to manufacture polio antibodies, thus providing immunity. Live-virus vaccine uses viruses that have been weakened, but not killed.

The Salk vaccine must be injected. Live-virus vaccine can be taken by mouth.

Live-virus vaccine sometimes spreads immunity to the unvaccinated. Salk vaccine does not.

The oral vaccine is easier to administer and scientists hope it may provide longer lasting immunity. Only years of experience can show how long immunity lasts.

HOW DOES THE SABIN LIVE-VIRUS VACCINE WORK?

Attenuation.—The viruses in oral vaccine are alive, but they are, in effect, "weak sisters." They have been selected and processed in the laboratory to make them harmless. When fed to a human being, they cause an actual polio infection. The viruses multiply in the intestinal tract and the body reacts, just as it does in an actual polio infection, by forming antibodies that fight off any subsequent polio attack.

Spread.—Oral vaccine viruses spread from people vaccinated to others in close contact with them in the same way polio viruses in nature are spread. This means that when one person in a family is fed a live-virus polio vaccine, other members of the family can "catch" the vaccine viruses from him and thus become "vaccinated" themselves. However, this spread has been found to be limited.

WHAT WAS THE ORIGIN OF THE SABIN LIVE-VIRUS VACCINE?

I. A mutant poliovirus isolated from the virulent Mahoney strain by Drs. Li and Schaeffer of the U.S. Public Health Service, a strain originally obtained by Dr. Thomas Francis, Jr., of the University of Michigan, from a child in Cleveland who was a victim of nonparalytic polio.

II. A naturally weak strain originally obtained from the stool of a healthy child in Louisiana by Dr. John P. Fox of the University of Tulane.

III. Mutant derived from a virus known as "Leon," named for the boy from whom it was obtained originally by Dr. J. F. Kessel of Los Angeles.

MARCH OF DIMES GRANTS TO DR. SABIN

The National Foundation, through March of Dimes grants, has supported all of Dr. Sabin's work on the live-virus vaccine. These grants have amounted to approximately $1,500,000.

Dr. Sabin recently made the following statement concerning March of Dimes support of his work:

"I wish to express my appreciation to the National Foundation for its faith in my work, expressed through grants of March of Dimes funds totaling $1,500,000.

"For 22 years, the National Foundation's broad medical research program has opened new doors in the whole field of virology. It was these breakthroughs that made antipolio vaccines possible.

"I wish also to express my thanks to the American people, whose contributions to the March of Dimes made it possible for the National Foundation to support my work."

BASIC MARCH OF DIMES RESEARCH IN LIVE-VIRUS POLIO VACCINE DEVELOPMENT

Among countless studies, the following were key advances:

(1) Discovery in 1949 by Dr. John Enders and associates at Harvard of poliovirus tissue culture techniques that revolutionized laboratory research procedures and won them the Nobel Prize. Without this technique, both killed and live-virus polio vaccines of today would be impossible.

(2) In 1950, scientists of the University of Southern California, Utah, Kansas, and Pittsburgh announced results of a 3-year poliovirus typing program establishing that three different viruses cause the disease. This information was essential to the development of any effective polio vaccine. The typing project was financed at a total cost of $1,190,000 in March of Dimes funds.

(3) In 1953, Dr. Renato Dulbecco, of the California Institute of Technology, announced development of so-called plaque technique method of obtaining genetically pure strains of the virus. This was, perhaps, the most significant contribution of basic research to live-virus polio vaccines. It made possible precise selections and isolation by scientists of indivdual virus particles with heredity characteristics. All strains of virus now included in the three live-virus polio vaccines were obtained by this plaque purification technique.

CURRENT MARCH OF DIMES SUPPORTED RESEARCH STUDIES AND TRIALS OF SABIN LIVE-VIRUS VACCINE

March of Dimes grants totaling $346,182 have gone to 4 scientists now conducting research studies and trials pertaining to forthcoming use of the Sabin live-virus vaccine. They are:

(1) *Viremia and reversion.*—Dr. Joseph L. Melnick of Baylor University, is seeking to learn if viremia occurs following vaccination with the Sabin live-virus product. In his study, he recently took blood samples from 650 prisoner volunteers aged 18 to 26. He will give Sabin vaccine to those who show lack of antibodies to one or more polio-virus types and test their blood frequently afterwards for presence of measurable virus. If he finds that viremia does occur often and to a considerable degree, authorities might have to reconsider whether live-virus vaccine is suitable, particularly for young adults and pregnant women.

Dr. Melnick and his associates are also conducting exhaustive studies on reversion—the extent to which weakened viruses in the vaccine regain some of their original virulence after passing from vaccinated to unvaccinated persons. Dr. Burney stressed this possibility as a reason for using Sabin vaccine on a mass community basis, rather than on an individual basis.

(2) *Administration, dosage, reversion, viremia.*—In addition to reversion and viremia studies, Dr. John R. Paul of Yale University, is conducting tests to determine the optimum administration and dosage schedules with the Sabin vaccine to produce the greatest likelihood of a take. The Burney statement

pointed out that interference with effectiveness of live vaccine poliovirus by other viruses circulating in a community probably will make it necessary to administer Sabin vaccine in three or more doses.

(3) *Administration and dosage in infants.*—Dr. Frederick C. Robbins, Western Reserve University, Cleveland, is studying effectiveness of Sabin vaccination in newborn babies and very young children, who do not always respond to immunization in the same way as do older children and adults. He is seeking to learn how early vaccination should start and what the dosage and administration schedule should be to provide full protection as early as possible in life. Infants are one of the so-called special groups referred to in Dr. Burney's statement.

(4) *Administration and dosage in infants.*—Dr. Randolph Batson, Vanderbilt University, Nashville, Tenn., a veteran of research on the effectiveness of Salk vaccination in infants, is conducting studies with Sabin vaccine similar to those of Dr. Robbins.

Mr. ROBERTS. What has been the role of the National Foundation with respect to the oral vaccine?

Dr. KURLANDER. Mr. Chairman, may I ask a question please, sir?

The questions that you address to us with reference to the National Foundation are questions that sir, are not within our province to know the answers to. We are not the National Foundation, we have no responsibility for the National Foundation, we have no access to their records, we do not determine their policy. I feel a bit embarrassed, sir, to ask them for information which they may or not be willing to give to us. We have no basic authority to ask for this. I have no assurances that they will give it to us.

And, frankly, sir, I feel rather uneasy about promising you something that is not within my province to see that it is carried out.

Mr. ROBERTS. I appreciate that situation. And we will make an attempt to get the National Foundation to join us in the hearings, and if we can't get it that way we will try other ways.

Dr. KURLANDER. Thank you, sir.

Mr. ROBERTS. Of course I am sure that you know about whether or not the armed services would be interested in the old vaccine, that is, for use by our forces abroad. Now, have the armed services so far as you know used the oral vaccine abroad?

Dr. MURRAY. We have no information on this matter.

Mr. ROBERTS. What has been the contact between the Public Health Service and the armed services with reference to this situation?

Dr. MURRAY. I can't speak for armed services policy, but whenever the question of using a biological product has come up in the past, the armed services have insisted on the use of a licensed biological product, one which has already been licensed, and, therefore, it would be my interpretation—this is just my interpretation of the situation—that they would not have used oral polio vaccine as a preventive medicine measure.

Mr. ROBERTS. But under the authority that is contained in the Public Health Service Act, it would be the function of the Public Health Service to cooperate with the armed services if such a request is made to the Public Health Service, would it not?

Dr. KURLANDER. That is correct, sir.

Mr. ROBERTS. Now, when did the Public Health Service decide to request the Bureau of the Budget to authorize funds for purchase of the oral vaccine?

Dr. KURLANDER. Mr. Chairman, we have this in the chronology. February 13, 1961.

Mr. Chairman, may I enlarge on that statement?

Mr. ROBERTS. Yes.

Dr. KURLANDER. The question of whether or not the Public Health Service should attempt to obtain a supply of oral polio vaccine for study and evaluation of its use in epidemics has been under discussion for quite some time in the Public Health Service and among those eminent public health people and scientists who are our advisers. The February 13 timing was a budgetary matter over which we had really no control. I state this only because there is really no significance to the date of February 13, other than that of the budget process.

But the philosophy, sir, behind this was in our minds many, many months ago, and it was the Public Health Service who formally presented this proposal to the Surgeon General's Advisory Committee on Poliomyelitis on January 23 and 24 in Atlanta.

But our proposals in discussion were much previous to that time.

Mr. ROBERTS. Now, was that the meeting of the Advisory Committee on Poliomyelitis control that was held in Atlanta January 23 and 24, 1961?

Dr. KURLANDER. Yes, sir.

Mr. ROBERTS. And this request was under consideration at that meeting, was it?

Dr. KURLANDER. Yes, sir. And it came out, sir, as a recommendation of the advisory group to the Surgeon General.

Mr. ROBERTS. Now, I asked Dr. Terry this morning about the figure of $1 million.

And I would like for you to elaborate just a little more on why this figure of $1 million was arrived at and the basis for the statement that it would buy approximately 3 million doses of the oral vaccine.

Dr. KURLANDER. Dr. Langmuir would answer that, and then I would like to follow.

Dr. LANGMUIR. We arrived, first of all, sir, at the estimate of 1 million doses of vaccine by sitting down with our intimate experience and saying, had we had a reserve at the beginning of the season in 1960, how many doses would we have been able to use effectively? And there was an epidemic in Providence, there was an epidemic localized in certain parts of Baltimore, there were a number of epidemics in groups of two or three counties in Pennsylvania, Maryland, western Maryland, in North and South Carolina, in Kentucky, and we put these together and said, "We think we could have used effectively about a million doses."

Then we realized that if we were going to plan ahead of time and make a commitment for such reserves in the future, we should be careful to have vaccine for each type. Granted that type 1 is the commonest type, type 3 on some occasions has been an epidemic type, and in some parts of the world even type 2 has been an epidemic type.

So that we arrived at this need of a million doses, and then we said we should have an adequate supply of each of the three types. An this was what we felt was a reasonable amount to handle this need of an epidemic reserve.

Mr. ROBERTS. Doctor, you realize, of course, that we are laymen. Would you give us the difference in types 1, 2, and 3?

Dr. LANGMUIR. These are determined only in the laboratory. There are certain differing characteristics that we observe in the field. But one cannot tell for sure except by testing in the laboratory. They are different, such as measles, and German measles. There is no real cross protection. One can have actually, theoretically, three separate attacks of polio. There have been a number cases where there have been two attacks of polio. The types are similar clincially but in testing in the laboratory they are different. So type 1 vaccine protects only in an epidemic against type 1 virus.

It was for this reason that we felt we had to have a supply of each of the three types. This can be determined rapidly, a matter of only 2 or 3 days. So by the time one sensed that there might be a problem here, and you had your first cases under study and you began to organize, it would take a little salesmanship, I think—not too much, maybe, but a few days, at least—and by this time you would know the kind of vaccine to give.

Mr. ROBERTS. When do you expect to be able to purchase the vaccine if the Congress appropriates the money you have requested?

Dr. KURLANDER. Mr. Chairman, we would purchase vaccine when the first licensed product becomes available to be purchased. That, we would hope, would be within a 6-month period. This, though, we cannot guarantee, the 6 months, that is.

Mr. ROBERTS. In other words, you would not consider purchasing the oral vaccine abroad?

Dr. KURLANDER. Mr. Chairman, the Public Health Service would not want to use vaccine that we would not permit to be sold and distributed within the United States.

Mr. ROBERTS. Well, is it available abroad?

Dr. KURLANDER. Vaccine?

Mr. ROBERTS. Yes, sir.

Dr. KURLANDER. Vaccine that would meet the licensing standards of the Public Health Service is not available for purchase anywhere, to the best of my knowledge.

Mr. ROBERTS. Would you care to comment on this question, that is, in what countries is it available, and to what extent has it been used in those countries?

Dr. KURLANDER. Dr. Murray will answer that.

Mr. ROBERTS. Dr. Murray?

Dr. MURRAY. Live vaccine in one form or another has been available in the U.S.S.R. and in some of the countries associated with the U.S.S.R. It has been manufactured in Czechoslovakia. And some has been manufactured in Poland. Vaccine has also been manufactured and used in the Union of South Africa. Vaccine is being processed just as it is in this country in such places as Great Britain and Canada.

If I might add a word to what Dr. Kurlander said, the question of availability of vaccine would have to follow the same rules for vaccine imported from abroad as it would for vaccine manufactured in this country. In other words, if vaccine were to be purchased abroad, sufficient vaccine would have to be manufactured in a licensed establishment, and the manufacturer would have to be licensed for the vaccine. In other words, he would have to meet the U.S. requirements.

Mr. ROBERTS. Now, would that still be true in view of the fact that last year we passed what was known as the International Health Research bill? Is there any authority in that legislation that would allow you to go into a mass experiment in other countries?

Counsel might rather answer that question.

Mr. ROURKE. To make it clear, I think there are two different things. I think there would be authority for the Public Health Service to conduct research abroad. I think what Dr. Murray was addressing himself to was the fact that you can't import the drug into this country for use in our population unless it meets the same standards as a domestic product. There is a difference from the research effort that might be conducted some place else.

Mr. ROBERTS. I knew under the terms of that bill we had authorized meetings of our medical people and scientists with the medical experts and scientists of other countries, and while there are no hard dollars in the program at the present time, we do have some of the currencies which are available in, I believe, some 19 countries, it might be more, that might be utilized for giving this oral vaccine to large numbers of people. I was wondering if there has been some discussion of this matter by the Public Health Service, and if any of you gentlemen had participated in those discussions and might give us some idea as to whether or not there is any plan being formulated as to this one particular vaccine and its use on a broad scale.

Dr. KURLANDER. Mr. Chairman, I am not aware of those discussions. They may or may not have taken place. I was not a party to them.

Dr. LANGMUIR. Let me add this:

In 1959, three of us from the Communicable Disease Center participated in the study in Costa Rica. But this was done in a consulting relationship with the Pan-American Health Organization rather than as something that the Public Health Service itself has initiated.

Mr. ROBERTS. It just occurs to me that if we could safely produce this vaccine it would certainly offer a wonderful avenue of good will in a way that we could very economically assist many of the underdeveloped regions of the world such as we do through the Pan-American Health Organization and various other activities in which we participate like the World Health Organization. If there have been any plans or discussions at a high level that could be supplied for the record, I would like very much to have any information that you could supply for this record.

Dr. KURLANDER. Mr. Chairman, we would be happy to get together what we can on this point. And if I may state first, I am in hearty agreement with the sentiments and the statements that you have expressed.

(The information referred to follows:)

INTERNATIONAL ACTIVITIES—POLIOMYELITIS CONTROL

In the spring of 1955, shortly after the announcement of the successful field trials of the Salk vaccine, the Department of State, at the direction of the President, distributed to all U.S. Embassies the formula for the manufacture of the Salk vaccine.

In the subsequent 2 years, because of the shortage of domestic supplies, an export quota was maintained by the Department of Commerce. When supplies became more freely available, the export quota was removed and substantial supplies have been shipped abroad by the manufacturers during the past 3 years.

From time to time, the subject of providing vaccine for other nations, as a possible gift from the United States, has been discussed within the Public Health Service. These discussions have been informal, however, and no formal proposal has been developed.

On January 24, the Surgeon General's Committee on Poliomyelitis Control, meeting in Atlanta, Ga., recommended that "The Surgeon General should encourage the development of programs to furnish immunizing agents to other countries for the control of poliomyelitis."

On February 16, 1961, the Surgeon General reported to the Committee that the Committee's recommendations had been presented to the proper authorities at the Department of State. In his statement the Surgeon General went on to say:

"The distribution of oral vaccine to underdeveloped countries will be discussed in detail when such a licensed product becomes available in this country for export. The wide use of parenteral vaccines is not feasible in many underdeveloped countries; however, the export of inactivated polio vaccine has been and will be expedited upon request by foreign governments."

The oral vaccine, as has been noted, has been widely used in the U.S.S.R. and in other nations in mid-Europe, and the U.S.S.R. reportedly has made quantities of the vaccine available to the Republic of China. The Public Health Service does not know whether this vaccine has been supplied as a gift. The vaccine supplied to Czechoslovakia, Hungary, and other nations was produced within the Soviet Union, but the precise arrangements between these nations is also not known to the Service.

Dr. KURLANDER. And also, for your information, the Surgeon General's Advisory Committee on Poliomyelitis at the January 24 meeting in Atlanta stated this resolution:

Assistance to other countries. The Surgeon General should encourage the development of programs to furnish immunizing agents to other countries for the control of poliomyelitis.

Mr. Chairman, may I please amplify how we arrived at the cost of the 3 million doses.

This morning the Surgeon General—and, I think, I too—said it was an educated guess. But for the purposes of the record, it was quite educated and less guess, within the limitations of economic knowledge available to us.

When Salk vaccine first became licensed, the price to the Federal Government was $7.13 for nine individual doses, which is approximately 80 cents per dose. The price of 33⅓ cents per dose that we estimate for the oral vaccine is based on approximately one half of the initial cost of Salk, since packaging and sterility control for the new live virus vaccine should be less.

Adenovirus vaccine, another new product needing sterile vials, sells at approximately 80 cents a dose. The current price of Salk vaccine to the Federal Government is approximately now 22 cents per dose. This allows the estimate for the live virus vaccine, a very new vaccine, to be slightly higher than a well-established product, the Salk vaccine, which we have had with us for 5 years, and still pay approximately 22 cents per dose.

Mr. ROBERTS. Now, going back to the statement with reference to imports; what section of the act was the statement with respect to imports based on, and does that section apply if the U.S. Government imports vaccine for use at home in an epidemic?

Mr. ROURKE. The provision of the act that controls imports is the same provision that controls the sale, barter, or exchange between States. It is section 351 of the Public Health Service Act. And if I may, I will read the first sentence of that, perhaps that will do. It is a rather long section.

No person shall sell, barter, or exchange, or offer for sale, barter, or exchange, in the District of Columbia, or bring for sale, or send, sell, carry, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession any virus, therapeutic serum—

and so forth.

In other words, the control applies both to exports, imports, and interstate commerce.

Mr. ROBERTS. Now, going back to this question of the safety factor, in your opinion is that one of the things that has held back the production of oral vaccine in the United States, that is, the fear of liability and the risk of the good name of the manufacturer in case something goes wrong?

Dr. MURRAY. I think this is a question that is more properly answered by the manufacturers themselves.

But I would refer to the summary that Dr. Furlander read this morning of the replies which were received to the November letter which was sent out by the Surgeon General.

Two of the manufacturers brought up the question of product liability without expressing just what was implied by the term "product liability" used in that sense.

Now, as far as the safety of the vaccine is concerned, the basic safety of the vaccine is considered to be covered by the acceptance of suitable strains, and by the establishment of the standards which set forth the testing which will be done on the product. In his conference on August 24, the Surgeon General announced the report of the Public Health Service Committee on Live Poliomyelitis Vaccine in which it was stated that the three sets of Sabin strains were considered safe and suitable for the manufacture of a vaccine.

Mr. ROBERTS. Then you would say that the safety factor has been pretty well taken care of?

Dr. MURRAY. The basic safety factor has been taken care of, because the strains will be licensed on the basis of a demonstration of safety to administration of at least a hundred thousand susceptible people.

Mr. ROBERTS. Now, do you know if there are other factors, that is, economic factors, that can play a part in the development of oral vaccine, such as large development costs? Are you familiar with that phase of it?

Can you say that it does require considerable original investment to go into the manufacture of this vaccine?

Dr. MURRAY. I think that we cannot answer these questions directly, because this is not the kind of information we can rightfully ask from manufacturers—as to why they came to a certain decision. This is a matter of their individual and privileged choice. However, there are certain facts which will emerge if one thinks about the problem. Here we are dealing with a vaccine which is not like a drug which is given in repeated doses time after time to a person. In other words, the market for the vaccine is limited by the population itself. And once you have given the basic number of doses to the population, you have for all practical purposes saturated the market, and from that time on the market only calls for the number of doses to immunize the newborn children as they come along.

This is just my personal guess as to one of the factors which are involved here; in other words, a horizon on the limits to which the material can be made available by a manufacturer profitably.

Mr. ROBERTS. Now, do you feel that the Public Health Service needs any new powers in this field in order to help developments along, or do you think the present powers are adequate?

Dr. KURLANDER. I think, broadly speaking, the authorities and powers that we have are adequate.

Would you have any comment on that, Counsel?

Mr. ROURKE. No. It depends on what happens, as the Surgeon General said this morning, on just the question of manufacture, it depends on what kind of situation you find yourself in in 6 months, 10 months, or a year from now. But as we stand, as far as I know what your proposals may be, Dr. Kurlander, I think you have adequate authority.

Mr. ROBERTS. Would you say that if we are at this same point a year from now that we should consider additional legislation?

Dr. KURLANDER. First, sir, I would hope that we are not 1 year from now at the point we are today. And second, if we are, I think much prior to that time we would have gone into very serious and lengthy discussions as to whether it is legislation that is needed to bring this product forth, or whether there is something else that needs to be done.

Frankly, sir, we have not looked at this matter in the recent past as a problem of legislation. I would, however, reserve the right to change our minds if the situation merits it.

Mr. ROBERTS. What I had in mind was this: that if we do not get some license applications in the mill, and in view of the fact that we have in the past in certain situations, as pointed out by Dr. Murray, developed our own vaccine, the question of protecting the public arises because of the failure of manufacturers to go into this field.

Would you say, then, that you might need additional powers or additional legislation?

Dr. KURLANDER. Mr. Chairman, if my understanding of our present authority is correct, we already have such authority. Is that correct, Counsel?

Mr. ROURKE. It all depends on what we are talking about. We have talked earlier today about indemnification. We have no authority to indemnify. If it becomes clear that the lack of this authority is what is holding up the program, presumably that would be considered at that time.

But you see, it is kind of speculative now. There are various things that might be done. It depends on the circumstances at the time.

Mr. ROGERS of Florida. I think what the chairman was getting at, as I understand him, you have the present authority to go into the manufacture of this if you have it, you do have the present authority, and you have done it before?

Mr. ROURKE. Yes.

Dr. KURLANDER. Mr. Chairman, Dr. Murray.

Dr. MURRAY. I would like to say one thing, in case there is some misunderstanding. We confidently expect that license applications will be filed in the forthcoming months, and as evidence of this, we have had transmitted to us samples of material for test.

So the matter is moving; it is just a question of when the manufacturers will have accomplished the necessary series of lots and completed their tests.

Mr. ROBERTS. Governor.

Mr. THOMSON. I would like to inquire whether in fact the development of the live vaccine has been slow. I have heard the term used "the slow development of the live vaccine." Are we indulging in a presumption that it has been slow? How does it compare with the development, for instance, of the Salk vaccine, and what are the inherent problems that must be weighed against the time within which it can be produced?

Dr. MURRAY. The main problem here is actually lack of manufacturing experience. Normally, when a product is in the course of development, it goes from the research laboratory through a development phase and perhaps pilot plant phase before it gets into actual production. In the case of the live vaccine, the information as to the vaccine itself and the strains was provided by the original research. Developmental work and pilot-plant operation were in fact lacking. One of the difficulties, and this has been perhaps the cause of slow development in this country, is to get sufficient industrial experience in order to make a vaccine which would meet standards which would be satisfactory to the informed scientists knowledgeable in this field in the United States.

Mr. THOMSON. Has the time been greater in development of the live vaccine than it was, for instance, in the development of the Salk vaccine?

Dr. MURRAY. I think that this is a very difficult question to answer. And I think the simplest answer that can be given to this is that both developments have been very rapid. Many of the studies which have been reported in the U.S.S.R. and elsewhere were in fact trials before the vaccine had been fully, as they put it, approbated.

Mr. THOMSON. Then your answer to my question is, as a matter of fact, the development of this vaccine, the live vaccine, has in fact been rapid?

Dr. MURRAY. It has in fact been rapid.

Mr. ROBERTS. The gentleman from Florida.

Mr. ROGERS of Florida. Continuing that just for a moment, I had the impression that you said it was not as fast as the Salk, because we are already using the Salk and we are not using the Sabin.

Dr. MURRAY. I am thinking in terms of from the time that the vaccine itself was developed until it got to the stage of being licensed.

Mr. ROGERS of Florida. You have not yet licensed any of the oral vaccine, is that correct?

Dr. MURRAY. That is correct.

Mr. ROGERS of Florida. How long has the Salk vaccine been licensed?

Dr. MURRAY. It was licensed in 1955. But development started some years prior to that.

Mr. ROGERS of Florida. I thought you also told me that the Sabin development started some time ago, 10 years ago, was it not?

Dr. MURRAY. I would like to correct that impression; I am sorry if I created it. Work on live polio vaccine has been going on for 10 years.

Mr. ROGERS of Florida. That is what I understood. I do not think that is too important. What I am concerned with now is, first of all, suppose I were a manufacturer, and I wanted to know what the standards were that you would permit, Public Health Service would permit me to use to develop an oral polio vaccine. What is the date that I could with assurance rely on the standards that you have set to begin my manufacture?

Dr. MURRAY. Can I preface that by this statement: That in a field which is developing rapidly, and where a great deal of research information must be collected, progress would be very slow if manufacturing were held back until standards were finally adopted. This would be one sure way of stopping it.

Mr. ROGERS of Florida. I understand that. You say they could go and get and be testing it. But I want to know, when could I, if I were a manufacturer, what date could I begin actual manufacture on the standards that you have set for oral polio vaccine?

Dr. MURRAY. We anticipate, as I have indicated, that these standards will be available somewhere about the end of this month.

Mr. ROGERS of Florida. So they have not yet really been established, is that right?

Dr. MURRAY. They have not been formally established as a legal entity. But the information has been available concerning the major provisions of these standards as early as August of 1959.

Mr. ROGERS of Florida. Could anyone be licensed before the end of this next month?

Dr. MURRAY. Theoretically, yes.

Mr. ROGERS of Florida. I mean as a practical matter.

Dr. MURRAY. As a practical matter, no, because this would require testing of the product, which in turn would occupy a period of some months.

Mr. ROGERS of Florida. So actually the manufacturers, even if they applied for a license, could not obtain one until the end of this period that you speak of, which should end this next month?

Dr. MURRAY. That is correct.

Mr. ROGERS of Florida. At which time they could come in and ask, and you could practically and legally grant a license?

Dr. MURRAY. Yes.

Mr. ROGERS of Florida. I had some impression that the manufacturers were a little more deficient than perhaps they really are.

Dr. MURRAY. They could apply with the knowledge that the T's and the I's of the standards had not yet been finally crossed and dotted.

Mr. ROGERS of Florida. Now, how long has it been since you have been working on an actual standard, how many years now would you say, actively working on a standard?

Dr. MURRAY. The Public Health Service started working on a set of standards immediately following the first International Conference on Live Poliovirus Vaccine here in June of 1959. And I would say that we started working on this in July of 1959.

Mr. ROGERS of Florida. I see. Now, what were the main factors in this period of time that determine—I think I know some of them, but would you just briefly state them—the main factors that have taken you a 2-year period?

Dr. MURRAY. All of the factors involved were not known, and there was no manufacturing experience in this country. It is as simple as that. And in the meantime, the principles involved have been gone over and added to and eventually formulated in the form of regulations, of proposed regulations, as of November 23.

The question has been asked as to what occasioned the delay in manufacturers getting into production. Coupled with this was the question of the time required to adopt standards. It must be emphasized that basic information is required in order to make a decision as to the suitability of live poliomyelitis vaccine as a principle. This information became available in the summer of 1960 following a series of conferences, the last of which was the International Conference on Poliomyelitis held in Copenhagen in late July. Complicating factors, particularly in the United States, were the questions raised by three sets of proposed strains; i.e., the Lederle, the Koprowski, and the Sabin strains together with other matters of a technical character which are referred to in the documents already submitted by Dr. Terry. I refer particularly to the paper which I presented at the midwinter clinical meetings of the American Medical Association on November 30, 1960. Reference should also be made to the World Health Organization Technical Report No. 203, Expert Committee on Poliomyelitis, Third Report, 1960. These matters were set forth in the report of the Public Health Service Committee on Live Poliovirus Vaccine dated August 20, 1960, which among other things, noted the Sabin strains had the favorable properties and recommended their use. (See appendix for foregoing documents.) This was based in large measure upon an evaluation of the comparative neurovirulence for monkeys of all the strains available. This is a key matter in the safety of the strains used.

As noted in the chronology submitted by Surgeon General Luther L. Terry, a report of the PHS Committee on Live Poliovirus Vaccine was submitted to potential manufacturers of oral vaccine on August 16. These recommendations, made available to all interested persons, virtually set forth the standards which should be met and were designed to encourage interested manufacturers to get into production with a knowledge of what the final regulations, which could only be more completely developed after some production experience has been gained, could be expected to cover.

Mr. ROGERS of Florida. Now, when you speak of manufacturing experience, what exactly does that imply?

Dr. MURRAY. This is the things that happened during the course of the manufacture of a product, the things that can go wrong, the accidents that can occur, the hazardous situations which might be encountered; these are unpredictable until there has been manufacturing experience. Some of them can be guessed at, and some of them were formulated.

Mr. ROGERS of Florida. Now, in your formulation of regulations, did you also outline manufacturing procedures?

Dr. MURRAY. No, sir.

Mr. ROGERS of Florida. Or simply what the vaccine must comply with at the end of the production line.

Dr. MURRAY. Any factors involved in production and in testing which influenced the safety and potency of the vaccine, but not manufacturing procedures in general.

For instance, in the live poliovirus vaccine one of the important things is to be sure that other viruses and agents are kept out of the manufacturing area. So one of the provisions is that it must be manufactured in separate facilities. This is one time that there is a requirement for a manufacturing procedure.

Mr. ROGERS of Florida. Particularly on the live vaccine.

Dr. MURRAY. Yes. But this concerns safety.

Mr. ROGERS of Florida. I have not got it clear in my mind—if you will bear with me, Mr. Chairman—is, would they just give you a batch of vaccine that they had manufactured for a couple of years, and turn it over to you and allow you to do the testing, would that be the normal procedure?

Dr. MURRAY. No; the normal procedure would be for the manufacturer to prepare the particular lot of vaccine or series of lots of vaccines—to complete all his testing and have this thoroughly documented, have this available for scrutiny, and submit samples for testing purposes, which would then be accomplished in the Division of Biologics Standards.

Mr. ROGERS of Florida. Yes.

What I was thinking of, does he give you a breakdown of each ingredient put in here and the different phases, and then give you the final lot?

Dr. MURRAY. He would submit a protocol which sets forth all of the essential procedures and the results of the tests which are required.

Mr. ROGERS of Florida. Now, what about the vaccine that has been used to give tests throughout our own country, although we are not yet licensed?

For instance, in my own State, in Miami, which we discussed earlier, did that have any clearance?

Dr. MURRAY. Such a vaccine does not come within the purview of the licensing responsibilities of the Public Health Service, because it is not for sale, barter, or exchange. And it was provided by the producer for experimental and research purposes at no cost.

Mr. ROGERS of Florida. Is there any authority that you have that you could withhold approval of allowing such an experiment?

Dr. MURRAY. If there is no violation of the provisions of sale, barter, or exchange, we have no authority other than, if somebody was indulging in a dangerous practice, it is presumed that there is sufficient authority within the broad provisions that the Surgeon General of the Public Health has for public health as a whole.

Dr. KURLANDER. Do you have any comments on that, Mr. Rourke?

Mr. ROURKE. No.

Perhaps, Dr. Murray, you meant to refer at the end there to the interstate quarantine authority, which under unusual circumstances is an authority to prevent the interstate transmission of a communicable disease. There is an authority there in an emergency that justifies the situation to actually detain persons, and so forth. If you have that kind of situation, you adopt proper regulations. This is a kind of reserve. We do not have a system going now to actually detain people, but it is a reserve authority that is there.

Mr. ROGERS of Florida. I did not realize that.

I would have thought before they can make a mass testing of even as many as 100,000, or 80,000, that there must be some check.

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Mr. ROURKE. The check is not only in the Public Health Service. The Federal Food, Drug, and Cosmetics Act applies to all drugs, and it has an exception that where proper research is being conducted and the regulations are complied with, then drugs may be distributed for research purposes without otherwise having to comply with other requirements of the act.

And it is under that research distribution that this occurs. The Public Health authority is, as Dr. Murray says, tied to sale, barter, and exchange, so if you give it away, you are not under the authority of that provision, the biologics provision.

But the Food and Drug Act, administered by the Food and Drug Administration of our Department, attempts to control a research distribution.

Mr. ROGERS of Florida. But there is no coordination with the Surgeon General on that; is there?

Mr. ROURKE. I would assume there is a working relationship.

Dr. KURLANDER. There is.

Mr. ROGERS of Florida. Is it required or not?

Dr. KURLANDER. Dr. Langmuir will speak to this.

Dr. LANGMUIR. In my position at the Communicable Disease Center I would know of any unusual disease arising in the country rather promptly.

If this were occurring as the result of something that had been shipped, or have any factor that we could identify, that somebody was doing something obviously dangerous, we would see that appropriate action was taken. If it was wholly within the State, I am sure the immediate action would be with the State health commissioner.

If it went beyond the range of a State, I feel confident that the Surgeon General's broad powers, if only his powers of persuasion, would stop this.

But we do not look on this as being a police power.

Now, in the Miami situation, you see, the State health department was fully participating and endorsing this experiment along with the local health department, and the Public Health Service participated on an informal, consultative basis.

Mr. ROGERS of Florida. Unless a pharmaceutical firm has actually manufactured batches of the vaccine, then the U.S. Public Health Service has no basis really for fixing the standards, would you say?

Dr. MURRAY. Not in its final form.

But from the very nature of the product, there are certain standards that can be defined right at the beginning from our knowledge of the peculiarities of the product. This is true in the case of live polio vaccine. There were such things as separation facilities, such things as the way the monkeys would be handled, and the exclusion of live viruses from the final product, other than the virus in question, safety test requirements, such as tests for neurovirulence. These are the major matters in the standards, and have been there from the beginning.

But details of new viruses that come along, like the "vacuolating agent," and so on, cannot be built in until some experience has been gained.

Mr. ROGERS of Florida. What would you say is the available supply of Salk vaccine?

Dr. KURLANDER. I do not have the figures with me. I can supply them. This changes, as you know. I shall supply them.

Mr. ROGERS of Florida. Would you say it is considerable, or just in general terms—I realize you do not have the details at this time.

Dr. LANGMUIR. There is quite a supply in the pipeline. And now that we have gotten up to a certain level, it is not anticipated that there would be any great run. It is in the several millions of doses, and believed to be adequate.

In 1958, you may remember—excuse me, in the spring of 1957—there was a great support of polio vaccination on a nationally organized basis from the American Medical Association and the State health departments. At that time the demand exceeded the supply for a time.

But this is the last real time there has been a shortage.

Mr. ROGERS of Florida. Thank you very much.

(The following information was submitted for the record:)

THE NATIONAL FOUNDATION

*Monthly report of poliomyelitis vaccine released and shipped, February 1961*

[In cubic centimeters]

| | Single antigen | | Multiple antigen | | Total | |
|---|---|---|---|---|---|---|
| | This month | To date | This month | To date | This month | To date |
| Released | 6,793,207 | 473,875,601 | 203,786 | 14,278,176 | 6,996,993 | 488,153,777 |
| Shipped: | | | | | | |
| National foundation | 427 | 15,244,979 | | | 427 | 15,244,979 |
| Public agencies | 1,232,129 | 165,644,148 | 52,692 | 923,687 | 1,284,821 | 166,567,835 |
| Commercial channels | 1,104,338 | 166,820,217 | 463,155 | 11,594,893 | 1,567,493 | 178,415,110 |
| Export | 3,159,349 | 100,170,944 | 19,757 | 526,208 | 3,179,106 | 100,697,152 |
| Total | 5,496,243 | 447,880,288 | 535,604 | 13,044,788 | 6,031,847 | 460,925,076 |
| Unshipped, end of month [1] | 14,641,466 | | 1,095,695 | | 15,737,161 | |

[1] Excludes outdated vaccine removed from inventory.

Mr. ROBERTS. Dr. Langmuir, do you think that for some period of time some doctors will use the oral, and others will prefer the Salk vaccine even after the oral vaccine is licensed and available for general public use?

Dr. LANGMUIR. That is my judgment, sir, which I actually stated in writing in the symposium held November 30. This was the outline that I made of the picture insofar as one can look into the future. I have tried this several times, and have not always been correct, but I would think certainly for a period of time, there will be some physicians who will tend to be more conservative, like the pediatricians who now give the quadruple antigen, who will like to watch and see the developments for a period of time. Others, of course, will use the oral vaccine as soon as it is available.

Then, of course, we will have improvements and new discoveries. Dr. Salk is talking on a scientific level of a single dose. Some of us think this may be a little optimistic. But this is ideal. A single dose of Salk vaccine that covered all three types in one dose, even though it carried a needle, would have many merits over having to give it in a sugar sirup four times, because the problem of reaching children

four times in the course of the first year of their life is a major organizational undertaking.

I think there will be a swinging of the pendulum for some time, maybe 5 or 10 years. Possibly both vaccines will remain with us for longer than that.

Mr. ROBERTS. Now, as to the potency of the two types, is there a period of time after which the Salk vaccine may no longer be sold?

Dr. MURRAY. The dating of the Salk vaccine or inactivated poliomyelitis vaccine at the present time is rather short. It is six months on the market, although a certain period of storage prior to issue by the manufacturer is permitted. It is anticipated, because of the rather higher stability of live vaccine, that it may be possible to have a longer dating period and 2 years has been suggested if it is kept in the frozen state.

We have no information as to how long it would keep in the form of candy. This would be a relatively short period of time. And if it is to be put out in the form of a liquid at room temperature, or to be thawed, then the period is very short after that, a matter of a week or so.

Mr. ROBERTS. Thank you very much.

Mr. Rourke, I don't know whether you want to add anything further to the question I asked you with respect to the present law prohibiting the importation and the use by the Government of unlicensed live vaccine manufactured abroad.

Mr. ROURKE. I may have misunderstood your question. I have not heretofore had to consider the question of whether the U.S. Government itself, if it wanted to purchase abroad some of this oral vaccine, could lawfully bring it in and use it.

Normally, as you know, regulatory statutes are not construed to apply to the sovereign government itself. I haven't had occasion to look at this question, because I think—as Dr. Murray pointed out, it didn't seem to him that the Public Health Service would buy and use in this country what it wouldnt permit to be manufactured in this country or used commercially.

Mr. ROBERTS. An epidemic might change that situation.

Mr. ROURKE. It may be. I conceive that it could.

Dr. KURLANDER. Mr. Chairman, I know we always have to deal in "ifs," that is part of our life. I would just like to emphasize that despite any concerns that all of us may or may not have about the availability of the oral vaccine, we have today in this country a highly effective vaccine which we are striving our best, even on this very day, to get used by these people who have not used it, yet, or have had it used on them.

And, in line with that, sir, so that we might present to the committee a rather detailed picture of what the situation is in this country today regarding poliomyelitis control, I would like, with your permission, to have Dr. Langmuir briefly discuss a document here which I hope we might give to the committee for such use as you may see fit.

But this will give one of the best pictures of the status of poliomyelitis control in this country today.

Mr. ROBERTS. The committee will be glad to have that.

Dr. LANGMUIR. This is material which was prepared for the Surgeon General's conference, and is an elaboration of material published

in the Journal of the American Medical Association presented at the symposium in November.

I don't propose to take your time for all of this, but there are one or two points I believe that are helpful to show you where we stand.

If you would turn to figure 1 on the back of the front page, it shows the trend of polio since 1933. Notice there was a sharp rise beginning in the 1940's and going to the peak in 1952. And then it drops off a little bit, but it was still a jagged line and high level above a rate of 20 per 100,000 through 1955. In 1956, the rate dropped abruptly, in 1957 it hit a low point, in 1958 it was horizontal, and in 1959 there was a little increase; and now in 1960 it has fallen to another low point.

There are some who argue, "See, the peak was in 1952, and it started down before the vaccine came."

I think that is a spurious argument. Throughout the world, with advancing standards of living, with more soap and water and better housing, there has been a delay in the age at which people get the polio infection. The rising trend has been associated with advancing standards of living.

I know of no basis for saying that there was a cycle and that we are entering into a period of a downward trend for spontaneous reasons. I believe that the great decline is due in very large part, possibly solely, to the vaccine program.

If you will turn to figure 3 you will see where there were epidemics and localized outbreaks in the 2 years 1959 and 1960. And we give a good deal of data here.

I would like briefly to have you also look at figures 4 and 5, because they show the consistent pattern of the change since polio vaccination became a common procedure.

In Chicago in 1952, the cases of polio in a severe epidemic covered the entire city and spread into the county in proportion to the concentration of the population. It hit all social classes.

In 1956 it was concentrated in definite sharp areas which were crowded slums, with very small numbers of cases in the other areas, differences of as much as eight times—eight-fold differences in the attack rates in different parts of the city.

In Kansas City, we compared 1952 and 1959. In Des Moines we compared 1952 and 1959. All epidemic areas since 1956 have been concentrated and localized, even the big epidemics in Chicago and Detroit. Cases have occurred among the least well-vaccinated populations, and among preschool children, even down to the 1- and 2-year-old infants.

Now, may I as a last point bring up figure 6, which is toward the end, it is the figure in the "ribbons."

This is based on the survey conducted in 1959 and again in 1960. In September of each year, a random sample of the population, as part of the labor force index, was asked about polio vaccine. If you will look at the key, each ribbon shows the level of immunization, the lower line in 1959, the upper line in each ribbon in 1960, and the solid upright line represents the improvement in that age group in the 12-month period.

Notice that if you take the four doses we have only reached in the 5- to 10-year group a 50-percent level. This is a substantial increase

over the last year, but still, to really provide adequate protection with present vaccine, we still have a good deal more work to be done even in the school age groups.

However, in the school age groups, if you take the three doses, you will realize that quite a good deal has been done.

In the older age groups vaccine is also recommended. Some polio still occurs among adults, but the risk is considerably less. From this chart I conclude that the really important group is the under-5-group, where we ought to have them right up there at the 70, 80, 85 percent level. When we achieve such levels and if the immunization is evenly distributed through the various population groups, I think we can see a much greater decline in polio than we have seen already.

I appreciate very much the opportunity of presenting this.

Mr. ROBERTS. Without objection, we will be glad to include this descriptive material in the printed record.

(The information referred to follows:)

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Communicable Disease Center

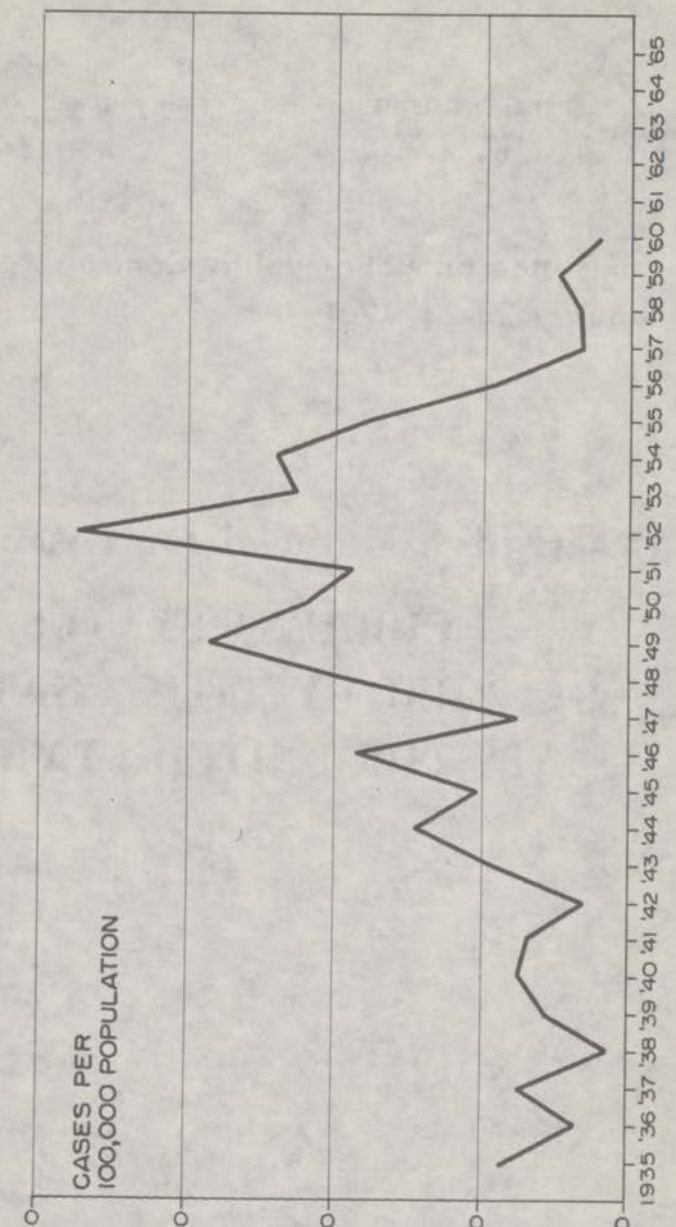
Committee on Poliomyelitis Control
January 23-24, 1961

# Descriptive Material for Discussion of

# CURRENT STATUS OF POLIOMYELITIS CONTROL IN THE UNITED STATES

Prepared by the
Poliomyelitis Surveillance Unit
and the
Statistics Section, Epidemiology Branch
Communicable Disease Center
Atlanta, Georgia

Figure I ANNUAL POLIOMYELITIS INCIDENCE RATES UNITED STATES, 1935–1960




SOURCE: NOVS

FIGURE 2

CURRENT U.S. POLIO INCIDENCE COMPARED WITH YEARS 1955-1959, APR.-DEC., BY WEEK

PROVISIONAL DATA SUPPLIED BY NATIONAL OFFICE OF VITAL STATISTICS

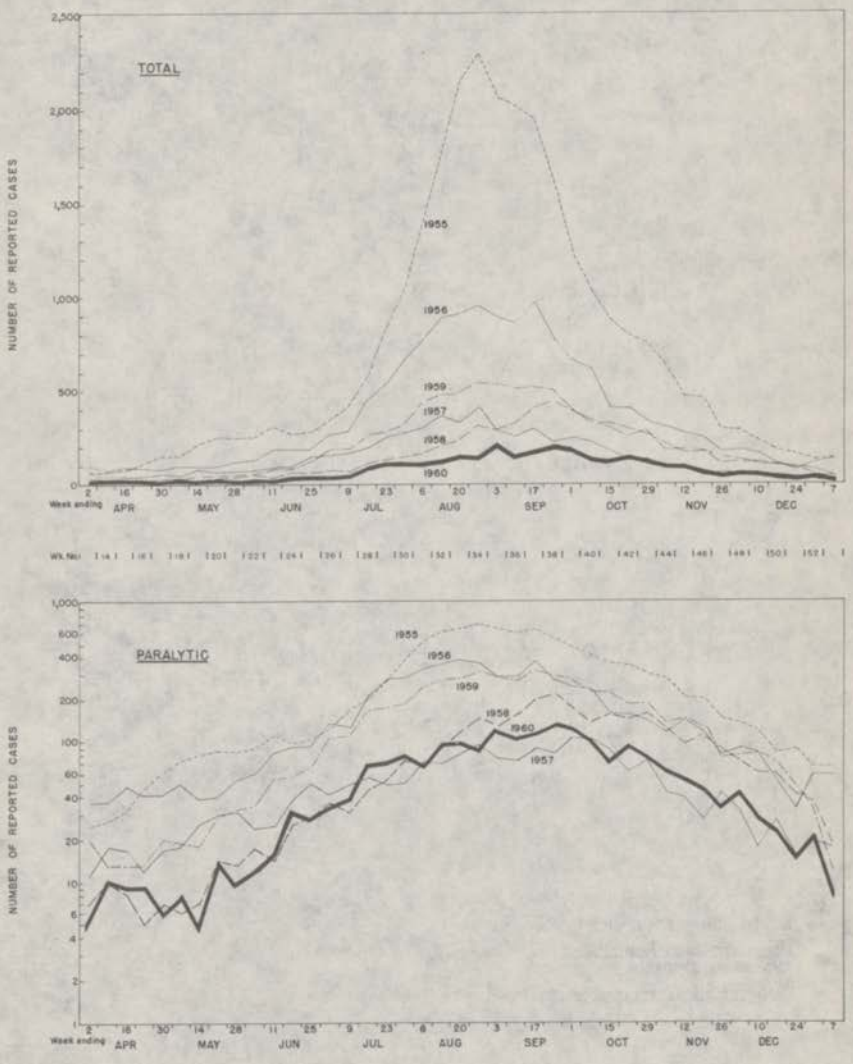


FIGURE 3

PARALYTIC POLIOMYELITIS - 1959



PARALYTIC POLIOMYELITIS - 1960

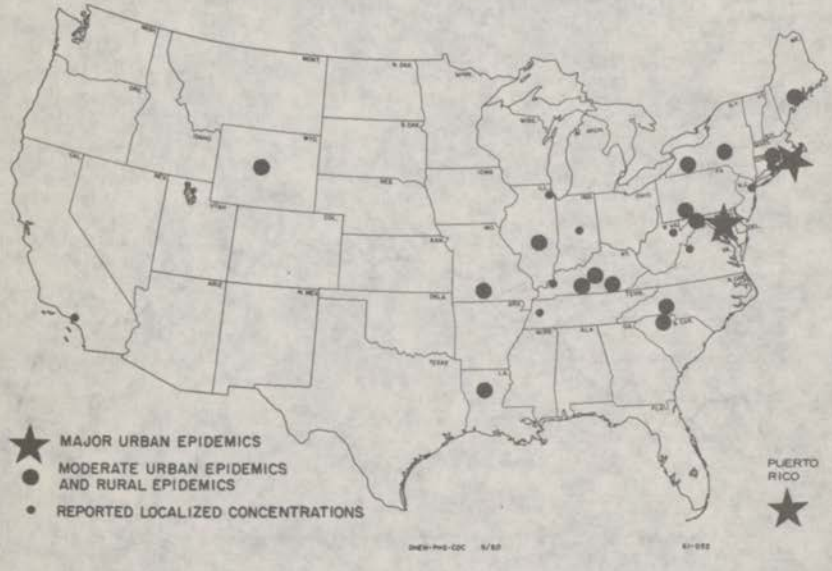


Table 1

INCIDENCE OF PARALYTIC POLIOMYELITIS - 1960
(Preliminary Data Based on PSU Forms
Submitted through December 24, 1960)

| LOCATION | ESTIMATED POPULATION* | PARALYTIC CASES | ATTACK RATE PER 100,000 | REMARKS |
|---|---|---|---|---|
| A. MAJOR EPIDEMICS | | | | |
| Baltimore, Md. Metropolitan | 939,024 | 96 | 10.2 | Type III |
| Providence, R.I. | 723,000 | 73 | 10.4 | Type I |
| Puerto Rico | 2,342,465 | 492 | 21.0 | Type I |
| B. MODERATE URBAN AND RURAL OUTBREAKS | | | | |
| Cumberland Co., Maine | 182,751 | 32 | 17.5 | Portland & vicinity |
| Windham Co., Connecticut | 68,572 | 14 | 20.4 | Contiguous to Rhode Island |
| Cattaragus Co., New York | 80,187 | 15 | 18.7 | Type III |
| Chenango Co., New York | 43,243 | 6 | 13.9 | Rural |
| Somerset Co., Pa. | 77,450 | 15 | 19.4 | Type III |
| Garrett-Allegany Cos., Md. | 104,589 | 12 | 11.5 | Type III |
| Cleveland Co., N.C. | 66,048 | 19 | 28.8 | Rural - Type I |
| Cherokee-Spartanburg Cos., South Carolina | 192,035 | 37 | 19.3 | Rural - Type I |
| Taylor County, Kentucky | 16,285 | 17 | 101.0 | Rural - Type I |
| Pulaski County, Kentucky | 34,403 | 13 | 37.8 | Rural |
| Barren County, Kentucky | 28,303 | 8 | 28.3 | Rural |
| Decatur, Illinois | 78,004 | 13 | 16.7 | Type I |
| Howell County, Missouri | 22,027 | 9 | 40.8 | Rural |
| Fremont-Natrona Counties Wyoming | 75,791 | 13 | 17.2 | Mining area |
| C. LOCALIZED CONCENTRATIONS | | | | |
| New London-Groton, Conn. | 44,293 | 7 | 15.8 | Contiguous to Rhode Island |
| Jersey City-Hoboken, N.J. | 324,542 | 18 | 5.5 | Low socio-economic group |
| Rockingham Co., Virginia | 40,485 | 6 | 14.8 | Religious sect |
| Preston Co., W. Va. | 27,233 | 9 | 33.0 | Rural |
| Monroe-West Monroe, La. | 67,434 | 6 | 8.9 | |
| Tipton Co., Tennessee | 28,564 | 6 | 21.0 | Rural |
| Mayfield, Kentucky | 10,762 | 4 | 37.2 | Small town |
| Indianapolis, Indiana | 476,258 | 30 | 6.3 | Urban-scattered |
| Chicago, Illinois | 3,550,404 | 19 | 0.5 | Puerto Rican population |
| Los Angeles Co., Calif. | 6,038,771 | 156 | 2.6 | Scattered |

* Based on latest available estimates.

Figure 4

LOCATION OF REPORTED POLIOMYELITIS CASES FOR EPIDEMIC YEARS
1952 AND 1956
CHICAGO and COOK COUNTY, ILLINOIS

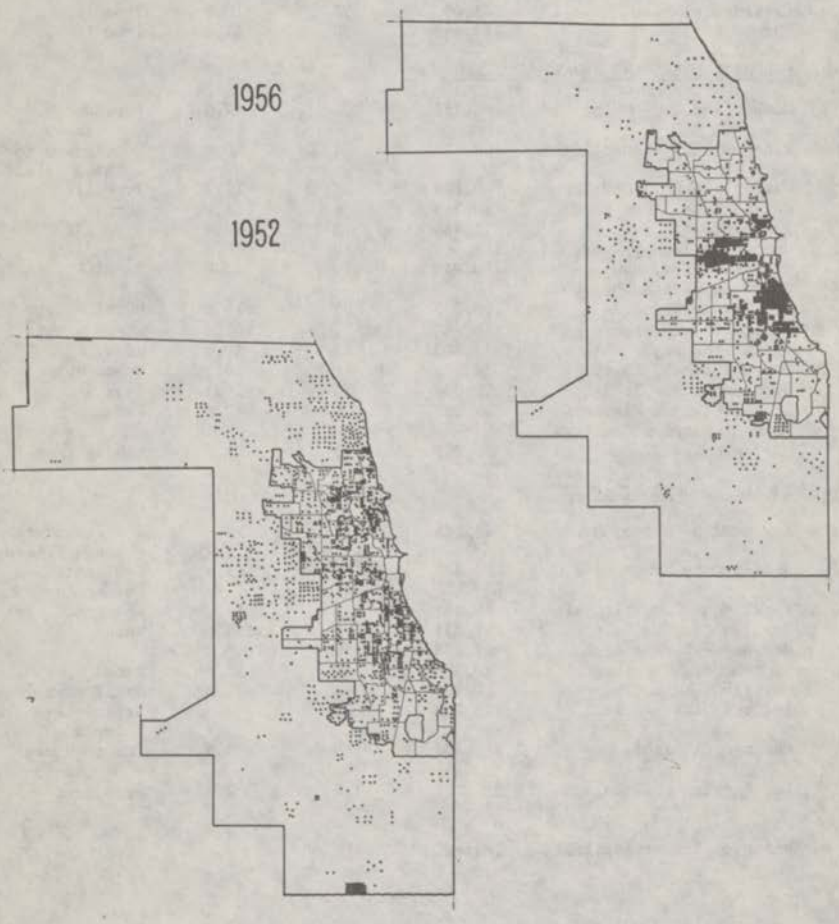
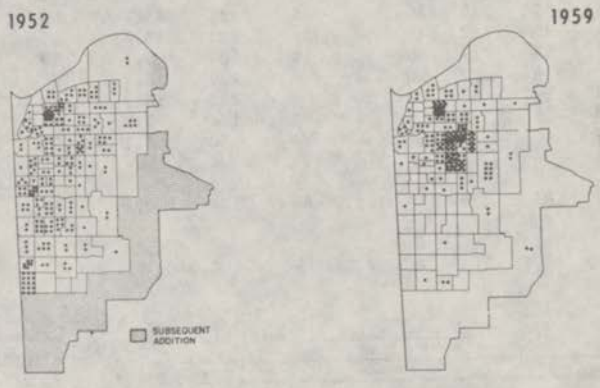


Figure 5

LOCATION OF REPORTED POLIOMYELITIS CASES FOR EPIDEMIC YEARS 1952 AND 1959 KANSAS CITY, MISSOURI, and DES MOINES, IOWA

KANSAS CITY




DES MOINES



Table 2

POLIOMYELITIS CASES BY PARALYTIC STATUS, VACCINATION HISTORY AND AGE GROUP, 1960

PERCENT DISTRIBUTION BY AGE AND DOSES OF VACCINE*
(Reported on PSU Preliminary Forms through December 24, 1960)

| Age Group | Paralytic Doses of Vaccine 0 | 1 | 2 | 3 | 4+ | Unk | Total | % | Crude Effectiveness Ratios** 3V | 4+V |
|---|---|---|---|---|---|---|---|---|---|---|
| 0–4 | 515 | 99 | 119 | 124 | 45 | 35 | 937 | 43.2 | 86 | 94 |
| 5–9 | 213 | 36 | 52 | 131 | 64 | 17 | 513 | 23.6 | 86 | 95 |
| 10–14 | 53 | 15 | 14 | 58 | 32 | 12 | 184 | 8.5 | 79 | 91 |
| 15–19 | 71 | 9 | 7 | 20 | 4 | 6 | 117 | 5.4 | 86 | 97 |
| 20–29 | 169 | 19 | 13 | 16 | 10 | 8 | 235 | 10.8 | 87 | 89 |
| 30–39 | 99 | 8 | 9 | 9 | 6 | 3 | 134 | 6.2 | 81 | 83 |
| 40+ | 45 | - | - | 1 | - | 4 | 50 | 2.3 | 75 | 100 |
| Unk | 3 | - | - | - | - | 1 | 4 | - | | |
| Total | 1168 | 186 | 214 | 359 | 161 | 86 | 2174 | 100.0 | 85 | 94 |
| PERCENT DOSES | 55.9 | 8.9 | 10.2 | 17.2 | 7.7 | - | 100.0 | | | |

| Age Group | Nonparalytic Doses of Vaccine 0 | 1 | 2 | 3 | 4+ | Unk | Total | % | Crude Effectiveness Ratios** 3V | 4+V |
|---|---|---|---|---|---|---|---|---|---|---|
| 0–4 | 71 | 14 | 13 | 24 | 16 | 12 | 150 | 24.1 | 80 | 84 |
| 5–9 | 35 | 16 | 21 | 46 | 40 | 16 | 174 | 27.9 | 70 | 83 |
| 10–14 | 10 | 7 | 5 | 33 | 29 | 4 | 88 | 14.1 | 36 | 55 |
| 15–19 | 18 | 1 | 10 | 23 | 13 | - | 65 | 10.4 | 38 | 55 |
| 20–29 | 35 | 8 | 6 | 30 | 12 | 10 | 101 | 16.2 | - | 37 |
| 30–39 | 11 | 2 | 5 | 6 | 8 | 4 | 36 | 5.8 | - | - |
| 40+ | 6 | - | 2 | - | - | 1 | 9 | 1.4 | - | - |
| Unk | - | - | - | 1 | 1 | 2 | 4 | - | | |
| Total | 186 | 48 | 62 | 163 | 119 | 49 | 627 | 100.0 | 59 | 74 |
| PERCENT DOSES | 32.2 | 8.3 | 10.7 | 28.2 | 20.6 | - | 100.0 | | | |

* Of those cases specified.
** Crude effectiveness ratios are calculated from National estimates of the vaccinated population as shown in Table 3.

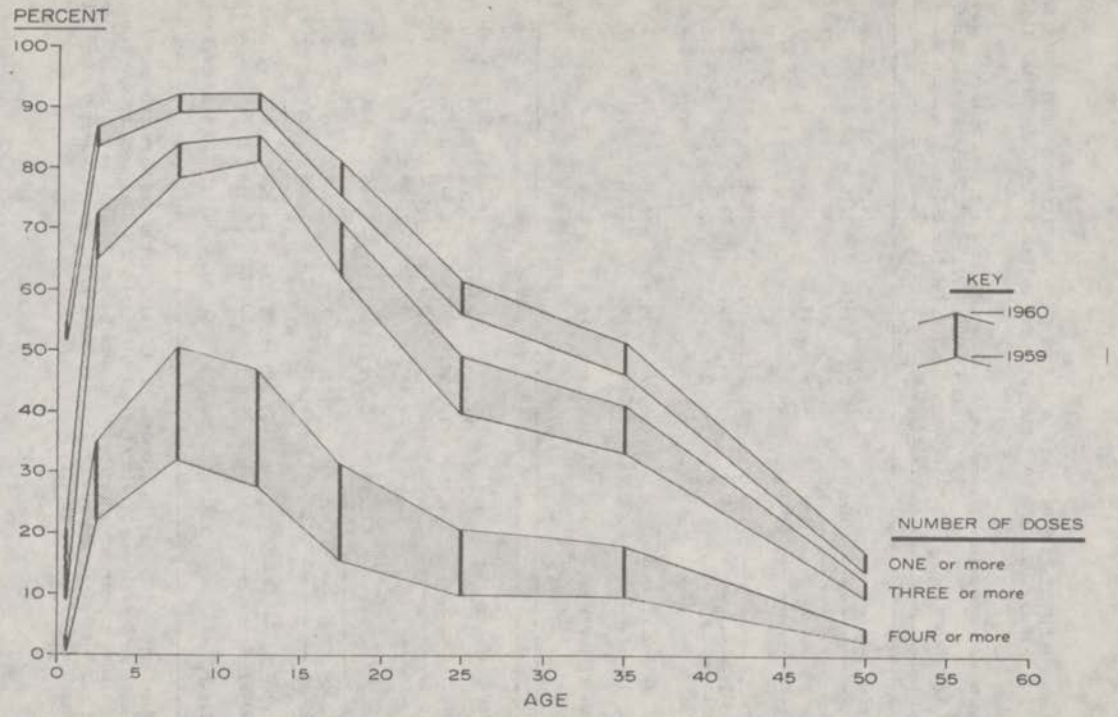
TABLE 3
POLIOMYELITIS VACCINATION STATUS OF THE CIVILIAN NONINSTITUTIONAL POPULATION UNDER 60 YEARS, BY AGE: UNITED STATES, SEPTEMBER, 1960

| Age (Years) | Population (1,000's) | Distribution by Number of Inoculations Received | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 or more Inoculations | | | | | No Inoculations |
| | | Total | 4+ | 3 | 2 | 1 | |
| | PERCENT DISTRIBUTION* | | | | | | |
| Under 1 | 100.0 | 54.8 | 2.7 | 17.8 | 21.7 | 12.5 | 45.2 |
| 1-4 | 100.0 | 86.6 | 34.6 | 37.6 | 10.8 | 3.6 | 13.4 |
| 5-9 | 100.0 | 92.3 | 50.6 | 33.3 | 6.2 | 2.3 | 7.7 |
| 10-14 | 100.0 | 92.7 | 47.1 | 38.3 | 5.5 | 1.9 | 7.3 |
| 15-19 | 100.0 | 80.6 | 31.5 | 39.5 | 7.3 | 2.3 | 19.4 |
| 20-29 | 100.0 | 61.3 | 20.5 | 28.8 | 8.9 | 3.1 | 38.7 |
| 30-39 | 100.0 | 51.5 | 17.8 | 23.2 | 7.4 | 3.2 | 48.5 |
| 40-49 | 100.0 | 23.8 | 6.7 | 10.9 | 3.9 | 2.2 | 76.2 |
| 50-59 | 100.0 | 8.2 | 1.8 | 3.6 | 1.7 | 1.1 | 91.8 |
| Under 20 | 100.0 | 86.7 | 39.6 | 35.7 | 8.2 | 3.1 | 13.3 |
| 20-59 | 100.0 | 37.4 | 12.1 | 17.2 | 5.6 | 2.5 | 62.6 |
| Total, Under 60 | 100.0 | 59.8 | 24.6 | 25.6 | 6.8 | 2.8 | 40.2 |
| | ESTIMATED NUMBERS OF PERSONS* | | | | | | |
| Under 1 | 4,232 | 2,318 | 116 | 752 | 919 | 531 | 1,914 |
| 1-4 | 16,679 | 14,445 | 5,775 | 6,268 | 1,797 | 605 | 2,234 |
| 5-9 | 19,385 | 17,894 | 9,808 | 6,447 | 1,193 | 446 | 1,491 |
| 10-14 | 17,308 | 16,041 | 8,145 | 6,622 | 947 | 327 | 1,267 |
| 15-19 | 12,965 | 10,454 | 4,088 | 5,115 | 952 | 299 | 2,511 |
| 20-29 | 20,743 | 12,721 | 4,259 | 5,966 | 1,846 | 650 | 8,022 |
| 30-39 | 23,623 | 12,176 | 4,195 | 5,477 | 1,738 | 766 | 11,447 |
| 40-49 | 22,294 | 5,302 | 1,498 | 2,425 | 878 | 501 | 16,992 |
| 50-59 | 18,022 | 1,482 | 319 | 655 | 303 | 205 | 16,540 |
| Under 20 | 70,569 | 61,152 | 27,932 | 25,204 | 5,808 | 2,208 | 9,417 |
| 20-59 | 84,682 | 31,681 | 10,271 | 14,523 | 4,765 | 2,122 | 53,001 |
| Total, Under 60 | 155,251 | 92,833 | 38,203 | 39,727 | 10,573 | 4,330 | 62,418 |

* Population estimates in 1,000's. Population estimates were provided by Dr. Monroe G. Sirken, National Office of Vital Statistics, Washington, D. C., based upon a national survey conducted by the Census Bureau in September 1960 (35,000 families). Estimates by age are independent estimates made by the Census Bureau and are not based on the survey itself.

FIGURE 6

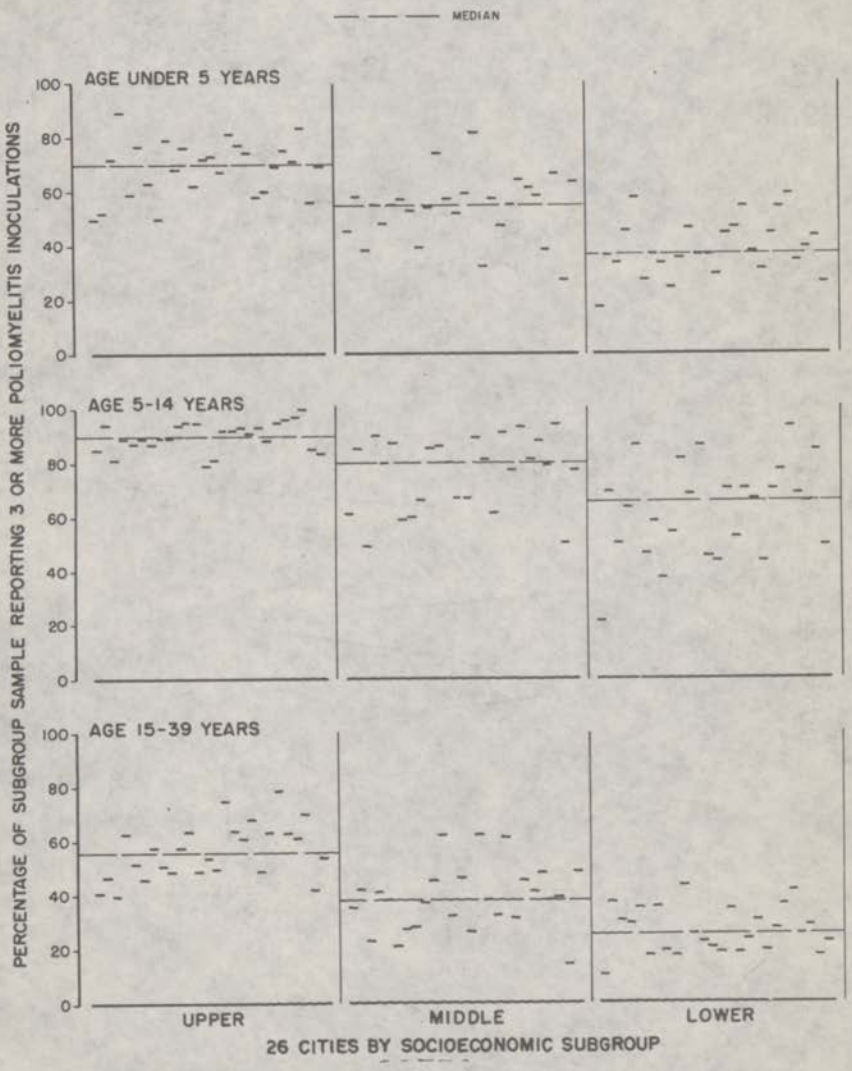
POLIOMYELITIS IMMUNIZATION BY AGE AND DOSES OF VACCINE RECEIVED
UNITED STATES — SEPT. 1959 and 1960




Source: NATIONAL POLIO IMMUNIZATION SURVEY - SEPT. 1959, 1960 (M.G. SIRKIN, NOVS)

FIGURE 7

POLIOMYELITIS IMMUNIZATION BY AGE AND SOCIOECONOMIC SUBGROUP OF THE WHITE POPULATION FOR 26 U.S. CITIES, JANUARY–JUNE, 1959




68776 O—61——12

FIGURE 8

QUARTERLY SHIPMENTS OF POLIOMYELITIS VACCINE
1955–1960

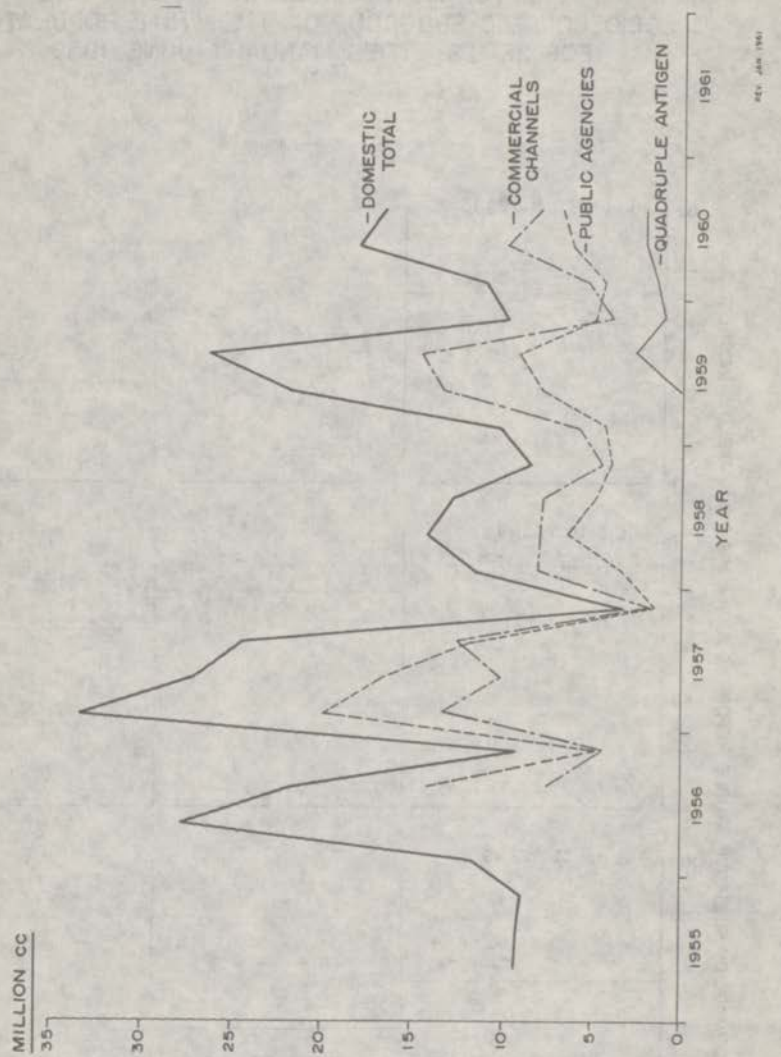


Table 4

QUARTERLY SHIPMENTS OF POLIOMYELITIS VACCINE; 1955 - 1960 (1,000 cc's)

| | National Foundation | Public Agencies | Commercial Channels | Quadruple Antigen | Domestic Total |
|---|---|---|---|---|---|
| 1955: | | | | | |
| Jan - Mar | - | - | - | | - |
| Apr - June | - | - | - | | 9,300 (est.) |
| July- Sept | - | - | - | | 9,200 (est.) |
| Oct - Dec | - | - | - | | 9,000 (est.) |
| TOTAL | 13,541 | 7,893 | 6,223 | | 27,657 |
| 1956: | | | | | |
| Jan - Mar | - | - | - | | 11,800 (est.) |
| Apr - June | - | - | - | | 27,800 (est.) |
| July- Sept | 2 | 14,178 | 7,509 | | 21,689 |
| Oct - Dec | 1 | 4,857 | 4,434 | | 9,292 |
| TOTAL | 194 | 45,588 | 24,784 | | 70,566 |
| 1957: | | | | | |
| Jan - Mar | 8 | 19,935 | 13,483 | | 33,426 |
| Apr - June | 143 | 16,738 | 10,277 | | 27,158 |
| July- Sept | 1 | 11,811 | 12,594 | | 24,406 |
| Oct - Dec | 2 | 1,542 | 1,712 | | 3,256 |
| TOTAL | 154 | 50,026 | 38,066 | | 88,246 |
| 1958: | | | | | |
| Jan - Mar | 100 | 3,419 | 8,079 | | 11,598 |
| Apr - June | 2 | 6,249 | 7,947 | | 14,198 |
| July- Sept | 101 | 4,903 | 7,801 | | 12,805 |
| Oct - Dec | - | 3,962 | 4,492 | | 8,454 |
| TOTAL | 203 | 18,533 | 28,319 | | 47,055 |
| 1959: | | | | | |
| Jan - Mar | 80 | 4,307 | 5,782 | - | 10,169 |
| Apr - June | - | 7,836 | 13,332 | 581 | 21,749 |
| July- Sept | 80 | 9,160 | 14,524 | 2,586 | 26,350 |
| Oct - Dec | - | 4,855 | 3,915 | 1,010 | 9,780 |
| TOTAL | 160 | 26,158 | 37,553 | 4,177 | 68,048 |
| 1960: | | | | | |
| Jan - Mar | - | 4,298 | 5,371 | 1,426 | 11,095 |
| Apr - June | - | 6,149 | 9,763 | 2,093 | 18,005 |
| July- Sept | 1 | 7,691 | 6,725 | 2,026 | 16,443 |
| Oct - Dec | | | | | |
| TOTAL | | | | | |

Mr. ROBERTS. Any further questions?

(No response.)

Mr. ROBERTS. Gentlemen, we appreciate very much the contribution you have made. We realize we have kept you here a long time, but we think it is a very important matter, and we hope we have not imposed on your good nature too much.

Dr. KURLANDER. Mr. Chairman, on behalf of the Surgeon General, myself and my colleagues, we appreciate the privilege of appearing before your committee.

Mr. ROBERTS. Thank you very much.

Our next witness is Dr. John B. Youmans, who will speak for the American Medical Association.

Dr. John B. Youmans, M.D., is the director of the American Medical Association's Division of Scientific Activities. He is in charge of—I believe this is correct—the AMA's Council on Drugs, which has the responsibility of determining the value and safety of drugs and is a part of the scientific division.

Dr. Youmans formerly was Director of Medical Research for the U.S. Army. During World War II, as a colonel, he was Director of the Army's Nutrition Division in the Preventative Medicine Service, Office of the Surgeon General. Previously he had served as a member of the Rockefeller Commission in Europe.

A graduate of and an instructor at Johns Hopkins, Dr. Youmans has been dean of the medical schools at the Universities of Vanderbilt and Illinois and president of the Association of American Medical Colleges.

In addition to being a member of the AMA, he is a fellow of the American College of Physicians, a member of the Association of American Physicians, a member of the American Society for Clinical Investigation, a member of the American Clinical and Climatological Association, vice president and member of the board and scientific director of the Grayson Foundation.

He was awarded the Legion of Merit by the U.S. Army and the Legion of Honor by the French Government.

Doctor, we are delighted to have you. I am sorry we are getting to you so late in the afternoon.

I appreciate very much the fact that you have been with us all day. We are delighted to have you, and we appreciate having you here.

You may proceed with your statement.

## STATEMENT OF JOHN B. YOUMANS, M.D., DIRECTOR, DIVISION OF SCIENTIFIC ACTIVITIES, AMERICAN MEDICAL ASSOCIATION

Dr. YOUMANS. Thank you very much, Mr. Chairman. I am pleased to be here. I have no prepared statement, but I would be very happy to answer any questions you may have to the best of my ability.

I would like to say that the American Medical Association is very greatly concerned with the health of the American people. They feel a great responsibility for it. And in an instance like this they have a great concern for the efficacy and the purity and the safety of products which it is intended, perhaps, to use. And that is one of the reasons why we are happy to be here on this occasion.

Mr. ROGERS of Florida. It is a real pleasure for us to have you, of course, as the chairman has said. And I would like for you to give us just a little background, although we have had a great deal of it given to us by the chairman here; you have had a most distinguished career.

I would like for you to give us just a little background of some of our work with polio. I know you have done a great deal of work in this field.

Dr. YOUMANS. No; I would not say that, Mr. Rogers.

I am an internist, I have had work in public health, and I have had some connection at times with microbiology, the general field of bacteriology, but I am not a biologist, and my competency in that field is limited to that of the sort of person I have described myself to be.

I did, however, attend the two meetings as an individual—I was a member—the two meetings of the Surgeon General's Committee on Poliomyelitis Control, one of which was held in Atlanta last October, and one held last January.

And I am also familiar with the situation to a certain extent because of the fact that the department of drugs and the council on drugs which handle these matters for the American Medical Association are in my division, and I have had close contact with them and consultation with them since I assumed my position.

Mr. ROGERS of Florida. Perhaps you could give us your feeling on the desirability of trying to perfect as rapidly as possible an oral polio vaccine.

Dr. YOUMANS. I believe it would be advantageous to proceed with all due speed, appropriate speed, and care in the perfection of an oral type of vaccine.

Mr. ROGERS of Florida I do not suppose there is any point in trying to get into a controversy as to which is the better vaccine, the Salk or the Sabin oral vaccine.

Do you see any advantage of one over the other, or do you want to comment on that?

Dr. YOUMANS. I would be glad to comment on that.

I think, like in many similar instances, there is a place for both, and you use the one which is best adapted to the circumstances under which you need to work.

And I think, as Dr. Langmuir, that there will be for at least a long period of time, and perhaps forever, until the disease is wiped out, a need and an opportunity for the use of both vaccinations, and because of that I think that it would be helpful and desirable to work toward a suitable oral vaccine which would give us two strings to our bow, as it were.

Mr. ROGERS of Florida Are there any particular situations that you are thinking about when you think of the oral vaccine, perhaps epidemic situations; is that what you had in mind, for instance?

Dr. YOUMANS. I think, because of the advantages it offers, or appears to offer, I believe it does, in the way of easier distribution, at times at least, easier administration at times, earlier immunity or earlier some degree of immunity, and its effect locally in the gastrointestinal tract, that it might at times be the preferred type of vaccine to use.

Mr. ROGERS of Florida. Do you feel that we are now at the stage in this period—I think they have testified today, you heard the testimony—at the end of the next month, I believe it is, that the Public Health Service participates and will be ready to license, do you feel that we are now ready to go into licensing and production of oral vaccine?

Dr. YOUMANS. I do not believe I can give a good answer to that, Mr. Rogers.

I would think that if companies were prepared to furnish a vaccine meeting the standards of the Public Health Service, there could be developed a program if the time is soon enough, but it will have to be very soon, because the times to use an oral vaccine in the way in which it is perhaps best used comes before the polio season is on us actually.

Mr. ROGERS of Florida. Do you think it is a good idea for us to appropriate $1 million to provide a reserve amount of oral polio vaccine?

Dr. YOUMANS. In answer to that, let me say that the general agreement, as I understood it, was that if and when we have a supply of the oral vaccine which is satisfactory, and it is not enough to use in mass application, that there should be a priority of use which would mean a reserve for the Public Health Service to use under a series of priority purposes, such as in a threatened epidemic, such as to use in pilot studies of its efficacy, such as to use with certain groups which are not at the present time in certain areas well covered with the Salk vaccine, and within those groups to use it within certain age limits which have been mentioned here; that is, very young, preschool, and the program that they propose, the breadwinner group.

Mr. ROGERS of Florida. So, generally, then, as I understand it, you do feel that if the standards are set and someone complies with them, that this is a good idea to set up a reserve for the Public Health Service to use in circumstances where a priority is necessary, and you speak for the American Medical Association, is that my understanding?

Dr. YOUMANS. Well, I speak for them without my statement having been approved by the board of trustees, but I would assume that they would agree with that position, since I have offered no objection to that.

Mr. ROGERS of Florida. I understand you have not had the board of directors approval, but unofficially you are speaking for them.

Dr. YOUMANS. I have no reason to believe that they would disagree with that point.

Mr. ROGERS of Florida. Thank you very much.

Mr. ROBERTS. Mr. Thomson?

Mr. THOMSON. No.

Mr. ROBERTS. There is one thing, I think, Mr. Youmans, that you might like to comment on. You remember, not so long ago we had a statement carried in one of the newspaper chains of the country quoting the AMA Journal as having contained an article saying that the Salk vaccine was, I believe, worthless, ineffective, and some other term was used?

I just wanted to know what your comment was about how that happened.

Dr. YOUMANS. Yes, sir. That is one of those unfortunate things that happen, and it has often been said it is no use trying to undo what has been done. But I would like to explain the circumstances. I think it would be well to not use the term, if you don't object, not use the term "article," because it was not an article, it was a response to a letter of inquiry.

We receive these letters all the time on a great variety of subjects, and there is a panel of persons to whom they are sent. These individuals are knowledgeable, generally, in certain fields, but need not be specifically the top authority in a small division of the field.

And the man to whom this went is a public health person and qualified in general, but I do not know that he would be qualified as the top expert in poliomyelitis vaccine.

As such—and these are routed more or less without specific direction—receiving this, he expressed a personal opinion of the value of the Salk vaccine.

Now, it is customary, and it is not infrequently done, that in such a situation we would publish a letter answering that inquiry, because, as I have already pointed out, it is not an official position, it is not a consensus, it is simply the answer of one man to a question, and we hope that in general it will be sound, but like all such things, you may have a difference of opinion.

In this case, there is a very sharp difference of opinion, and the American Medical Association through Dr. Blasingame, the executive vice president, and I believe Dr. Price, the chairman of the board of trustees, has already expressed the fact that we do not accept this point of view or this opinion.

Mr. ROBERTS. And it did not reflect the opinion of the American Medical Association, and the American Medical Association still supports the use of the Salk vaccine, that is the official position, is it not?

Dr. YOUMANS. Yes, sir. And we reiterated the support which we gave following the meetings in Atlanta, following the symposium which was held here, I believe, on November 30, last year, in which we strongly recommended a program of the use of the Salk vaccine, and certainly during that interval, this period, urged such a campaign, and urged the support by all medical societies and physicians.

Mr. ROBERTS. May I suggest this. It would be well for the record to show the statement that was carried in the AMA Journal, and the statement of Dr. Blasingame, if that could be supplied.

(The documents referred to follow:)

POLIOMYELITIS IMMUNIZATION

To the EDITOR:

If we assume that a yearly booster injection of poliomyelitis vaccine is needed because of the lack of potency in the present injectable vaccine, are we not inconsistent in principle to say that the patient who had the last injection—be it the third or the fourth—2 to 4 years ago can get the same protection by only one booster injection as the one who had the last injection 1 year ago? Furthermore, is it true that by next year the oral vaccine will have solved this problem?

M.D., *Wisconsin.*

Answer. The question rightly recognizes that recommendations of additional injections of the Salk vaccine relate to its low and variable potency. On April 19, 1955, only 7 days after the Francis report and the promulgation of minimal requirements for the licensing of the vaccine, the USPHS found it necessary

to reduce potency standards by two-thirds. The problem worsened late in 1955 when, to insure safety, it was necessary to introduce additional filtration during inactivation. This additional filtration resulted in a tenfold to thirty-fold loss in antigen (Illinois Medical Journal 118: 85–93, 1960; and 118: 160–168). Kelly and Dalldorf (American Journal of Hygiene 64: 243–258, 1956) reported a 600-fold variation in the potency of the Salk vaccine on the open market, from negligible potency upward. The difficulty became enhanced when, on May 17, 1957, the Division of Biological Standards permitted lots of vaccine which had failed to meet minimum potency requirements to be retested, so that if the manufacturer then obtained a positive potency test, earlier negative tests could be disregarded. It is now generally recognized that much of the Salk vaccine used in the United States has been worthless.

It follows, then, that the true issue for the physician and patient is not how many injections, or how often, but whether the vaccine given or to be given contains dependable amounts of viral antigen. With the Salk vaccine this cannot be determined because it is an unstandardized product of an unstandardized process. Therefore, for the physician who prefers to know what he is giving, the choice rests with either the recently licensed killed poliovirus vaccine which is concentrated to a known and optimal weight of inactivated virus antigen, and which has substituted the Parker strain for the dangerous Mahoney strain, or with the standardized attenuated live poliovirus vaccine promised for next spring. In either instance, a complete course of vaccination is indicated, irrespective of the number of injections of the Salk vaccine given.

HERBERT RATNER, M.D.

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[News release from the American Medical Association]

CHICAGO, March 1.—The American Medical Association disagreed today with what it termed "a sensational story" distributed to Scripps-Howard Newspapers to the effect that the AMA believes that more than "3,500,000 doses of Salk vaccine given so far have been wasted."

"This statement is untrue and does not reflect the official position of the American Medical Association relative to the Salk vaccine," said Dr. F. J. L. Blasingame, executive vice president of the AMA. "The Scripps-Howard story, emanating from Washington, leaves readers with a highly distored and inaccurate picture."

The story was based on a correspondent's question from an unnamed Wisconsin physician which appeared in the February 25th issue of the AMA Journal. The correspondent, Dr. Herbert Ratner, Oak Park, Ill., health commissioner, said in part that "It is now generally recognized that much of the Salk vaccine used in the United States has been worthless."

"This," said Dr. Blasingame, "is the correspondent's opinion and not the opinion of the American Medical Association. Medical science advances because of conflicting viewpoints, and Dr. Ratner, a well-known public health leader, has a right to his opinion."

Dr. Blasingame clarified the American Medical Association's position regarding Salk vaccine by quoting a resolution adopted by the AMA house of delegates at its clinical meeting in Washington, D.C., last December. The resolution said:

"In view of the fact that oral polio vaccine will not be generally available in sufficient quantity in 1961 for any large scale immunizing effort, the board of trustees of the AMA strongly recommends that the medical profession encourage the widest possible use of the Salk vaccine for prevention of poliomyelitis. The Salk vaccine has been proved to be effective and since there are still many segments of the population not immunized against poliomyelitis every effort should be made to encourage the general public to take advantage of the Salk vaccine without delay."

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[News release from the American Medical Association]

AMA JOINS BIG POLIO DRIVE; TARGET: LOW INCOME GROUPS

CHICAGO.—With 40 percent of the Nation's population not yet inoculated against polio, the American Medical Association announced today that it is taking the leadership against this year with the U.S. Public Health Service and the national foundation in an all-out drive to stimulate State and county medical societies throughout the country in a spring polio campaign.

"Polio still remains a serious health menace," said Dr. Julian P. Price, Florence, S.C., chairman of the AMA board of trustees, "and State and county medical societies will be urged to cooperate with the U.S. Public Health Service and the national foundation in getting more people to take their polio shots."

The AMA, the Public Health Service, and the national foundation are cooperating at the national level in the drive, dubbed the "Babies and Breadwinners" campaign for 1961.

Dr. Price said the campaign will be aimed primarily at the younger age groups in the lower economic area and is designed to stimulate all-out effort by the local organizations.

Dr. Price announced that the Advertising Council of New York again is volunteering its services in launching the 1961 polio campaign in April.

"Timing of the campaign is important," Dr. Price said, "in order that everyone can receive at least three polio shots before the summer polio season."

He said that success of the campaign depends on joint activity at the local level. The local campaigns, sponsored by medical societies, boards of health, and voluntary health agencies, will be tied in with the nationwide campaign.

The AMA leader assured all sponsoring groups of receiving wholehearted cooperation from the more than 2,000 State and county medical societies throughout the country.

"Contrary to recent reports," Dr. Price said, "the AMA is strongly behind every effort to encourage the public to take advantage of the Salk vaccine without delay. This is the official policy of the AMA as enunciated in a resolution adopted by the AMA house of delegates at a meeting in Washington, D.C., last December."

He pointed out that this year's campaign is an extension of similar drives led by the AMA the last 3 years in an effort to persuade every unvaccinated person to protect himself, his family, and his neighbors with Salk vaccine shots.

Dr. Price said that 38 percent of all children 5 years old and younger have not yet been inoculated against polio. In addition, 63 percent of men, aged 20–40, and 48 percent of the women in this age group have not been inoculated. A high proportion of this group is from low-income areas.

"These are segments of the population never reached by previous polio appeals and they should be the special targets in the 1961 polio campaign. As long as 'islands of unvaccinated persons' exist even within well-vaccinated communities, polio epidemics remain a serious threat. Consequently, the campaign should be directed primarily toward low-income groups not normally reached by private physicians in their offices or even by special polio clinics."

Goals and priorities for the 1961 program follow:

(1) Every person should be fully immunized against polio.

(2) Immunization campaigns should be intensive in neighborhoods with less than 85 percent vaccination in groups under age 6, where epidemics are most likely to occur.

(3) The first priority groups to receive "complete and early coverage" should be infant and preschool groups under 8 years of age. Other children under 10 and parents of young children comprise the second priority group.

Dr. Price urged that all community-sponsored polio immunization programs be planned and carried out in close cooperation with local medical societies. He said that the schedule of Salk vaccine shots will remain about the same—the second shot to be given 1 month after the first, the third, 7 months after the second or before the next polio season, and the fourth 1 year later. This applies to all persons except infants under 6 months.

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[From the AMA Journal, Apr. 22, 1961]

PRELIMINARY STATEMENT OF THE AD HOC COMMITTEE ON POLIOVIRUS VACCINES OF THE COUNCIL ON DRUGS OF THE AMA

The ad hoc committee on poliovirus vaccines of the Council on Drugs, in considering the present status of poliomyelitis vaccination, recently reviewed the accumulated experience with regard to Salk vaccine in the United States and other countries and noted the following observations:

(1) It was found repeatedly that Salk vaccine was at least 80 percent effective when three or more doses were given. Both general surveys and specific studies of outbreaks disclosed, time after time, with one notable

exception, that the disease occurred primarily in the unvaccinated rather than the vaccinated. This observation has been strongly confirmed in studies of the Rhode Island outbreak last summer. The only significant exception that has been reported, the Massachusetts outbreak by type 3 virus, could apparently be correlated with an exceptionally widespread use of Salk vaccine in that State in 1956, at the time when the potency of the vaccine was lowest.

(2) The potency of the vaccine has been rising steadily for the past 2 years; therefore, the relatively unsatisfactory results which have sometimes appeared in the past need no longer be expected.

(3) Effectiveness similar to that reported in the United States has been observed in a number of other major countries in which it has been used, in which 75 percent to 95 percent protection has been reported, according to the most recent WHO Expert Committee report.

In the light of these findings the Council on Drugs of the AMA not only wishes to reiterate its belief in the effectiveness of the Salk vaccine but also calls attention to the fact that Salk vaccine is now well established as one of the most effective vaccines of any kind presently available; thus, there is every reason for, and no reason against, every unvaccinated person's being vaccinated with Salk vaccine, especially those under 40 years of age. We urge all physicians to lend their support to this kind of program in their communities in whatever way they feel will be most effective; particular emphasis should be given to the "Babies and Breadwinners" program.

The live poliovirus vaccine is now under study, but the fact that this vaccine will not be available for use in 1961 emphasizes the need for utilization of the Salk vaccine.

Mr. ROBERTS. Mr. Rogers?

Mr. ROGERS of Florida. Are you familiar with a Koprawski vaccine and Cox vaccine?

Dr. YOUMANS. Yes, sir.

Mr. ROGERS. And Sabin, I know you are.

Dr. YOUMANS. Yes.

Mr. ROGERS of Florida. Can you give us some statement about your feelings on these two vaccines?

Dr. YOUMANS. No; I think not. I am sorry to say I don't think I am competent to compare them. There are three oral live vaccine types. The Cox I know has been used experimentally, the Koprawski some, and as far as I know, the Sabin has been used much more widely in an experimental way.

Mr. ROGERS of Florida. Do you know if it is the Cox vaccine that has been used in Miami, Fla.? Are you familiar with that?

Dr. YOUMANS. No, sir; I do not know.

Mr. ROGERS of Florida. Thank you.

Mr. ROBERTS. Thank you very much, Doctor.

This will conclude our witnesses this afternoon.

I would like, Mr. Borchardt, without objection to have the copy of the President's press release on the request for a million dollars included in this record, if you have that available.

(The press release is as follows:)

THE WHITE HOUSE,
*March 13, 1961.*

President John F. Kennedy announced today his intention to request a $1 million appropriation for the purchase of oral polio vaccine when it becomes available because of its potential for combating epidemics.

The sum is contained in a supplementary request for funds being submitted to the Congress on March 14 for the Department of Health, Education, and Welfare. The appropriation, if approved by the Congress, will be used by the Public Health Service to set up a reserve supply of approximately 3 million doses upon which States and local communities threatened by epidemics could draw without cost to them.

In requesting the appropriation, the President said, "I want to insure that there will be no delay, due to lack of funds, in having available to the Public Health Service, at the earliest possible moment, a supply of oral vaccine that can be used in event of epidemic situations."

President Kennedy also urged wider use of the presently available Salk vaccine. "I have been informed by Dr. Luther L. Terry, Surgeon General of the Public Health Service, that very little oral vaccine will be available for this summer," the President said.

"It becomes more important than ever that every effort be made to use the present Salk vaccine. I am happy to endorse wholeheartedly the vaccination drives being undertaken this year by the Public Health Service, the medical profession and other groups. We have the means for stamping out polio. It would be nothing short of tragic if we did not take advantage of the opportunity we now have to prevent the toll of suffering which paralytic polio brings," the President concluded.

The Public Health Service and other health authorities, among them the Surgeon General's Committee on Poliomyelitis Control, have emphasized that the ease of administration of an oral vaccine, permitting a start in protecting thousands of people in a single day, makes it a potentially more valuable weapon in epidemic situations than the present vaccine. Health authorities believe that it gives some protection in a matter of days after it is taken, sooner than the Salk vaccine.

Mr. ROBERTS. This will conclude the hearings for this afternoon, and the committee will stand in recess until 10 a.m., tomorrow at the same place.

(Whereupon, at 3:35 p.m., the committee recessed, to reconvene at 10 a.m., Friday, March 17, 1961.)

# POLIO VACCINES

FRIDAY, MARCH 17, 1961

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND SAFETY OF THE
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 10 a.m., in room 1334 New House Office Building, Hon. Kenneth A. Roberts presiding.

Present: Representatives Roberts, O'Brien, Rogers of Florida, Nelsen, and Thomson.

Also present: Kurt Borchardt, legal counsel.

Mr. ROBERTS. The subcommittee will please be in order.

We are to continue hearings today on the subject of the oral vaccine.

As I stated yesterday, we called the hearings at this particular time primarily because the President requested $1 million to buy a reserve supply of the oral vaccine.

We had yesterday the Surgeon General, Dr. Terry, and his colleagues, and they took most of the day with their testimony. We also had Dr. John Youmans, who testified on behalf of the American Medical Association.

Today we have with us a man who has been outstanding in the work of developing the live vaccine. He has spent over 30 years in working on this problem. He has appeared here before when we had our scientific panel presentation on poliomyelitis vaccine in June of 1955.

We are very happy today that even on short notice this distinguished gentleman is able to come and talk to us today.

I am speaking of Dr. Sabin, who is at the Children's Hospital Research Foundation at the University of Cincinnati.

Doctor, you are so well known in this field that I think you certainly need no introduction. We are happy that you are able to give us some of your time in view of your very busy schedule, and we will be happy if you will come around and occupy the witness chair at this time.

Just for the record, Doctor, would you tell us a little bit about your medical training. We would like to have it on the record.

## STATEMENT OF DR. ALBERT B. SABIN, CHILDREN'S HOSPITAL RESEARCH FOUNDATION, UNIVERSITY OF CINCINNATI

Dr. SABIN. I received my M.D. from New York University in 1931. I interned at Bellevue Hospital in New York City for 2 years. Then I had a National Research Council Fellowship working in England

for a year. I returned to this country and worked for 5 years at the Rockefeller Institute in New York. Since 1939 I have been in Cincinnati.

My work over the years has been concerned with the study of infectious diseases, mostly those caused by viruses. I began my work on poliomyelitis in 1931.

This completes 30 years, and I hope I can go on to something else now.

Mr. ROBERTS. Now, will you give us something of the history of the development of the Sabin vaccine?

Dr. SABIN. In order to be able to use a vaccine of this type, it was necessary to know the natural history of the infection; it was necessary to have the most complete intelligence of how it behaves in man and in nature. And if I were asked when the work began, I would say, at least for my part, it began more than 20 years ago with the determination of how the virus gets into the body, where it multiples and what it does.

But the actual attempts to develop and study strains of modified poliovirus that would be harmless for human beings did not begin until early 1953. This involved a tremendous amount of work on experimental animals and finally human volunteers, because the animals could not provide us the answers.

And here I must say that young men who had committed crimes against society and were in the Federal Reformatory at Chillicothe, Ohio, tried to make up for their transgressions by serving as volunteers in the earliest studies.

It was not until after 5 years of extensive experiments that at the end of 1956 we arrived at a point where we believed that we had modified polioviruses of each of the three types that could be used for more extensive field studies in human beings. And it was at that time that with the aid of one of the pharmaceutical companies in this country—the Merck, Sharp & Dohme research laboratories—that large lots of each of the three types of vaccine, Type 1, Type 2, and Type 3 were prepared, and tested by myself originally in this country. The pharmaceutical company, I should say at this point, provided all this cooperation without any charge.

The National Foundation, which was supporting all of my research, offered to pay them for their expense in preparing these lots of vaccine which contained at least 2 million doses of each of the three types, but they refused the money and offered it as their contribution.

After satisfactory preliminary tests in this country on small groups of children and adults, the question then arose of tests on the larger scale that were necessary before one could know whether or not these vaccines could be used with safety and effectiveness for the complete elimination of poliomyelitis.

In this country Salk vaccine was being used with increasing effectiveness. Even though there were many people who had not taken it, it was believed that a complete answer regarding the safety and effectiveness of the oral vaccine could not be obtained properly in this country. Moreover, there were those who believed that large-scale trials of the oral vaccine might interfere with the attempts that were being made to get more people to use the Salk vaccine that was available.

It was in 1957, then, that the World Health Organization expert committee on poliomyelitis recommended that it was time to have tests with oral vaccine on a larger scale. Scientists from different countries then asked me if they could have portions of these same large lots of vaccine that we had prepared for tests in this country for their own studies in their countries under their conditions.

Accordingly, portions of these large lots were given to individual scientists in Mexico, Holland, U.S.S.R., and a number of other countries, in which tests were first carried out on small groups—hundreds, leading up to thousands.

The first actual large-scale use of this particular vaccine was in Singapore in 1958, under the direction of British scientists who were there at the time. And then the first application for still larger amounts came from Czechoslovakia through the World Health Organization. And I supplied them with some portions of these same lots.

Scientists from the Soviet Union who had come to this country in 1956 to learn how to produce Salk vaccine also became interested in my studies on oral vaccine, and they obtained portions of the large lots that I had prepared, and carried out a series of careful investigations, first on hundreds, then on thousands of children.

By the end of 1958, the scientists in Czechoslovakia, U.S.S.R., and Mexico had decided that the time had come to carry out large-scale field trials.

They obtained enough vaccine from me for about 600,000 children. In the U.S.S.R. they then produced vaccine for additional millions of children, using the vaccine they obtained from me as seed.

1959 was a year of great international scientific collaboration in extensive field tests. Those carried out in places where the number of children and adults who had gotten Salk vaccine was not very large, and where the number of susceptibles was greater than in the subtropical and tropical areas, where previous tests had been performed, were of special significance.

The results of these extensive studies were reported at several international conferences. By the end of 1959 the results of these field trials had established that the oral vaccine was safe for those who received it, that it was safe for susceptible children and adults, that it was safe for those in the community who might have become immunized by contact infection—this is a phenomenon peculiar to this vaccine—and, furthermore, that it was effective both as measured by the changes that take place in the blood that one can measure, and by the marked diminution in the number of cases of polio that occurred even in the unvaccinated in those areas where only 50 percent of the susceptible population had received the vaccine.

It was at that stage, at the end of 1959, that the decision was made in the Soviet Union—since the largest trials were carried out in that country—that this oral vaccine should be given to the entire population under 21 years of age.

1960, then, became the year in which an attempt was made to determine, not just the effectiveness of vaccine for those who received it, but its effectiveness in completely eliminating the disease from the community when as many as 85 or 90 percent or more of the susceptible children get it. This was done on a large scale in eastern

and central European countries, mostly with vaccine produced by the Moscow Institute for Poliomyelitis Research.

But we wanted to know what the effects would be on a large scale in American communities with this particular vaccine, particularly because there were some here who said that communitywide programs can perhaps be carried out only under dictatorships, and that under the American voluntary system such a thing would not be very successful.

The Board of Health of Cincinnati provided the opportunity when it decided to determine just what that response would be in an American community.

The program was started in April of 1960, using the same lots of oral vaccine that were prepared at the end of 1956. And we, with the help of funds that we had from the national foundation for our research, decided to determine just how effective such a program would be, effective as measured by the immunity that would be produced under natural conditions—among people of low income groups and higher income groups; also the effectiveness and the capacity of this vaccine to stop polio not only in those who received it, but by preventing the spread of the paralyzing viruses in the community, also in those who were not vaccinated.

The results of this program involving 181,000 persons, mostly preschool children and school children, have been submitted in a paper that will shortly be published in the American Medical Association Journal under the title "Diseases of Children."

I have a copy of this report with me that I could submit for your committee if you wish it.

Mr. ROBERTS. Do you have that with you?

Dr. SABIN. Yes, sir.

Mr. ROBERTS. Without objection, I would like for that to be supplied for the record.

(The document referred to is as follows:)

# EFFECTIVENESS OF COMMUNITY-WIDE VACCINATION WITH ORAL, ATTENUATED POLIOVIRUS VACCINE IN CINCINNATI

Albert B. Sabin, M. D., Richard H. Michaels, M. D., Ilya Spigland, M. D., William Pelon, Ph. D., Johng S. Rhim, M. D., and R. Eugene Wehr, M. D., Cincinnati.

From The Children's Hospital Research Foundation, University of Cincinnati College of Medicine; and the Cincinnati Health Department.

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The extensive field trials of 1959 on very large numbers of susceptible persons of various ages that were carried out in many countries outside of the U. S. A. not only established the safety and effectiveness of an oral live poliovirus vaccine, but also suggested the possibility that the disease as well as the causative paralytic viruses could, under certain conditions, be completely eliminated[1-8]. The purpose of the present communication is to report the results of studies carried out in connection with the first community-wide use in a large American city of the attenuated, oral poliovirus vaccine, developed by one of us and previously employed in the extensive field trials mentioned above. The community-wide program in Cincinnati was initiated in April, 1960, by the Board of Health in an attempt to determine whether the voluntary public acceptance of the new oral polio vaccine would be sufficiently great to eliminate poliomyelitis from the city.

The attempted elimination of the disease and the causative viruses from the vaccinated as well as from the unvaccinated members of a community is predicated on effecting a break in the chain of transmission of the polioviruses which can be expected when a sufficiently large number of susceptible persons develops intestinal resistance to infection. Since this intestinal resistance can be produced by the oral vaccine and not by the killed-virus vaccine, it is essential in any such program to give the oral vaccine to all persons, regardless of the number of doses of Salk vaccine they might have had - - and especially to the maximum number of pre-school children,

who are the most important spreaders of the polioviruses.

To provide some basis for evaluation of the results, the following studies were carried out:

1. Extent of use of Salk vaccine among different groups in the community.
2. Immune status of pre-school children, with and without Salk vaccine, just before the oral vaccine program.
3. Antibody response to oral vaccine.
4. Extent of infection with enteric viruses among pre-school children of different socio-economic groups just before feeding the oral vaccine.
5. Spread of poliovirus from vaccinated to unvaccinated within the family and outside.
6. Persistence of polioviruses among vaccinated and unvaccinated.
7. Clinical and virologic surveillance of suspect viral infections of nervous system during and after oral vaccine program.

## Vaccine Used, Dosage, and Plan of Administration

Each of the 3 types of vaccine used were portions of the original large (22 to 25 liter) lots that were prepared by one of us (A.B.S.) in December, 1956, in cooperation with the Merck, Sharp and Dohme Research Laboratories, and tested for identity, potency, and absence of extraneous

microbial agents in the Cincinnati laboratory[9, 10]. These same lots of vaccine were used in numerous small scale and large scale human studies in the U. S. A. and abroad since 1957, and also constituted the seed for the production of additional vaccine that had been fed to more than 50 million persons in different parts of the world,[4,6] before the Cincinnati program began at the end of April, 1960.

The undiluted vaccine, distributed in 1 ml. quantities in ampules, had been stored at -15° to -20°C. Early in 1957, the potency measured in plaque forming units (PFU) per 1 ml. in cynomolgus monkey kidney tissue cultures was $4.2 \times 10^7$ for type I, $3.6 \times 10^7$ for type II, and $4.3 \times 10^7$ for type III. Potency tests in subsequent years suggested little or no loss for type I, and some loss of potency in the type II and III vaccines. Twofold and even threefold differences in titer are of doubtful significance because tissue cultures from different monkeys can vary in sensitivity, and different batches of serum used for growing the tissue cultures and in the agar overlay for determining the number of PFU can vary in their content of nonspecific inhibitors for the vaccine strains. Accordingly it was decided that the dose should be 0.01 ml. of the undiluted types I and III vaccines, and 0.02 ml. of the type II vaccine. The types I and III vaccines were therefore diluted 1:10, and the type II vaccine 1:5, about 1 week before use and distributed in dropper bottles which were then stored at about -20°C. The droppers were selected to have a bore that would deliver 0.1 ml. in 2 drops when the

droppers were held perpendicularly; held at an angle or horizontally, the same droppers delivered up to 40% more per 2 drops. Based on tests performed on the frozen, diluted vaccines at the time they were used, the 0.1 ml doses contained $2 \times 10^5$ PFU of type I, $3 \times 10^5$ PFU of type II, and $1 \times 10^5$ PFU of type III.

During the period of actual administration, the diluted vaccine was at room temperature, and portions that had not been used up were stored in an ordinary refrigerator at about $+5^{\circ}C$ for periods not exceeding 7 days. Only slight or doubtful loss in potency was detected in tests on vaccine that was returned to the laboratory by clinics and private physicians at the end of the program. Just before administration two drops of diluted vaccine were added to a teaspoonful of syrup. Simple syrup (U.S.P.) was used in the clinics, and many physicians used a commercially available preparation of cherry syrup, which we had previously determined to be without effect on the potency of the vaccine. We discovered that two commercially distributed preparations of "wild cherry syrup" were unsuitable because they destroyed the viral activity on "momentary" contact.

The plan was to administer the 3 types separately in the order of I, III, and II, because the available data indicated that this was the procedure of choice for avoiding mutual interference among the 3 types, and for obtaining not only the maximum antibody response but also the maximum resistance to reinfection of the intestinal tract [11]. Although an interval of at least

6 weeks between any two types is considered preferable, an interval of 4 weeks was used, because the Cincinnati program was not initiated until the end of April and it was desired to administer the last type of vaccine (i.e. type II) by the end of June, before the usual seasonal increase in poliomyelitis. Similarly only one week was designated for the administration of a single type, although for a community the size of Cincinnati 10 to 14 days would be more desirable, to allow for unavoidable periods of inclement weather. There are two important scientific reasons for administering each type of vaccine in the shortest possible time during a community-wide program: 1) to avoid the interference which may be expected from the simultaneous spread in the community of more than one type, and 2) to create as quickly as possible the largest possible number of resistant intestinal tracts, as a means of quickly breaking the chain of transmission of the naturally occurring polioviruses in the community.

Organization of Program and Extent of Vaccination

The Cincinnati Health Department, executing the directives of the Board of Health, had the administrative responsibility for the program, which included the necessary public information to bring the vaccine and the people together. The extraordinary public response to the challenge of an attempt to eliminate poliomyelitis from Cincinnati resulted in a progressive extension of the program which originally was limited to the preschool children of the city. The vaccine, produced in 1956 free of charge

by the Merck, Sharp and Dohme Research Laboratories and tested and prepared for administration with funds supplied by The National Foundation for Infantile Paralysis (currently The National Foundation) was distributed without charge at The Children's Hospital to the participating private physicians and clinics, who administered the vaccine as a public service free of charge. During the first week of the program, which began on April 24, 1960, the type I vaccine was administered in the private offices of 265 physicians and in 34 health department and hospital clinics to a total of 76,205 persons - predominantly pre-school children, but in the doctors' offices also to about 5,000 school children and 1,714 parents. The important role of the 265 private physicians working in their own offices scattered throughout the city in reaching the pre-school children is evident in the fact that they administered 44,074 doses out of the total of 76,205 during the first week. During the week beginning May 22, this original group received the type III vaccine, and the type II vaccine was given during the week beginning June 19. The overall return rate was 91% for type III, and 83% for type II, while in the offices of the private physicians 97% returned for the type III vaccine and 89% for type II.

The unexpected public demand for the vaccine led to a decision by the Board of Health and Board of Education to give the vaccine in the schools to all children whose parents requested it by signing cards that were distributed in all the schools. During the 5 days beginning May 16,

teams of public health physicians and nurses together with cooperating private physicians and volunteer members of the Parent Teachers Association administered 87,341 doses of the type I vaccine in the public, parochial and private schools within the city limits of Cincinnati. Many pre-school children, living in Hamilton County communities adjacent to Cincinnati received the oral vaccine in the private physicians' offices, and the schools of 12 communities, outside the Cincinnati city limits, also administered the vaccine at the end of May to 16,450 children. Since the schools closed for summer vacation early in June, administration of the type III vaccine was postponed until November, 1960, and of the type II vaccine until January, 1961.

Altogether 181,784 persons received the type I vaccine - 67,634 in the 3-month to 5-year group, 111,127 from 6 years to end of high school (about 18 years), and 3,023 adults (1755 parents of vaccinated children and 1268 hospital and school personnel). To obtain some idea of the proportion of pre-school children in Cincinnati and surrounding Hamilton County that received the oral vaccine, Mr. Eugene R. Porter of the Cincinnati Health Department calculated the total population in this age group from the recorded numbers of births and deaths, leaving out of consideration emigration and immigration on the assumption that they were about equal, since there was no significant change in the total population of Cincinnati between 1950 and 1960. An examination of the vaccine records also suggested that about 75% of the pre-school children resided in Cincinnati and in the

separately incorporated communities of Norwood, St. Bernard and Elmwood, which are surrounded by the city, and for our statistical purposes were therefore included within the Cincinnati city limits. Precise data were of course available on the number of children in the schools. The summary presented in table 1, indicates that in Cincinnati approximately 73% of the pre-school children and 79% of the school children received the type I vaccine, while in the remainder of Hamilton County it was about 35% and 26% respectively.

Recommendations Regarding Contraindications

The only contraindication specifically indicated was that children obviously ill with vomiting, abdominal pain, diarrhea or fever of 102°F or more should not receive the vaccine for two reasons: a) to avoid possible interference with the effect of the vaccine, and b) to avoid giving the vaccine to children who might be in the incubation period of a naturally acquired poliovirus infection. Minor respiratory illnesses, penicillin sensitivity, or steroid therapy were not contraindications. In the various countries in which millions of children had received the oral vaccine in 1959 and early 1960, surgical operations in the throat and mouth were not regarded as contraindications, and no associated cases of poliomyelitis were encountered. Although there is also no theoretical reason why infection with attenuated polioviruses should represent an extra hazard to persons with such surgical operations, it was, nevertheless, desired to avoid any possible complicating situations in connection with tonsillectomies and adenoidectomies during this initial vaccine program in Cincinnati. Accordingly, the health department

recommended that the oral vaccine should not be given to children who had had pharyngeal surgery within two weeks, and also that elective tonsillectomies and adenoidectomies should not be performed on vaccinated children or their familial associates for at least 2 weeks after feeding the oral vaccine. Since the 3 different types of oral vaccine were given at 4-week intervals during the period of April 24 to the end of June, this meant in effect that elective pharyngeal surgery was to be suspended until about the middle of July. Actually, this recommendation was for the most part not heeded because 1677 tonsillectomies and/or adenoidectomies were performed in only 11 Cincinnati hospitals during the period of April 15 to July 14. Data obtained from 5 of these hospitals, showed a total of 1151 such operations for the same period in 1959 as compared with 1129 in 1960. It is noteworthy, therefore, that there were no cases of poliomyelitis in any of these children or in the several thousand others who had tonsillectomies and adenoidectomies during the remainder of 1960.

## Reactions to Oral Vaccine

No immediate reactions were reported, and there were no unusual manifestations subsequently to suggest any minor illness specifically associated with the oral vaccine. As was to be expected the usual childhood diseases continued as before, and there were many instances in which children became ill within a day or more after vaccination. There was no indication that there was any modification in the course of the illness when measles, chickenpox or mumps occurred shortly after vaccination, even

in those few with mumps meningitis or chickenpox encephalitis (see subsequent discussion under surveillance).

Salk Vaccine Status of Population in Cincinnati

The records obtained on the children given the oral vaccine indicated the number of doses of Salk vaccine they had had, and in most instances also the Salk vaccine status of their parents. Based on an analysis of 45,651 records of pre-school children, who came for the oral vaccine to the offices of private physicians, and to 10 of the 34 clinics, Mr. E. R. Porter of the Cincinnati Health Department indicated that the incidence of 3 or more doses of Salk vaccine was 73 per cent among those that came to the physicians and hospital clinics (predominantly from middle and higher income groups) 53 per cent among those who came to all clinics, and only 34 per cent among those who came to the clinics in the poorest neighborhoods. The records on over 24,000 parents of pre-school children indicated that 46 per cent of the fathers and 24.5 per cent of the mothers had received not even a single dose of Salk vaccine.

Polio Antibody Status Among Pre-School Children Just Before Administration of Oral Vaccine

Blood specimens were obtained by venepuncture from more than 700 children who came to the clinics and private physicians for oral vaccine at the end of April, 1960. The sera were screened for the presence of antibody for the 3 types of poliovirus by testing the effect of 0.2 ml. of a 1:4 dilution of unheated serum against approximately 100 $TCD_{50}$ (50% tissue

culture doses) each of the 3 types of poliovirus. The serum-virus mixtures were incubated for 4 hours at 37°C and overnight in a refrigerator, before 0.2 ml. quantities were added to each of two monkey kidney tissue culture tubes containing 2 ml. of medium. The cytopathogenic effect was recorded at 3 to 4 days and at 8 days, and a serum was recorded as negative when it failed to delay the appearance of the cytopathogenic effect. The data presented in table 2 are based on this method, which in most instances detects low-avidity as well as high-avidity antibody. With few exceptions most of these sera were also tested quantitatively by the pH metabolic inhibition test in the laboratories of the Pitman-Moore and Wyeth companies, to whom we are deeply grateful for their cooperation. The results obtained by the pH test in one of these laboratories correlated very well with those we obtained by the cytopathogenic test, while in the other laboratory a considerable number of sera which we found to be positive at 1:8 (i.e. both tubes protected at 1:4) in the cytopathogenic test were negative at 1:8 in the pH test - this occurred with type I in 18 sera, with type II in 7 sera, and with type III in 42 sera. No obvious explanation for the discrepancy was found, especially since both laboratories agreed to follow the same procedure.

In a small proportion of sera from both unvaccinated and Salk-vaccinated children, the pH method in both laboratories detected antibody in titers of 8 to 64, and sometimes even higher, which was not detected by our cytopathogenic test at a dilution of 1:4, despite the prolonged incubation of the serum-virus mixtures and the early reading of cytopathogenic

effect.

A more detailed analysis of the antibody studies will be presented in another communication.

The results shown in table 2 are those obtained by the cytopathogenic test and are only for children from 7 months to 5 years of age inclusive, who either had no Salk vaccine at all or had only 3 doses. Most of the children, who had no Salk vaccine, came from the lower income families, and the tests on their sera serve as an index to the spontaneous dissemination of the 3 types of poliovirus in this population group in Cincinnati in recent years. Thus, the occurrence of 40% positives for type I, 32% for type II, and 26% for type III among the children aged 7 months to 23 months, without Salk vaccine indicates that all 3 types of poliovirus have been circulating rather extensively during the preceding two years; actually, since the 7- to 11-month-old children in this group had as high an incidence of the 3 types of antibody as the 12- to 23-month-old children, most of this poliovirus dissemination must have occurred in 1959, a year in which the incidence of paralytic poliomyelitis was also higher in the city (27 cases in 1959 as compared with 15 in 1958 and 8 in 1957). The incidence of 88%, 87%, and 84% positives respectively for types I, II and III in the 7- to 23-month-old children of this socio-economic group, who had had 3 doses of Salk vaccine, obviously reflects the combined effect of the vaccine and natural immunization.

Although we had blood specimens on only 9 pre-school children without Salk vaccine, from higher income families, it is, nevertheless,

evident that the extent of natural immunization among them was less than among the lower income families. Thus, even if we assume that natural immunization played no role in the production of antibodies among the 7- to 23-month-old children from the higher income families, who had had 3 doses of Salk vaccine, it is evident that in this group of children no antibody was detected in at least 43% for type I, 30% for type II, and 29% for type III.

Antibody Response to Oral Vaccine

The antibody response was determined by tests on paired serum specimens that were obtained from about 600 children just before the oral vaccine was given at the end of April and again at the end of July, which was 4 to 5 weeks after the last of the 3 types had been fed. Two types of tests were carried out. In the Cincinnati laboratory we used the cytopathogenic test mentioned above only on the postvaccination sera of the children that lacked one or more types of antibody in the prevaccination specimens; these sera were tested only at the 1:4 and 1:16 dilutions, and at lower dilutions in the few instances in which it was indicated. In the Pitman-Moore and Wyeth laboratories the pre- and post-vaccination sera were tested simultaneously and quantitatively in twofold dilutions from 1:8 to 1:1024 in duplicate, by the pH method, using serum-virus mixtures that had been incubated for 3 hours at 37°C prior to addition of the cells.

It is evident from the data shown in table 3 that, among the children who received all 3 types of the oral vaccine, there were none who failed to develop antibody to all 3 types. Among the children without antibody before the oral vaccine, listed in table 3, there were 22 triple-

negatives, and the antibody titers of 19 of these were determined quantitatively by the pH method (see table 4). The quantitative tests on Salk-vaccinated children, who already had various levels of antibody, indicated that the oral vaccines exerted a marked booster effect. Representative data on 30 young children from higher income families, who had received from 1 to 7 doses of Salk vaccine prior to the oral vaccine, are shown in table 5.

Extent of Infection with Enteric Viruses Among Pre-School Children of Different Socio-Economic Groups Just Before Feeding of the Type I Vaccine

There have been many observations indicating that infection with other enteric viruses may under certain conditions interfere with the implantation or adequate multiplication of the orally administered poliovirus vaccine strains [3,11]. Accordingly in any scientific evaluation of the effectiveness of the oral vaccine it is important to know the extent of infection with enteric viruses. Another reason for a pre-vaccination virologic survey is to obtain an indication of the extent and type of poliovirus dissemination in the community prior to the introduction of the vaccine strains. Since the incidence of enteric viral infection is known to be higher among children in lower socio-economic groups and in institutions (nurseries, orphanages, etc.), the present study included children from higher as well as lower income families and limited itself to those living at home.

Rectal swabs were obtained from children who came for oral vaccine at 11 different clinics and at the private offices of 44 pediatricians on the staff of the Children's Hospital whose excellent cooperation made this study

possible. The physicians were supplied with vials containing 4 ml. of lactalbumin hydrolysate tissue culture medium with 2,000 units penicillin, 2 mg. streptomycin and 100 units of mycostatin per ml. They were directed to moisten a sterile cotton swab in this fluid, insert it in the anal canal, move it about in the rectum and then rinse thoroughly in the vial; the process was repeated with another swab. The specimen bottles were kept in an ordinary refrigerator for a few hours to not more than 48 hours until they were brought to our laboratory, where they were stored in an electric freezer at about -65°C until they were tested in tissue cultures. Each specimen was tested in both rhesus kidney and human epithelioma (HEP 2) tissue cultures - 3 tubes of each inoculated with 0.2 ml. per tube - which were then observed for 14 days with appropriate changes of medium. This double tissue culture method greatly increased the incidence of virus isolations, as was already found in our studies in the Mexican city of Toluca [3]. Each isolate was again passaged in monkey kidney and HEP 2 cells and identified as a poliovirus or nonpoliovirus by qualitative and serologic properties.

The results obtained on specimens from 1,000 pre-school children (see table 6), in approximately equal numbers in the different age groups from <1 year, 1, 2, 3, 4 and 5 years from lower and higher income families, indicated that: a) the incidence of non-polio enteric viruses as well as of polioviruses, which was twice as high in the lower income families, was very low by comparison with the results obtained by the same technique in children of the same age group in Toluca, Mexico [3]; b) this low incidence

occurred at the end of April when Cincinnati was already having unseasonably warm weather (with temperatures as high as 89°F); c) the 3 strains of poliovirus were all type I; d) the actual spontaneous carrier rate of type I poliovirus among these children was already probably about 1% (multiplying the actual incidence of virus recovery by a factor of 3 on the basis of previously reported studies[3]). It was thus evident that many hundreds of pre-school children were already disseminating type I poliovirus at the end of April in Cincinnati before the type I poliovirus vaccine was administered.

Since 100% of the children without antibody for type I poliovirus developed such antibody after the oral vaccine (see table 3), the question arose whether or not there was significant interference in the children from whom non-polio enteric viruses were recovered just before they received the oral vaccine. Paired serum specimens were available on 9 such children; 3 of these, with similar high titers of type I antibody in the pre- and post-vaccination specimens, probably were not infected because of specific intestinal resistance; in the remaining 6 there was evidence of multiplication of type I virus, because 4 without demonstrable antibody in the pre-vaccination serum exhibited high titers in the post-vaccination serum, and the 2 others showed a marked increase in titer in the post-vaccination specimen. These data, of course, do not prove that there might not have been some interference initially, which subsequently disappeared, permitting either the originally ingested vaccine virus or virus acquired by contact with other vaccinated children to multiply in them. At any rate it would appear that under the

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conditions of the community-wide use of the oral vaccine, even the small number of children who were infected with other enteric viruses developed immunity.

Spread of Poliovirus from Vaccinated to Unvaccinated Within the Family and Outside

Many previous studies have shown that children, especially very young children, infected with poliovirus vaccine strains can spread the infection to susceptible intimate contacts - the degree varying chiefly with the age of the children, the number of contacts without naturally acquired immunity, and hygienic conditions [10,12-15]. We took advantage of the fact that the oral vaccine program in the schools did not begin until 2 1/2 to 3 weeks after the pre-school children had received the type I vaccine to determine how much spontaneous spread of poliovirus there may have occurred among unvaccinated children with and without familial contact with orally vaccinated pre-school children. We tested rectal swabs from a total of 291 children, about equally divided among lower and higher income families, and the results are shown in table 7. Twenty strains of poliovirus were isolated and all were type I. Although the numbers in any one category are not very large it is evident that: a) a marked increase in dissemination of type I poliovirus had occurred, b) the incidence was the same among school-age children whether or not they had familial contact with an orally vaccinated child, c) among unvaccinated pre-school children in the lower income families the incidence of spread seemed definitely higher within the family than outside,

d) poliovirus was recovered twice as often from the school-age children in the higher income families than in the lower income families - this paradox most likely being due to the fact that more children of this age group in the lower income families have naturally acquired immunity and therefore partial or complete intestinal resistance. If the incidence of actual virus recovery is multiplied by a factor of 3 to obtain an estimate of the number that may actually have been infected during this period (based on data in our Toluca study [3]), it is evident that a very large proportion of susceptible pre-school and school-age children - and probably also the young parents of pre-school children - who did not receive the oral vaccine directly became infected by contact.

Persistence of Polioviruses Among Vaccinated and Unvaccinated

The persistence of poliovirus among orally vaccinated was first studied in a group of 587 persons about 1 month after they had received the last of the 3 types of vaccine in the order of I - III - II at monthly intervals. Thus the specimens were collected about 3 months after type I, about 2 months after type III, and 1 month after type II. It is not surprising, therefore, to note in table 8 that among the 145 strains of poliovirus that were recovered there was not a single type I. Type III was still recovered from about 4% of the children (24 strains) 2 months after ingestion, which actually means that at the end of July and early August there were still at least 3,000 of the vaccinated pre-school children, and probably many contacts, still disseminating type III poliovirus in the Cincinnati area. The

type II virus, which was fed last, was still being excreted by an amazingly high proportion of vaccinated persons in sufficient concentration to be detected in the minute amount of fecal matter that is obtainable on a rectal swab. It should be noted here that the majority of these type II strains were recovered in the HEP 2 cultures and not in the monkey kidney cultures, which led us to carry out a series of tests that showed that the line of HEP 2 cells we were using was more sensitive to the type I and type II vaccine strains, but not the type III or wild type I strains, than are rhesus kidney cells. At any rate, it is evident that at the end of July, there were probably at least 15,000 vaccinated pre-school children still shedding type II virus, not to mention those who must have been infected by contact. It is also noteworthy, that in the higher income families, the incidence of type II virus excretion was as high among the small number of vaccinated parents and school-age children as among the pre-school children, suggesting that a high proportion of them had no naturally acquired immunity for this type of poliovirus.

In view of the above results it was of particular interest to sample a large number of orally unvaccinated as well as vaccinated children at the end of September, which is one of the peak months for dissemination of enteric viruses in Cincinnati, to determine whether the massive dissemination of these artifically introduced polioviruses is self-limited, as we found it to be in Toluca, Mexico [3], or whether it persisted especially in the children who did not receive the oral vaccine. Accordingly we tested 620 unvaccinated and 680 vaccinated children - a total of 1300 - aged 1 month

to 16 years, from both lower and higher income families. The chief results, shown in table 9, may be summarized as follows. In the lower income families: a) no polioviruses of any type were recovered from the orally vaccinated pre-school children, although the isolation of other enteric viruses was now at a peak rate of 23%; b) from 258 orally unvaccinated children, aged 1 month to 5 years, two strains of type II poliovirus were recovered - one from a 5-month-old baby who was a sibling of a vaccinated 2-year-old child, and the other from a 1-year-old baby without known contact; c) no polioviruses were recovered from either the unvaccinated or the vaccinated school children most of whom had received only the type I vaccine in the middle of May, and therefore can be considered under the unvaccinated category as regards the type II and III viruses. In the higher income families: a) no polioviruses were recovered from any of the 330 unvaccinated children, nor from a group of 55 school children who had received only type I vaccine in mid-May, nor from the 240 vaccinated pre-school children; b) only one strain of type II poliovirus was recovered from a 13-year-old child -- one of 105 school children tested who had received all 3 types of the oral vaccine - indicating that the type II vaccine virus can in an occasional person continue to be excreted for at least 3 months. These data clearly indicate the self-limited nature of the dissemination of polioviruses, when they are introduced on a massive scale within a short period among the pre-school children in a community. Table 10 presents a summary of all the virus isolation data only on pre-school children at different times after administration of the 3 types of oral vaccine. It

is evident that dissemination of the polioviruses was halted at a time of year that was most conducive to the spread of enteric viruses. The only poliovirus that still persisted was type II, the last of the vaccine strains to be fed 3 months earlier, and that was recovered from only 2 unvaccinated young babies in the lower income families among a total of 948 pre-school children tested in all categories.

Clinical and Virologic Surveillance of Suspected Infections of Nervous System During and After Oral Vaccine Program

Careful clinical and virologic surveillance of all patients with any manifestations suggesting possible nonbacterial infection of the nervous system was instituted at the very beginning of the oral vaccine program and continued until the end of 1960. Patients with any degree of nuchal or spinal rigidity associated with a febrile illness, and those with facial or other paralysis, or with encephalitic signs, were hospitalized and submitted to a diagnostic lumbar puncture. By special arrangement with all Cincinnati hospitals, cerebrospinal fluid, rectal swabs, pharyngeal swabs and blood were obtained on admission, and our laboratory was immediately notified. Two of us (R. H. M. and I. S.) clinically examined and followed up almost all of the reported cases. Immediately after admission to the hospital an attempt was made to obtain two consecutive stool specimens, or enema returns if the patient was constipated, and another blood specimen 1 week after admission. A special effort was made to obtain permission for necropsies on fatal cases. The specimens for virologic study were

inoculated in rhesus kidney cultures (3 to 5 tubes per specimen), which were observed for 14 days with a change of medium at 8 days. Serologic tests for poliovirus and other antibodies were carried out when they were necessary to elucidate the diagnosis.

During the entire period we investigated a total of 57 patients from Cincinnati and the remainder of Hamilton County, and an additional 30 patients who were admitted to Cincinnati hospitals mostly from neighboring Ohio and Indiana counties within a radius of about 50 miles. Prior to the oral vaccine program, one case of paralytic poliomyelitis was reported to the health department in April, but our investigations showed that the diagnosis was not warranted on either clinical or virologic grounds; this was a patient with an antecedent history of upper respiratory infection followed by partial paralysis of one leg with increased deep tendon reflexes and no pleocytosis, no demonstrable poliovirus in the stools, no antibodies for either type I or III poliovirus and a low titer of high-avidity antibody for type II, which was the same in the early acute and convalescent phase serum specimens. During the remainder of the year a great variety of clinical syndromes, listed in table 11, were encountered among vaccinated and unvaccinated persons. During the period of oral vaccine administration and the subsequent months of July and August there was not a single, clinically diagnosed case of poliomyelitis in Cincinnati or the remainder of Hamilton County.

On September 10 within 13 days after returning to Cincinnati from an 8 weeks' stay in Massachusetts, an unmarried 25-year-old man developed

paralytic poliomyelitis, which we showed to be due to type I poliovirus both by virus isolation and concurrent development of antibody. This patient had never had either Salk vaccine or the oral vaccine and had no known contact with any orally vaccinated person. Since in human beings the incubation period between known isolated exposures and development of paralysis is known to be as long as 36 days, with an average of 17 days [16], and in orally infected, isolated chimpanzees as long as 31 days, with an average of 16 days [17], we believe it to be most probable that this patient contracted his infection while he was away from Cincinnati. This was the only case of paralysis, due to a poliovirus, that occurred in Cincinnati and Hamilton County during the entire year of 1960. There were, however, a number of other cases with varying paralytic manifestations among vaccinated and unvaccinated (listed as encephalomyelitis, facial paralysis, infectious polyneuritis, intracranial hemorrhage in table 11), which were not associated with infection by polioviruses. Without critical clinical and virologic studies, some of these might have been reported as poliomyelitis. Thus, the 2 cases of facial paralysis, were without fever or pleocytosis, and were associated with earache or clinically discernible otitis media. The 3 cases of infectious polyneuritis, all of them fatal, were clinically characteristic, except that 2 of them, with the expected absence of pleocytosis, exhibited no increase in cerebrospinal fluid protein - and yet necropsy studies on these two patients revealed the characteristic lesions of infectious polyneuritis. The 2 cases, listed as encephalomyelitis associated in one instance with Coxsackie B 4 and

in the other with ECHO 6, might have been reported as poliomyelitis if it had not been for our virologic studies, and brief mention of their history and clinical findings may be illuminating.

The Coxsackie B 4 case occurred in Hamilton County, adjacent to Cincinnati, in a 20-month-old baby, who had had 3 doses of Salk vaccine (the last in March, 1960) and type I and type III oral vaccines at the end of April and May respectively. He became ill September 9 with fever of 104°, convulsions and upper respiratory infection for which he received intramuscular injections of antibiotics in both buttocks. On September 11 he was observed to drag his right foot, which progressed to a definite foot drop and decreased motion at right knee with, however, definite loss of sensation to pin-prick over the right foot, and areas of induration were found in the buttocks at the sites of the previous intramuscular injections. Although there was no nuchal rigidity, there was a pleocytosis of 133 leukocytes with 77% monocytes. Coxsackie B 4 virus was isolated from his stools, and tests on paired serum specimens showed no change in the high titers of high-avidity antibody for all 3 types of poliovirus. Two months later, the paralysis and sensory defect were still the same. There is no question that he had a Coxsackie B 4 infection, and the pleocytosis indicates that he had involvement of the central nervous system, but it is not clear whether his foot drop and sensory defect are due to a nerve injury following intramuscular injection of antibiotics or Coxsackie B 4, or both.

The ECHO 6 case occurred in Hamilton County, adjacent to Cincinnati,

in a 6-year-old girl who had had 3 doses of Salk vaccine (the last in 1959), and the type I oral vaccine in mid-May, 1960. On 9-23-60 she developed a febrile asthmatic bronchitis for which she was given an intramuscular injection of adrenalin and penicillin in both buttocks; 4 days later she had pain in both buttocks and was noted to limp. On 9-28, afebrile, but neck stiff and paralysis of left leg. Hospitalized 9-29; pleocytosis of 180 mononuclear leukocytes; flaccid paralysis of most of left leg without any disturbance in sensation or position sense. Temperature fluctuated from 98.6° to 100.6° for 3 days. Some urinary retention with distention of bladder from 9/30 to 10/11. ECHO 6 virus was recovered from stools obtained on 9/29, 9/30, 10/7 and 10/10, and when tested against the patient's strain the titer of antibody was <4 in the 9/29 serum and 125 in the 10/18 serum. The patient had high titers of high-avidity antibody for all 3 types of poliovirus in the 9/29 serum, which remained the same in the 10/11 and 10/18 specimens, pointing against concurrent infection with any poliovirus. On 10/3 a right facial paralysis affecting only the mouth was noted, on 10/6 bilateral parotitis appeared, and on 10/8 the facial paralysis was no longer evident. The fact that the 10/7/60 serum still was negative for mumps, viral complement fixing antibody, which appeared in the 10/18/60 serum, would eliminate the mumps virus from consideration in the etiology of the earlier neural manifestations, but there remains some doubt whether a localized inflammatory process in the parotid gland may have produced the lower facial paralysis at least 3 days before gross swelling of the parotid, or whether

this was a transitory supranuclear facial paralysis. On 1/14/61 (3 1/2 months later) there was still residual paralysis of the left leg, although some return of muscle power was evident. Although many instances of paralysis, associated with ECHO 6 virus have been reported before, recovery within about 2 months was the rule [18].

The clinical and virologic data on the 6 children, who exhibited neural signs within 30 days after receiving oral vaccine, are summarized in table 12. In 2 instances, the illness was an acute tonsillitis with meningismus without pleocytosis. In a third case, with mumps developing 3 days after the oral vaccine, the subsequent meningitis was not associated with excretion of poliovirus in the stool. In patient K. Gr., an acute encephalitis appeared within 24 hours after administration of the type I oral vaccine, but the absence of poliovirus from stools obtained 4 and 6 days later, as well as the very high titer of type I antibody 3 days after ingestion of the vaccine, indicated that this child was naturally immune to type I poliovirus before he received the vaccine. In patient K. Sm., the febrile illness with otitis media, widespread petechial rash, and meningitis, which appeared 9 days after ingestion of the type III vaccine was not associated with excretion of poliovirus. The circumstances in patient M. Ra., are of special interest because a varicella encephalitis appeared 4 days after ingestion of the type II vaccine, in a child without type II antibody and with active multiplication of type II poliovirus in the intestinal tract - and the course of neither infection was apparently modified by the other. It is clear from these data that we are

dealing here with intercurrent infections in no way connected with the ingestion of the oral vaccine.

Among the 26 unvaccinated patients with neural signs listed in table 11, there were 11, who were familial or playmate contacts of orally vaccinated children, and from none of these was poliovirus isolated. The illnesses in the 11 contacts - 3 cases of mumps meningitis, 4 of aseptic meningitis, 2 of infectious polyneuritis, 1 of otitis media, and one of Bell's palsy with otitis media - occurred throughout the year without any special relation to the time the contacts had received vaccine (1 in May, 4 in June, 1 in July, 2 in August, 1 each in October, November and December).

It is furthermore noteworthy that with the exception of the isolation of type II poliovirus from the child with varicella encephalitis, 4 days after ingestion of the type II vaccine in June, and of type I poliovirus in September from the one "imported" case of paralytic poliomyelitis, no poliovirus was recovered from any of the other 55 patients listed in table 11.

Among the 30 patients that we studied from outside of Hamilton County, there were 2 with paralytic poliomyelitis (one type I and one type III) from 2 different towns in Ohio, 20 to 30 miles from Cincinnati. The remainder included 2 cases of infectious polyneuritis, 2 mumps meningitis, 13 aseptic meningitis (including some with ECHO 6, Coxsackie B 4, and 3 unidentified enteric viruses), 7 encephalitis of unknown etiology (6 of them from adjacent areas in Indiana), 1 varicella encephalitis, and 3 miscellaneous without involvement of central nervous system - from none of these was

poliovirus isolated.

COMMENT

The community-wide program of vaccination with oral, attenuated poliovirus vaccine in Cincinnati in the spring of 1960 was highly effective by the following criteria:

1. The extraordinary response on the part of the public and physicians to the challenge of an attempt to eliminate poliomyelitis from the city, despite the fact that the program was definitely an experiment with a vaccine that at the time had not yet been officially approved for licensure in the U. S. A.
2. 100 per cent of pre-school children who were without antibody developed antibody for all 3 types after receiving the 3 types of oral vaccine separately at monthly intervals in the order of I - III - II.
3. The initial extensive dissemination of polioviruses, and consequent immunization by contact of a large number of those that did not receive the oral vaccine, was self-limited, so that at the end of September neither type I nor type III poliovirus was detected among vaccinated or unvaccinated children, and type II only rarely.
4. With the exception of a single imported case in September, there were no cases of poliomyelitis either in the city or the surrounding county with a total population of about 940,000,

thus achieving the objective of the vaccination program.

Several points deserve special emphasis and comment. While the rapid administration of the vaccine to all the school children, whose parents requested it, was readily achieved during a brief recess in each school, the success of the pre-school program depended on the cooperation of 265 physicians, whose private offices became centers for administration of the vaccine for one or more periods of a few hours during the week designated for the administration of one particular type of vaccine. In the poorer neighborhoods of the city special methods employed by the health department in bringing the pre-school children to the clinics also played an important role. The return rate of 97% for the type III vaccine, and of 89% for the type II vaccine to the offices of private physicians, even without provisions for make-up visits that might under different circumstances be made for those who happened to be sick, indicated that the need for giving the 3 types separately presented no great problem. It should be remembered, however, that the need for giving 3 doses of the oral vaccine is not comparable to that of giving multiple doses of Salk vaccine, because the first dose of type I oral vaccine provides immunity for the type of poliomyelitis that is responsible for 85 to 90% of the paralytic disease. It should also be remembered that reaching 70 to 75% of pre-school children with the oral vaccine in a community-wide program is quite different from reaching a similar proportion with killed virus vaccine, because with the former the unvaccinated are also benefited in two ways: 1) initially by contact immunization and 2) subsequently by a break in the chain

of transmission of polioviruses.

The 100 per cent conversion rates, under field conditions of administration in Cincinnati in many different clinics and doctors' offices, are perhaps the result chiefly of two factors: 1) the very low incidence of other enteric viruses during the spring months among children living at home exerted little or no interference, and 2) the use of more sensitive tests for antibody including the longer incubation of serum-virus mixtures. It should be pointed out, however, that closely comparable results have been obtained by others with the same mode of administration and same dosage of the same lots of vaccine under field conditions; in Czechoslovakia [7] the conversion results were 95%, 93%, and 94% for the 3 types respectively; in New Haven, Conn. during the winter of 1960, using a less sensitive paper method for antibody tests, the conversion rates were, nevertheless, 100%, 98%, and 87% for types I, II, and III respectively[19]; in Kragujevac, Yugoslavia, during the winter of 1960 the conversion rates for high-avidity antibody among 115 triple-negative children were 91%, 91% and 98% for types I, II and III respectively, and 95%, 95% and 97% among single and double-negative children[20]. In Mexico, the same doses of the same lots of vaccine (each type administered separately) gave 100% conversion rates for each of the 3 types in children without interfering enteric viruses[21], while under field conditions the conversion rates varied from 72% to 89% for type I, 74 to 87% for type II, and 52% to 80% for type III[8] in different cities in which the administration of each type of vaccine was spread out over a period of many weeks and covered only

a small proportion of the child population. On the other hand, in a subsequent field trial with the same lots of vaccine, in which a mixture of all 3 types in the same dose was administered within a few days to 86% of the children in the Mexican city of Toluca, under conditions of most massive infection with other enteric viruses, the conversion rates were 68%, 82% and 43% for types I, II and III respectively; this was raised to 96%, 96% and 72% in a small group of children, who were given a second dose of the trivalent vaccine 5 months later[3].

From all of these data and the results reported from the U. S. S. R.[4,5], it is evident that the circumstances, which determine the incidence of other enteric viruses, will also determine the mode of administration of the oral vaccine and the need for fortifying the initial administration of the 3 types of vaccine by an additional dose of trivalent vaccine. In this sense the requirements for pre-school children living at home in American cities during the winter and spring months would be different from those living in orphanages or regularly attending nurseries, where the incidence of enteric viruses is high throughout the year. For the same reason the schedule adopted for pre-school children in most cities of the U. S. S. R.[4], where most of the children are in nurseries while their parents are at work, may have to be more intensive than that in American cities for children living at home. The results of the present study as well as those obtained by Paul and Horstmann[19] in tests on hundreds of families in New Haven, indicate that in community-wide programs in American cities, the separate administration of the 3 types during

the winter and spring months may be regarded as adequate, until such time as future virologic and serologic surveillance may indicate whether or not further immunization by a trivalent dose of vaccine is necessary either for maintaining antibody or sufficient intestinal resistance to curb the dissemination of polioviruses in the community.

The results obtained in Cincinnati also indicate that children, who have had all 3 types of the oral vaccine, do not need any killed-virus vaccine, and that there is no scientific need for the killed virus vaccine when enough oral vaccine becomes available for everyone.

The Cincinnati experience also provided additional evidence for the harmlessness of the dissemination in the community of each of the 3 types of poliovirus excreted by thousands of orally vaccinated children during the warm months of the year. The fact that 46% of the young fathers and 25% of the mothers of orally vaccinated pre-school children in the higher income families did not have even a single dose of Salk vaccine suggests that a fairly large number of susceptible adults as well as unvaccinated and incompletely vaccinated children had contact with the excreted viruses. Among these, obviously, there were also a large, although undetermined, number of pregnant mothers.

The first demonstration, under field conditions, that the initial massive dissemination of polioviruses, which follows community-wide use of oral, attenuated vaccine, is self-limited and is followed within a few months by an extraordinary reduction in the spread of polioviruses in the

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community took place in Toluca, Mexico, in 1959, where 5031 specimens were tested and 2711 enteric viruses were isolated[3]. The present study in Cincinnati, under different climatic and hygienic conditions, and under different conditions of vaccine administration, by tests on a total of over 3,200 specimens supplied even more striking evidence that the chain of transmission of polioviruses is broken within a few months after community-wide administration of the vaccine to most but not all of the pre-school children - and this has been demonstrated at the end of September, one of the peak months for the spread of enteric viruses. The only 3 polioviruses, that were recovered from the 1300 children tested at the end of September, were all type II and were similar to the vaccine strain in possessing the rct/40- marker, i. e. lacked the capacity to produce cytopathogenic effect in rhesus kidney cultures at 40°C.

The extensive clinical and virologic surveillance that we carried out in connection with the oral vaccine program in Cincinnati indicated that, with the exception of one undoubtedly imported case in September, there were no cases of aseptic meningitis or paralytic poliomyelitis due to poliovirus in Cincinnati and the remainder of Hamilton County, with a total population of about 940,000. One of us (A. B. S.) has been pursuing studies on poliomyelitis in Cincinnati since 1939, and this is the first time, that anything like this has happened. The health department records for 1940 to 1955 do not distinguish between nonparalytic and paralytic poliomyelitis, and to obtain an estimate of the paralytic cases one would be justified in dividing in half the reported number of cases, which (divided in half) ranged from a low of 8 in 1943

to highs of 92 in 1954 and 54 in 1955 for Cincinnati and Hamilton County. The incidence of reported paralytic cases since then has been 34 in 1956, 9 in 1957, 17 in 1958 and 30 in 1959. Our surveillance data indicate, however, the need for critical, clinical and virologic studies, if other neural disorders, bearing some resemblance to poliomyelitis, are not to be reported as poliomyelitis on clinical grounds. In our opinion, facial paralysis should join the aseptic meningitis syndrome in the category of clinical diseases that cannot be diagnosed as poliomyelitis without supporting virologic evidence. The fact that other enteroviruses have been implicated in human paralytic disease, emphasizes the need of virologic studies in such cases also - and this is further supported by the association in the present study of Coxsackie B 4 and ECHO 6 viruses in two of the patients with paralysis, who exhibited no evidence of concurrent infection with polioviruses. Poliomyelitis will officially never be eradicated from any region in which cases of facial paralysis and sporadic cases of other types of paralysis will continue to be reported as poliomyelitis on clinical grounds without supporting virologic evidence.

While 1959 was the year of most extensive field trials with the oral, attenuated poliovirus vaccines, 1960 was the year in which community-wide programs of vaccination were carried out in many countries in an attempt to eliminate the disease. According to a personal communication from Professor M. P. Chumakov of the Institute for Poliomyelitis Research in Moscow, about 76 million persons received oral poliovaccine in the U. S. S. R. in 1960, and, including other countries allied with the U. S. S. R., the total number is over

100 million. In September of 1960 one of us (A. B. S.) visited Hungary and Czechoslovakia, where extensive community-wide programs of oral vaccination were carried out, and had an opportunity to examine the results of their extensive studies. Hungary, which has had recurrent severe epidemics of paralytic poliomyelitis in recent years, did not have a single confirmed case in 1960 during the peak months of July, August and September; the only 3 reported suspect cases, which were not confirmed, included one facial paralysis, one transitory postinfectious myelitis with foot drop and incontinence of stools and urine, and one transitory post-measles myelitis. Tests performed by Dr. I. Domok and his associates of the State Institute of Hygiene in Budapest on hundreds of stool specimens from young children showed that polioviruses were not circulating, and a serologic survey for poliovirus antibodies on young children in August yielded positive results in at least 94%, 96% and 96% respectively for types I, II and III. In Czechoslovakia, where clinical and virologic studies were also made of the few sporadic cases reported during the summer and autumn of 1960, comparable negative results were obtained. In the U. S. S. R. and East Germany, there was also an unprecedented disappearance of poliomyelitis with only small numbers of sporadic cases being reported, and the data regarding their confirmation have not yet been transmitted to us, although Professor Chumakov indicated, in a personal communication, that most of the sporadic cases reported after the completion of the oral vaccination program in a given region were not poliomyelitis. One of us (A. B. S.) also visited Yugoslavia in September, 1960, where type I oral vaccine (prepared locally from vaccine we supplied) was administered rapidly on a mass scale to

more than 1 million children in more than 10 different regions where poliomyelitis outbreaks began in July; in all instances the outbreaks ended abruptly in accord with the known incubation periods of poliomyelitis in man. The results of all these European experiences with oral, poliovirus vaccine in 1960, which were transmitted to us, will soon be published by the investigators in each of these countries.

The results reported in the present communication, taken together with those in the various European countries mentioned above, indicate that in oral poliovirus vaccine we now have a simple tool with which the complete elimination of poliomyelitis can be attempted. Although the Salk vaccine has prevented thousands of cases of paralytic poliomyelitis in the U. S. A., thousands of cases are continuing to occur annually in unvaccinated and inadequately vaccinated persons. On the basis of the results obtained with oral vaccine in 1960, the future occurrence of such cases can be prevented by programs comparable to or better than that carried out in Cincinnati in 1960. This oral vaccine, prepared according to standards set up by the U. S. Public Health Service, has been accepted for licensure in the U. S. A. and as soon as enough of it has been manufactured the following programs would offer the best promise of the most rapid elimination of poliomyelitis from the country. Phase one would involve community-wide oral vaccination during the winter and spring months of the year of the largest possible number of persons, regardless of how many doses of Salk vaccine they may have had, with special emphasis on the pre-school children, who are the most important disseminators of polio-

viruses. The purpose of this phase is not only to immunize those who are not now immune, but also to break the chain of transmission of the polioviruses and thus protect also those who failed to receive the vaccine. Phase two would involve the continuing oral vaccination of all newborn children during their first year of life as part of their regular medical care when they go to their own physicians or clinics to receive the other immunizations. Only time and future serologic, virologic and epidemiologic surveillance will tell, whether or not, and, if yes, when it may be necessary to fortify this immunity by re-feeding of vaccine.

## SUMMARY

During the spring of 1960, type I oral, attenuated poliovirus was given within a short period of time to 181,784 persons in Cincinnati and adjacent Hamilton County - 67,634 pre-school children, 111,127 school children, and 3,023 adults. Most of the pre-school children, some of the adults, and a small number of school-age children also received the type III vaccine at the end of May, and the type II vaccine at the end of June. The vast majority of the school children received the other two types of vaccine in November, 1960, and January, 1961. There were no untoward reactions to the vaccine, and, with the exception of one imported case in September, there were no cases of poliomyelitis during the entire year in the entire area with a total population of 942,000.

A serologic survey carried out prior to the oral vaccine program indicated the presence of large numbers of very young children without

poliovirus antibodies among the unvaccinated in the lower income families, and also among those who have had 3 doses of Salk vaccine in the higher income families. Among the young parents of the pre-school children in the higher income families, 46% of the fathers and 25% of the mothers had not received even a single dose of Salk vaccine. After ingestion of each of the 3 types of oral vaccine at monthly intervals, 100% of the pre-school children, who were without antibody, developed antibody to all 3 types, and a marked booster effect was also obtained in Salk-vaccinated children from higher income families with various pre-existing levels of antibody.

Virologic studies on rectal swabs obtained from about 3200 children at various times before and after the oral vaccine program indicated: 1) a very low incidence of other enteric viruses at the end of April even among the children from the poorest homes, 2) rather extensive spread of polioviruses to unvaccinated, susceptible persons both within the family and outside, and 3) a rapid disappearance of polioviruses from the community within a few months after the oral vaccine program.

The results obtained in Cincinnati in 1960, as well as those being reported from central and eastern European countries where community-wide programs of oral vaccination were carried out in 1960, indicate that in oral poliomyelitis vaccine we now have a simple tool with which the complete elimination of poliomyelitis can be attempted. A program for elimination of poliomyelitis from the U. S. A. is proposed.

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TABLE 1. - Proportion of Child Population Within Cincinnati City Limits and in Remainder of Hamilton County Received Type 1 Oral, Polio Vaccine - Spring, 1960

| Region and Total Population | Age Group Years | Total Population in Group | Total No. Vaccinated | % Vaccinated |
|---|---|---|---|---|
| Cincinnati City Limits | 3/12 - 5 | 69,150 | 50,726 | 73.4 |
| | 6 - 18 | 118,500* | 93,195 | 78.6 |
| 549,300 | 3/12 - 18 | 187,650 | 143,921 | 76.7 |
| Remainder of Hamilton County | 3/12 - 5 | 48,850 | 16,908 | 34.6 |
| | 6 - 18 | 67,950* | 17,932 | 26.4 |
| 392,800 | 3/12 - 18 | 116,800 | 34,840 | 29.8 |
| Hamilton County including Cincinnati | 3/12 - 5 | 118,000 | 67,634 | 57.3 |
| | 6 - 18 | 186,450* | 111,127 | 59.5 |
| 942,100 | 3/12 - 18 | 304,450 | 178,761** | 58.7 |

* These population figures include only the children registered in the schools up to the end of High School.

** The additional 3,023 adults who received the vaccine brings the total to 181,784.

TABLE 2. - Polio Antibody Status of Pre-School Children in Cincinnati Just Before Mass Administration of Oral Vaccine, April, 1960

| Group | Age Years | Type 1 Positive | | Type 2 Positive | | Type 3 Positive | |
|---|---|---|---|---|---|---|---|
| | | No Salk | Salk X 3 | No Salk | Salk X 3 | No Salk | Salk X 3 |
| Clinics Mostly Lower Income Families | 7/12 - <2 | 40 % (28) * | 88 % (41) | 32 % (28) | 87 % (45) | 26 % (27) | 84 % (45) |
| | 2 - <6 | 58 % (31) | 88 % (78) | 43 % (30) | 98 % (79) | 63 % (30) | 87 % (77) |
| Private Doctors Mostly Higher Income Families | 7/12 - <2 | 0 (2) | 57 % (23) | 0 (2) | 70 % (23) | 0 (2) | 71 % (21) |
| | 2 - <6 | 14 % (7) | 72.5 % (80) | 14 % (7) | 92 % (79) | 43 % (7) | 70 % (79) |

* Numbers in parenthesis = numbers of children tested.

TAB 3.

## ANTIBODY RESPONSE IN 3-MONTH TO 6-YEAR OLD CHILDREN RECEIVING LIVE, ORAL POLIO VACCINE DURING COMMUNITY-WIDE PROGRAM IN CINCINNATI

| DOSAGE & SCHEDULE: | | | |
|---|---|---|---|
| | TYPE 1 - $2 \times 10^5$ PFU | — | END OF APRIL, 1960 |
| | TYPE 3 - $1 \times 10^5$ PFU | — | END OF MAY, 1960 |
| | TYPE 2 - $3 \times 10^5$ PFU | — | END OF JUNE, 1960 |

| TYPE | NO. NEGATIVES TESTED | PER CENT CONVERTED TO POSITIVE | |
|---|---|---|---|
| | | 1:16 or more | 1:3 or more |
| 1 | 108 | 99.1 | 100 |
| 2 | 66 | 98.5 | 100 |
| 3 | 121 | 97.5 | 100 |

TABLE 4. - Level of Antibody Response by pH Test in Triple Negative Children One Month After Receiving Types I, III and II Oral Vaccine Separately at Monthly Intervals

Note: All of the prevaccination sera tested in the unheated state by the cytopathogenic test were negative at a dilution of 1:8; they were also negative when tested simultaneously with the postvaccination sera by the metabolic inhibition method.

| Sera Tested at [n] | Child No. | Age Years | No. Doses Salk Vaccine Before Oral Vaccine | Titer of Antibody for Indicated Type I | II | III |
|---|---|---|---|---|---|---|
| Laboratory A | 829 | 2 | 0 | 1536* | 96 | 256 |
| | 828 | 3 | 0 | 1536 | 512 | 8;(7 32)** |
| | 827 | 5 | 0 | 1536 | 96 | 256 |
| | 661 | 9/12 | 2 | 1536 | 1536 | 1024 |
| | 657 | 1 | 2 | 1536 | 1536 | 768*** |
| | 616 | 19/12 | 3 | 1536 | 1536 | 384 |
| | 671 | 2 | 3 | 1536 | 1536 | 384 |
| | 676 | 30/12 | 3 | 1024 | 1536 | 512 |
| Laboratory B | 242 | 7/12 | 0 | 1024 | 128 | 128 |
| | 130 | 8/12 | 0 | 1536 | 384 | 256 |
| | 230 | 9/12 | 0 | 768 | 384 | 192 |
| | 196 | 11/12 | 0 | 512 | 16 | 96 |
| | 206 | 18/12 | 0 | <8;(3)† | 256 | 758 |
| | 213 | " | 0 | 96 | 1536 | <8;(3)† |
| | 283 | " | 0 | 768 | 768 | 96 |
| | 247 | 3 | 0 | 768 | 768 | 64 |
| | 282 | 10/12 | 2 | 192 | 64 | 48 |
| | 579 | 8/12 | 3 | 1024 | 1024 | 1536 |
| | 581 | 16/12 | 3 | 64 | 64 | 384 |

Legends on following page.

Legends for TABLE 4.

n = the tests carried out in the two different laboratories are presented separately because the titers obtained at Laboratory B were consistently lower, and sera which they found to be negative at 1:8 were very often positive by the cytopathogenic test in our laboratory at dilutions of 1:8 or higher.

* The titer 1536 means that both tubes at the 1:1024 dilution of serum showed neutralization and higher dilutions were not tested; accordingly the actual titer may be 1536 or greater.

** Figure in parenthesis indicates titer of 32 or greater obtained in cytopathogenic test in which sera were not tested beyond a dilution of 1:16.

*** The prevaccination serum of this child had a titer of 1:16 in the pH test but was negative at 1:4 in the cytopathogenic test.

† The titer of 1:3 was obtained in the same cytopathogenic test in which the prevaccination serum was negative at 1:2.

TABLE 5. - Booster Effect of Oral Vaccine on Antibody in Salk-Vaccinated Children Measured by pH Method in Laboratory A

| No. Doses Salk Vaccine Before Oral Vaccine | Age of Child Years | Titer of Antibody for Indicated Type in Serum | | | | | |
|---|---|---|---|---|---|---|---|
| | | Before Oral Vaccine | | | After Oral Vaccine | | |
| | | I | II | III | I | II | III |
| 1 | 4/12 | 768 | 256 | 384 | 1536* | 1024 | 1024 |
| | 5/12 | 24 | 64 | 128 | 1536 | 1024 | 768 |
| | 1 | <8;8** | 12 | 16 | 1536 | 1536 | 1536 |
| | 1 | 32 | 48 | 24 | 1536 | 1536 | 1536 |
| 2 | 4/12 | 64 | 64 | 32 | 1536 | 1024 | 1024 |
| | 6/12 | 96 | 128 | 96 | 1536 | 1536 | 1536 |
| | 9/12 | 48 | 64 | <32;4** | 1536 | 1536 | 768 |
| | 9/12 | 64 | 128 | <8;4** | 1536 | 1536 | 1536 |
| | 1 | 192 | 24 | 24 | 1536 | 1536 | 1024 |
| | 4 | 16 | 128 | 12 | 512 | 768 | 256 |
| 3 | 21/12 | 24 | 32 | 16 | 1536 | 1536 | 1536 |
| | 2 | 64 | 192 | 64 | 512 | 1536 | 1536 |
| | 3 | 48 | 96 | 24 | 1536 | 1536 | 1536 |
| | 4 | 32 | 64 | 6 | 1024 | 1024 | 192 |
| | 5 | 48 | 192 | 48 | 1024 | 1536 | 1024 |
| 4 | 2 | 12 | 24 | 32 | 1536 | 1536 | 1536 |
| | 2 | 192 | 64 | 384 | 1536 | 1536 | 1536 |
| | 3 | 64 | 384 | 64 | 1536 | 1536 | 1536 |
| | 4 | 48 | 192 | 24 | 1536 | 768 | 768 |
| | 5 | 384 | 384 | 32 | 1024 | 1536 | 512 |
| 5 | 2 | 6 | 64 | 64 | 1536 | 1536 | 1536 |
| | 3 | 16 | 24 | 24 | 768 | 1536 | 128 |
| | 3 | 192 | 384 | 64 | 1536 | 1536 | 1536 |
| | 3 | 192 | 96 | <8 | 1536 | 1536 | 1024 |
| | 5 | 96 | 384 | 96 | 1024 | 1536 | 384 |
| 6 | 4 | 48 | 64 | 512 | 1024 | 1536 | 1536 |
| | 5 | 96 | 128 | <8 | 768 | 1536 | 256 |
| | 5 | 48 | 192 | 12 | 512 | 1536 | 192 |
| | 5 | 384 | 256 | 48 | 1536 | 1536 | 512 |
| 7 | 4 | 384 | 768 | 192 | 1536 | 1536 | 768 |

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...BLE 6.

INCIDENCE OF POLIOVIRUSES AND OTHER ENTERIC VIRUSES IN RECTAL SWABS OBTAINED FROM CINCINNATI CHILDREN JUST BEFORE MASS ADMINISTRATION OF TYPE 1 ORAL VACCINE TO PRE-SCHOOL CHILDREN

SPECIMENS OBTAINED DURING WEEK OF APRIL 18, 1960 FROM 3-MONTH TO 6-YEAR OLD CHILDREN

| SPECIMENS OBTAINED BY | NO. TESTED | POSITIVE | | ESTIMATED INCIDENCE POLIOVIRUS CARRIERS |
|---|---|---|---|---|
| | | NON-POLIO | POLIO | |
| CLINICS MOSTLY LOWER INCOME FAMILIES | 493 | 22 (4.5%) | 2 (0.4%) | 1.2% |
| PRIVATE DOCTORS MOSTLY HIGHER INCOME FAMILIES | 507* | 11 (2.2%) | 1 (0.2%) | 0.6% |
| TOTAL | 1000 | 33 (3.3%) | 3 (0.3%) | 0.9% |

*AN ADDITIONAL 32 CHILDREN, 7 TO 16 YEARS OF AGE, YIELDED NO VIRUSES.

## SPREAD OF TYPE 1 POLIOVIRUS TO CHILDREN WHO DID NOT RECEIVE ORAL VACCINE

INCIDENCE OF POLIOVIRUS AND OTHER ENTERIC VIRUSES 2½ TO 3 WEEKS AFTER MASS FEEDING OF TYPE 1 VACCINE TO PRE-SCHOOL CHILDREN IN CINCINNATI DURING THE WEEK OF 24 APRIL TO 1 MAY, 1960

| SPECIMENS OBTAINED BY | AGE GROUP YEARS | FAMILIAL CONTACT WITH ORALLY VACCINATED | NO. TESTED | POSITIVE | | ESTIMATED INCIDENCE POLIOVIRUS CARRIERS |
|---|---|---|---|---|---|---|
| | | | | NON-POLIO | POLIO | |
| CLINICS | 3/12–6 | YES | 10 | 0 | 3–30.0% | 90.0% |
| | | NO | 46 | 2 | 6–13.0% | 39.0% |
| MOSTLY LOWER INCOME FAMILIES | 7–15 | YES | 33 | 4 | 1– 3.0% | 9.0% |
| | | NO | 63 | 1 | 2– 3.2% | 9.6% |
| | ALL | ALL | 152 | 7 | 12– 8.0% | 24.0% |
| PRIVATE DOCTORS | 5–6 | YES | 8 | 0 | 0 | |
| | | NO | 5 | 0 | 0 | |
| MOSTLY HIGHER INCOME FAMILIES | 7–15 | YES | 50 | 2 | 3– 6.0% | 18.0% |
| | | NO | 76 | 1 | 5– 6.6% | 20.0% |
| | ALL | ALL | 139 | 3 | 8– 5.8% | 17.0% |

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TABLE 8.

Recovery of Polioviruses and other Enteric Viruses from Vaccinated Persons in Cincinnati
1 Month after Feeding Last of 3 Types of Poliovaccine in Order of I–III–II at Monthly Intervals
Rectal Swabs Collected July 20 — August 3, 1960

| SPECIMENS OBTAINED BY | AGE GROUP YEARS | NUMBER TESTED | PER CENT POSITIVE | | | | |
|---|---|---|---|---|---|---|---|
| | | | NON-POLIO | POLIO I | POLIO II | POLIO III | POLIO-TOTAL |
| CLINICS Mostly Lower Income Families | 3/12-5 | 274 | 10 | 0 | 17 | 3 | 20 |
| PRIVATE DOCTORS | 3/12-5 | 236 | 4 | 0 | 24 | 5 | 29 |
| Mostly Higher Income Families | 6-16 | 41 | 0 | 0 | 22 | 7 | 29 |
| | 22-48 | 36 | 0 | 0 | 28 | 0 | 28 |
| TOTAL | 3/12-48 | 587 | 6 | 0 | 21 | 4 | 25 |

TABLE 9.

RECOVERY OF POLIOVIRUSES AND OTHER ENTERIC VIRUSES FROM VACCINATED AND UNVACCINATED CHILDREN IN CINCINNATI

*3 MONTHS AFTER FEEDING LAST OF 3 TYPES OF POLIOVACCINE IN ORDER OF I-III-II AT MONTHLY INTERVALS*

*RECTAL SWABS COLLECTED SEPTEMBER 24, ——— OCTOBER 1, 1960*

| SPECIMENS OBTAINED BY | AGE GROUP YEARS | VACCINATED | | | UNVACCINATED | | |
|---|---|---|---|---|---|---|---|
| | | NO. TESTED | PER CENT POSITIVE | | NO. TESTED | PER CENT POSITIVE | |
| | | | NON—POLIO | POLIO | | NON—POLIO | POLIO |
| CLINICS | 1/12 — 6/12 | — | — | — | 99 | 13 | 1(III) SIB. CONT. |
| MOSTLY LOWER INCOME FAMILIES | 7/12 — 5 | 187 | 23 | 0 | 159 | 27 | 0.6(II) NO. SIB. CONT. |
| | 6 — 16 | 85* | 6 | 0 | 32 | 13 | 0 |
| | TOTAL | 272 | 18 | 0 | 290 | 21 | 0.7 |
| PRIVATE DOCTORS | 1/12 — 6/12 | — | — | — | 86 | 5 | 0 |
| MOSTLY HIGHER INCOME FAMILIES | 7/12 — 5 | 240 | 6 | 0 | 177 | 12 | 0 |
| | 6 — 16 | 168** | 4 | 0.6(III) | 67 | 1 | 0 |
| | TOTAL | 408 | 5 | 0.25 | 330 | 8 | 0 |
| TOTAL | 1/12 — 16 | 680 | 10 | 0.15(III) | 620 | 14 | 0.32(III) |

* 69 OF THESE HAD ONLY TYPE I VACCINE, AND ONLY 7 HAD I+III+II

**55 " " " " " " " " , " 105 HAD I+III+II

TABLE 10.

**Recovery of Polioviruses and other Enteric Viruses from PRE-SCHOOL Children in Cincinnati**

Before and at Different Times After Community-Wide Use of Oral Poliovaccine

Dates Vaccine Given: Type I - end April; Type III - end May; Type II - end June

| RECTAL SWABS OBTAINED BY | DATE COLLECTED | TIME IN RELATION TO VACCINE | ORAL VACCINE GIVEN | NO. TESTED | PER CENT POSITIVE | |
|---|---|---|---|---|---|---|
| | | | | | POLIO | NON-POLIO |
| CLINICS | MID-APRIL | BEFORE | NONE | 493 | 0.4 I | 4.5 |
| Mostly | MID-MAY | 2-3 wks. POST I | " | 56 | 16 I | 4 |
| Lower | END-JULY | 1 month " II | I + III + II | 274 | 20 II + III | 10 |
| Income | END-SEPT. | 3 mos. " II | I + III + II | 187 | 0 | 23 |
| Families | " " | " " " II | NONE | 268 | 0.7 II | 21 |
| PRIVATE DOCTORS | MID-APRIL | BEFORE | NONE | 507 | 0.2 I | 2 |
| Mostly | END-JULY | 1 month POST II | I + III + II | 236 | 29 II + III | 4 |
| Higher | END-SEPT. | 3 mos. " II | I + III + II | 240 | 0 | 6 |
| Income | " " | " " " II | NONE | 263 | 0 | 10 |
| Families | | | | | | |

TABLE 11. - Cases with Neural Signs From Cincinnati and Surrounding Hamilton County Studied Clinically and Virologically from Beginning of Oral Polio Vaccine Program in April to End of 1960

| Final Diagnosis | No. of Patients | | |
|---|---|---|---|
| | Vaccinated | Unvaccinated | Total |
| Meningitis - mumps | 4 | 6 | 10 |
| " - aseptic** | 13 | 7 | 20 |
| " - H. Influenza | 1 | - | 1 |
| Encephalitis - (1 varicella; 1 ECHO 18) | 3 | 1 | 4 |
| Encephalomyelitis - Coxsackie B 4 | 1 | - | 1 |
| " - ECHO 6 | 1 | - | 1 |
| Encephalomyocarditis (newborn) - Coxsackie B 4 | - | 1 | 1 |
| Infectious polyneuritis - fatal | - | 3 | 3 |
| Facial paralysis - Bell's palsy | 1 | 1 | 2 |
| Paralytic poliomyelitis - type I polio | - | 1* | 1 |
| Miscellaneous - lead encephalopathy, drug poisoning, intracranial hemorrhage, febrile convulsion, otitis media, etc. | 7 | 6 | 13 |
| Total | 31 | 26 | 57 |

* This 25-year-old man, who had no contact with any orally vaccinated person, spent the summer in Massachusetts and became ill September 10, within 13 days after returning to Cincinnati.

** 7 of these yielded non-polio enteric viruses - 1 each of Coxsackie B 2, ECHO 4, ECHO 9, untyped Coxsackie A, and 3 unidentified.

TABLE 12. - Clinical and Virologic Data on Persons Exhibiting Neural Signs within 30 Days After Receiving Oral Vaccine

| Name Age Years | Salk Vaccine No. Doses | Oral Vaccine | | Onset Illness Date | Clinical Signs | Virus Isolation in Rhesus Kidney | | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | Date | Type | | | Specimen Date | Result | |
| J.Cu. 6 | 4 | 4-24 | I | 4-29 | Fever 104° - 106°; abdominal pain, vomiting, neck stiffness, tonsillitis; no pleocytosis. Rapid recovery. | | | Tonsillitis wit meningismus |
| T.Ba. 5 | 5 | 4-28 | I | 5-18 | Fever, nuchal rigidity, positive Kernig and Brudzinski, no pleocytosis, tonsillitis. Rapid recovery. | T.S. 5-19<br>R.S. "<br>CSF " | 0<br>0<br>0 | Tonsillitis wit meningismus |
| K.Gr.* 9 | 1 | 5-19 | I | 5-20 | Fever, vomiting, convulsions, delirium, rash, gingivo-stomatitis, nuchal rigidity, positive Kernig, pleocytosis - 180 lymphs. Recovered 5-23. | T.S. 5-22<br>Stool 5-23<br>" 5-25 | 0<br>0<br>0 | Encephalitis in type I immune child |
| F.Ac. 7 | 3 | 5-19 | I | 5-22 | Mumps 5-22, neck stiffness and drowsiness. 5-26, pleocytosis - 200 mono. Recovered 6-1. | R.S. 5-26<br>CSF " | 0<br>0 | Mumps mening |

See continuation.

TABLE 12. - continued.

| Name Age Years | Salk Vaccine No. Doses | Oral Vaccine Date | Oral Vaccine Type | Onset Illness Date | Clinical Signs | Virus Isolation in Rhesus Kidney Specimen Date | Virus Isolation in Rhesus Kidney Result | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| K.Sm. | 4 | 4-25 | I | 6-1 | Fever 104°, headache, vomiting, petechial rash, face, trunk and extremities, otitis media, pharyngitis, nuchal rigidity. CSF: 6/2 - 500 cells, mostly polys; Sugar 37 mg. 6/4 -350 cells, mostly mono. Treated with antibiotics. Completely recovered 6-8. | R.S. 6-4 | 0 | Aseptic ? meningitis |
| 5 | | 5-23 | III | | | Stool 6-7 | 0 | |
| | | | | | | CSF 6-4 | 0 | |
| M.Ra.* | 0 | 4-27 | I | 6-24 | Varicella skin lesions 6-24, headache 6-26, ataxia, lethargy and confusion 6-27, temp. 99.2°, no nuchal rigidity, but CSF - 162 cells, mostly lymphs. Complete recovery. | Blood clot 6-27 | 0 | Varicella encephalitis during early phase of infection with type II vaccine strain of poliovirus |
| 5 | | 5-25 | III | | | T.S. " | 0 | |
| | | | | | | R.S. " | 0 | |
| | | 6-22 | II | | | Stool 6-28 | Polio II | |
| | | | | | | " 7-8 | " II | |

T.S. = throat swab. R. S. = rectal swab. CSF = cerebrospinal fluid.

* Polio antibody tests:

| Patient | Date of Serum | Type I | Type II | Type III |
|---|---|---|---|---|
| K. Gr. | 5-23 | >4,096 | <4 | <4 |
| | 6-11 | 2,048 | <4 | <4 |
| M. Ra. | 6-27 | >4,096 | <4 | 2048 |
| | 7-8 | >4,096 | 512 | 4096 |

Dr. SABIN. May I hold onto it for reference in case any questions come up later?

Mr. ROBERTS. Surely.

Dr. SABIN. In brief, the results were that a communitywide program under the American system of voluntary participation is quite an extraordinary phenomenon.

If any of you have ever read of, or been in, a mining town where just one man was trapped, and there was still some chance of saving his life, and everybody in the community had stopped what they were doing to try to help him, that was the type of spirit that was displayed in Cincinnati in response to the challenge—it was not a promise—it was a challenge. The challenge was to determine whether or not through a communitywide program of vaccination carried out in the spring the city could be freed of polio. The response of business enterprises who gave up their advertising space in newspapers and their time on radio and television, the response of parent-teachers groups and service organizations was the most extraordinary display of community spirit the people of Cincinnati have experienced.

Mr. ROBERTS. How was this administered to the children, Dr. Sabin?

Dr. SABIN. It was administered in two ways. To reach the preschool children 265 private physicians opened their offices for periods of several hours during the particular week that was set aside for this program and said that anybody who would come with their preschool children during that time to their offices would get it. The vaccine was supplied free, because it was prepared and tested with funds that I had from the national foundation, and the cost of its production was gratis by the Merck, Sharp & Dohme Research Laboratories. The physicians also gave it free. That was 265 doctors' offices scattered throughout the city becoming centers for administration of the vaccine to preschool children so that mothers wouldn't have to travel long distances.

But for people who didn't have their own doctors, the health department and the hospitals established 34 clinics in different parts of the city, some of them in churches, some of them in firehouses, some of them in schools, in which the preschool children were brought to receive the vaccine.

In the schools, it was administered during a brief session that was set aside, and in 1 hour as many as 1,000 children received the vaccine. A total of 111,000 school children received the vaccine in that way in a very brief period of time.

Mr. ROBERTS. Now, when was this vaccine prepared? How old was it at this time?

Dr. SABIN. It was almost 4 years old by this time. The vaccine keeps very well in the frozen state, and the potency now is not significantly different from what it was in December of 1956 when it was prepared.

The participation, then, was very gratifying, and the results were too, because 100 percent of preschool children who were without demonstrable immunity by blood tests before, and who received the three different types of oral vaccine, showed evidence of having developed immunity later. Not a single case of polio occurred in the city or surrounding Hamilton County during the entire year. Our laboratory had a very active program to test every suspect case of possible infection of the central nervous system.

This program is now being continued in Cincinnati, still with vaccine that we have from those original 1956 lots. Beginning yesterday, March 16, in the City of Cincinnati all children who were born since January 1960 and up to the beginning of February 1961, and all preschool children who for one reason or another did not participate last year are now receiving the vaccine to maintain the immunity in the community through the cooperation again of about 215 private physicians who are giving it in their offices to their own patients, and through clinics established by the health department.

This, then, was the result in one American community.

Rochester, N.Y., starting a little later, carried out another such program which did not work out as well because they did not have enough time; they started later. But even there 114,000 children received the vaccine, but only about 27 percent of the preschool children were involved in this. They did not utilize the efforts of private physicians. Everything was done in clinics. And it rained for 4 of the 7 days of the week that they set aside for this program.

At the present time the Yale University Department of Public Health is also engaged in carefully studying the community response in an American city. In January of this year, again using some of the portions of these same lots of original vaccine, the city of Middletown, Conn., with full cooperation of all the groups in that city, and the Yale Department of Public Health have been engaged in studying very carefully the response of an American community.

In the eastern and central European countries last year, where communitywide progams had been carried out well in advance of the summer season, and where I have personally had an opportunity to study the records of the few suspect cases that occurred, it can be said that in Czechoslovakia, with about, I think, 14 million or so people, and Hungary with 10 million people, there had not been a single confirmed case of poliomyelitis after July 1, 1960.

My conclusion, sir, is that the studies of 1960 on communitywide programs in countries outside of the United States, and especially our own experience in Cincinnati, makes me believe that this procedure provides a means for the complete elimination of poliomyelitis that gives us the most reasonable hope of finishing the job. The job was started with Salk vaccine, and a tremendous amount of paralytic polio has been prevented with it. But we have a hard residue that for various reasons we cannot get rid of or have not gotten rid of in this country.

Mr. ROBERTS. What are some of those reasons, Doctor?

Dr. SABIN. Well, they have been told you before, but I don't mind repeating them.

No. 1, for one reason or another it has been difficult to reach a fairly large proportion of the American population with Salk vaccine. Three doses of the Salk vaccine, as has been reported by the Public Health Service, is about 80 percent effective. Four doses are much better, 90 percent or more effective. And with the Salk vaccine, even if it were 100 percent effective, you would be able to protect only those who receive the vaccine; and, furthermore, it would still take many months and usually longer to administer the four doses, so that the very young children, beginning with a few months of life, by the time they get to be 1½ years of age may not be as well protected as they ought to be.

But even with four doses of Salk vaccine you would still be protecting only about 90 percent of those who receive the vaccine. It has no effect on the spread of the virus in the community, and does not provide a means of breaking the chain of transmission of the paralyzing viruses in the community.

Now, this is a function which is fulfilled, it has been demonstrated, with the oral vaccine. It can break the chain of transmission and thereby protect the parents of children who for one reason or another have not themselves been vaccinated with Salk vaccine, and can also protect indirectly those in the community who have not received the vaccine.

In Cincinnati, we found that almost 50 percent of the young fathers of preschool children have not had even one dose of Salk vaccine.

Mr. ROBERTS. Yesterday you were quoted as having said that the Sabin vaccine could be produced much cheaper than the other type vaccine. Would you go into some of the processes of manufacture which you think make this possible?

Dr. SABIN. I have supplied the strains of vaccine and the manufacturing process to every pharmaceutical company in this country, Canada, Europe, and elsewhere that has asked for it, and there have been many of them.

And I am in intimate contact with their experiences.

The oral vaccine is made from the same kind of tissue culture as the Salk vaccine. And these tissue cultures are made from the kidneys of monkeys.

Now, while one cubic centimeter of such a culture fluid provides only one dose of the Salk vaccine, one cubic centimeter of such a culture fluid has already, not just in the laboratory, but on the basis of actual manufacturing experience, supplied as much as 100 to 500 doses of the oral vaccine.

I know that at least one pharmaceutical company producing the vaccine in Great Britain, has obtained in series results such that the kidneys from 1 monkey have given anywhere from 500,000 to 2 million doses—1 monkey yielded as much as 500,000 to 2 million doses of the oral vaccine.

Now, I do not expect on this basis that the cost of the oral vaccine should be one one-hundredth as much as the cost of a single dose of Salk vaccine, because in the production of the oral vaccine a certain proportion of the tissue is not used. About 25 percent has to be set aside merely for observation, a certain number of monkeys have to be discarded because the tests do not justify their inclusion.

But even if you have one-third left—I know that that is possible—one-third of all the monkeys that you use, ending up with usable vaccine, and this is usable vaccine by the American criteria—the U.S. Public Health Service criteria—you still have many millions of doses from small numbers of monkeys that you process.

Now, I know that the cost of a product is influenced by many factors. Mass production is always different than model production. Therefore, if a company only makes a hundred liters of vaccine and tries to charge off the cost of all the initial tests that are required to fulfill the license requirements, that would make it quite expensive, to be sure.

But if it would then proceed to make vaccine in hundred liter lots—and some of the very costly tests can be carried out on hundred liters just as readily as on 5 or 10 liters—and if the initial investment is not charged off on the first lots that are produced but spread out over a long period of time—and that is not an unreasonable procedure—the cost is very different. I have already had discussions with the president of one of the companies, whom I asked whether or not it would be considered unbusinesslike, even if it would be humanitarian, to spread out the original investment over many years so that the first vaccine that became available would not be so much more expensive than subsequent mass-produced lots. Well, he told me that in business, as in other things, you have to mix humanitarianism with other considerations, and it would not be unreasonable to spread out the original investment over a long period of years.

It is for that reason that I believe that if these factors are taken into consideration the cost of oral vaccine should be at least one-tenth, not one-hundredth or one five-hundredth, at least one-tenth per dose of the present cost of Salk vaccine to begin with, and perhaps less later on.

In saying this, I am not merely guessing and pulling these figures out of the air, but this has already come under consideration, and I would like to document it with the following experience:

One of the pharmaceutical companies in Great Britain already has about 50 million doses of each of three types that it is ready to distribute, made according to British requirements. Governments in Latin America, such as Brazil, Uruguay, and others have for a long time been interested in starting such programs in their countries. And this company had to figure whether or not they could meet the budgetary possibilities of such governments, governments that might be able to affort 1 or 2 cents a dose and not 20 or 30 cents a dose.

If you will permit me not to mention the name of the company, I can say that they were prepared to meet such budgetary requirements at that low level.

I think it is possible to produce it at that low price, and it would be of greater importance even in other parts of the world than in our own to have this vaccine produced at the lowest possible price so that it can be made available to the largest number of people in the shortest possible time.

Mr. ROBERTS. What countries seem to have the highest incidence of this disease?

Dr. SABIN. Countries that are using the least Salk vaccine, are among the highest. And countries that are just now emerging, so to speak, to the civilized state from a polio point of view that we achieved in 1916 or 1917. And there are many such countries emerging now. For example, Egypt, in 1957–58, in 1 year, had admitted to its Cairo Hospital 1,700 children with paralytic polio, most of them under 3 years of age. Israel in 1958 also had, despite the extensive use of Salk vaccine, almost 700 or more cases of paralytic polio. There are countries in Asia that are just beginning to have polio epidemics for the first time. When I served with our Armed Forces during World War II, I was called to Tientsin in 1946 because of an outbreak among our Marines that turned out to be polio. Three men died within a week, and about 40 others were sick, and I made a careful

investigation as to the possible occurrence of polio in China. In Tientsin, there was no polio among the children at the time and the local doctors didn't know of any in the area for many years.

But there was evidence that the polio viruses were spreading among the population without producing obvious disease.

Last year, as part of our U.S.S.R. exchange program, I went to Moscow along with representatives of the Public Health Service who are here present. And one of the representatives from China said that for the first time since 1952, I believe it was, or 1953, they have begun to have epidemics involving thousands of children in Chinese cities. Japan has been having more than before. European countries that are just emerging hygenically, Middle Eastern countries, and in Africa, where it has been a relatively low-incidence disease, with the larger movements of population and travel there are also epidemics of polio appearing with greater frequency.

Mr. ROBERTS. Does this seem to be worse in the tropical countries than it is in temperature zones?

Dr. SABIN. It is not worse in tropical countries. The viruses seem to spread throughout the year, and those who become infected get it very early in life and usually become immune without getting the disease.

And up until recently the price they paid in paralysis for the natural immunization was low.

But, again, for reasons that might require too much technical analysis, tropical and subtropical countries are beginning to have epidemics to an extent that they have not had before.

Mr. ROBERTS. Now, you mentioned that the largest program of immunization had occurred in the U.S.S.R.

Dr. SABIN. Yes, sir.

Mr. ROBERTS. Are you familiar with the manufacture of the vaccine in Russia?

Dr. SABIN. Yes, sir.

Mr. ROBERTS. Do they use the same methods that are used by the pharmaceutical people in this country who make it?

Dr. SABIN. The methods of production are the same; some of the tests are not the same.

Mr. ROBERTS. We had some testimony yesterday that with your vaccine comes the problem of eliminating the simian viruses. Would you go into this a little bit?

Dr. SABIN. Yes, sir. While there are many viruses in the intestinal tract of monkeys, just as there are many in that of man, the cultures that are prepared from their kidneys have a relatively limited number. And, actually, with quarantined monkeys that are used for production of this vaccine, only two agents or viruses, one of them known as vacuolating and the other as foamy, have presented problems, because they are not in the intestinal contents of the monkeys, but because they remain in the kidneys of the animals without doing them any harm.

The vacuolating virus, about which we didn't know until about 10 or 12 months ago because it took a very special African monkey tissue culture to show up its presence, has been administered now by mouth to millions of children, and we know from studies that we have carried out, also from studies that have been carried out in Eng-

land, that when it is taken by mouth it doesn't multiply, and it doesn't have any demonstrable effect in the children.

On the other hand, children receiving injections of Salk vaccine have been found to produce a reaction in the blood which indicates that it was either present in the Salk vaccine in unmodified living form or in very large amounts in the killed form.

So the Salk vaccine is not necessarily free of this same agent, and you cannot be sure that it is not there unless you actually test for it.

But let us assume that the vaccine that we want to use in this country shall be free of any demonstrable agents other than the polio viruses. I will go along with that; I will not argue with that. That does not mean that you cannot make vaccine under those conditions. You can. Because all it means is that monkeys which happen to have this particular agent in their kidneys you do not use. And instead of being able to use every 75 out of 100 monkeys that you process, you may be able to use only half of that number, or 25 or 30. That still does not prevent one from making this vaccine under those conditions. It has been made in Great Britain under those conditions, and some of the American companies working on a small scale have shown that it can be made here under those conditions.

I do not regard that as an obstacle in itself to the production of vaccine; it just means you throw away some material that you might otherwise use.

Mr. ROBERTS. Now, assume that the agent is not removed in the manufacture, what could be the results to other parts of the body?

Dr. SABIN. This is not a theoretical question, sir; it is one that can be documented, because, as I said, millions of people have received vaccine with this agent in it. Nothing happened. It is just like putting it down the drain, because it is swallowed, it doesn't multiply, it is excreted, it goes out, and nothing happens.

Some of the countries have decided that it is not important to test for this particular agent, and are using vaccine regardless of the presence of this agent.

I think that that is true of the Soviet Union.

I have just had word that in Yugoslavia, where they have also started to make vaccine from my strains, and they have now given their own manufactured vaccine, beginning early February, to over 4 million of their children—I haven't got the last word, but I think they also have not considered it necessary to test for this agent.

The Swiss Federal Government has released vaccine produced from my strains by a Belgian company without requiring tests for this particular agent.

We have no evidence that it causes any harm whatever, or that it multiplies.

Mr. ROBERTS. You remember when we had the other panel there were some fears along that line expressed by Dr. Mayer, if I remember correctly, one of the biochemists who was here on the panel. And if I remember correctly, he said that if these agents were not removed, we might have a problem of—I don't know whether he used the term hepatitis, but I believe he said there was some danger of possible liver damage or kidney damage.

Dr. SABIN. Without knowing exactly what he said, since he mentioned hepatitis, I can tell you where that is a problem: The sug-

gestion has been made of using certain human tissue cultures instead of monkey tissue cultures.

And the decision has been against using human tissue cultures because of the possible problem of hepatitis virus (jaundice) for which we have no tests at the present time, and cannot be sure whether it is in there or not.

Mr. ROBERTS. Doctor, yesterday we had quite a bit of discussion about why no applications have been filed for licenses to manufacture the Sabin vaccine in this country. I might say that we did have some testimony that indicated that the applications would be made within a short time; we had testimony to the effect that the standards would be published by the end of this month in the Federal Register.

I would like to know as to whether or not you have any knowledge of whether any of the pharmaceutical firms are planning to file such applications.

Dr. SABIN. I have been in close touch with pharmaceutical companies ever since the International Conference in 1959 here in Washington, which indicated that the field trials were coming along so well that the possibility of using oral vaccine was imminent.

A pharmaceutical company cannot begin to prepare vaccine which it could submit for license here until it knows the final requirements that it will have to fulfill. It has been said that with all the good intentions of the committee working for the Public Health Service, there were a series of recommendations, one following the other, that read more like research projects than directions for how to make a vaccine.

Now, there were those forward-looking individuals or groups who began to work before the last "t" was crossed and "i" dotted. But there were others—and I think from a business point of view perhaps justifiably so—who took the position that until they can see the final requirements as to just what they will have to do and fulfill, they cannot begin to manufacture a single lot for licensure.

Now, these final requirements are yet to come out at the end of this month, we have been told.

Therefore, personally I cannot argue with any man in charge of management who says that he had to postpone appropriating money for actual production until he could read those final requirements and calculate what his investment would have to be.

I would say that that is one reason, but only one of many other reasons.

Until about 10 days ago I was not very optimistic that even by the end of 1961 or early 1962 there would be more than a dribble of oral polio vaccine.

And on the basis of production in this country, I would say that my attitude would still be the same.

But after a conference that I have had—and since the name has appeared in the public press there is no point in my not mentioning it, Pfizer International, working in its plant in England—it became apparent to me that they, who have started quite early, are perhaps more advanced than the others, that they are making vaccine to the best of their ability in accord with the requirements of the U.S. Public Health Service as they had reason to believe they would finally be, because last August there was an indication of what they would be;

so they did not wait for the last word on this, and if the tremendous effort and investment that they are putting into their England plant continues to yield as much vaccine as they are now producing per month, and if their vaccine passes—you notice all the "ifs" that I put in—if their vaccine fulfills and passes the licensure requirements, that company alone may be supplying by the end of December in my estimate, and up to about March 1962, either 40 to 50 million doses of each of the three types, or, if the dosage requirements are modified, perhaps even a 100 million.

On the other hand, the actual production in this country is quite different. I have had altogether five different pharmaceutical companies make contact with me about production of this vaccine. I should like to make it clear that whatever agreements I have, I counsel with all pharmaceutical companies without any monetary return whatsoever, either personal or institutional or any other kind, and that of the five that approached me one decided not to continue after making a very great initial serious effort, because they believed that they couldn't do anything until they read the final requirements. Another company that started building a separate production plant for this also decided against even starting until the final requirements were published. A third company—I hope I have got all my fingers all in order—a third company decided that they would play with it and see if they could make small lots of vaccine to fulfill the licensure requirements, but had made, as of now, no plans whatever to produce the amounts of vaccine that might be desired and needed in this country.

Only one company, which is not engaged in the production of Salk vaccine, has been putting an effort into this in this country, but they started rather later than the English company, and I am sorry to say that in my contacts with them they are more inclined to complain about the rigidity of the U.S. Public Health Service requirements than saying, "This is a fact of life, and we are going to work with it," as I know it can be worked with.

Now, some of the companies have indicated that until they know what the ultimate policy will be for use of Salk vaccine and oral vaccine in this country, they have no way of evaluating what the need will be. Some of the companies have definitely indicated that they are very much concerned about possible damage suits that might occur.

When you go out and give anything to 10 million children, and then observe them over a period of several months, we know that there are going to be some cases of polio among them, because a few will be in the incubation period of the disease. And unless scientific opinion makes it clear that this is the sort of thing to be expected, they fear that they may have damage suits.

Now, other companies say that those are facts of life with which they live, and have decided to go ahead in spite of it. Others have not.

There may be many more factors, but all in all I would say that clarification of policy of what will be needed in the way of oral vaccine in this country and elsewhere, and the final publication of the U.S. Public Health Service requirements, which are imminent, may influence subsequent policy in this direction.

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But, as regards actual production in this country now, unless the English-produced vaccine passes the requirements, we will not have very significant amounts for the 1962 polio season.

Mr. ROBERTS. Yesterday, it was testified by one of the witnesses that the oral vaccine was complementary to the Salk vaccine rather than competitive with it.

Would you care to comment on that statement?

Dr. SABIN. Mr. Chairman, I hope you will permit me a philosophical introduction. Among people of good will and equal information there may be justifiable differences of opinion regarding strategy and tactics.

Now, the recommendations for how the two vaccines are to be used ultimately that were made before this committee yesterday and in the press and through the Surgeon General's announcements before were made on the advice of my closest friends, for whom I have the greatest respect and admiration, and it is no reflection on them at all if we differ in strategy, because even in military operations generals who are supposed to be equally informed differ in strategy.

Now, with that introduction, I would like to tell you why I believe that the strategy of indiscriminate use of one vaccine or the other vaccine as an individual physician may be moved to decide is not the best way to eliminate the residue of poliomyelitis from this country as quickly as possible.

I believe that the quickest way to get the most out of oral vaccine is, first of all, to have communitywide programs on the Cincinnati model, which means that during the months of, let us say, November to May or June in most of this country, the vaccine would be administered on a communitywide basis. And from what has happened in Cincinnati, and what has happened in some of the central European countries in 1960, we have reason to believe that even if only 70 to 80 percent of the preschool children were reached that way, poliomyelitis might be brought to a stop within a given season.

Now, this would naturally involve perhaps some changes in the usual mode of administering immunizations to children, in communities. But after that, the best way to continue is to give the vaccine to children as they are born during the first year of life as part of their regular medical care when they come to their own physician—or clinic if they have no physician then that would be the way to maintain it.

I would like to point out that this particular recommendation is also the recommendation that has been made by a committee established by the Surgeon General of the Public Health Service known as Subcommittee No. 1.

And I believe you now have the document that was submitted to you by the Public Health Service people yesterday in which precisely this procedure has been recommended for the use of oral vaccine when it becomes available.

This committee also agreed that when that is done, there is no need, no scientific need, also to use the Salk vaccine or other immunization until further notice.

Mr. ROBERTS. In other words, you are saying that it is complementary in the sense that a Ford automobile is complementary to a Chevrolet automobile?

Dr. SABIN. That is a very vivid way of saying it. But I would say that there is one modification, that at a time when you didn't have enough automobiles but you also have horses and buggies, you should use both and in that way they would be complementary.

But as soon as we can get mass production to give us the automobiles, I think that horses and buggies have a place for sport.

Mr. ROBERTS. You described the very fine community effort made in Cincinnati, with the complete cooperation of the local physicians. Do you think that you would find the same climate in other communities, or do you think that it will require energetic leadership on the part of organizations such as the American Medical Association to bring about a similar climate?

Dr. SABIN. I have already had some experience which makes me believe that a formal consideration of such programs by the leadership of the American Medical Association, the Academy of General Practice, would be most helpful as a guide to individual county medical societies.

I do not have documents with me, sir. I was attending a cancer conference yesterday in New York when I was called to this meeting. But I can supply it. Some months ago the president-elect of the American Medical Association was asked whether or not any modification in the usual patient-doctor relationship that might be required in an initial communitywide program would draw any objections, basic objections from the American Medical Association. And he expressed himself that he could see no reason why it should.

After the Atlanta January 23 meeting of this year, the officers of the Academy of General Practice—I understand they represent about 24,000 general practitioners in this country—released a statement regarding their endorsement of the use of oral vaccine, and they also asked me to make a recording for them on the way in which I thought it ought to be used.

And I, essentially, gave the recommendations of subcommittee No. 1 to the Surgeon of the Public Health Service.

Now, why do I think it would be helpful to have the leadership of these important organizations provide a guide to the county medical societies in this country?

There are some of the officers in county medical societies who regard the free administration of the vaccine in the schools as a breach of the usual medical practice, and, as a matter of fact, in Cincinnati the county medical society—this is no secret, because it was published in all the Cincinnati newspapers—came out against the free administration of the vaccine in the schools under the supervision of a physician. And the board of education, board of health, and city council took that into consideration, but decided nevertheless that this was a public health function, and that if 110,000 or so children could receive the vaccine very easily in an hour, that the end of public health would be achieved much better that way than have them go individually to so many doctors.

In some areas, the county medical societies have had no objections to this whatever.

In New York State, for example, I was informed by Dr. Hilleboe, State health commissioner, that the county medical society had no objection to it being done that way in Rochester, N.Y.

In Middletown, Conn., I was informed that there was no objection. There are differences in local opinions. I think that if the leadership of the American Medical Association and Academy of General Practice would consider what is involved and give their considered opinion on this, it would be a great help.

And I think it would be well for them to remember that any modification of the doctor-patient relationship would apply just once during the communitywide programs which is the first step in providing a blockade to the spread of polioviruses because, after that, the vaccine will be given during the course of the first year of life of children as they are born, as part of their regular medical care.

When a child is taken to the doctor to get whooping cough and diptheria shots it can get a few drops of the vaccine by mouth without any extra effort, and in the usual medical practice without upsetting the established medical principles of practice.

Mr. ROBERTS. Doctor, if you have concluded your main statement, I think at this time the Chair will reserve any other questions so that the other gentlemen here may have an opportunity to ask whatever questions they have in mind.

The gentleman from Minnesota?

Mr. NELSEN. No.

Mr. ROBERTS. The gentleman from New York?

Mr. O'BRIEN. I have just one question.

Doctor, how much after the final publication of licensing requirements do you think the companies can be in sufficient production to provide comprehensive protection of American children?

Dr. SABIN. Mr. O'Brien, if I understand your question—permit me to repeat it—if the licensure requirements are published, let us say at the end of this month, how long would it take for some of the American companies that are now tooled up to go into production to provide large quantities of the vaccine?

I have asked that question in advance of one particular company that said that they were making just enough vaccine to fulfill the licensure requirements. And they said that if they had assurance of a market—so that the investment they would put in they could get back by selling the vaccine—they could expand their production now, so that by the end of 1961 or early 1962 they would have not 100 liters of each type—100 liters is 10 million doses—but they could have 10 times that much, because they are all set up to go.

Mr. ROBERTS. Mr. Thomson?

Mr. THOMSON. Dr. Sabin, you said that the cost of the vaccine might reasonably be expected to be one-tenth of the cost of the Salk vaccine?

Dr. SABIN. Yes, sir.

Mr. THOMSON. The cost in the early stages was double what it is at the present time, isn't that correct?

Dr. SABIN. I understand that that was the case, or more.

Mr. THOMSON. And in your estimate were you thinking of the original cost or the present cost? In other words, how many doses of this vaccine will $1 million reasonably be expected to buy?

Dr. SABIN. As I pointed out before, it depends on the policy that is adopted by a pharmaceutical company. If they would spread out the initial investment over many years and not try to recover it im-

mediately, if they will calculate on the basis of ultimate mass production, then it ought to be as low as I indicated.

But, if they do not, I have no way of knowing, and they themselves do not yet know, because they have made no cost analysis, because they have had no basis for making a cost analysis.

But permit me to point out one other thing, if I may. The cost of the vaccine by itself is not the only social problem connected with elimination of polio by vaccination. I have had many letters from people all over the country, after publication of an article that I was asked to write by the American Medical Association entitled "Ten Facts You Should Know About the New Oral Vaccine." It was published in a Sunday magazine distributed throughout the country. I haven't got the letter with me, but I could provide it. The most vivid and characteristic one came from a mother in Texas. They have four children, both parents are young, and when they, the six of them, go to their doctor to get one shot of Salk vaccine for each of them, it costs them $25.

Now, that is not true of the entire country. They said that they are not poor, but they are not rich. And this also has been, I think, one of the social factors that has changed the picture in such a way that while poliomyelitis has not been eliminated from the middle and higher income groups by Salk vaccine, it has been so disproportionately diminished in them, so markedly and so disproportionately raised in the lower income groups that it is now almost a matter of socioeconomic status, and it is not enough to say, "Well, you can get it free." Some places they can get it free without having to say anything at all, although in others they practically have to declare themselves paupers. Again, in many of the letters I have received, there is something in the average American spirit against publicly saying, "I am in a category where I can't afford to get it." Some of the people have written me that they would rather not get it at all.

So we do have a social problem here which goes quite beyond the cost of the vaccine itself—so that, we might say, that the 3 cents or the 30 cents may be a small matter when it is compared to $5 per dose ultimate cost to the recipient.

Mr. THOMSON. Thank you very much, Doctor.

Mr. Chairman, I would just like to observe that we have in the audience this morning Dr. Gunnar Gunderson, former president of the American Medical Association, with some of his contemporaries in the State of Wisconsin. I don't know whether he expects to testify or not, but we are pleased to see him here.

Mr. ROBERTS. Thank you, Governor.

We are certainly happy to have you, Doctor.

The gentleman from Florida?

Mr. ROGERS of Florida. Dr. Sabin, I enjoyed very much your testimony, and I am grateful to you for giving us the benefit of your views. And, of course, we take pride in the wonderful accomplishments you have made in this field.

I want to find out just a little more for my own knowledge about the manner in which your vaccine is given. Is it given with water? For the three types must you give three doses, or can it be combined in one dose? Can you just give us a little testimony on that?

Dr. SABIN. Yes, sir.

The administration is a matter of convenience. In Cincinnati, we had to set up our own vaccine distribution, and so we diluted the vaccine and put it in an eye dropper bottle, which was then given out to the doctors and to the clinics. They lined up rows of plastic spoons into which they put some ordinary sirup, put two drops of vaccine in the sirup, and it went down the line this way. That is one way of doing it.

The Russians have incorporated the vaccine into a candy ball. And you have had some testimony about that yesterday, I understand.

Mr. ROGERS of Florida. Yes; we saw it.

Dr. SABIN. Which makes the distribution particularly for children over 1½ to 2 years of age, those who have their teeth and can do a little something to it, very much simpler.

Now, the process of candy production which they have worked out was transmitted to me in the greatest detail, and I have transmitted it both to our own manufacturers and manufacturers in Canada and Europe with all the details of the engineering problems that are involved in getting it to come out just right.

I myself was interested in testing how uniform the dose was in such candies, and I tested 130 individual pieces of candy and found that it was exactly what they said it was; it was uniformly distributed, and I think it is a simple procedure.

But there is a much easier way in which you can make our own candy. If you distribute instead of a lot of plastic spoons one of these half inch sugar cubes and put the two drops of the vaccine on the sugar cube and take that in your mouth, you have got your own candy. And what I am particularly concerned with is that the package should not cost more than the vaccine.

Now, so much for the different ways of administering it.

Now, about the three types. The three types, or the three doses of oral vaccine, do not have the same significance as three or four doses of Salk vaccine, for the following reason: The multiple doses of Salk vaccine are needed to build up the immunity, because this is a killed virus vaccine that does not multiply, and you have to build up the immunity with larger quantities of it over a period of many months.

The three different doses of oral vaccine represent the three different types of virus against which one must protect.

Now, it is important to remember that type 1 is responsible for at least 85 percent of all the paralytic disease, and with few exceptions, for most of the epidemics. And when you have taken one dose of the type 1 oral vaccine within a matter of a few days, certainly within a matter of a week, you already have immunity against that most important type of polio whether or not you take any more doses.

The subsequent doses are given to provide immunity against type 3 and type 2, which have a lower incidence in causing paralysis.

Now, under conditions obtaining in this country, in which there are not too many interfering viruses in the intestinal tract—and our study in Cincinnati showed that during the spring that was no problem—the best results are achieved by giving them separately at 4- to 6-week intervals.

On the other hand, studies that we have carried out in subtropical and tropical countries on a really extensive scale show that at any one time the children are full of all sorts of other viruses in their

intestinal tracts which can interfere with the proper effectiveness of the oral vaccine unless you use old military tactics, which are that if your enemy numbers a thousand, outnumber him, and to outnumber him means to give all three types of vaccine simultaneously, let them find their place wherever they can in the intestinal tracts of the susceptible children, and then the children spread it one to the other. Under those conditions, it was found—and this was carefully studied in a city of 100,000 in Mexico in 1959—under those conditions it was found that two doses of a mixture of all three types constitutes an efficient way of doing it.

But in this country the administration of the three types separately does provide the best approach on the basis of our present knowledge.

Mr. ROGERS of Florida. May I ask how long you do feel that this vaccine is effective?

Dr. SABIN. The absolute determination of how long it will be effective, in my opinion, will not be possible until communitywide programs have been carried out, so that the circulation of the naturally occurring polio viruses has been cut down tremendously or completely eliminated, so that natural reinfections will not occur; but on the basis of studies on my own children who were without any immunity to any of the three types of polio, when they got the oral vaccine in 1957, and also on some of their playmates—they were captive guinea pigs on whom I could carry out detailed studies—and since they did not acquire polio immunity during the pervious period of 5 to 10 years, it is not likely that under the conditions they lived they would have acquired infection subsequently—we have reason to believe that, certainly, it will last several years without any modification.

And if it behaves like the naturally occurring infection which produces immunity, in the vast majority of the population, it may last a lifetime, but we will not know, sir, until time and study tell us.

Mr. ROGERS of Florida. Now, I should like to ask as to the progress for licensing that we are going through in this country which I understand, of course, is at a high level—and it may be that we have moved as rapidly as we possibly can in licensing polio vaccine, but I wanted to get your opinion as to whether you feel we have progressed as rapidly as we could.

And could you give the committee the benefit of your thought as to how our progress might be improved with other vaccines, since I understand we have others, and what should have been done with licensing requirements?

Dr. SABIN. I hope you will permit me to overlook the past entirely. I do not want to say what I would have done in 1958 or 1959 or 1960. I am interested only in the future. And, therefore, I would like to address myself to what, in my opinion, is needed to get material that will be submitted for license, as quickly as possible now that the requirements will be published.

I think, first of all, to help our pharmaceutical companies in their planning, a clear statement should be made as to whether or not Salk vaccines will have a large place in immunization against polio, once live vaccine becomes available, so they can plan.

You now have six companies or so making Salk vaccine. If they find out that the opinion of the people who have studied this question is that once immunization is carried out, let us say, in accord with the

recommendation of the Subcommittee No. 1 of the U.S. Public Health Service there will be little place except for individual preferences for Salk vaccine, they would modify—they would not, naturally, continue with intensive activities with a product that would not have much use.

That is point No. 1, to clarify how it will be used and what the place for the different vaccines will be.

Mr. ROGERS of Florida. That is by the Public Health Service?

Dr. SABIN. I think if the Public Health Service adopts the recommendations of Subcommittee No. 1, that is spelled out there, I think that would have a great deal of influence on planning, both medical and commercial.

Point No. 2, perhaps, individual companies will deny in public that they will not put any effort into it unless they have assurance of some sale in mass-produced lots, but that is indeed what was told to me in private.

Therefore, it is my opinion that if we could plan not only for the production of small lots but for programs that would take in not only our interests in this country alone but also the international health program on which the United States spends so much money, helping others, then they could mass-produce it rather than model produce it, and we would gain not only by cheaper price for the United States, but also in my opinion, by having something that can become part of the American international health program.

That, I believe, would help to get it going once the license requirements have been published.

I hope very much that we can get such production started in this country even though I am very hopeful that the vaccine production by Pfizer in England may be a very excellent source if it passes the licensing requirements.

It is for that reason that I believe the recommendation of $1 million to buy vaccine when it becomes available is a nice step on a long journey. But I hope I will be pardoned and not appear to be hypercritical if I say that I think it is a small step, and I think that it is a small step, also, if we consider that it is to be used as was recommended to the President, as an epidemic reserve.

Now, permit me to say, in my opinion—and I think I can confirm it with data that my good colleagues of the Public Health Service have accumulated—that the problem in the United States now is not so much epidemic. There have been a few last year, the year before, we may have one this year. They constitute a small proportion of the total residue. The total residue is the increased summer incidence that occurs throughout the country.

Therefore, it seems to me unwise to have millions of doses lying in reserve that could be used immediately in community programs to prevent occurrence; it is much better to prevent, than come in after you think you have an epidemic; to my mind an epidemic reserve would not be the best way to use the oral vaccine.

Therefore, it would be my judgment that it might help to reconsider the recommendations of Subcommittee No. 1, to the Surgeon General of the Public Health Service and to plan in the light of the fulfillment of that program rather than the small step of a million dollars for only a small part of it.

Mr. ROGERS of Florida. May I ask you a question as to the Subcommittee No. 1 of the Surgeon General: Is that subcommittee a permanent one or one that was formed at the conference in Atlanta?

Dr. SABIN. You have the record on that, sir. This is a committee that was appointed by the Surgeon General to prepare material for the conference in Atlanta. I do not know whether it is an ad hoc committee or a continuing committee, but you have that in your documents.

Mr. ROGERS of Florida. I wonder if you could give us your thoughts or, at least, recommendations for the future to improve or step up, if it is necessary, the determination of requirements for licensing?

Dr. SABIN. Mr. Rogers, I think there may be justifiable differences of opinion in requirements for licensing, but I would not want any differences of opinion about that to be an obstacle in the way of immediate operation.

I think that immediate operations are possible with the present requirements.

The most important difference, for example, between American requirements and British requirements, are that in the British requirements, once the product is made, free of other viruses, except the polio immunizing viruses in the vaccine, no extensive tests on children, on consecutive lots, are required in order to obtain a license.

Maybe one or two minimal demonstrations.

In the American requirements, copying mostly the procedure that was used with the Salk vaccine, which is an entirely different product, five consecutive lots must be tested. And that is really a very terriffic job. It can be done. And it will be done and it will not be an obstacle, but I would say that if the Public Health Service wants to have something for epidemic use in 1961, they may have some lots that would actually be available in June and July if the letter of this requirement of having all five consecutive lots fulfilling this particular test repeatedly tested in hundreds and hundreds of children is not required.

But please, I do not want this to be an issue, because I do not want anybody to fall back on the excuse that they will not and cannot make the vaccine because it cannot be made according to present requirements.

My opinion is that it can be made and it has been made and it should not be an obstacle.

Mr. ROGERS of Florida. Do you recall offhand how many cases of polio we had in this country last year?

Dr. SABIN. I may be off on the fourth digit—it was 2,000-some-odd which was very, very gratifying.

Permit me, if I go beyond your question and say that in 1959, however, it was 6,200. And that in 1960, also, in the American territory of Puerto Rico, with only a population of 2.5 million or so, there were close to 500 paralytic cases. And that we have no way of knowing whether it be less in 1961 or more, and more in 1962, but that it will continue and that it may continue to be greater in proportion to the extent of vaccination of the population, there is no question at all.

Canada produces as good Salk vaccine as we do in this country, I know. It is a nation of 17 million. In 1959, they had close to 2,000 cases of paralytic polio. Mostly in those who were unvaccinated or inadequately vaccinated, but they, also, have not been able to get it out to the people enough. That is 2,000 for about 17 million. You

multiply this for 180 million, and there is, at least, a potential that we might face.

Mr. ROGERS of Florida. Will you reiterate for me the countries that had no cases where the oral polio vaccine had been used last year during the polio season? I believe you cited two examples.

Dr. SABIN. Czechoslovakia, Hungary—I mentioned only those two, because there careful tests for confirmation of suspect cases were carried out.

This is, also, true in some of the republics in the Soviet Union where tests were carried out.

A report on what happened there, particularly, on what happened in Czechoslovakia, will shortly be published in the Journal of the American Medical Association. Manuscripts were sent to me, I transmitted them to the editor, and he will publish it.

Also, a preliminary report on just what was done in the Soviet Union will appear in a forthcoming issue, perhaps in a week or so, again in the Journal of the American Medical Association. So it will be on record.

Mr. ROGERS of Florida. As I understand it, it is your feeling that with the children in an active program in this country, especially using the oral polio vaccine, we can approach a record of almost wiping out the disease; in other words, certainly reducing greatly even the polio that now exists?

Dr. SABIN. I would say that this is not a theoretical, but a practically demonstrable possibility; on the basis of achievement in different areas where that was done, we have good reason to expect just that.

Mr. ROGERS of Florida. That is very encouraging and I hope we will, and I feel sure that subcommittee, Mr. Chairman, will do what it can to see that this gets on the crash program.

Mr. ROBERTS. Doctor, when Salk vaccine was first used, was there an assured market for it?

Dr. SABIN. The definition of an "assured market" is one I would not like to attempt. I think Mr. O'Connor is sitting behind me and you will have an opportunity to question him.

I think the National Foundation did a very fine thing during those days. There was no vaccine at all. And while he will quote the precise figure that the National Foundation invested in cooperation with the manufacturers even before the field trials were finished to make sure that they would continue in operation so that as soon as it was licensed there would be some material to use, I cannot help, personally, but feel that that was a great impetus; and the paralysis and death that this prevented far outweighed the cost to the National Foundation, which is, after all, the American people who supply it with its money.

And when you consider the cost of caring for one paralyzed person, child or adult, every case that is prevented repays ultimately even in dollars and cents the investment that you make in preventing it.

Mr. ROBERTS. You have had quite a bit of experience in the international health field; in fact, I would say you are one man who has had to do with international health. Do you think we would be crippled in our international relations unless we get the oral vaccine manufactured in a short time?

Dr. SABIN. Mr. Roberts, "crippled" is a strong word. By comparison with all of the other problems in this world, I know that polio is a relatively little problem. But if we tackle the little problems one by one, they add up.

I would not say that lack of oral polio vaccin would cripple our international relations, but I must say that it has entered into the field of international competition for favor with, let us say, uncommitted nations. There are many nations in this world who cannot afford polio vaccine, need it, and want it. One of the recommendations that was made to the Surgeon General at the Atlanta meeting was that it would be a very good idea if the United States could help countries that cannot help themselves with immunizing material against poliomyelitis.

I think that if we do not ourselves make such material available to other nations, that the Soviet Union, probably, will, and has the capacity of doing so. They are producing or have been producing, when I was there in Moscow in May 1960, at the rate of about 20 million doses a week of oral vaccine. And while up to the present they have mostly either given it or sold it—they do not always give it away free, I discovered that East Germany has to buy it—they, nevertheless, have enough vaccine on hand now to give it to others.

I have, sir, made a proposal to the World Health Organization that this, indeed, is one of the functions for which the World Health Organization was set up, to help countries that cannot help themselves with the elimination of poliomyelitis.

And my proposal included two steps:

One, that all of the nations that made more vaccine than they could use for themselves should contribute it to the World Health Organization. And then have the World Health Organization give it to the nations that need it and cannot afford it.

And the other is that the World Health Organization train key personnel.

But I am afraid we are not in position now to contribute anything except a promise.

Mr. ROBERTS. You will remember last year this committee had a part in passing legislation which carried out Senator Hill's bill which authorized such a proposition on research, but did not authorize to go into the field of preventive medicine. Do you think that on the basis of international health research such a bill could be used as a vehicle to promote the use of the oral vaccine?

Dr. SABIN. I think that there is a place not only for extensive use of oral polio vaccine but for research as you suggested because, while available data suggest that we may have reason to believe that extensive use on a communitywide basis in some subtropical or tropical areas, in underdeveloped countries, will quickly stop the further occurrence of polio, studies have to be carried out over a long period of time to see what happens when you pursue the designated program for a year or 2 years. Polio has existed with mankind since earliest evolutionary times and I am not so naive to think that we have got all of the answers now—we have some answers on which to act, but study is still required.

And the type of thing you suggest would constitute a very important international health research contribution and one which this country could very profitably contribute.

Mr. ROBERTS. Thank you, Doctor. Any more questions, gentlemen?

Again, I want to express the thanks of the Chair and the members of the subcommittee for your appearance here today. You always contribute to our hearings and to our work.

(Dr. Sabin submitted the following documents for the record:)

LAKE JACKSON, TEX., *January 30, 1961.*

ALBERT B. SABIN, M.D.,
*University of Cincinnati,*
*Cincinnati, Ohio.*

DEAR DR. SABIN: As a mother of four children I want to compliment your excellent article about oral vaccine. I cannot tell you in words how grateful I am for this opportunity to immunize my children, my husband, and myself.

It is so sad that this vaccine is not yet available to us. I am especially concerned because this is the time when our booster shots are due. Do you know that in order for the six of us to get his booster that our doctor will charge us $25. To me this seems an appalling sum. Especially since I know it is available for something like 10 cents a shot. We are not hungry; however, it is not easy to stretch the salary my husband makes.

Yes; there is something like relief in this community where if you obtain your doctor's signature saying you are in need of medical care and are financially destitute the county will give you care. We do not need this kind of help. What I'm saying is that in order to help yourself you must pay, pay, pay. Can't there be a balance somewhere?

Why am I writing this to you? You are indeed a dedicated man and thank you for thinking above yourself. You are urging the masses to get their shots—to fight polio. Well, I, for one, want to show you that it is not always as easy as it may seem.

Sincerely yours,

MRS. H. L. WOLF.

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THE CHILDREN'S HOSPITAL RESEARCH FOUNDATION,
*Cincinnati, Ohio, October 22, 1960.*

Dr. L. E. BURNEY,
*Surgeon General, Public Health Service,*
*U.S. Department of Health, Education, and Welfare,*
*Washington, D.C.*

DEAR DR. BURNEY: This letter is about two closely related matters, which your early departure from Atlanta on October 11 prevented me from discussing with you in person. These two matters are:

(1) A plan that would stimulate American pharmaceutical companies to produce the relatively small amounts of live, oral polio vaccine needed in the United State, and at the same time—at little extra cost if any—to provide a large surplus that the United States could distribute (through WHO or directly if need be) to economically underdeveloped countries that need it but cannot afford to buy it.

(2) A plan that the United States may find advisable to propose at the next World Health Assembly, for the WHO to develop a program to help those nations that cannot help themselves in the elimination of poliomyelitis from their own countries.

REASONS FOR URGENCY IN CONSIDERING SOME PLAN FOR STIMULATING PRODUCTION OF LIVE POLIO VIRUS VACCINE IN THE UNITED STATES

(1) Properly organized communitywide programs utilizing oral polio vaccine in the winter and spring of 1960 in the United States and elsewhere have resulted in the complete or almost complete elimination of poliomyelitis during the 1960 season.

(2) Inquiries that I made, just before the October 11 meeting in Atlanta, of the American pharmaceutical companies that have expressed their intention to produce vaccine from my strains indicated that—

(*a*) Pitman-Moore—management had not yet given orders to start.

(*b*) Wyeth—are working on a minimal scale.

(*c*) Lederle—had very few monkeys in quarantine and work on small scale was only starting at end of October.

(*d*) Pfizer—in their plant in England are far ahead of the others, but are not prepared to start large-scale production without some sort of contract.

(3) On this basis, unless something is done very soon, there will not only be no oral vaccine for licensure prior to the 1961 polio season but it is very doubtful that enough vaccine will be available by the end of 1961 to implement plans of communitywide programs, currently under consideration by the U.S. Public Health Service, that might be put into operation prior to the 1962 polio season. Failure to achieve this will be paid for with thousands of preventable cases of paralysis and death in the United States.

(4) Only about 1,000–2,000 liters of oral vaccine of each type (total of about 3,000–6,000 liters) would be needed for the initial phase of communitywide programs in which about 100 million children and young adults could be vaccinated in the United States.

This relatively small amount should be compared with the approximately 80,000–100,000 liters of Salk vaccine that American pharmaceutical companies have been making annually in recent years. The Salk vaccine has recently been sold to public agencies at 10 cents per cubic centimeter—and 1 cubic centimeter of oral vaccine, made from the same kind of tissue culture as the Salk vaccine, would be sufficient for 50 to 100 doses.

If the oral vaccine (which can be readily stored in the frozen state for many years) were made in quantities comparable to those of Salk vaccine, the price per cubic centimeter may be somewhat greater but probably not more than twice as much (based on an assumption that 50 percent of the lots might have to be discarded for one reason or another). If production were limited to the very small quantities needed by the United States, the price would undoubtedly be very much higher if the pharmaceutical companies are to recover their expenditures and make a justifiable profit. (Automobiles produced in small numbers are invariably much more expensive than those which come off the assembly line in mass production.)

(5) I am suggesting that the Federal Government subsidize, by contract to buy or otherwise, the production by American pharmaceutical companies of at least 30,000 liters of the oral vaccine. This, in my opinion, may achieve the following:

(*a*) Provide the necessary business incentive for American companies to produce the vaccine;

(*b*) Provide not only enough vaccine for the first phase of communitywide immunization programs, which holds the promise of eliminating poliomyelitis from the United States in 1 year, but also enough for at least several years of the second phase, which involves the immunization of newborn children during the first year of life;

(*c*) Permit the United States to use the surplus vaccine in a truly humanitarian way, as part of its international health program, to help those economically underdeveloped countries that want it and cannot afford to buy it.

(6) This plan would probably not involve the expenditure of much more money than public agencies (State and city governments, etc.) are now spending annually for the purchase of Salk vaccine. In 1959, public agencies bought about 26,000 liters, and from 1955 to 1960 a total of about 166,000 liters.

(7) Whether it be this plan or some other plan, unless something is done soon, the U.S. Public Health Service may develop fine plans for the elimination of polio from the United States with the aid of the oral vaccine—only to find that there is little or no vaccine to use.

### BACKGROUND AND PLAN FOR PROPOSAL AT NEXT WORLD HEALTH ASSEMBLY REGARDING ROLE OF WHO IN ELIMINATION OF POLIOMYELITIS ON WORLDWIDE SCALE

(1) The pilot study which I carried out together with my associates in Mexico in the city of Toluca (pop. 100,000) showed the effectiveness of two trivalent doses of oral polio vaccine in immunizing the susceptible children under conditions of most massive natural infection with poliomyelitis and other entire viruses. The Toluca experience reported in the J.A.M.A. (Aug. 6, 1960), 173: 1521–1526, can serve as a model for such vaccination programs in most economically underdeveloped countries.

(2) Many economically underdeveloped nations have in recent years been suffering from epidemics of infantile paralysis, and on the basis of inquiries that I have received from India, Egypt, Africa, Latin America, etc., there is a desire to use the oral, live polio virus vaccine for elimination of poliomyelitis in their countries. Most of these countries either cannot afford to buy it or

could afford it only at the very cheap price that would result from mass production of the vaccine.

(3) Live polio virus vaccine is now in mass production in the U.S.S.R. In May 1960 I was told that the Moscow Institute for Poliomyelitis Research was producing 25 million doses weekly at a cost of 1.3 kopeks per dose of liquid vaccine and 2.3 kopeks per dose in candy—this is equivalent to one-seventh cent and one-fourth cent, respectively, at the tourist rate of exchange of 10 rubles to 1.

(4) Even during the early part of 1960, when vaccine was badly needed in the U.S.S.R., the following nations received vaccine from the U.S.S.R.: East Germany, 5 million; Hungary, 2.5 million; Bulgaria, 2 million; Czechoslovakia, 3.5 million (type 2 and 3 only); North Vietnam, 1.5 million. With 65 million already vaccinated in the U.S.S.R. in 1960, the home needs will be less in the future and the U.S.S.R. should have large quantities available for free distribution or for sale (some of the U.S.S.R. allied countries are buying vaccine from Moscow).

(5) Pharmaceutical companies in the United States, Canada, Britain, West Germany, Austria, Italy, Belgium, France, and the Institute of Poliomyelitis in South Africa, who are already producing or have made arrangements for production of vaccine from my strains, have the potential to produce within a year enough oral vaccine for the entire world—provided they had the stimulus of a business contract.

(6) Production of the vaccine in the mass quantities required for worldwide use, may cost little more than if production were limited to the smaller quantities needed by the countries that can afford to buy it.

(7) Poliomyelitis, to a greater or lesser extent, is a worldwide problem. In oral, live polio vaccine we now have a tool with which we may reasonably attempt to eliminate not only the disease but also the causative viruses. Its elimination from any one country would be beneficial not only to its own inhabitants, but also to neighboring and other regions because it would result in a very marked reduction in the dissemination of the paralyzing polio viruses.

(8) The U.S.A., the U.S.S.R. and other nations, who can produce more of this vaccine than they need for their own use, have a choice of helping the needy nations individually, and perhaps even competitively, or by uniting their efforts through the World Health Organization, which was set up by the United Nations to perform such a function.

(9) Help through the WHO would be in line with American policy, most recently reemphasized in President Eisenhower's last address to the United Nations.

(10) Accordingly, it seems to me that it would be highly desirable to bring up such a proposal at the next World Health Assembly. The basic ingredients of such a proposal would be:

(*a*) that the WHO assume the fuction of helping those nations that cannot help themselves in the elimination of poliomyelitis, and that it develop a program for this purpose as quickly as possible;

(*b*) that all nations, which will produce more of the oral polio vaccine than they need for themselves, should be asked to contribute their surplus vaccine to the WHO for distribution to other nations that need it, want it, but cannot afford to buy it;

(*c*) that WHO obtain the cooperation of member nations in training key personnel in the administration of poliomyelitis elimination programs.

I would appreciate it very much if you would consider these proposals and let me know what you think about them. If you should find these proposals impractical, I would be greatly indebted to you if you could let me know of any alternative plans that you may have under consideration that would achieve as rapidly as possible the goal that you announced on October 11 at Atlanta, i.e., "eradication of poliomyelitis with oral, live poliovirus vaccine."

I have several lecture engagements in the next few days dealing with eradication of poliomyelitis—October 24, Baltimore; October 25, New York; November 3, San Francisco (American College of Preventive Medicine). It is not unlikely that there will be press interviews—and I should like you to know my position. An abstract of my remarks for the New York and San Francisco lectures is enclosed.

I am sending copies of this letter only to Drs. J. Smadel and R. Murray, because I have previously discussed with them certain aspects of these proposals.

With kindest personal regards.

Sincerely yours,

ALBERT B. SABIN, M.D.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
*Washington, D. C., November 4, 1960.*

ALBERT B. SABIN,
*Professor of Research Pediatrics, University of Cincinnati College of Medicine, Children's Hospital Research Foundation, Cincinnati, Ohio.*

DEAR DR. SABIN: This is in reply to your letter of October 22, relative to suggestions for stimulating the production of oral polio vaccine and assistance in making it available to economically underdeveloped countries. As Dr. Kurlander indicated to you in a recent telephone conversation, we appreciate your suggestions and are giving them very careful study and consideration. It is not possible at this time, however, to forecast the likelihood of any such programs being adopted by the Federal Government, or to give you any preliminary appraisal of the feasibility of your proposals.

As you can well appreciate, these proposals involve considerations of new legislative authority, involving basic questions as to the relationship of the Federal Government to the pharmaceutical industry, as well as considerations of policy and program priority in international relations and U.S. participation in the programs of the World Health Organization. All of these considerations will require very careful analysis and wide consultation within the executive branch, apart from any congressional considerations that may be involved if legislation is to be proposed.

Even when we complete our analysis of the desirability and feasibility of such actions from the standpoint of the Public Health Service there will remain the necessity of discussion and final determination at the policy levels within the administration. In view of the forthcoming elections and the likelihood of some changes in policy officials, regardless of the outcome, it appears highly unlikely that any resolution of these considerations can be anticipated before the early part of 1961.

Again let me express our appreciation of your suggestions. I hope you and others who are close to this problem will continue your concern with the total problem of effective immunization policies and programs.

Sincerely yours,

(Signed) LEE BURNEY,
*Surgeon General.*

8-A Cincinnati Enquirer Sunday, April 23, 1961

# Protect Your Pre-School Children

## FREE SABIN POLIO VACCINE

BY MOUTH



Cincinnati's Dr. Albert B. Sabin gives a child a teaspoon of sugar syrup containing five drops of polio vaccine.

# "Children's Crusade" April 24-May 1

Cincinnati has been chosen as the first city in America to receive voluntary mass polio immunization of pre-school children. The program is also an international demonstration of cooperation in a free society.

In order to achieve protection against polio for every pre-school child here, the Cincinnati Board of Health brings you this important message in the form of questions and answers:

**How old does a child have to be to receive Sabin vaccine during this week's "Children's Crusade?"**

From 3 months to 6 years of age.

**What does your child get?**

Two drops of polio vaccine in a teaspoon of sweet syrup. It is completely harmless.

**What's the result?**

Your child can then neither get nor transmit polio. The immunity brought about by the Sabin vaccine lasts for years and possibly for a lifetime.

**But my child has had the Salk shots—isn't that enough?**

No. With Salk shots your child will not get paralytic polio but he can still transmit it to others—you, for instance. But with the easy-to-take two drops of Sabin vaccine, a child cannot get or transmit polio.

**Is the Sabin vaccine proved?**

Yes, with more than 50,000,000 children and adults throughout Europe, Africa and Mexico. The Children's Crusade here is jointly sponsored and approved by the Academy of Medicine of Cincinnati, the Cincinnati Pediatrics Society, the Southwestern Ohio Society of General Physicians and the Cincinnati Board of Health.

**Why limit the free vaccine to the pre-school group?**

Because they are the least protected and the most susceptible. Over the past several years more than half of the paralytic polio cases in Cincinnati were in this age group.

**Is all this really free?**

Free beyond any question of doubt. Your family doctor receives the Sabin vaccine free. He offers his medical services without cost for this great crusade to protect your children. The vaccine is provided free because of grants from the National Polio Foundation to Dr. Albert Sabin for its development.

As a matter of fact, many family doctors and child specialists are holding open house this afternoon, Sunday, April 24, to administer the Sabin vaccine. Check with your family doctor. If for any reason you do not have a family doctor or pediatrician, call the Cincinnati Health Department, GA 1-5700, or Children's Hospital, AV 1-6161, line 277.

**What's the easiest way to get the Sabin vaccine?**

Just call your family doctor or children's doctor and make an appointment. Or if you prefer, take your children to any of the Hospitals or Clinics on the day and at the hours that the Sabin vaccine is being given. See the complete list of days and times on this page. No Hospital or Clinic appointment is necessary.

## Hospital and Clinic Hours For Free Sabin Vaccine by mouth

### Monday, April 25

C. & O. Play Center, 8-11 AM, 1-4 PM
4th and Cutter

Robinson Memorial Church, 1-4 PM
2109 Ravine Street

St. Rose Church, Basement of School, 1-4 PM
2501 Eastern Avenue

YMCA, 8-11 AM
Columbia Parkway and Delta, 2nd floor

Immaculate Church, 1-4 PM
Pavilion and Guido

Millvale Administration Building, 8-11 AM, 1-4 PM
1901 Millvale Cr.

Senior Citizens Center, Peebles Corner, 8-11 AM
795 E. McMillan

12th Street Health Center, 8-11 AM, 1-4 PM
212 W. 12th Street

Shoemaker Health Center, 8-11 AM, 1-4 PM
1041 Cutter Street

Mohlberg Health Center, 8-11 AM, 1-4 PM
3845 Wm. P. Dooley By-Pass

Madisonville Health Center, 8-11 AM, 1-4 PM
5915 Madison Road

Findley Street Clinic, 8-10 AM, 1-3 PM
940 Findley Street

Christ Church Clinic, 8-10 AM
4th & Sycamore Streets

### Tuesday, April 26

English Woods Administration Building, 8-11 AM, 1-4 PM
1990 Sutter Avenue

Price Hill YMCA, 8-11 AM, 1-4 PM
Considine and Warsaw Avenue

St. Mark Church, 8-11 AM, 1-4 PM
Montgomery and Duck Creek

St. Cecilia School-Gym, 8-11 AM
3105 Madison Road

Stratford Manor Administration Building, 1-4 PM
5327 Eastwood Drive

12th Street Health Center, 8-11 AM, 1-4 PM
212 W. 12th Street

Shoemaker Health Center, 8-11 AM, 1-4 PM, 6-7 PM
1041 Cutter Street

Mohlberg Health Center, 8-11 AM, 1-4 PM
3845 Wm. P. Dooley By-Pass

Madisonville Health Center, 8-11 AM, 1-4 PM
5915 Madison Road

Findley Street Clinic, 8-10 AM, 1-3 PM
940 Findley Street

Christ Church Clinic, 8-10 AM
4th and Sycamore Streets

Children's Hospital, 9 AM-Noon
240 Bethesda

Good Samaritan Hospital, 9 AM-1 PM
Clifton and Dixmyth

### Wednesday, April 27

Winton Terrace Administration Building, 8-11 AM, 1-4 PM
4848 Winneste Avenue

Rev. Tucker-Station, 1-4 PM
730 State Avenue

Avondale Community Center, 8-11 AM, 1-4 PM
Blair and Hartford

Elmrose Community Center, 8-11 AM
5701 Kellogg Ave., California, Ohio

Our Lady of Loretto School, 1-4 PM
2944 Reeves Place

Riverside Methodist Church, 8-11 AM
3488 Henrietta

12th Street Health Center, 8-11 AM, 1-4 PM, 6-7 PM
212 W. 12th Street

Shoemaker Health Center, 8-11 AM, 1-4 PM
1041 Cutter Street

Mohlberg Health Center, 8-11 AM, 1-4 PM
3845 Wm. P. Dooley By-Pass

Madisonville Health Center, 8-11 AM, 1-4 PM
5915 Madison Road

Findley Street Clinic, 8-10 AM
940 Findley Street

Christ Church Clinic, 8-10 AM
Fourth and Sycamore Streets

### Thursday, April 28

St. Aloysius Church, 8-11 AM
Portage and Whipple, Seyler Park

St. Bonaventure School, 1-4 PM
1708 Queen City Avenue

Swifton Center, Basement of Rental Office, 8-11 AM
1878 Yorktown Road

Mt. Washington Library, 1-4 PM
2049 Beechmont Avenue

12th Street Health Center, 8-11 AM, 1-4 PM, 6-7 PM
212 W. 12th Street

Shoemaker Health Center, 8-11 AM, 1-4, 6-7 PM
1041 Cutter Street

Mohlberg Health Center, 8-11 AM, 1-4 PM
3845 Wm. P. Dooley By-Pass

Madisonville Health Center, 8-11 AM, 1-4 PM
5915 Madison Road

Findley Street Clinic, 8-10 AM, 1-3 PM
940 Findley Street

Christ Church Clinic, 8-10 AM
4th and Sycamore Streets

Cincinnati General Hospital, 3-5 PM
3231 Burnet

Good Samaritan Hospital, 9AM-1 PM
[illegible] and Dixmyth

St. Mary's Hospital, 2 PM-Closing
[illegible] Betts Street

Jewish Hospital, 1:30-3:30 P.M.
Burnet Avenue

### Friday, April 29

Memorial Community Center, 8-11 AM, 1-4 PM
1607 Mansfield Street

Bethel Baptist Church, 1-4 PM
2712 Alms Place

12th Street Health Center, 8-11 AM, 1-4 PM
212 W. 12th Street

Shoemaker Health Center, 8-11 AM, 1-4 PM
1041 Cutter Street

Mohlberg Health Center, 8-11 AM, 1-4 PM
3845 Wm. P. Dooley By-Pass

Madisonville Health Center, 8-11 AM, 1-4 PM
5915 Madison Road

Findley Street Clinic, 8-10 AM, 1-3 PM
940 Findley Street

Christ Church Clinic, 1-3 PM
4th and Sycamore Streets

Children's Hospital, 9AM-Noon
240 Bethesda

### Saturday, April 30

Christ Church Clinic, 8-10 AM
4th and Sycamore Streets

A RESOLUTION

Whereas in the course of the presentation of an award by the Wittstein Middleman Post No. 524, the American Legion, Cincinnati, Ohio, Department of Ohio, to Dr. Albert Sabin of the University of Cincinnati, Ohio, Medical College, recently for the magnificent research work in the field of poliomyelitis, it was deemed fitting and proper to present this resolution by the Wittstein Middleman Post to the U.S. Public Health Service in Washington, D.C., for action by the Congress of United States; and

Whereas it has been clearly demonstrated that the general use of Dr. Sabin's oral vaccine has eliminated many cases of polio within the limits of this city; and

Whereas the treatment of this oral vaccine has met with tremendous success in many foreign countries where it has been given a thorough trial thereby saving the lives of untold millions of children; and

Whereas properly organized communitywide programs which have used the oral polio vaccine in the winter and spring of 1960 in the United States and elsewhere; it has shown the result of an almost complete elimination of poliomyelitis during the 1960 season; and

Whereas many foreign undeveloped countries whose children have been suffering from this most dreaded disease are unable to help themselves toward its elimination because of its probable excessive purchase price: Therefore be it

*Resolved*, That the Federal Government subsidize by contract to buy sufficient amounts of this oral polio vaccine from the pharmaceutical companies so that it could be an incentive for them to manufacture in sufficient amounts so the price of the same would be less costlier. This would accomplish a twofold purpose; first, it would assist in the elimination of this most dreaded disease from our children and, secondly, save the lives of many newborn children during the first year of life.

A plan should be formed to stimulate the American pharmaceutical companies to produce relative amounts of this oral polio vaccine which is needed in our country; but that any surplus amount should be made available for distribution to economically undeveloped countries who could use it, but cannot afford its proposed price; be it further

*Resolved*, That unless action is not taken immediately there will be little or no oral polio vaccine available for license prior to 1961 polio season. It is believed that it is extremely doubtful that a sufficient amount of oral polio vaccine can be available by the end of 1961 to implement plans for communitywide programs currently under consideration by the U.S. Public Health Service that might be put into operation prior to the 1962 polio season. If this is not done, probably thousands of preventable cases of paralysis and death may result. If production of this oral vaccine should be limited to only small needed quantities, the price of it would undoubtedly be very expensive and the pharmaceutical companies would not be prone to manufacture it because their profit would be very small. If the Federal Government would see fit to subsidize this oral polio vaccine so that it could be used soon, it would be performing a generous and noble act to humanity and mankind; and be it further

*Resolved*, That the Wittstein Middleman Post No. 524 of the American Legion, Department of Ohio, herein assembled go on record to petition and advocate this subsidy to be carried out because of its great urgency and need.

JAMES B. FALK, M.D.
FRANK L. GARRETT,
*Commander.*
MAURICE BRAUER,
*Adjutant.*

Mr. ROBERTS. Our next witness has contributed very much to the work of the National Foundation. I think it is especially appropriate that he appear here on St. Patrick's Day; at least, one of the gentlemen on the subcommittee will welcome his appearance for this reason alone

We will be glad to have the Honorable Basil O'Connor, president of the National Foundation, to appear here.

68776 O—61——18

## STATEMENT OF BASIL O'CONNOR, PRESIDENT, THE NATIONAL FOUNDATION, NEW YORK, N.Y.

Mr. O'CONNOR. Mr. Chairman, I am not quite sure what position I have in this field of science. I have been connected with the polio problem for 35 years, and I have been president of the National Foundation for 22 years, ever since it started, which was formerly known as the National Foundation for Infantile Paralysis.

I am not a doctor. I am not a scientist. And I pretend to be neither.

I think the committee has, probably, seen some of the problems, therefore, that a layman has in this sort of a situation. It is bad enough when doctors disagree, but when scientists disagree, that is something above that. And there is not much the layman can do about it or try to do anything about it.

The American people, through the National Foundation and the March of Dimes, has supported entirely financially the creation of the killed virus vaccine and the live virus vaccine. And, therefore, we should be objective and we are objective and we take sides neither way.

In situations like this, of course, however, there are not only scientific problems but there are some practical problems that have to be considered. And certainly, in that area, a layman, I think, has a right to function and exercise his judgment and opinion.

We do not manufacture the vaccines. We do not sell the vaccines. Nor do we license the vaccines. We are in what would be a humorous situation if it did not relate to the lives and the disabilities of children, by being charged with having pushed the Government prematurely into licensing the killed vaccine and now being accused, in some quarters, of preventing the Government from licensing the live virus.

The National Foundation is really a great organization, but it is not that great. And such talk, of course, is nonsense, although, apparently, believed in some quarters. We have nothing to do with the delaying of or speeding up of the licensing of anything that anyone may make.

What we are interested in, however, is in preventing, primarily, paralytic polio, and we have been interested ever since we started in eliminating polio itself. And have spent considerable of your money in connection with it other than in connection with the live vaccine, trying to find some drug or substance that would eliminate polio itself.

On the other hand, from a purely practical point of view, I do not suppose any of us are much interested in a virus or a bacterium that does no one harm, or there is an effective method of preventing it from doing harm, even though we still may have the desire to eliminate it.

The situation that we are confronted with is this: We are delighted that the killed vaccine has proved successful. We are delighted there is every indication that the live virus vaccine will prove to be, likewise, successful. And we hope it will be available just as soon as possible.

All we can say is that when it becomes available, we have two vaccines. And how they will be used is not for us to say; but I think our experience leads us to believe that primarily they will be used in whatever way the doctors and the public health men choose to use them.

Some doctors will prefer the killed vaccine and some will prefer the live vaccine. But, in any event, again that is not a matter with which we have concern.

We do have concern at the moment with eliminating what really is the negligible amount of paralytic polio that we are having now.

Not by way of argument, but by way of facing the practical situation which, I think, is the job of the layman, in the 6 years of the use of the killed vaccine paralytic polio in this country has decreased in numbers about 90 percent.

Let me say that any figures I use, and there will not be many, are based on what is, probably, the greatest piece of work of its kind that has ever been done, and that is under Dr. Langmuir and his associates in Atlanta in the Public Health Service in this epidemiological survey that they have kept ever since the Salk vaccine was first given.

I am sure that nothing like that has ever been done before, and I am very sincere and serious when I say that it is the kind of work that has not been propagated around and the kind of work that few realize has been done and therefore few appreciate.

But it is really an incredible piece of work, to put it in lay language. He has kept the record of every case that presumably had the killed virus vaccine where paralysis appeared. And were it not for that work, we would not have the information we have.

No other organization could possibly have done it. This is the first time that that sort of a job has been done.

I hope I will not torture his figures—if I do, I will hear from him later—when I say it decreased about 90 percent in number, that is approximately correct. Paralytic polio in this country last year was reduced to, approximately, 1.26 cases per 100,000.

For all practical purposes, current paralytic polio, if that continues, is at a rate that would not put it in the category of a serious situation.

We still have serious problems with polio.

This is not for propaganda, but we have 50,000 cases that were paralyzed before there was a killed vaccine. But I think we should face the fact that paralytic polio over these 6 years—not consistently declining every year, but declining—has declined through those years to these figures I have indicated.

And we may add, to be sure, we may have epidemics, although Dr. Sabin has stated, presumably publicly, there are no more epidemics. And I suppose we may have epidemics in diphtheria or whooping cough.

But that is of the kind of thing for which there is some prognostication and opinion and speculation as to what the facts will be before the facts are found out which can be found out, eventually, even though not now.

Despite the fact that we still have these low epidemic areas of which you have heard much, despite that, paralytic polio has been reduced to that almost irreducible figure.

And 80 percent of the paralytic cases we had last year came from, primarily, two age groups—that is, the children 0 to 4 and the young adults 20 to 29, in which you find most of the young married people.

If we could increase, at least, up to 85-percent inoculation in the 0–4 age group, instead of 62 percent which now exists in that group, as was recommended in Atlanta, I think, what would happen to that ratio of 1.26 per 100,000, is a matter of hieroglyphics.

And, therefore, one of the things that bothers us is, despite our tremendous interest in both of these vaccines, that while we talk, and quite rightfully, about one that we do not yet have, we are afraid that it will prevent the use of the one vaccine we do have, that will prevent paralytic polio, on the theory that people will wait for something else that is coming along. We would regret that very much.

And while everybody has been fair enough and scientific minded enough in this whole situation to reiterate the point that the public should continue to use the Salk vaccine, the public, as you know, including ourselves, does not always follow the advice that it is given.

The situation today is that despite the fact that less than half of the people of the United States have been vaccinated with the killed-virus vaccine, we have made that incredible reduction in paralytic polio. And what we want to do for the time being, at least, is to continue to have the use of the killed-virus vaccine proceed.

Whether it will be easier to get, in these uneconomic areas, the public to accept one kind of a vaccination instead of another, whether price, as yet unknown, will be a factor in that—those are things I think none of us know. We may find out that it is the reverse of what we may now think.

Where we are having our greatest difficulty in getting the killed vaccine used is in what is usually included in the phrase "low economic area," which means a low intelligence area. And what will affect that, we have found, is bringing the vaccine to their doorstep and trying to get it accepted that way; so that whether that problem would be true in connection with some other vaccine is yet to be found out.

Obviously, we want the live virus vaccine very much. We have always said that so far as we were concerned, we did not care how many vaccines there were if they were safe and effective. And I repeat, it is not for us to say how many there shall be or how they shall be used or when or where they are licensed.

We are familiar, because of the killed vaccine, with the problems that the Government has in licensing any vaccine of this nature, and we have no reason to believe that the Government is not proceeding in the way that it should proceed. But we would hope that, while we are trying to get this live-virus vaccine, we could continue to handle this situation with the killed virus vaccine and for all practical purposes and without prognosticating as to the future presumably eliminate paralytic polio entirely in this country.

You will find, as we all have found, there is not complete agreement among scientists in this area on several phases of it. I am not competent to discuss those matters and I do not intend to.

What I have tried to do is to present to you the situation from a practical point of view, as we see it. That is the function and obligation of an association, such as the National Foundation, who are in this kind of a situation.

In connection with the killed-virus vaccine, the National Foundation purchased an amount of vaccine to keep the manufacturers in production.

They have been manufacturing the vaccine for the National Foundation in experimental work and they have been manufacturing it for use in the tremendous field trial that we put on involving 1.8 million children to test the efficacy of that vaccine.

Pending the results of that test, the manufacturers did not feel that they could stockpile a lot of vaccine because of the possibility that it might be determined to be ineffective. If they had ceased production in July of 1954, it would have taken them, at least, 120 days to get back into operation.

What the National Foundation did was gamble about $9 million, which we did not have, to buy production from all of the manufacturers from July 1954 to the end of that year, primarily to keep them in shape to continue producing if the killed virus vaccine was found to be effective.

In connection with the killed virus vaccine, the Federal Government itself spent $66 million in research of killed vaccine and its administration, but apart from the instance that I have indicated, it has never been the job of the National Foundation to finance the manufacture of production of any vaccine. That is not our area, nor do we have the money.

But what we sincerely hope is that we will have two good vaccines as soon as possible. But in the meantime, we would do those things that the normal human being would do in the circumstances.

Mr. ROBERTS. Thank you, Mr. O'Connor.

You mentioned the decision of the Foundation to purchase the Salk vaccine, particularly from the manufacturers. Would you care to state what would have happened if the Foundation had not decided to do that, to proceed that way?

Mr. O'CONNOR. Well, yes, I will be glad to. And probably, I should not say this, but I think that the situation then is a little bit different, probably, than it is now. They had been manufacturing successfully the killed vaccine for experimental purposes.

That vaccine was tested in Dr. Salk's laboratory in Pittsburgh. It was tested by the manufacturers, and, also, tested by the NIH. And the problem left was, really, to what extent would it be effective, if at all.

The problem we were confronted with was not to get them to manufacture a vaccine for commercial purposes in toto, but to keep them in production during that 6-month period, so that if the Salk vaccine was found to be effective, as it was, they would not have a delay of 120 days or more in retooling up to go into commercial production. And that vaccine, which we purchased, we gave free to the first- and third-graders across the country in schools.

Mr. ROBERTS. You mentioned the fact that you had this unvaccinated group, that did not use the Salk vaccine. Has that group increased any since the introduction of the Salk vaccine?

Mr. O'CONNOR. My guess would be that it would not because the group which would be going out or coming in, the zero to four group, and the 20 to 29 age group—in these there could be, of course, increases as such in those but normally, it would be an intake and outflow from one group to the next group.

But it is in those two areas that we had roughly 80 percent of our paralytic polio last year, the sum of 2,000-odd cases of paralytic polio.

Mr. ROBERTS. I believe you said in your opinion that it was down from what it was when the National Foundation started to more or less secure the manufacture and production of killed vaccine.

I will ask this question that I would like to have you answer, if you feel that perhaps there is a need for somebody, perhaps the Government, to take steps which will in the case of oral vaccine have the same effect as the Foundation's decision and the Government's decision did in the case of the killed vaccine?

Mr. O'CONNOR. Well, I have always taken a position on that, that the Government should do whatever it thinks the public wants done. And if, as it apparently thought in connection with the killed vaccine, it thinks the public expects it to buy and make available certain amounts of it, if that is what they think the public expects them to do, then the Government, presumably, I think, will follow in that line.

The situation is not clear, and again I hesitate to discuss some of these things for fear that one will be charged with taking sides which would be rude, of course, for me to do, but there are some differences.

You will have a very large part of your public vaccinated at the time that the live virus vaccine comes out. And then what the Government, apart from this stockpiling against epidemics, might or might not do, will depend on a lot of factors, I think.

One factor is that if you are talking about community immunization, it will depend upon the attitude of the public health men in the counties and States, because they are the primary authorities. And I think it is impossible to say now that when we have a live virus vaccine the Government should do this or that unless that is connected with some plan that someone now thinks is not only sound but feasible.

Mr. ROBERTS. Do you think that we would be wise to look at the action of the President in asking for $1 million for stockpiling for an epidemic to see whether or not we should consider obtaining the supply for immunization instead of an epidemic?

Mr. O'CONNOR. Well, there again I think, and I am only hesitating because I want to make as intelligent an answer as I can—there again, I think one has to weigh the factors that will exist at that time that did not exist when there was no vaccine at all.

And they will, also, have to decide what you are stockpiling that against, what sort of a plan you are stockpiling against.

When the Government spent their $66 million for killed vaccine, they were doing that against a situation where there was no question about it being needed, susceptible to use, as there will be no question when the live virus vaccine is available for use.

But how it will be used, whether it will just come on as another vaccine or whether there will be some plan for large community giving of the live virus vaccine and what those plans involve—all of those things, I think, have to be thought out before you could make an intelligent answer as to whether or not the Government should stockpile for use and how much it should stockpile.

Mr. ROBERTS. I know that you say you are a layman. But I know you have had a tremendous amount of experience in this field. And

yesterday Dr. Terry agreed that the safety factor does not enter into the live vaccine, that it is being made as well as it can be made to make it safe.

Do you subscribe or go along with that opinion?

Mr. O'Connor. I really have no opinion on it. I am informed to that effect, too, and I think reliably so.

Mr. Roberts. Thank you.

Mr. O'Brien. There is less urgency now as to this than there was at the time that the Salk vaccine came into being. At that time we had practically nothing and there was this great feeling of relief on the part of the American people. It is true to say that as the result of the Salk vaccine we reduced these figures very much. But do you not think that we can reduce them more, or eliminate them entirely, by providing them for the public at reasonable cost, so as to persuade that 38 percent who are not now vaccinated to use it?

Mr. O'Connor. To me it does not make any difference how you persuade them. If you can persuade them to take either one of the vaccines, that is all I am interested in.

When you get into an area of undetermined factors as yet, one could not make a choice anyway. Any way to persuade or induce this particular group to take an effective vaccine would be good.

Mr. O'Brien. You mentioned the low economic groups and such as that, including some ignorant people. There is this fear to the use of a needle, which is very real, that there would not be in putting a piece of sugar in their mouths. There are all of those factors. You have done a splendid job, you and your organization. But I think that if we can get into a field that we can persuade 90 percent of the people to take this vaccination, we are better off.

Mr. O'Connor. And not in an attempt to prove anything, one way or the other, I was shocked because I was sure that when I was the head of the Red Cross that one reason people did not give blood was fear of the needle, and I was sure that not taking the killed virus vaccine was largely that. We had a very careful study made by outside people, and to my surprise, of four or five things, of those the needle was the last.

They ran something like this: apathy, ignorance, and so forth and so on, and the needle came last.

So that, however, does not disprove anything you say, I think those are some of the things, when you get to a comparative state, that we don't know about. We do not know which would be more acceptable to those people. I think I have to say there are some people that have as much objection to pills as they do to anything else or what they think may be pills. That, again, is not argumentative.

I am only stating these things we do not know yet. We do not know them.

Mr. O'Brien. When the first drive was on to persuade people to have their choice to be vaccinated with Salk vaccine, were there any instances of such complete success as we have had reported to us, concerning the experiments with the live vaccine in Cincinnati? Were there any such reports?

Mr. O'Connor. I could not honestly answer that one way or the other. Dr. Langmuir is the one to answer that question.

Mr. O'Brien. What puzzles me, you—apparently, you feel we have a good vaccine now.

Mr. O'CONNOR. I think everybody admits that.

Mr. O'BRIEN. It is possible that on the way there is a better vaccine.

Mr. O'CONNOR. No; I do not think I would say that. I say that everybody agrees that we, too, have a good vaccine. And I do not want any time lost by not using that as against another good vaccine that may be available tomorrow or next month or 2 or 3 months from now but is not now available.

Mr. O'BRIEN. You are desirous to have as many people get one or the other vaccine?

Mr. O'CONNOR. Oh, yes; decidedly so.

Mr. O'BRIEN. If you came to the conclusion that the live vaccine and the way of administering it would be more acceptable to more people, that would be in line with the thinking of you and your organization?

Mr. O'CONNOR. Yes. Of course, I have to say to you that we may express opinions but, after all, it gets down to the people who are going to use it and that is the doctor, unless you have some other plan in mind—I mean like a compulsory requirement of the use of the vaccine which is, I think, true now in some of our States.

But apart from that, if you have two or three vaccines, the selection will, generally speaking, be made by the doctor and not by anything I say or the National Foundation says. We do not enter into that field. That is not our field.

Mr. O'BRIEN. This is true, that 110,000 children were run through this line in schools, and I wonder all along how many of those children would have received it if we did not have this oral vaccine.

Mr. O'CONNOR. I cannot answer that. I think you could get an answer to that if you made checks between places where there have been relatively small mass giving of killed vaccine. But I cannot answer it.

Mr. ROGERS of Florida. It is a pleasure to see you here. We appreciate your testimony. And I guess everyone in the room has contributed to the organization that you helped to build. And we are mighty proud of what has been done.

I think it is encouraging that the foundation has helped to promote the live oral vaccine as well, and that your attitude is, certainly, that you want to see it used where it can be used effectively.

And I notice that the Surgeon General in August of 1960 published a statement stating that the live polio vaccine is considered suitable for use in the United States. We are now told that they will be ready to license it, probably, this month or the beginning of next month. So that perhaps it is an educational process now to help get it, as you say, to many people who do not see the advantage of taking a vaccination and particularly if it can be administered in a very simple way, say, on a lump of sugar or with water, as it has been effectively used, as I understood, in certain areas. In fact, we have one in Miami, Fla., that will be watched very carefully, and I think it has been successful so far.

Also, it is encouraging that the American Medical Association has indicated its support of that test. We had that in the testimony yesterday.

Also, I noticed in the chart submitted to the committee by the Public Health Service on the current status of polio that the chart shows

that the figures are still fairly low on those who have taken the four shots.

And so I think, perhaps, when we look at the figures we can see the need for increasing our efforts in trying to get, as you say, more into the program of using the oral polio vaccine in addition to the Salk vaccine.

I appreciate the testimony you have given.

Mr. ROBERTS. Thank you.

Mr. NELSEN. No questions.

Mr. ROBERTS. Thank you again, Mr. O'Connor.

Mr. O'CONNOR. Thank you.

Mr. ROBERTS. I am informed Dr. Salk will be here this afternoon at 2:30 o'clock. At that time I will read into the record a statement by the Chas. Pfizer & Co., Inc., on the present production status of polio vaccine.

The subcommittee will recess until 2:30 this afternoon in this same room.

(Whereupon, at 12:30 p.m., a luncheon recess was taken until 2.30 p.m.)

AFTERNOON SESSION

Mr. ROBERTS. The subcommittee will please come to order.

We have as a witness this afternoon, Dr. Jonas E. Salk, who is director of the Biological Research Laboratory of the University of Pittsburgh, and, of course, is well known as the developer of the Salk vaccine. And he has been before the committee in previous years, and served as a member of the panel—although he did not vote, if I remember correctly—the panel that did recommend the use of the Salk vaccine, I believe, in 1955.

It is a real pleasure, Dr. Salk, to welcome you here this afternoon. And you may proceed, sir, with your statement as you desire.

Before we get into your statement, Dr. Salk, would you indulge me in this: Mr. O'Connor wanted to make a correction in a statement he made for the record this morning.

Mr. O'Connor?

Mr. O'CONNOR. Thank you, Mr. Chairman.

I am told that I said this morning that we had reached the irreducible minimum in paralytic polio. I think I would be the last to say that. We still have 2,000 paralytic polio cases in 1960. And what I have no doubt about is that if we could immunize that zero or four age group further we could cut it down to as close to zero as you ever get.

Thank you very much.

Mr. ROBERTS. One other thing I would like to do before we proceed with Dr. Salk is to state again that there has been a statement for inclusion in the record by Charles Pfizer & Co., Inc., on the present production status of the oral vaccine. And at the conclusion of the testimony of this witness, I will ask the reporter to include this statement in the record.

All right, Dr. Salk.

## STATEMENT OF DR. JONAS E. SALK, DIRECTOR OF THE VIRUS RESEARCH LABORATORY, UNIVERSITY OF PITTSBURGH

Dr. SALK. Mr. Chairman, when I was asked if I would appear before this committee I expressed a willingness to do so only if the committee, and through this committee the public, wished to have my views about the present state of the problem of poliomyelitis in the United States, and some indication of the likely trends.

It is unfortunate that an air of competition exists. I can assure you that I do not share such feeling, and, as a scientist, I do not wish to be associated with any such situation.

As a scientist, I set out to determine whether or not a killed virus vaccine could control and eventually approximate extinction of a virus disease such as polio.

As you know, many were of the opinion, and some still are, that this is not possible, and that only when a live virus vaccine is available will this be possible.

Such opinions have created an atmosphere suggesting that we are faced with a situation such as existed in 1954–55, when there was not yet available any means for the control of this disease.

Perhaps it would be helpful if you were to see for yourselves the present picture that you may then understand the factors that have been operative and the measures that need to be applied in the period immediatedly ahead.

May I have the first slide (fig. 1), please?

[Slide.] Now, this slide (fig. 1) indicates—and if I may, Mr. Chairman, go to the screen, I would like to emphasize some points.

Mr. ROBERTS. Surely.

Dr. SALK. This slide (fig. 1) is drawn from data obtained by the U.S. Public Health Services Surveillance Unit, and also from the Bureau of the Census. It indicates the number of cases by week occurring in the months of March through December in 1949, and this reflects the total number of cases paralytic and nonparalytic as well.

If one were to redraw this chart and reflect the paralytic cases only, then one would end up with figures that were roughly on the average, perhaps, about 60 percent of these that are there now.

The point of importance is that there had occurred the sharp epidemics each season until the time of the field trial (1954) and the first use of vaccine (1955), following which there was a rather sharp reduction, which has been fairly well maintained.

Now, in the year 1960 a total of about 3,000 cases have occurred both paralytic and nonparalytic for the entire year. And you will observe that in 1952 there were many weeks running when more than 3,000 cases occurred in any one week.

The point of showing this slide (fig. 1) is to indicate the extent to which the disease has been brought under control in the United States even when but a fraction of the population has been vaccinated.

And the point that I will make first is on the degree of efficacy of vaccine in those who have been so treated, but also the extent to which there seems to have been a dampening influence on the spread of the virus in the population. This leads one to believe that there will occur a further progressive reduction in incidence of disease because of the reduced spread due to mechanisms that have been operative up

until now. This is reflected in reduction, not only in the paralytic disease, but in the nonparalytic as well, suggesting a total reduction in the amount of virus circulation.

The next slide (fig. 2), please.

[Slide.] Now, I read in the paper this morning a statement to the effect that the effectiveness of the injected vaccine is delayed, and also that the effect may not be very durable. We have followed this one child (fig. 2), and a great many others, first vaccinated in 1953. The point is to illustrate the rapidity of the rise in antibody for all three types. The numbers on this scale indicate the extent to which the child's serum can be diluted and still protect, or neutralize virus.

You will observe (fig. 2) the rise in antibody of all three types, and at 7 months later when the booster injection was given there was a sharp rise, followed by a decline over a period of months.

The idea that the effectiveness of the killed virus vaccine might be of short duration was predicated on studies that were always of short duration when this sort of a drop was observed, with the expectancy that the projection of the decline after the booster would continue all the way.

You see that what we have found, which is essentially, you might say, a new observation, is that there is a plateau in the level of antibody that continued over the remainder of the 7-year period. It seems that the child, once altered, so to speak, is permanently altered, just as might be the case in hay fever; as you know, once you have hay fever and are sensitive to ragweed, you tend to remain that way the rest of your life.

It appears as though a similar mechanism is involved. Some might say, this is just one child. We have similar data for many children, both with respect to the speed at which antibody appears, and also its persistence.

Some may say that this doesn't always happen.

And we reply to that, that is true, but it does happen if a group of individuals receive a vaccine that has more than a certain minimum amount of virus in it. If it doesn't happen the first time, it could happen after the second dose, or after the third dose, but eventually it does happen.

Now, it will happen after a fewer number of doses the more potent the material is to begin with, as I will try to show in just a moment.

The emphasis that I wish to place here is that there is implicit in the killed virus vaccine idea persistence of immunity and not that immunity is of short duration, and there is every reason to believe that these effects will remain for many years to come, perhaps for a lifetime.

It is a misconception that only with a live virus vaccine does one get durable immunity. We now have evidence that this is not so, that it can be induced by a killed vaccine, and it gives us hope that if this is true for three viruses (types 1, 2, and 3 polioviruses), it can be true for 10, 30, and perhaps a hundred different viruses, all of which might conceivably be incorporated in a single preparation some day.

The next slide (fig. 3).

[Slide.] Here you see the degree of persistence, not only following a primary injection and the booster, but you see the same degree of persistence is true even after primary stimulation only. This plus

other evidence leads us to believe that by pursuing this thesis further, it will be possible to accomplish objectives such as this with a single injection, and to accomplish this for many viruses injected simultaneously.

This may seem to be irrelevant and beside the point, but emphasis is placed upon the nature of research these days, whether it is basic or applied. Well, you might look upon this as a basic observation in the sense that this, then, leads to an opening in a wide field that has a bearing on the question of the control of virus diseases in general.

This has been the underlying question in our studies. It is for this reason that I feel that you might like to have the background against which the observations to which I refer may be placed.

This child (fig. 3) has been observed now for 3 more years, or a total of 6 years, and the persistence has been maintained.

The next slide (fig. 4), please.

[Slide.] Here is another slide (fig. 4) that is of interest. Let me try to explain this. In 1959—for these data we are grateful to Dr. Langmuir and the surveillance unit—an analysis was made of the paralytic rate in the 0 to 4 age group, in all the children under 5 years of age who had paralytic polio in 1959.

It is estimated that 4.7 million had had no vaccine; 1.8 million had had one dose; 3.6 million, two doses; 5.4 million had had three doses; and 3.6 million had had four doses. There were 1,508 cases among those who had had no vaccine; 234 cases among those that had one dose; 209 among those that had two; 267 among those that had three; and 51 cases among those that had four doses.

When this was calculated in terms of rate per 100,000 it came to 32 for the none; 18 for one dose; 5.8 for two; 3.6 for three; and 1.4 per 100,000 for four doses.

And when plotted on a chart in this way, using the logarithmic scale for the rate per 100,000, the points fell on a straight line.

Now, this was something we had not anticipated. But it has an important bearing on the mechanism whereby vaccine works. And it has bearing on the question of the possibility that a single dose would be effective if the vaccine was so constituted.

What this means is that if a single dose reduced the amount of disease by about 50 percent, protecting 50 percent of the population, then a second dose would protect 50 percent of the remainder, or a total of 75 percent. A third dose would reduce the size of the susceptible group by the same proportion of 50 percent, with an increasing number vaccinated each time each dose would have the same proportional effect.

This is like the line showing radioactive decay. And it is reminiscent of that kind of a curve. But what this suggests is that if vaccine potency is increased to the point where one dose is about 90 to 100 percent effective, the line would be much more vertical.

I think you will understand this from another chart.

The next slide (fig. 5), please.

[Slide.] This shows that the relationship between number of doses and effectiveness is true not only for the zero to four age group, but it is also true for the 5- to 19-year-old age group, and the 20 to 39.

Therefore, this law appears to apply generally to individuals at all age levels.

There are other details that I won't bother you with, other than to show that this has general applicability.

The next slide (fig. 6), please.

[Slide.] You see the linear relationship in 1959, and the same relationship is true in 1960. From this chart you can read that four doses have been 96 percent effective; three doses about 90 percent effective; two doses about 80 percent effective; and one dose about, close to 60 percent effective. And thereafter each additional dose reduces the proportion of the number of susceptibles to the same extent.

If, however, the vaccine was more potent, then the line would be much more vertical, and one would be able to accomplish the same effect with fewer number of injections.

The next slide (fig. 7), please.

[Slide.] With the evidence that vaccination can be approximately 95 to 96 percent effective with four doses, the question arises as to why have localized outbreaks occurred in recent years, why has the disease as a whole not been reduced to that extent? Even though a great many have not been vaccinated it has been reduced to the extent of about 90 percent.

And some of the clues to this come from experience such as this that occurred in Detroit in 1958. This is characteristic of regions throughout the country where localized outbreaks have occurred in recent years.

Detroit has a white population of 1.48 million and a nonwhite population of 420,000. The number of whites are such that when plotted on a scale of rate per 100,000, you see the sharp outbreak in the nonwhite segment of the population, and a very low rate in the white section of the population, suggesting that the amount of vaccine used in this part of the population had dampened the spread of the disease and reduced the amount of the disease, whereas such outbreaks tend to occur in those segments of the population where vaccine has not been used.

And this would be true no matter what vaccine was used, if it was not used in quantities that would be effective.

The next slide (fig. 8), please.

[Slide.] Looking at the country as a whole in 1959—it is evident that the largest number of cases occurred in the zero to four age group with the next largest group in the five to nine. A total of about 64 to 65 percent of all the cases in 1959 occurred under the age of 10.

The next largest was the 20- to 29-year age group, and this now explains why the Public Health Service has suggested as a slogan for this year, "Vaccination of Babies and Breadwinners."

The solid black portion of the column refers to cases that have occurred in those who had no vaccine, or less than three doses.

But what you might refer to as failure to use vaccine is indicated by the extent to which the black column exists, and the so-called vaccine failures at the three dose level are indicated by the open spaces at the top.

Therefore, this presents a picture both of age groups in which cases have occurred primarily, and it also reflects the extent to which the prevalence of disease has been due to failure to use vaccine rather than vaccine failure.

Now, keep this in mind, and we will see the next slide (fig. 9), which indicates as of April 1960 the proportion of the individuals in the different age groups that have been vaccinated with three or more doses. And you see that about 58 or 59 percent had three or more doses in the under 5 age group, and only 80 percent and 82 percent of the 5 to 9 group and the 10 to 14, respectively, and then the proportion diminishes.

If you will bear in mind that in 1960 the overall incidence of polio was reduced by about 90 percent from the prevaccine period average, and you see (fig. 9) that no single group was vaccinated to the extent of 90 percent, it should be clear that if the group (ages zero to four) especially, which one can pinpoint fairly closely, is vaccinated, that the bulk of the cases that have been occurring in recent years would be eliminated, and the likelihood is, from all the surveillance group evidences, that when 85 percent of individuals in this group (age zero to four) had three or more doses, then outbreaks do not occur.

Therefore, it is important to bear in mind the extent to which the disease has been reduced in spite of the fact that vaccination has not been extended to the entire country.

The next slide (fig. 10) please.

[Slide.] I draw your attention to the incidence of polio in all forms in three other countries—in Australia, Denmark, and Sweden, where the numbers of cases were as indicated in the prevaccination period. The lower part of the chart indicates how the disease has been reduced to the point where, as in Denmark there were a total of three cases this last year, only one had been triply vaccinated; in Sweden a total of seven cases and none in individuals who had had three doses of vaccine.

Now, there is a difference between these countries and the United States in that there has been a more general saturation of individuals in the lower age groups. You will see that the degree of reduction in disease on the average in these countries is such that it has been reduced by the use of the killed vaccine to the extent of about 99½ percent in 1960 as compared to the 1950–54 average and not 100 percent of the population was vaccinated, but particular saturation was accomplished in individuals in the lower age groups.

Next slide (fig. 11), please.

[Slide.] Looking back to 1915—and this is charted on a logarithmic scale—there is a peculiar high in the 1916 epidemic and a peculiar low in 1938. You will observe that there is a fluctuation in incidence, and an increased incidence of the disease in the late 1940's and the early 1950's. With the introduction of vaccine, the incidence dropped, and we had a rate in 1959 which was not beyond the range of fluctuation normally observed, and a continued decline. In the Scandinavian countries and Australia the overall average was near our peak in 1952—and they are now down near the bottom of the scale.

I would expect that in this country we will soon reach that level in the normal course of events, and certainly as one saturates the younger members of the population which we can certainly do between now and next summer.

The way in which viruses spread among nonvaccinated individuals is perfectly clear. In the vaccinated population there is a tendency for the spread to be dampened, and consequently there will eventually be a sharp reduction not only in the spreaders, but in the susceptibles.

Now, there is an important difference in point of view as to how polio is spread.

Some are of the opinion that it is spread primarily by the contents of the intestines, by fecal contamination. Others are of the opinion that an important mode of spread, particularly in a country such as ours, is through the pharyngeal route. The reason for believing that this is likely to be the case is, first, that paralytic polio becomes a problem when hygienic conditions of the country improve to the point where fecal contamination of the environment is reduced. Individuals are not exposed early in life, and there is then the tendency for them to reach later ages fully susceptible, and even under better socioeconomic conditions one sees the spread of the virus.

One can find virus very readily in the pharynx. Also in studies that have been done with live virus vaccines it has been shown that the spread within a family unit occurs primarily if there is an infant under 18 months of age that is in diapers. Therefore, the spread by and large is by fecal contamination where feces are obviously present. But in a society such as ours, I believe, this is not the normal mode of distribution of the virus. I think it is spread by the kind of association that occurs within a family household or between playmates, and that is by the pharyngeal route, just as measles, for example, tends to spread.

Now, the presence of antibody in the bloodstream in a vaccinated individual will prevent the virus from getting from the intestine to the pharynx, just as it prevents it from getting into the central nervous system, and in that way vaccination cuts down the number of effective spreaders in the community. And it is for this reason that vaccination could be expected to dampen the spread of virus. Hence it is clear that a killed virus vaccine does in absolute terms, not relative terms, tend to reduce the amount of virus that is distributed in the population.

This is not too surprising, because diphtheria toxoid is not a living agent at all; it is a chemical substance, it is a toxin from the diphtheria bacillus that has been treated with an agent to render it nontoxic. This, too, when given to a segment of the population prevents the spread of a disease like diphtheria. You don't have to vaccinate 100 percent of the population to prevent diphtheria.

This has certainly been true in our studies of influenza. Working with closed groups that were partially vaccinated it is perfectly clear that it is possible to reduce the spread of this disease by means other than the use of living viruses.

The next slide (see fig. 1), please.

[Slide.] Now I show you this once more just by way of a frame of reference. I tried to indicate the basis upon which these effects have been observed, and the forecast in terms of probability of continued reduction is certainly implicit in the trends that have been observed thus far.

The next slide (fig. 12), please.

[Slide.] I think this is possibly the last one.

I want simply to show that there are three other diseases for which vaccination is available, namely, pertussis (whooping cough), diphtheria, and tetanus. From 1950 to 1959, you see the number of cases of pertussis that occurred. The trend has been declining with a new effort toward immunization in diphtheria because of outbreaks in the late 1940's and 1950's. And there are about 500 cases of tetanus each year with about three to four hundred tetanus deaths each year. These are also problems.

Polio is simply one of many problems with which we are confronted. Our hopes and expectations are that the procedures but the prevention of diphtheria, tetanus, and whooping cough, which require injection, will simply have added to them the other antigens, whether they are for polio or others, and eventually there will develop practices that will result in an elimination, not only of polio, but of all others as well. Polio cannot be separated and isolated from all other health procedures, but practice for the solution of the polio problem would be used to draw along some of the other problems for which good public health and medical practices are desired.

May I have a few more minutes, Mr. Chairman?

Mr. ROBERTS. At this point, Doctor, I will ask you to make the slides available for the record.

Dr. SALK. Yes.

Mr. ROBERTS. And without objection, I would like for the charts to be properly inserted in the printed record.

(The documents referred to are as follows:)

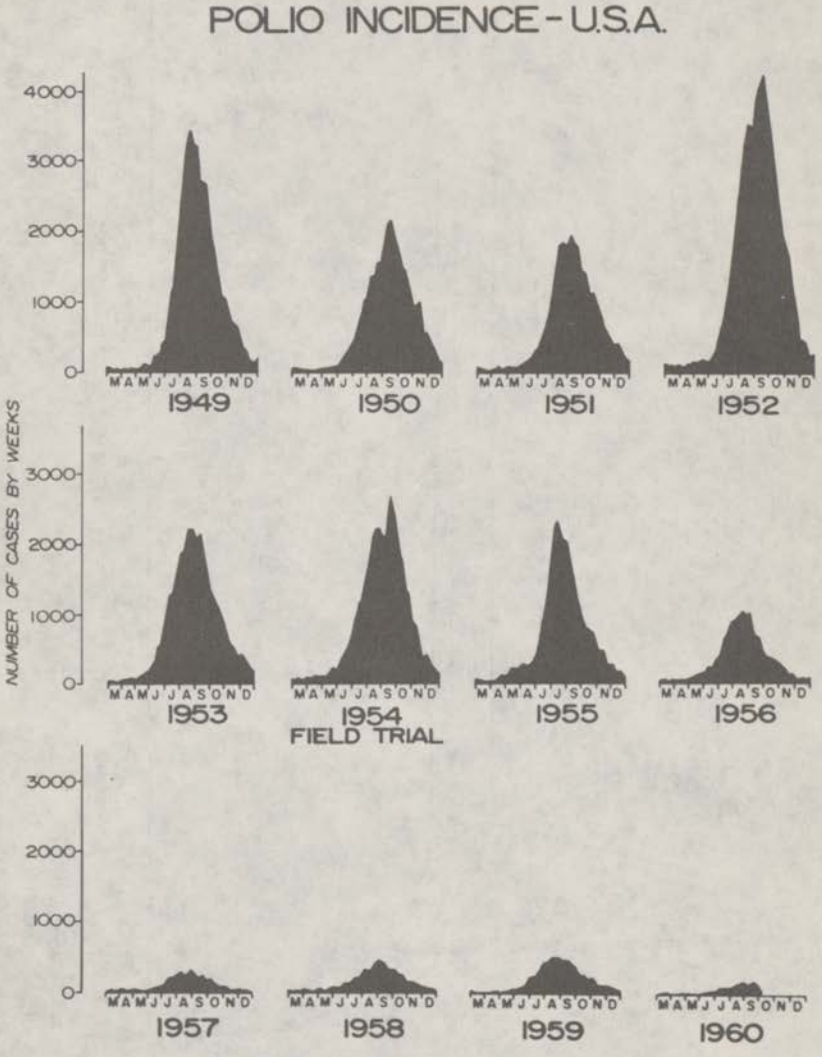



FIGURE 1

68776 O—61——19

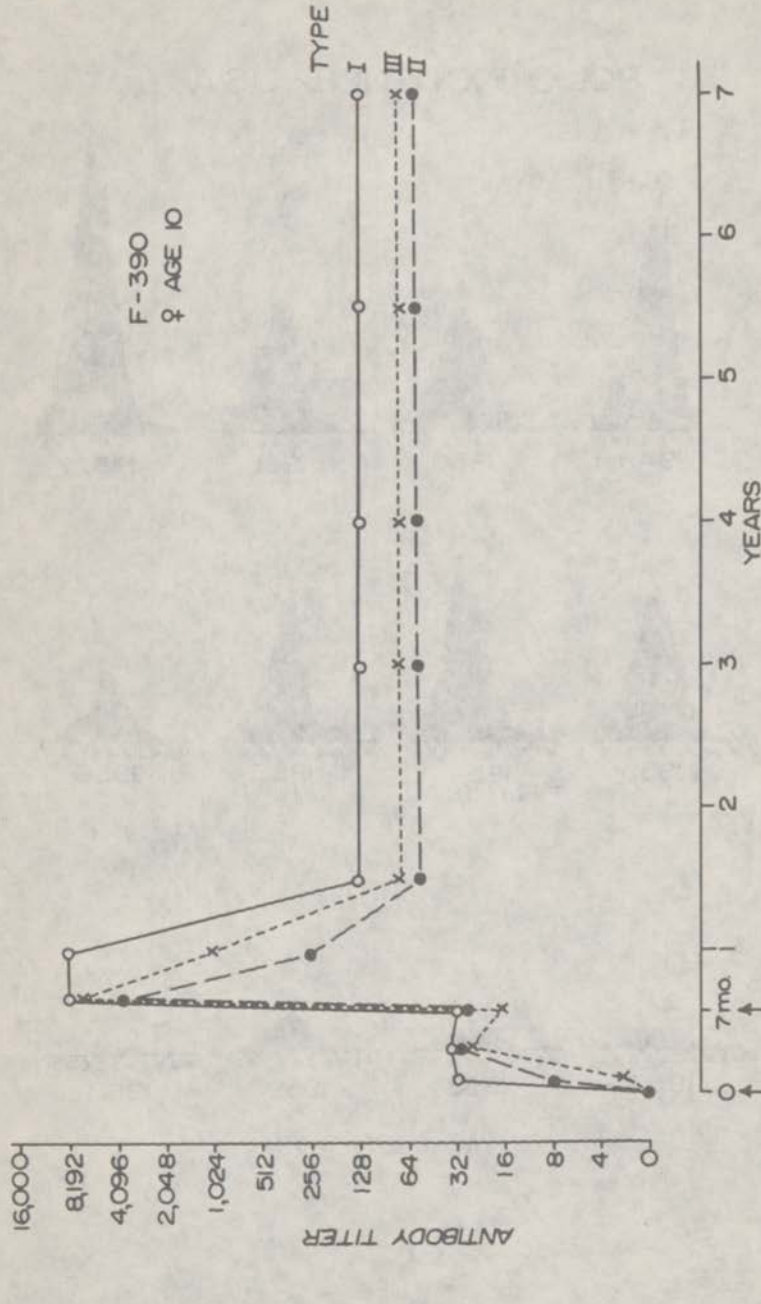

F-390
♀ AGE 10
TYPE
I
III
II
ANTIBODY TITER
16,000
8,192
4,096
2,048
1,024
512
256
128
64
32
16
8
4
0
0
7 mo.
1
2
3
4
YEARS
5
6
7
Vacc. 13 Vacc. 18
0.6 ml. I.M. 1 ml. I.M.

FIGURE 2

# PERSISTENCE OF ANTIBODY THREE YEARS AFTER PRIMARY VACCINATION

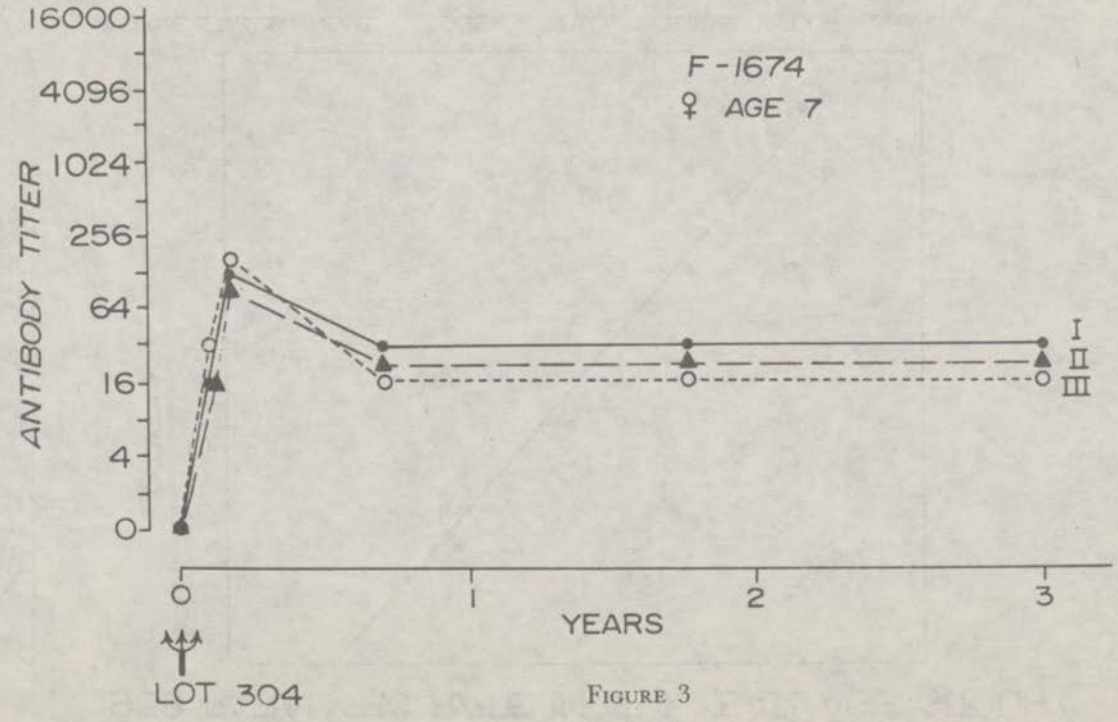



FIGURE 3

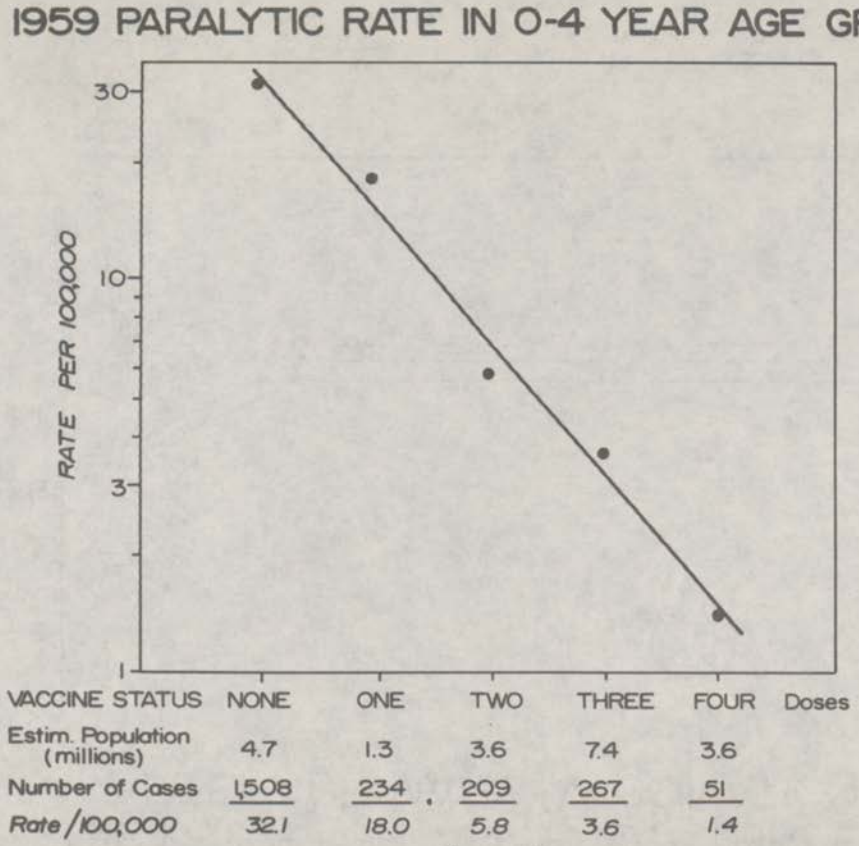

1959 PARALYTIC RATE IN 0-4 YEAR AGE GROUP
RATE PER 100,000
30
10
3
1
VACCINE STATUS
NONE
ONE
TWO
THREE
FOUR
Doses
Estim. Population (millions)
4.7
1.3
3.6
7.4
3.6
Number of Cases
1,508
234
209
267
51
Rate/100,000
32.1
18.0
5.8
3.6
1.4

FIGURE 4

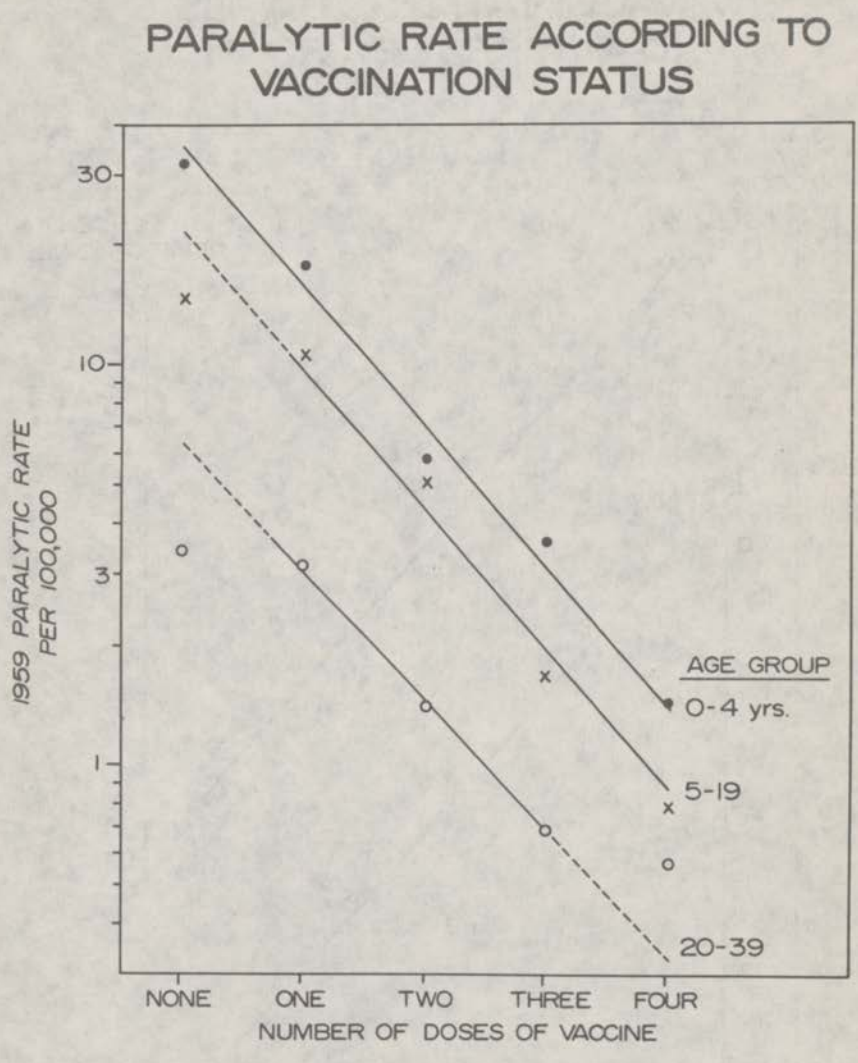

PARALYTIC RATE ACCORDING TO VACCINATION STATUS
1959 PARALYTIC RATE PER 100,000
30
10
3
1
AGE GROUP
0-4 yrs.
5-19
20-39
NONE
ONE
TWO
THREE
FOUR
NUMBER OF DOSES OF VACCINE

FIGURE 5

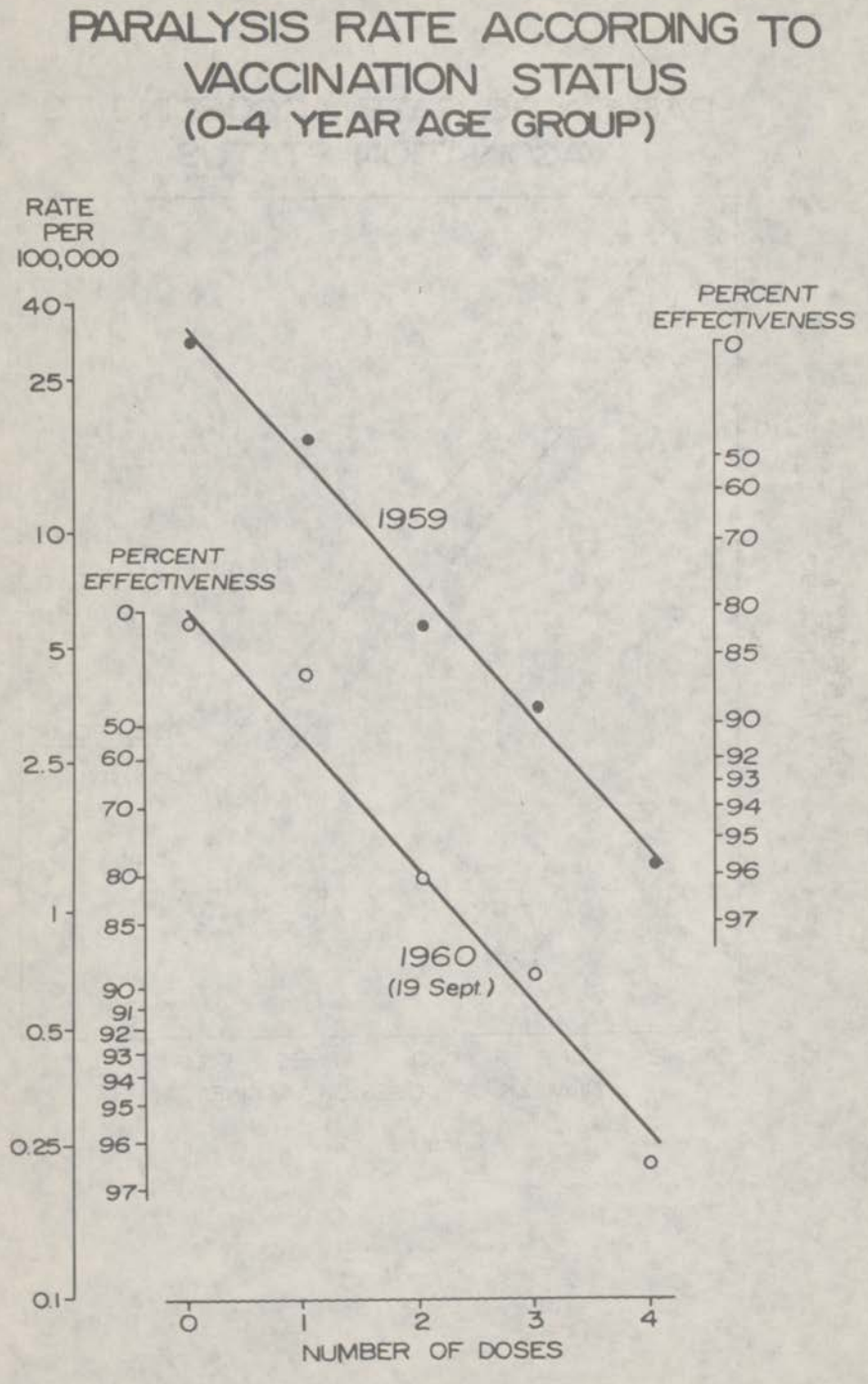

PARALYSIS RATE ACCORDING TO VACCINATION STATUS
(0-4 YEAR AGE GROUP)
RATE PER 100,000
40
25
10
5
2.5
1
0.5
0.25
0.1
PERCENT EFFECTIVENESS
0
50
60
70
80
85
90
91
92
93
94
95
96
97
1959
1960
(19 Sept.)
0
1
2
3
4
NUMBER OF DOSES

FIGURE 6

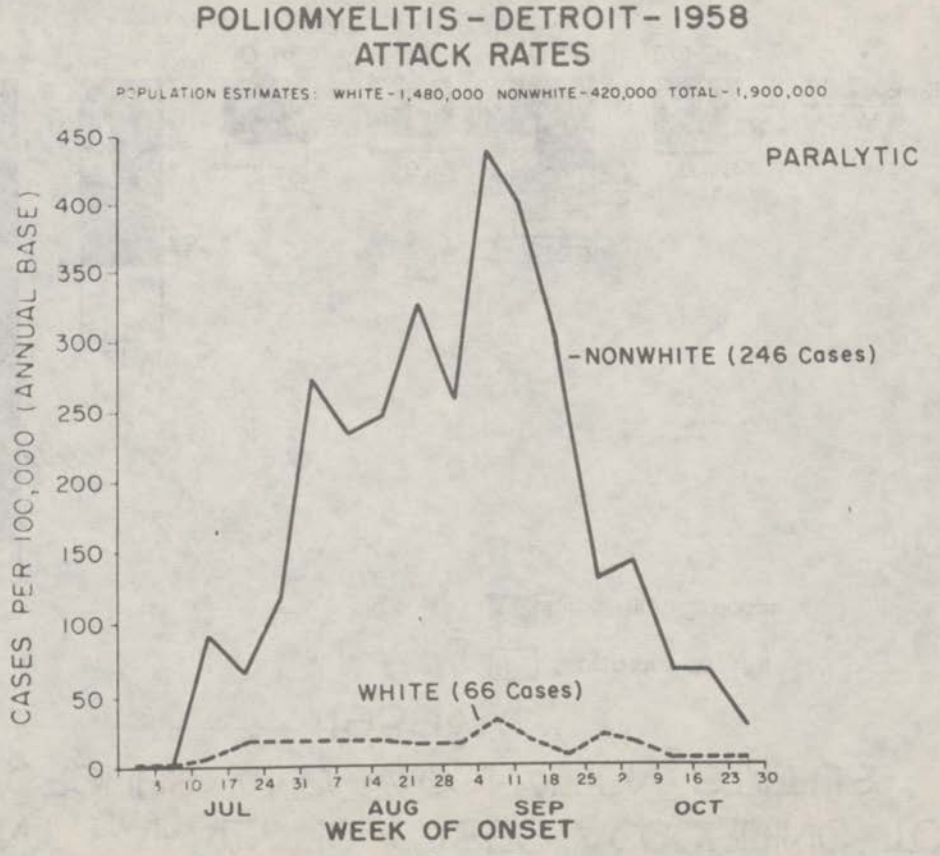

POLIOMYELITIS - DETROIT - 1958
ATTACK RATES
POPULATION ESTIMATES: WHITE - 1,480,000 NONWHITE - 420,000 TOTAL - 1,900,000
PARALYTIC
CASES PER 100,000 (ANNUAL BASE)
450
400
350
300
250
200
150
100
50
0
NONWHITE (246 Cases)
WHITE (66 Cases)
5 10 17 24 31 7 14 21 28 4 11 18 25 2 9 16 23 30
JUL
AUG
SEP
OCT
WEEK OF ONSET

FIGURE 7

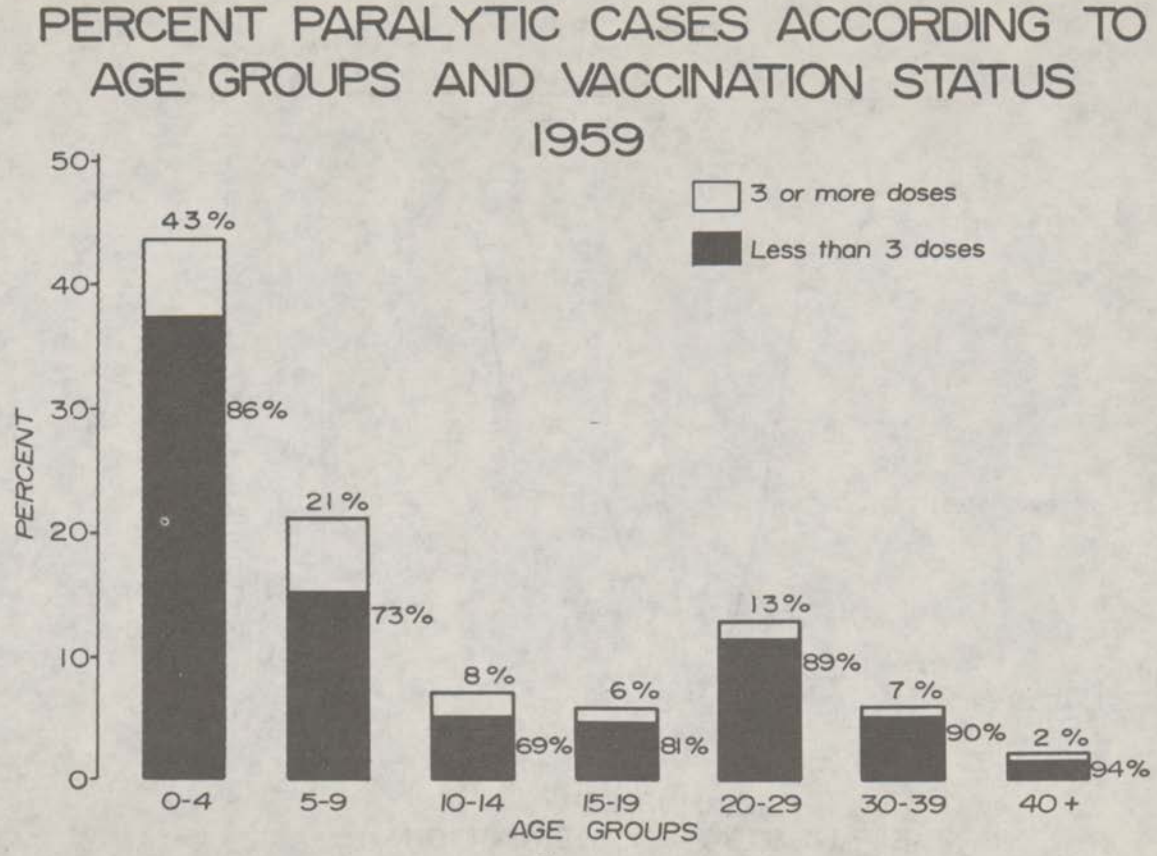

PERCENT PARALYTIC CASES ACCORDING TO AGE GROUPS AND VACCINATION STATUS 1959
3 or more doses
Less than 3 doses
PERCENT
50
40
30
20
10
0
43%
86%
21%
73%
8%
69%
6%
81%
13%
89%
7%
90%
2%
94%
0-4
5-9
10-14
15-19
20-29
30-39
40+
AGE GROUPS

FIGURE 8

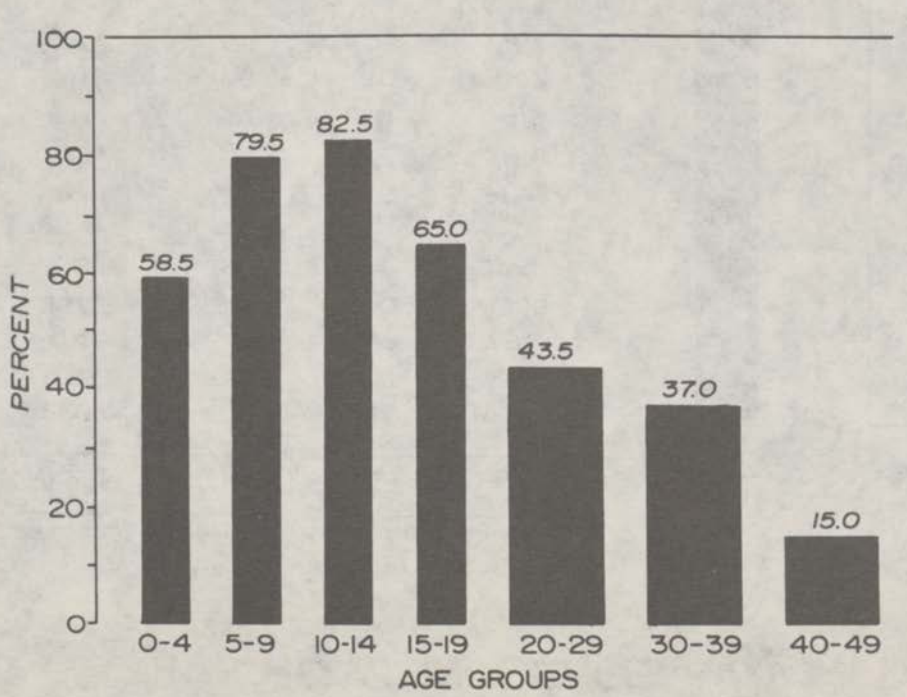
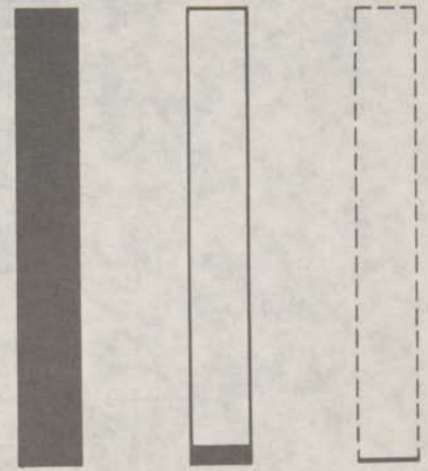

ESTIMATED PERCENT WITH 3 OR MORE DOSES
APRIL, 1960
PERCENT
100
80
60
40
20
0
58.5
79.5
82.5
65.0
43.5
37.0
15.0
0-4
5-9
10-14
15-19
20-29
30-39
40-49
AGE GROUPS

FIGURE 9

# POLIO INCIDENCE

| | Australia | Denmark | Sweden | COMBINED |
|---|---|---|---|---|
| POPULATION-millions | 10 | 4.5 | 7.4 | 21.9 |
| 1950 | 2267 | 1572 | 1718 | 5557 |
| 1951 | 4736 | 383 | 551 | 5670 |
| 1952 | 1743 | 5676 | 492 | 7911 |
| 1953 | 1677 | 1591 | 5090 | 8358 |
| 1954 | 1906 | 352 | 1009 | 3267 |
| 1955 | 874 | 70 | 486 | 1430 |
| 1956 | 1274 | 191 | 551 | 2016 |
| 1957 | 141 | 21 | 250 | 412 |
| 1958 | 110 | 66 | 191 | 367 |
| 1959 | 75 | 26 | 56 | 157 |
| 1960 | (26) | (2) | (7) | (35) |




| | 1950-54 AVER. | 1959 | 1960 |
|---|---|---|---|
| CASES | 6152 | 157 | (35) |
| RATE/100,000 | 26.7 | 0.68 | (0.15) |
| RATIO | 100 | 2.5 | (0.5) |

FIGURE 10

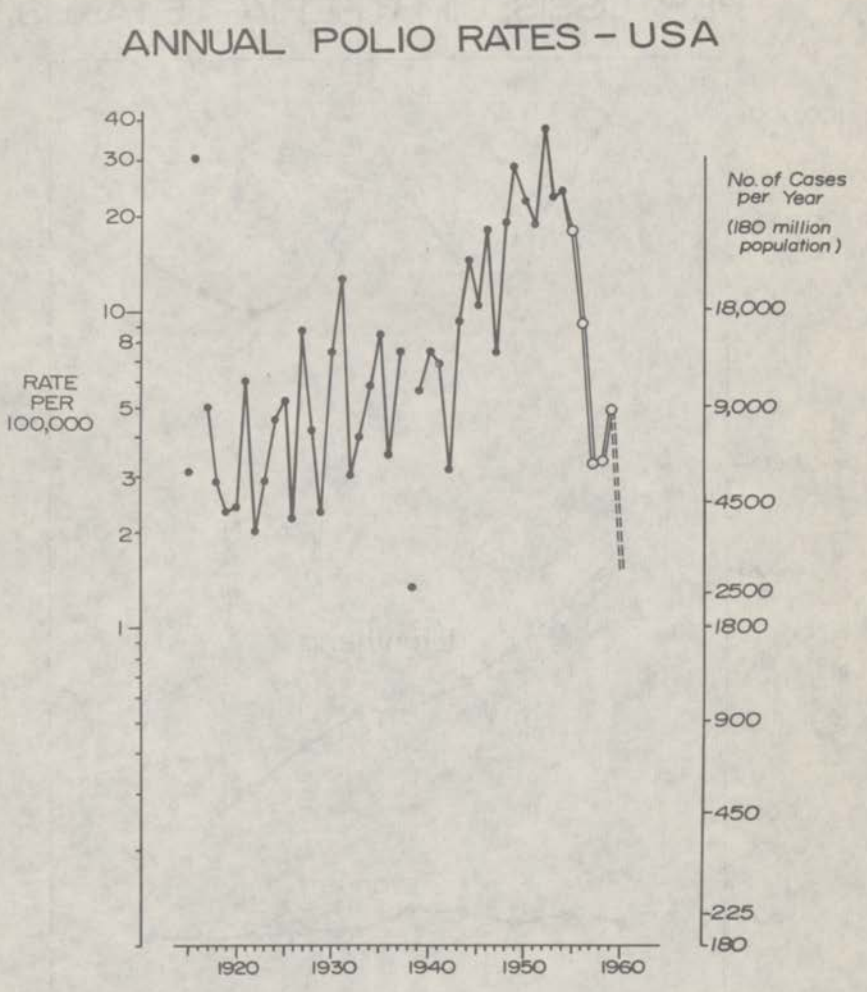

ANNUAL POLIO RATES – USA
RATE PER 100,000
40
30
20
10
8
5
3
2
1
No. of Cases per Year
(180 million population)
18,000
9,000
4500
2500
1800
900
450
225
180
1920
1930
1940
1950
1960

FIGURE 11

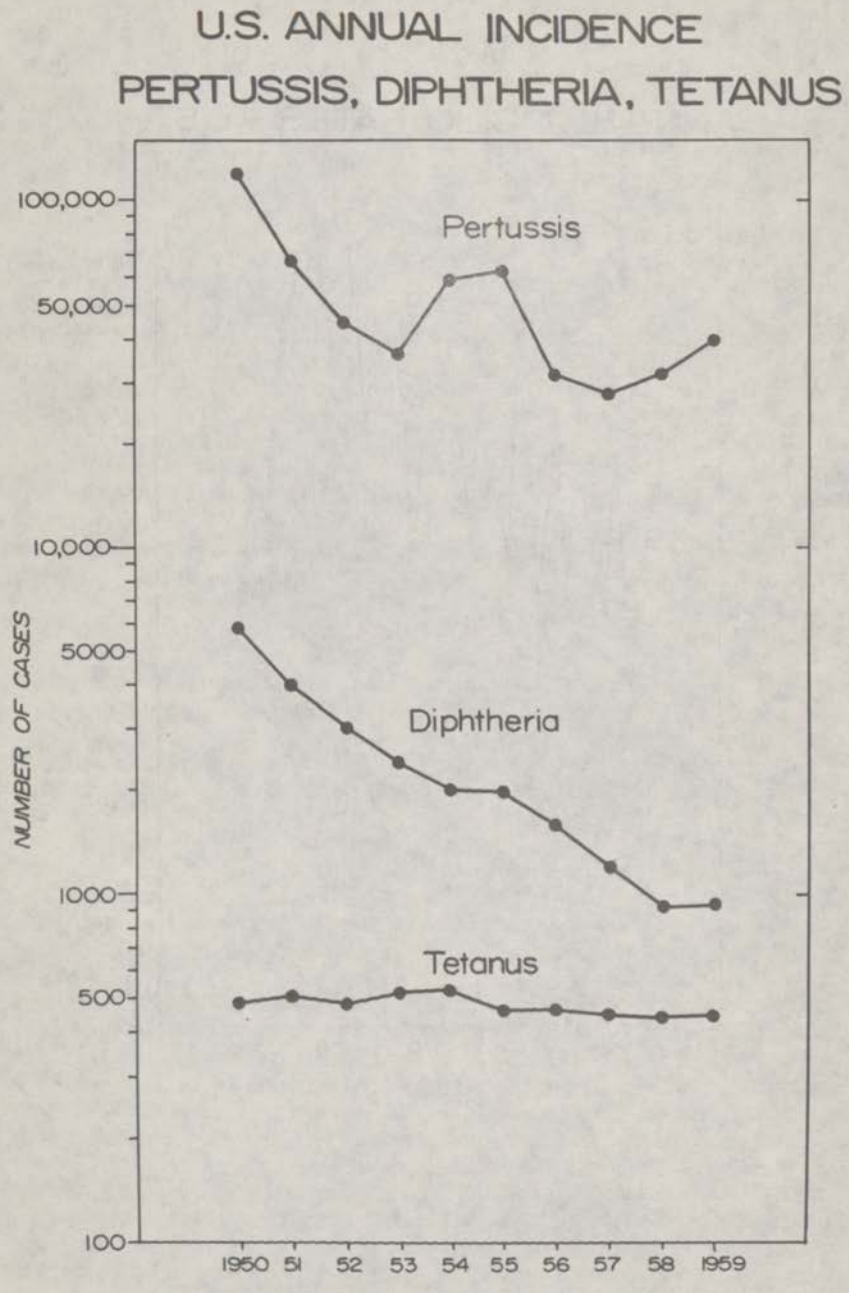

U.S. ANNUAL INCIDENCE
PERTUSSIS, DIPHTHERIA, TETANUS
NUMBER OF CASES
100,000
50,000
10,000
5000
1000
500
100
Pertussis
Diphtheria
Tetanus
1950
51
52
53
54
55
56
57
58
1959

FIGURE 12

Dr. SALK. Now, what does all this mean?

I think that it means, first, that a means for immunization is available that reduces the probability of paralytic polio by about 96 percent, but has the potential, if used a bit more widely, to reduce the likelihood of epidemics by dampening the spread of virus, and, therefore, it has the potential for approximating the extinction of the disease.

It seems, also, that the effects so induced are durable.

Therefore, all that is required to approximate effects such as have been achieved, for example, in the Scandinavian countries and Australia, is to administer vaccine to a sufficient percentage of the susceptible population, particularly the youngest age groups. It seems that this could be done before and into next summer by three or four doses given approximately a month apart.

Therefore, it seems that the problem with which we are confronted is not a scientific or a technical problem, but it is one that involves a mechanism for the distribution of medical care. Any new vaccine will be bought and will be used by those who have already been vaccinated. It will not solve the problem of the unvaccinated. This is not unlike the problem with which we are confronted economically, where, as the gross national product increases, it simply increases the wealth of those who already have money and does not affect the group that one might call the poverty group.

The problem here is the development of practices for bringing those who need what is needed and those who can administer what is needed together.

Regardless of the kind of preparation that is involved, this is the basic issue.

Now, the ease of administration of any preparation is admirable, the fewer the number of treatments that are required the more desirable.

But there is also the problem, as I have tried to point out, of immunization against diphtheria, tetanus, and pertussis and other diseases for which immunization will be developed in the future, for which we now understand the basic principles, some of which I have tried to emphasize this afternoon. I say that polio is just one part of the broad problem in maintenance of health. To some the importance of polio has always been exaggerated, and now its magnitude is such that its final touches require a pinpoint focus that is clearly evident.

The question, it seems to me, is, should we prepare for an emergency for next summer, or should we do what seems to be clearly indicated to prevent such emergencies and in the meantime develop methods for extending the benefits of the advances of science to that segment of the population in greatest need of motivation to help themselves?

The live virus vaccine issue has brought to the fore a neglected condition, and it seems that it is still being neglected.

Why should an appropriation not be made to provide health officers with presently available vaccine, so that they may proceed forthwith in responding to joint community and county medical society campaigns to disolve the pockets of susceptibles where epidemics are likely to occur?

Every health officer knows where such neighborhoods exist. Every physician in the country would be willing to volunteer his services in a door-to-door campaign if necessary, and there is ample community

leadership to organize the details of bringing the needy and the physician together at the same place to perform the brief procedure that will benefit not only the individual but the community.

The catalyst that would make this reaction proceed would be the provision of funds for vaccine to those health officers who could not otherwise proceed.

Initiative and imagination and ingenuity has brought about such striking effect in the Scandinavian countries and Australia, and wherever good effects have been obtained with killed or with live vaccine, these are attributable not to any special magic of one over the other kind of preparation, but to a mechanism for distributing their particular procedure for the maintenance of health. The problem is a social and an economic one, and if we persist in believing that there is a profound scientific issue, other than that we now know the killed virus can be effective, and that this principle can be extended to dozens of other viruses, then we are missing the essential point.

As a scientist who set out to find out something, I am satisfied. As a member of the human race and a citizen of this country, I am gratified that the United States has been so successful, and that this is true of other countries as well.

However, to go all the way—we must not be deceived, to go all the way we must promptly proceed, and we must apply promptly the procedures that we know must be applied and not merely prepare for an emergency that need not arise.

I would like to say in closing that I have been very conscious of this problem, and I have indicated that I thought that the discussion about live virus vaccine has brought to the fore a long-neglected problem, of which we have been aware. I felt it incumbent upon myself last fall to discuss this matter with the executive vice president of the American Medical Association, because I did not feel that another year could go back without my bringing the matter to the attention of someone in a position of responsibility to act upon what is clearly a social need.

And I should like, if I may, to read the contents of a letter that I wrote to Dr. Blasingame on the 22d of November of 1960. It followed the visit with him. And I indicated:

> After leaving your office I realized that at the outset of our conversations, the purpose of my visit to you was not yet clear; but, that you did understand my purpose before I left. I am not concerned how the problem of paralytic polio is ultimately solved. In this respect, I am like the average man on the street. However, in another respect, I am different, inasmuch as I am engaged in studying the question of immunization against virus diseases. On the basis of reasoning set forth in my papers, and for additional reasons, to which I referred in our conversations, I believe that the pursuit of the idea of the use of killed viral antigens will be the most fruitful for the control of virus diseases generally. This is a scientific question, the resolution of which will require additional time and, therefore, should be kept separate from the practical question of the control of paralytic polio now.
>
> It is clear that the physicians of this country have been instrumental in applying a procedure that appears to have 96 percent probability of preventing paralytic polio when four doses of vaccine are administered; when three doses are given the probability of prevention of paralysis is something in excess of 90 percent. When three or more doses have been administered to 85 percent or 90 percent of the younger age groups in a community, it appears that localized outbreaks have not developed. However, outbreaks have occurred in neighborhoods, particularly in urban areas but also in rural areas, where the rate of vaccine application has been low. Furthermore, the largest majority of cases

has been in individuals who have been inadequately vaccinated or have had no vaccine at all. Thus, the principal residual problem is failure to use vaccine rather than vaccine failure.

In spite of the extent to which vaccine has not been used, it is remarkable to observe the extent to which the prevalence of this disease has declined as compared with the prevaccine period. The intensity of outbreaks in the poorly vaccinated segments of the population, such as those in the lower socioeconomic groups, and in Negro neighborhoods suggests that if vaccine had not been applied that the outbreaks in recent years might have been more severe than in the prevaccine era. That outbreaks have been largely confined within the poorly vaccinated neighborhoods and have not spread in reasonably well-vaccinated groups, suggests that if vaccine had been used more uniformly in all segments of the population then community outbreaks would not have occurred even in the lower socioeconomic groups. The small proportion who fail to be protected after three or four doses could be expected to be protected by virtue of the community protection afforded by sufficiently extended use of vaccine in all groups including those that have shown less initiative in seeking vaccination, especially in the lower socioeconomic groups.

It is clear from the foregoing that we are confronted with a social problem rather than a technical or scientific one. Even if we had in our possession at this time a killed-virus vaccine that would, with a single dose, immunize with a probability of 90 to 95 percent or more, we would still be confronted with the problem of its administration. Even if there was available a live-virus vaccine which was to be administered either in one does or three or four doses, the problem would be the same. We do not now have either of these variations of an immunizing preparation, nor is it likely that we will, prior to the summer of 1961, have anything but the preparations now available. Therefore, if we are to take advantage of what we now know concerning the degree of efficacy of vaccination, the durability of its effect, and the extent to which the spread of virus in the community is dampened by vaccination, and if we are to discharge our responsibility toward maintaining the health of the country, and of the communities of which each of us is a part, we must now plan to apply the methods now available in the manner suggested by our experience thus far.

If I were to specify what I had in mind when I came to see you it would be the following: First, to consider with you means whereby the prevalence of paralytic polio could be further reduced by vaccination before the summer of 1961, and at least to an extent comparable to that which has already been accomplished in some of the Scandinavian countries or Australia where vaccine administration, especially in the younger age groups, has been much more complete than in this country. Secondly, to consider whether or not some initiative on the part of the American Medical Association, and its county medical societies, might not be of great value if the local societies were to declare that they will take the lead and will enlist the support of local service organizations and voluntary groups as fully and completely as necessary to accompish the desired objective. It is hardly necessary to point out that if specific programs were organized under the auspices of the county medical societies the community could be saturated with vaccine. I doubt that an effective countrywide vaccination program can be carried out without this kind of medical society initiative and support and I can see great value in bringing about the further reduction in incidence of polio by a voluntary community contribution of this kind.

A copy of this letter was sent to Surgeon General Burney, who acknowledged his concurrence with these views.

There are many other thoughts that have occurred to me, but I think I will let that suffice for the moment, Mr. Chairman.

Mr. ROBERTS. Doctor, if you will go back to the witness chair, you will be more comfortable, and we may have some questions.

I believe you said you sent a copy of the letter to Dr. Burney. Would you make it available for the record?

Dr. SALK. Yes.

Mr. ROBERTS. Without objection, it will be included in the record.

(The letter follows:)

NOVEMBER 22, 1960.

Dr. F. J. L. BLASINGAME,
*Executive Vice President, American Medical Association,*
*Chicago, Ill.*

DEAR DR. BLASINGAME: After leaving your office I realized that at the outset of our conversations, the purpose of my visit to you was not yet clear; but, that you did understand my purpose before I left. I am not concerned how the problem of paralytic polio is ultimately solved. In this respect, I am like the average man on the street. However, in another respect, I am different, inasmuch as I am engaged in studying the question of immunization against virus diseases. On the basis of reasoning set forth in my papers, and for additional reasons, to which I referred in our conversations, I believe that the pursuit of the idea of the use of killed viral antigens will be the most fruitful for the control of virus diseases generally. This is a scientific question, the resolution of which will require additional time and, therefore, should be kept separate from the practical question of the control of paralytic polio now.

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In spite of the extent to which vaccine has not been used, it is remarkable to observe the extent to which the prevalence of this disease has declined as compared with the prevaccine period. The intensity of outbreaks in the poorly vaccinated segments of the population, such as those in the lower socioeconomic groups, and in Negro neighborhoods suggests that if vaccine had not been applied that the outbreaks in recent years might have been more severe than in the prevaccine era. That outbreaks have been largely confined within the poorly vaccinated neighborhoods and have not spread in reasonably well-vaccinated groups, suggests that if vaccine had been used more uniformly in all segments of the population then community outbreaks would not have occurred even in the lower socioeconomic groups. The small proportion who fail to be protected after three or four doses could be expected to be protected by virtue of the community protection afforded by sufficiently extended use of vaccine in all groups including those that have shown less initiative in seeking vaccination, especially in the lower socioeconomic groups.

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initiative on the part of the American Medical Association, and its county medical societies, might not be of great value if the local societies were to declare that they will take the lead and will enlist the support of local service organizations and voluntary groups as fully and completely as necessary to accomplish the desired objectives. It is hardly necessary to point out that if specific programs were organized under the auspices of the county medical societies the community could be saturated with vaccine. I doubt that an effective country-wide vaccination program can be carried out without this kind of medical society initiative and support and I can see great value in bringing about the further reduction in incidence of polio by a voluntary community contribution of this kind.

The data reviewed with you will be prepared for publication in the JAMA. I am enclosing photo copies of some of the charts for any use they may be to you at this time. If I can be of any help at any time, I hope you will feel free to call upon me.

Sincerely,

JONAS E. SALK, M.D.

---

NOVEMBER 22, 1960.

Dr. LEROY BURNEY,
*Surgeon General,*
*U.S. Public Health Service,*
*Washington, D.C.*

DEAR DR. BURNEY: In view of our conversations in Atlanta, I thought that you would be interested in seeing a copy of a letter I am sending to Dr. Blasingame.

The continued gratifying results of vaccine effectiveness point up strikingly the benefits to be gained toward the solution of the polio problem by use of vaccine in a way that might well reduce the 3,000-odd cases of polio in 1960 to 300-some in 1961.

Sincerely,

JONAS E. SALK, M.D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
*Washington, D.C., December 21, 1960.*

JONAS E. SALK, M.D.,
*Virus Research Laboratory,*
*University of Pittsburgh, School of Medicine,*
*Pittsburgh, Pa.*

DEAR DR. SALK: Thank you for sending me the copy of your letter to Dr. Blasinghame.

I join with you in the hope that American physicians will undertake to do their utmost in getting the vaccine to those groups who are the least protected.

As you may know, an opportunity presented itself at the 1960 clinical sessions of the AMA to bring the profession up to date on present vaccination status and to provide some general guides for the immediate future.

I am enclosing copies of the papers presented at that time in which you will note that the Service intends once more to exert a substantial effort to promote vaccinations.

In it, we shall need all the help we can get; and, as you point out in your letter to Dr. Blasinghame, the medical profession is one of the key factors.

With all good wishes.

Sincerely yours,

———, *Surgeon General.*

Mr. ROBERTS. First of all, I would like to say that I regret that the subcommittee is not able to give you more notice of our hearing. We called it on rather short notice following on the heels of the President's announcement in which he requested $1 million for a reserve supply of the oral vaccine, and because prior to that announcement, there had been in the press some confusing statements with respect to the efficacy of the Salk vaccine which arose from something like a question and answer column in the American Medical Association Journal. I am sure you are familiar with the treatment that that story received in the press throughout the country.

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I certainly want to commend you highly for placing the emphasis which you do on the problem, that is, the socioeconomic and political problem. And I would like to go into that just a little bit.

Following the announcement of the results of the field tests of the Salk vaccine the pharmaceutical industry received from the National Foundation and from the Federal Government some measure of support. Under the legislation with which you are familiar, I believe some $68 million was spent by the Federal Government in trying to make the vaccine available. I would like your comment on whether or not you think that—considering that we have passed through some of our most productive years as far as gross national product is concerned and as far as capital income is concerned—within those years that we might have made more progress in the area of the unvaccinated?

It seems to me that if we did not make such progress in this time of high income, what is the hope that we will get to this large area of people who have not been inoculated in the future?

Dr. SALK. Mr. Roberts——

Mr. ROBERTS. I know my question is not too clear, and I am sorry.

Dr. SALK. No; it is quite clear to me. If you want to restate it, I will be glad to hear it.

Mr. ROBERTS. What I am trying to say is this: that in view of the fact that all the efforts that have been made on the part of the National Foundation and on the part of the Federal Government in the last 5 years, 5 or 6 years, when you say that we still have this large area of people who are not taking advantage of the vaccine, do you see anything in the present effort of education that would indicate that we are going to reach this particular group, in the lower socioeconomic area?

Dr. SALK. I suppose that a proper question would be, Do we know why vaccinations have not been carried out in such groups?

Mr. ROBERTS. Yes.

Dr. SALK. If we knew why, we might then be able to apply the proper treatment, I suppose.

In the older age groups I think there is the general attitude that it cannot happen to me. And if no one will take any personal offense, it is interesting to observe the extent to which cigarette smoking is carried on when there are such strong indications that it may have some association with cancer of the lung. There are fluctuations in terms of scare, it is down and then it is back up again—I think it is in this category.

Mr. ROBERTS. We used to have a "no smoking" sign up here, but it has been removed.

Mr. ROGERS of Florida. May I have the floor for just a minute?

Mr. ROBERTS. Yes.

Mr. ROGERS of Florida. I wish you would say that once more for the benefit of the chairman.

Dr. SALK. I do not know if he is worse off for smoking; he seems to be a rather agreeable man, and perhaps he is helped by smoking.

However, it seems to be that way in the upper age groups. But what about the situation of children under 5? In fact, children should be vaccinated in the first year of life.

The problem here is one of either education or, you might say, an indoctrinated system of health care. And what has been revealed by the experience of the last few years, perhaps, is a symptom of a fundamental problem which is not indigenous to or unique to polio, but it points to something fairly broad and fairly general, because I tried to point out that diphtheria, tetanus, and pertussis still are problems.

I do not know what the reason for it is. If one is going to make comparisons between this country and other countries and say that if they are highly successful in distributing medications of this kind, preventives of this kind in the U.S.S.R., in Hungary, in Denmark, and Scandinavia, is it because of the methods that they have for administration of medical care, or is it because of some other reason?

You see, the question you have asked, I have unfortunately turned back in the form of another question, because I do not really have an answer, I merely have a question.

Mr. ROBERTS. Now, in the first instance your vaccine, I believe, was used in Canada; is that right?

Dr. SALK. In the United States first.

Mr. ROBERTS. It was used first in the United States?

Dr. SALK. Then in Denmark and in Canada and a number of other countries simultaneously.

Mr. ROBERTS. And you referred to Australia and to Sweden.

Was your vaccine used in both those countries?

Dr. SALK. Yes.

Mr. ROBERTS. And did you reach a higher percentage of the population in, say, Sweden than we have reached in this country?

Dr. SALK. Yes, certainly in the younger age groups.

Mr. ROBERTS. And also the same thing was true in Denmark?

Dr. SALK. And in Australia.

And in Canada there has been a large pocket of the French Canadians around Montreal that have resisted vaccinations, and because of this there was a large outbreak in 1959, which one must regard as separate from that of Canada as a whole.

Mr. ROBERTS. And now in order to get complete protection would you say that the four doses of the Salk vaccine are preferable?

Dr. SALK. Preferable to what, Mr. Chairman?

Mr. ROBERTS. Well, preferable to three.

Dr. SALK. The difference between three and four is, in my way of reckoning, according to the line I put on the board, about 6 percent.

You see there is the law of diminishing returns with each additional treatment, because you get the large bulk with the first treatment, and it is for this reason that I think that both theoretically and practically it is sound in the future to recognize this, to have a single dose preparation. But to talk about what we have at the moment, if three doses can be administered to those who have not yet been vaccinated, particularly in the under 10-year age group, let us say the babies and the breadwinners that the Public Health Service speaks of, there will be a 90-percent reduction in probability of acquiring paralytic polio in individuals so treated.

Mr. ROBERTS. Now, in the chart—you pointed out in one chart the field trial.

Dr. SALK. Yes.

Mr. ROBERTS. Now what was the largest number of persons inoculated under that field trial, and when was that?

Dr. SALK. That was in 1954. And if my memory doesn't fail me completely, I think there were about 400,000 individuals who actually received vaccine, and then there were control groups.

Mr. ROBERTS. Had they received any other type of vaccine prior to the injection of the Salk?

Dr. SALK. None. There wasn't any available prior to that time.

Mr. ROBERTS. As to the effectiveness of the Salk vaccine, would you care to make a comparison between it and the live vaccine?

Dr. SALK. The only direct comparisons of which I am aware are those that have been carried out in Mexico. And this puts the live virus vaccine at a distinct disadvantage, because in Mexico at the time when these trials were conducted in such children there was a very high incidence of virus infections of the intestinal tract due to viruses other than polio, and as you probably know, when such virus infections are present, then it constitutes an interfering effect, and the vaccine that is fed doesn't take, so to speak.

Now Dr. Sabin has done some very splendid studies to try to overcome this problem, and has done some successfully. But this indicates the difficulty of making direct comparisons.

In that particular study, if I recall the figures correctly, there was approximately a 59 percent reduction in paralytic polio among those who received the live virus preparation, and in those who received approximately two doses of the killed vaccine, there was about an 82 percent reduction.

Now you provide me with an opportunity to make the most important point that I think needs to be made. I would say that there is probably little difference between the two preparations so far as effectiveness is concerned. The most important point is that either one be administered to a sufficient segment of the susceptible population.

And if you want to make comparisons you may make them between the overall effects that have been observed in the various eastern European countries, and the Scandinavian countries and the United States, and you will see that in all instances it is possible to reduce the incidence of disease not only in those so treated, but also to dampen the spread of virus generally with either preparation.

Mr. ROBERTS. We had some testimony to the effect that live vaccine was effective—the onset of effectiveness was faster than the Salk. Would you care to comment on that statement?

Dr. SALK. Yes, I tried to show in one of the charts that the onset of effectiveness can be after the first dose. And this is clearly evident when you see that there is about a 50 or 60 percent reduction—that about 60 percent of those given a single dose are protected, therefore, there is onset of protection within a matter of a week or two following a single dose. There is no theoretical reason why there should be a difference between the two. And I would say that the important point is whether or not the first dose, whether live or killed, takes at that time.

In either case, if it takes, the onset of effectiveness is prompt.

We have been able to demonstrate this again and again in experimental animals, and I could show you much more information on the promptness of the onset of effectiveness which varies with different doses of vaccine, different quantities of virus in the vaccine, vaccines

of different degrees of potency, the more potent the material the higher proportion will be affected favorably after the first dose.

And as one reduces the amounts, then there are some who are not protected after the first dose, but do respond after the second.

Mr. ROBERTS. As to the potency factor, how long—under whatever conditions you preserve the vaccination, how long is that vaccine effective?

Dr. SALK. I think that the Public Health Service has established a time limit which was based on a rather limited amount of information initially. In our own laboratory, and I know that in the laboratory of many manufacturers, the material has been stable for several years, in fact it is possible for manufacturers to do a fresh potency test at or about the expiration date, and have an extension of the useful life of the vaccine simply on the basis of retesting. And, by and large, this is successfully accomplished.

Mr. ROBERTS. Other than the experience that we had with the Cutter batch, have you had any other experiences with bad batches of vaccine?

Dr. SALK. None like the Cutter episode.

Mr. ROBERTS. And could you say approximately how many manufacturers now make the Salk vaccine in the United States?

Dr. SALK. In the United States?

Mr. ROBERTS. Yes.

Dr. SALK. Well, there are six in the United States and, of course, there is Canada, England, France, Australia, South Africa, and many others.

Mr. ROBERTS. You used the figure of 400,000 who participated in the 1954 field trial. What is the largest mass immunization that has been done with your vaccine?

Dr. SALK. I don't know what the cumulative figure is throughout the world.

Mr. ROBERTS. I mean in specific field trials.

Dr. SALK. That was the largest.

Mr. ROBERTS. There has not been one of comparable size?

Dr. SALK. I don't think there have been any other field trials of the same kind any place ever. Trials have been carried out, but they have not been of the same character, they have been more or less use trials.

Mr. ROBERTS. That is all I have at the present time.

Mr. NELSEN. No questions.

Mr. ROBERTS. Mr. Rogers?

Mr. ROGERS of Florida. Thank you, Mr. Chairman.

Dr. Salk, of course, we all have a great admiration for the work you have done and are continuing to do, and your testimony has been most helpful and enlightening. I am interested to know, now, about the three types of polio.

How do you handle that with your vaccine? Do you combine all three into one shot?

Dr. SALK. Yes.

Mr. ROGERS of Florida. Could you explain that to us just a little?

Dr. SALK. The viruses are grown separately, and they are converted into the noninfectious form separately, and then they are combined in a proportion, the purpose of which is to produce corresponding effects with each of the three types.

Mr. ROGERS of Florida. So when you take a series, say, of four shots, these four cover all three types of polio, is that correct?

Dr. SALK. That is right.

Mr. ROGERS of Florida. So you don't have to take different shots for different types?

Dr. SALK. No. And at the moment in our own laboratory we are experimenting with the inclusion of many more viruses into the same inoculum.

Mr. ROGERS of Florida. I see. I wanted to ask you, too what the amount of Salk vaccine now available in the United States is? Are you familiar at all with that?

Dr. SALK. No. I get the reports, but I don't pay any more attention to them than I do to the stock market.

Mr. ROGERS of Florida. What generally is true—or maybe you cannot generalize—what is true as to the live virus vaccine and the killed virus vaccine as far as effectiveness? For instance, smallpox, I think, is alive, is it not?

Dr. SALK. Yes.

Mr. ROGERS of Florida. Have they ever had a killed vaccine?

Dr. SALK. I see what you are asking.

Mr. ROGERS of Florida. I would like to know what experience you have had.

Dr. SALK. During the war I worked with the Commission on Influenza on influenza virus vaccine. And the degree of effectiveness of the material that was prepared at that time was something of the order of magnitude of about 80 percent. That was influenza A.

Then there was an outbreak of influenza. Influenza B, I think, was about 90 percent. And then in 1947 the strain changed, and the effectiveness virtually could not be demonstrated.

And so there has been some feeling that a killed virus has been ineffective essentially. In other words, the experience with influenza A, although favorable and positive, has not given the feeling of confidence that the disease has been brought under control. So far as I know, polio is the first virus disease that has been brought under as effective control as has been demonstrated now.

Mr. ROGERS of Florida. With the killed vaccine, which is yours?

Dr. SALK. Yes—well, it is not mine——

Mr. ROGERS of Florida. I understand.

Dr. SALK. For the record I had to say that.

Mr. ROGERS of Florida. We all give you credit for it anyhow.

Dr. SALK. On the other hand, the same principles have been used for the preparation of the typhus vaccine, the vaccine for diphtheria, and tetanus toxoids. This is a fairly general principle, but in quantitive study I have tried to convert the preparation of vaccine from an art to a science, so to speak. This is something that we have concentrated on, so that we can understand what the parameters are that are required to produce a consistent effect.

Mr. ROGERS of Florida. Is there any way to provide for a killed vaccine to be taken orally?

Dr. SALK. No.

Mr. ROGERS of Florida. No possibility?

Dr. SALK. No. There are not very many other agents that can be so administered.

Mr. ROGERS of Florida. Do you feel that there is an advantage in oral—in administering a vaccine orally above a hypodermic?

Dr. SALK. Well, I am sure that everyone has his own preference. I prefer to try to answer the question from my viewpoint as a scientist, and that is that I would like to extend the principle of the killed vaccine to the point where we may have 100 different viruses included in the same innoculation. It is obvious that this is my scientific interest.

From the human point of view, I wouldn't care if the stuff was put into the water supply, or put into the air-conditioning system, if it would produce an effect. I don't think it matters.

Mr. ROGERS of Florida. I was thinking maybe for easy acceptance.

Dr. SALK. I don't think that a 9-month-old baby or a 6-month-old baby knows the difference.

Mr. ROGERS of Florida. I was thinking of 6-year-old children.

Dr. SALK. That is fine, if they prefer candy—by that time, it is too late.

Mr. ROGERS of Florida. Now, I want to ask this. When was it you actually came upon the discovery of your vaccine?

Dr. SALK. Well, it wasn't a discovery, it was a planned attack.

Mr. ROGERS of Florida. Your development, then.

Dr. SALK. We began our first animal experiments in October 1951, and the first human inoculations at the end of June 1952.

In September of 1952 we thought we had something. But November we were sure. And at the end of January 1953 at a meeting in Hershey, Pa., I reported on this for the first time.

And from that point, the work moved rather rapidly.

Mr. ROGERS of Florida. It actually was licensed when?

Dr. SALK. This was in 1955. The field trial began in the spring of 1954, and after Dr. Francis' report on April 12, 1955, the licensing took place.

Mr. ROGERS of Florida. Do you feel that our licensing procedures are handled in as rapid a manner as possible, or do you have any suggestions as to future handling that might be helpful in licensing new vaccines?

Dr. SALK. I have only the highest commendation for the developments of the Division of Biologic Standardization since 1955 when there was a great deal of interest and activity in the question of biologic standardization as a result of the experiences as of that time. And I think that we have perhaps one of the finest organizations and staffs for this purpose anywhere.

Mr. ROGERS of Florida. Do you feel then that everything that has been done is being done as it should be at the present time?

Dr. SALK. I think so. I have not been close enough to the Division of Biologic Standards since a few years ago but I have no reason to think from contacts that I have had that they are not as efficient and as expeditious as they should be.

Mr. ROGERS of Florida. I am not criticizing them.

Dr. SALK. I know that.

Mr. ROGERS of Florida. I was wondering about the procedure—do you think it is necessary to test many times? Or is testing once, twice, or three times of the batches of vaccine sufficient? I wondered if you had any thoughts along that line, as to procedure?

Dr. SALK. This is one where, let us say, the statisticians come along, you know—and they have reason for setting numbers of that kind, because they can then talk in terms of probability.

As you know, it is difficult to talk in absolute terms. And the point that I hope I have made effectively is that when one uses the vaccine, all you do is reduce the probability of something happening that might otherwise have happened.

When we say that a vaccine is 96 percent effective, it does not mean that it is 96 percent effective in any one individual. It just means that 96 out of 100 people will react in a certain way under the circumstances; and, therefore, in the testing of one batch or two or three or four or five, you would have an increasing degree of confidence in estimates of probability of whatever it is you are attempting to determine.

Mr. ROGERS of Florida. So you have no particular suggestion along those lines?

Dr. SALK. I think so far the use of the No. 5 in the killed vaccine, probably, has influenced the Public Health Service in using that magic number, if they continue to use it. I presume they will.

Mr. ROGERS of Florida. I am not sure. I think that is still used. Are you familiar with the number of tests made in other areas overseas?

Dr. SALK. I could not tell you but my feeling is that by and large the U.S. Public Health Service's procedures have been followed in most places.

Mr. ROGERS of Florida. Thank you very much.

Dr. SALK. Thank you.

Mr. ROBERTS. Mr. Thomson.

Mr. THOMSON. I have one question, Dr. Salk.

I got the impression that you felt the need for wider immunization, since the vaccine was effective. Why not move ahead with the existing vaccine rather than wait until the live vaccine has been licensed? We could do a great deal with this rather than wait until 1962.

Is that your position?

Dr. SALK. Precisely.

Mr. THOMSON. Thank you.

Mr. ROBERTS. Dr. Salk, again I want to thank you for appearing. We are very happy to have had you here to give this information to the committee and very happy to have you before the committee again. We know you are a very busy man. I am delighted that you could come. I think we have all of the exhibits that you wish to place on the record taken care of.

Dr. SALK. I have already given them.

Mr. ROBERTS. And the charts and the like that you presented, to be included in the permanent record.

Dr. SALK. Yes, sir.

Mr. ROBERTS. Again I want to thank you for your appearance. We deeply appreciate your coming.

I note the appearance of the Surgeon General, Dr. Terry. I want to again thank you, Dr. Terry, for your fine cooperation and that of the Public Health Service, for your splendid statements. And, also, to thank the gentlemen who were with you here yesterday and who have been here today.

I would like to thank all of the witnesses who have participated in the hearing.

I would like to say that the Public Health Service has, in my opinion, done a fine job thus far in the face of very difficult problems. We feel that the time has come to review the vaccine picture in the light of all of the testimony in these hearings in order to reach new decisions, some of which are scientific and technical in nature and others administrative and political.

We think that a factual review should be made by the Public Health Service and the results of such review should be submitted to the Secretary of Health, Education, and Welfare. In the light of all the facts, alternative, practical programs might be outlined by the Public Health Service for the Secretary and for this committee so that the merits of alternative approaches may be considered.

The Chair would like to say that we would expect the Public Health Service and the Department of Health, Education, and Welfare to submit at an early date reports on the progress made in such review and the preparation of alternative programs to meet the problems dealt with by the witnesses in these hearings.

(NOTE.—The information requested is being printed as a separate report entitled "Vaccines and the Public's Health.")

Mr. ROBERTS. I have one other statement that I mentioned earlier, the statement by one pharmaceutical manufacturer.

Mr. Clerk, if you will read that at this time, we will then conclude the hearing.

Mr. WILLIAMSON (reading):

STATEMENT OF CHAS. PFIZER & CO., INC., READ BY W. E. WILLIAMSON

Statement by Chas. Pfizer & Co., Inc., on the present production status of Sabin-type oral polio vaccine, submitted to the Subcommittee on Health and Safety of the House of Representatives Committee on Interstate and Foreign Commerce:

This progress report on the development of oral vaccines against poliomyelitis is presented at the invitation of the Subcommittee on Health and Safety of the House of Representatives Committee on Interstate and Foreign Commerce.

Chas. Pfizer & Co., Inc., has a medical, social, and economic interest in the development of any drug product which will cure illness, alleviate human suffering, or prevent serious disease. It has successfully demonstrated this interest in its extensive research efforts; in its mass production of penicillin during World War II when it provided a major part of the penicillin used by the U.S. Armed Forces; in its discovery and development of the broad spectrum antibiotics, terramycin and tetracycline, both in wide use today; and in its development and marketing of Diabinese, an oral antidiabetic used by thousands for whom its use is suited.

Over the years it has been the policy of the company to invest time, manpower, and money in new developments when such developments hold promise of extending public use of medicines to prevent disease.

Pfizer first began preparations for the production of the Sabin-type oral polio vaccine at our English subsidiary, Pfizer, Ltd., in the summer of 1959 with the technical assistance of Dr. Albert B. Sabin, professor of research pediatrics at the University of Cincinnati College of Medicine.

Seed virus work began early in 1960 on types I, II, and III strains, all of which are required for full protection against poliomyelitis.

The production of three different types of seed virus has now been completed and the initial production lots required for licensing by the Division of Biologics Standards of the National Institutes of Health and the British Medical Research Council are in process and being tested. Bulk samples of lots of two of the three types of vaccine to be marketed have been forwarded to the National Institutes of Health for their testing and bulk samples of the remaining type

are expected to be submitted shortly. Government representatives are scheduled to inspect our facilities in Sandwich, England, this month.

All of these steps, carried out in close collaboration with Government representatives, are part of the necessary procedures followed by our company in making application for a license to produce and market the Sabin-type oral vaccine.

We expect to submit our formal application following the issuance of final Government regulations providing standards for live vaccine production. Meanwhile, our work has been carried out in conformity with the proposed regulations for live polio vaccine published in the Federal Register of November 23, 1960.

We are now operating our English facilities at maximum capacity to produce live oral polio vaccine. At this time it is extremely difficult to make projections as to future availability of the oral vaccine. There are still problems to be solved, such as the formulation of the final dosage form and the standardizing of vaccine potency determinations.

However, on the basis of our experience to date within the framework of the proposed regulations, we are pleased to give the committee our best present estimates as to future availability of vaccine from our plant. If our Pfizer plant in England is licensed to produce oral vaccine by next winter and approval is given for importation to the United States, we believe substantial quantities—sufficient to vaccinate millions of individuals—can then be made available.

Our company currently has submitted samples of production lots of the Sabin-type vaccine to the British and Japanese Governments in preparation for the sale of the vaccine in these countries when it has been approved.

Within recent weeks there has been discussion in the public press and otherwise on the possible dosage price of the oral vaccine. At this time it is still too early for us to comment on a possible selling price because of the many variables in the situation.

The new vaccine will be administered by mouth instead of by injection. It could be incorporated, for example, in a flavored sirup, distilled water, or with ordinary granulated sugar for ease of administration. To combat the three different types of polio, three different types of oral vaccine are required, as mentioned earlier, and present thinking indicates that these will probably be administered in separate doses.

As stated earlier, Pfizer began preparations for the production of the Sabin-type oral polio vaccine in the summer of 1959. At that time, there were no assurances that an oral polio vaccine would be accepted in the United States or that the Sabin strains would be adopted as the standard for manufacturing.

Although Pfizer manufactures Salk-type vaccine at both Terre Haute, Ind., and Sandwich, England, Pfizer proceeded with the live vaccine only at its Sandwich plant. The English facilities were chosen primarily because of the Pfizer British group's well advanced production and marketing program for the Salk-type vaccine and the fact that it was in a position to pursue the necessary research and development work at the time this project was undertaken in 1959.

Once the decision was made to produce live polio virus vaccine at Sandwich, facilities for production, laboratory work, safety testing, and animal holding were constructed at an accelerated rate. All installations were built to comply with the tentative regulations available at that time.

Pfizer has invested millions of dollars in staff and facilities to produce vaccine at Terre Haute and Sandwich, and the company is now able to supply a highly potent Salk-type vaccine throughout the world. In this program we have been provided the finest type of cooperation and assistance by Dr. Jonas Salk.

In the program to produce oral polio virus vaccine we have been similarly benefited by the excellent cooperation and scientific guidance provided by Dr. Sabin. His work has been invaluable, since he has not only provided the original seed virus for the Pfizer program, but has also visited the company's English facilities and has advised our scientists from time to time.

In pursuing this program from its early laboratory beginnings, we have received cooperation of the highest order from the U.S. Public Health Service, as well as the Medical Research Council in England. Our scientific personnel have been benefited materially through guidance from the Public Health Service in all phases of the program and this has enabled us to proceed expeditiously in our production to the present point.

Pfizer will continue to pursue its Sabin-type oral vaccine program and to cooperate whenever and wherever possible with the appropriate governmental authorities in seeing the program successfully culminated.

Until such time, however, we urge all unvaccinated children and young adults not to wait for the availability of an oral vaccine, but to get their Salk shots now.

Mr. ROBERTS. Thank you, Mr. Williamson.

Also, the Chair received a wire from Dr. Hilary Koprowski, offering to testify at the hearings, and I would like to say, before the record is closed, he will be given an opportunity to file a statement. His telegram will be made a part of this record.

(The telegram follows:)

PHILADELPHIA, PA., *March 16, 1961.*

Representative KENNETH ROBERTS,
*House Health and Safety Subcommittee, House Interstate and Commerce Committee, New House Office Building, Washington, D.C.:*

If the committee hearings on oral polio vaccine extend beyond Friday I'm available to testify on background of development of the oral vaccine and express my views on the national and international regulations related to manufacture and use of the vaccine. I was the first scientific investigator to report successful immunization with oral polio vaccine. Because of speaking at Yale Medical School symposium am unable to come to Washington until after Friday.

HILARY KOPROWSKI, M.D.

(Dr. Koprowski later submitted the following letter:)

PHILADELPHIA, PA., *April 14, 1961.*

Representative KENNETH ROBERTS,
*Chairman, House Health and Safety Subcommittee,*
*House Interstate and Foreign Commerce Committee,*
*New House Office Building, Washington, D.C.*

DEAR SIR: I appreciate your invitation to submit a statement to the congressional subcommittee which is considering the status of the oral polio vaccines made from live poliovirus.

Since the first feeding of live virus to humans in 1950, I and my associates have conducted experimental studies in this field, and since 1957 our strains have been used in large-scale field trials. At present they are being used exclusively or predominantly in Poland, Yugoslavia, Sweden, and Switzerland, as well as in a clinical trial in our own city of Philadelphia. On the basis of these studies I hold the following views concerning the best approach to the problem of immunization against poliomyelitis. Some of these are at variance with the current policies and views of those in the U.S. Public Health Service who are in charge of these problems.

Of first importance at the present time, I feel, is the fact that the Division of Biologics Standards continues to insist that the production of live poliovirus vaccine be in monkey kidney tissue culture. As a monkey kidney tissue culture is host to innumerable simian viruses, the number found varying in relation to the amount of work expended to find them, the problem presented to the manufacturer is considerable, if not almost insuperable. He is faced with the prospect of having to discard most of his manufacturing lots of vaccine. This will inevitably raise the cost of the vaccine, and as our technical methods improve we may find fewer and fewer lots of vaccines which can be called free from simian virus.

We believe that it would be sounder scientifically to switch to human cell strains for the production of live poliovirus vaccine. The likelihood of simian viruses being present in these cells is small. The cost of production would be even less than if primary monkey kidney material were used. The only objection that can be raised to the use of these cells is that they may be "cancerous." In fact, however, not a shred of evidence exists suggesting that this is the case. Indeed, one could make out a case for the presence of a hypothetical cancer agent in monkey kidney with perhaps greater factual support.

I feel that this aspect of the situation has great practical value, quite aside from its theoretical importance to scientists. I feel that it should receive thorough and immediate consideration by the DBS, in view of the promise it holds for overcoming one of the major obstacles to getitng this new type of polio vaccine on the market and available to the population.

Another aspect of this situation on which I hold views differing from those of the officials of the U.S. Public Health Service concerns the regulations as to which strains of attenuated polio virus may and may not be used in vaccine production. As you are probably aware, the strains which have been developed in my laboratory do not have the official approval of the PHS, even though it is known that they have been safely used in the immunization of millions of people throughout the world and even though the former Surgeon General has said that so far as safety in man is concerned, all currently available strains (those developed by me and by Lederle Laboratories as well as Dr. Sabin's) are probably equal. The basis for the exclusive endorsement of the Sabin strains by the PHS was that they gave the best results in monkey neurovirulence tests.

It is my opinion that this is a most unsound basis for decision, in view of all available scientific data, for the following reasons:

1. The difference in monkey neurovirulence between the Sabin strains and mine are of doubtful biological and statistical significance. I am enclosing a table which makes this point clear.

2. The results of this monkey neurovirulence test are difficult to reproduce, which again calls into question the observed differences on which this important decision was based.

3. As you know, live virus vaccines spread from vaccine to contact and therefore the properties of the excreted virus are as important as the vaccine virus. It has been demonstrated in many laboratories that all type 3 strains, including Dr. Sabin's, change in the intestinal tract into viruses which are more virulent for monkeys than any of the vaccine strains proposed for use. It therefore seems unsound to reject certain vaccine strains on the basis of monkey neurovirulence when excreted virus of an improved strain is more virulent. As a matter of fact we have found in our laboratory that it is possible to improve considerably the stability of type 3 strains. We have developed a new strain which is now ready for clinical trial.

In this connection, I feel that it is important to note that when the World Health Organization Expert Committee on Poliomyelitis met to consider the problem of worldwide standards for production of live polio virus vaccine, its decision was not to select any particular set of strains which must be used, but recommend the use of any set of strains which had been tested thoroughly in man. Two other countries, England and Switzerland, have similarly not discriminated against any set of strains in their regulations.

All of these views I have repeatedly presented to the U.S. Public Health Service and I appreciate the opportunity to present them for the consideration of your consideration. I shall be happy to add further information if necessary.

Sincerely yours,

HILARY KOPROWSKI, M.D.

*Monkey neurovirulence of type 1 strains*

| Route | Vaccine | Testing laboratory | Dose of virus inoculated (PFU [1]) | Clinical signs | Histologic lesions | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Intracerebral | Koprowski | Division of Biologics Standards [2] | 7.6 | 0/5 | 2/5 | | |
| | | | 6.6 | 0/5 | 2/5 | | |
| | | | 5.6 | 0/5 | 2/5 | | |
| | | | 4.6 | 0/5 | 2/5 | | |
| | | | 3.6 | 0/5 | 6/5 | | |
| | | | 2.7 | 0/5 | 0/5 | | |
| Do | Sabin | do [2] | 7.4 | 0/9 | 0/9 | | |
| | | | 6.4 | 0/4 | 0/4 | | |
| | | | 5.4 | 0/5 | 0/5 | | |
| | | | 4.4 | 0/3 | 0/3 | | |
| | | | 3.4 | 0/3 | 0/3 | | |
| Do | do | do [2] | 7.4–7.7 | 0/3 | 0/3 | | |
| Do | do | Melnick [4] | ([5]) | 0/12 | 1/12 | | |
| | | | $10^{-1}$ | 1/7 | 1/7 | | |
| | | | $10^{-2}$ | 1/7 | 1/7 | | |
| | | | | | L | C | BS |
| Intramuscular | Koprowski | Division of Biologics Standards [3] | 7.7–7.9 | 2/4 | 2/4 | 1/4 | 2/4 |
| | | | 6.7–7.2 | 0/12 | 1/12 | 1/12 | 1/12 |
| | | | 6.2–6.4 | 0/2 | 0/2 | 0/2 | 0/2 |
| Do | Sabin | do [3] | 8.7–8.9 | 0/4 | 3/4 | 0/4 | 0/4 |
| | | | 8.7 | 0/3 | 3/3 | 2/3 | 2/3 |
| | | | 7.7–8.7 | 0/5 | 4/5 | 1/5 | 3/5 |
| | | | 7.9 | 0/14 | 5/14 | 2/14 | 1/14 |
| | | | 6.7–7.2 | 0/4 | 0/4 | 0/4 | 0/4 |

[1] Plaque-forming units in log to the base of 10. L—lumbar enlargement of cord; C—cervical enlargement of cord; BS—brain stem.

[2] Murray, R. et al. Comparative virulence for Rhesus monkeys of poliovirus strains used for oral administration. Pan American Health Organization Scientific Publication No. 44:39, 1959.

[3] Kirschstein, G. et al. Neurovirulence after intramuscular inoculation of monkeys. Pan American Health Organization Scientific Publication No. 50:90, 1960.

[4] Malnick, J. et al. Studies on live poliovirus vaccine: Its neurotropic activity in monkeys and its increased neurovirulence after multiplication in vaccinated children. J.A.M.A. 171:1166, 1959.

[5] Undiluted.

Mr. ROGERS of Florida. Mr. Chairman, I just want to say that I have personally been impressed with the Public Health Service, the work they are doing in this field. And I want to compliment these gentlemen.

Also, I was glad to see the interest by someone from the industry, the Pfizer Co., and also Mr. Frank Duckworth, a member of that industry, who is an old friend of mine, who happens to be here in Washington for the first time. I have great confidence in him. And I think the statement of cooperation on the part of this drug company is most helpful.

Mr. ROBERTS. I, certainly, would like, in closing, to associate myself with the tribute the gentleman paid to the Public Health Service and to the industry.

I also would like to thank all of the witnesses who have made themselves available, and to thank the members of the press for the fine services given our hearing, which will close our hearings on this matter.

And, also, we appreciate very much the fine attendance shown here today.

(The following material was submitted for the record:)

BAYLOR UNIVERSITY COLLEGE OF MEDICINE,
DEPARTMENT OF VIROLOGY AND EPIDEMIOLOGY,
*Houston, Tex., March 8, 1961.*

Hon. KENNETH A. ROBERTS,
*House of Representatives, Washington, D.C.*

DEAR CONGRESSMAN ROBERTS: I have learned through an article in the New York Times of your interest in the discussions regarding possible ineffectiveness of the Salk poliomyelitis vaccine. I gather that your concern arises from a letter in the Journal of the American Medical Association. In view of your interest, I am taking the liberty of enclosing a few copies of an editorial which I wrote on this subject a couple of weeks ago, on invitation from the editors of Medical Record and Annals. You might be interested particularly in the conclusions which are stated in the last paragraph.

Respectfully yours,

JOSEPH L. MELNICK, *Professor and Chairman.*

[Reprinted from Medical Record and Annals, Houston, Tex., January 1961 issue, vol. LIV, No. 1, pp. 1 and 2]

EFFECTIVENESS OF SALK VACCINE IN HOUSTON AREA[1]

Recent epidemiological and virological studies have emphasized that complete control of poliomyelitis has yet to be attained in spite of there having been an effective vaccine generally available since 1955. There has been a feeling among some sources that Salk vaccination has not been as effective as had been anticipated, particularly because of the increased incidence of poliomyelitis in 1959, during which year 5,472 paralytic cases were reported in the United States. In the Houston area alone, there came to the attention of the virus laboratory at Baylor Medical College 251 patients who were hospitalized with paralytic and nonparalytic poliomyelitis in 1958–59. These patients came largely from the clinical study center of the Texas Institute for Rehabilitation and Research and from the pediatric service of Jefferson Davis and other hospitals in the area. They constituted virtually all cases of acute central nervous system disease severe enough to be hospitalized during this period.

In an attempt to assess the effectiveness of Salk vaccination in the Houston area, the Baylor laboratory data have been analyzed to determine to what extent

[1] The study on which this editorial is based was supported by a grant from the National Foundation to the department of virology and epidemiology, Baylor University College of Medicine.

the polioviruses and other enteroviruses were causing these illnesses, and to what extent adequately Salk-vaccinated persons were involved.[2]

Of the 126 cases which were diagnosed clinically as paralytic poliomyelitis, 102 yielded a virus in monkey kidney cultures. All but two of the viruses isolated were polioviruses (86 type 1 and 14 type 3) ; the other two enteroviruses isolated were a Coxsackie B2 strain, in 1958, and an ECHO 7 strain, in 1959.

During the same period, 125 cases diagnosed as aseptic meningitis were studied, with 53 of them yielding enterovirus isolations. Of these, only 23 were polioviruses (21 type 1, and one each of types 2 and 3), while 30 were found to be other enteroviruses. The nonpolio strains which have been fully identified to date include 12 ECHO strains (four ECHO 9, three ECHO 11, two ECHO 7, one each of ECHO 4, 16, and 17), and 8 Coxsackie strains (four B2, two B3, one each of A9 and B5).

Thus in 98 percent of the paralytic patients from whom any virus could be isolated, the clinical diagnosis of paralytic poliomyelitis was confirmed by the laboratory. In contrast, more of the viruses isolated from the aseptic meningitis cases proved to be nonpolio enteroviruses than were identified as polioviruses, 57 percent as against 43 percent respectively.

The relationship of Salk vaccination to the incidence of laboratory-confirmed cases of paralytic poliomyelitis is shown by the fact that only 3 of the 100 such cases studied had received 3 or more Salk vaccine inoculations, whereas 87 were completely unvaccinated, and 10 had been inadequately vaccinated, having been given only 1 or 2 inoculations.

The overall incidence of aseptic meningitis in those yielding virus was less markedly related to vaccination status: of the 46 cases in which a virus was isolated and vaccination history was available, 14 (30 percent) were in those with a history of 3 Salk inoculations. However, when the distinction is made between those excreting polioviruses and those excreting nonpolio enteroviruses, it becomes clear that aseptic meningitis associated with intestinal carriage of polioviruses occurred rarely in persons who had received a full course of 3 or more Salk inoculations—only 2 of the 23 poliovirus-associated aseptic meningitis cases studied. Among the poliovirus excretors, this syndrome was seen chiefly in those who had not received any vaccine at all (17 of the 23). The incidence of aseptic meningitis in which viruses other than polioviruses were isolated bore no relationship to the history of Salk vaccination, for 12 of 23 such cases were in the triply vaccinated group.

Thus, in the Houston area, with an analysis limited to laboratory-proved cases, it is clear that Salk poliovaccine has continued to provide highly effective protection against paralytic poliomyelitis in persons who have had a series of three or more inoculations. In confirmation of other studies, vaccination is shown in this study to have had a suppressing effect on incidence of nonparalytic poliomyelitis also, that is, on cases of aseptic meningitis in which the agents isolated were polioviruses.

These findings constitute additional documentation that the effectiveness of Salk vaccine, when evaluated on the basis of proven cases, is greater than superficial documentation would indicate. It is concluded that poliomyelitis continues to appear in clinical form because of the failure by physicians and public health officials to administer vaccine to susceptible persons. No better results can be expected of any vaccine—either the inactivated one in current use, or the living attenuated one now under consideration in this country—unless it is fully utilized in the susceptible population.

JOSEPH L. MELNICK, Ph. D.,
*Professor and Chairman, Department of Virology and Epidemiology, Baylor University College of Medicine, Huston, Tex.*

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LEDERLE LABORATORIES,
*Pearl River, N.Y., March 22, 1961.*

HON. KENNETH A. ROBERTS,
*Chairman, Committee on Interstate and Foreign Commerce,*
*House of Representatives, Washington, D.C.*

DEAR CONGRESSMAN ROBERTS: Though no formal invitation was received by Lederle to participate in the recent hearings on the status of the oral polio-vaccine held by the House Commerce Committee's Subcommittee on Health and

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[2] Melnick, J. L., Benyesh-Melnick, M., Peña, R., and Yow, M., "Effectiveness of Salk Vaccine." An analysis of virologically confirmed cases of paralytic and nonparalytic poliomyelitis. J.A.M.A., in press, 1961.

Safety, we are pleased to avail ourselves of the opportunity to file a statement in accordance with the subcommittee's general invitation to do so tendered at the close of the hearings, March 17, 1961.

The Lederle Laboratories Division, American Cyanamid Co., initiated the pioneering research program in 1946 to develop an attenuated live virus oral poliovaccine because of the conviction that immunization with such an oral vaccine would be long-lasting, would break the chain of transmission of natural infections and might ultimately eradicate poliomyelitis.

This program was carried out under the direction of Dr. Herald R. Cox at Lederle whose research group succeeded in attenuated a poliovirus strain and safely feeding it to a human, after fully adequate testing, as far back as 1950.

The conviction of Lederle scientists in the soundness of this research program coupled with progressively promising results explains why in 1953 Lederle on the one hand offered its experience and facilities for the production of Salk vaccine, but at the same time expressed the hope that its people and facilities would not be required in that program because its research on the attenuated live virus vaccine would be interrupted or delayed.

While we are gratified that this conviction of Lederle scientists has been justified and that Lederle has played a significant role in bringing about this breakthrough, it should be pointed out that all our work, up until September 1960, was done with the Lederle-Cox strains of attenuated polioviruses. This included clinical testing throughout the world, financed by Lederle, in some 2 million persons. Other companies, however, had been working with the Sabin vaccine at least 9 months previous to this date.

When word was received in August 1960 of the Surgeon General's decision to accept the Sabin type I strain as the reference strain for manufacture of the oral vaccine, Lederle nevertheless stated the very next day after the decision that it would "comply with the decision of the Surgeon General and undertake the manufacture of approved strains as soon as all licensing and Division of Biologics Standards requirements could be met."

Since that time, we have vigorously pursued this project, fully utilizing our new $3 million facilities constructed for the new vaccine. However, drawing upon our not insubstantial experience in the field, it must be said that important technical problems remain to be resolved in the production, distribution and administration of the vaccine as constituted by the additional standards: (42 CRF pt. 73) issued by the Division of Biologics Standards. These are gone into more fully in attachments "A" (Nov. 29, 1960, letter to Surgeon General Burney from L. C. Duncan) and "B" (production outline).

If the currently available licensing and production requirements are successfully met, there remains what is in our opinion a major obstacle to the successful continuing distribution and administration of the vaccine as now constituted. (At this writing the Division of Biologics Standards has not yet issued final licensing requirements, nor are the official reference strains necessary for testing in compliance with the tentative standards yet available from the Government.)

As has been established by the experience with the Salk vaccine, the importance of getting adequate immunization to adequate numbers of people is fundamental to the success of any immunization program no matter how potent the immunizing agent. We at Lederle were made aware of this problem when we were administering the Lederle-Cox oral vaccine in monovalent doses as a part of our extensive clinical programs. For this reason we developed a trivalent oral vaccine with the Lederle-Cox strains that would be effective in one or two doses without the necessity of maintaining complex immunization records for each individual. Indeed, several public health officers with experience in the field have voiced grave doubts about the acceptability or feasibility of a monovalent vaccine as an effective enough weapon in the fight against polio. This problem, coupled with the limited stability of the Sabin vaccine as defined in the tentative standards, poses serious professional problems both from the standpoint of the public health officer, and certainly for the physician in private practice. It must be a serious loss to the American public if the vast and effective network of private physicians is not to be able to effectively participate in the necessary continuing mass immunization program.

In closing, may I reiterate that Lederle is doing all in its power to comply with the available standards. We would, however, be remiss in our responsibilities if we did not, as we have done in the past, endeavor to produce the most useful and effective vaccine possible as a contribution to the public health problem of poliomyelitis.

Sincerely yours,

L. C. DUNCAN, *General Manager.*

ATTACHMENT A

NOVEMBER 29, 1960.

Surgeon General LEROY BURNEY,
*U.S. Public Health Service,*
*Washington, D.C.*

DEAR DR. BURNEY: This will reply to your letter of November 9, 1960, addressed to Dr. W. G. Malcolm, inquiring about the progress we have made in our program for the manufacture of live polio virus vaccine. In the letter you asked us to provide answers to four specific questions which I will attempt to do in as direct a manner as possible.

Your first question asked for a statement as to whether or not we had made a definite decision to manufacture live polio virus vaccine.

As you well know, we embarked on a program to develop a live polio virus vaccine in 1946 and have pursued it without interruption ever since that time in the firm belief that such a vaccine will provide the only final and satisfactory means of possibly eradicating polio.

As soon as we were advised officially in August 1960 that the Public Health Service had adopted standards which would rule out the three "Cox" strains and make the three Sabin strains the only ones acceptable for licensing purposes, we immediately took steps to secure the Sabin strains to begin work on them. After preliminary discussions we invited Dr. Sabin to visit us in Pearl River and bring along the strains as we were determined to reach an agreement and to this end secure the strains immediately in order to avoid delays. This was accomplished on August 31. We immediately initiated an extensive development program aimed at determining if uniform lots of acceptable vaccine can be produced with the Sabin strains in successive production batches.

These seed strains, as you are aware, contained the extraneous virus, the "vacuolating agent," which had to be eliminated before a pool of seed virus could be established. Intensive work has been going on in this direction and we are completing final tests which we think will demonstrate that this extraneous virus has been eliminated. In order to save time, we have gone ahead with initial production of our seed virus pool and have completed the first production runs of the three strains.

Since one of the most serious production problems is the availability of monkeys free of foamy agents and "vacuolating agents," we sent one of our veterinarians to India to arrange for the isolation of monkeys. This program has not been fully evaluated to determine if monkeys procured in this way are, to a greater degree, free of these agents.

Extensive studies have been established to determine stability properties of the Sabin strains under a number of conditions. While it is far too early to know of the success of these studies on the Sabin strains, previous work on the Cox strains which had indicated stability far greater in degree than those specified in the additional standards leads us to believe that the same result can be accomplished with the Sabin strains.

Thus, you can see we have made significant progress in our development program. It is impossible, however, to give you at this writing a definite answer as to our decision to produce this vaccine on a commercial basis.

Our past experience has been that at this stage in the development of a biological product our technical people have acquired sufficient process experience to permit them to sit down and work out with the technical representatives of the Division of Biologic Standards the testing requirements for proving the safety and efficacy of the product. In the present case we do not yet have such experience with the Sabin strains, nor have our technical people had time to study the additional standards: Poliovirus vaccine, live, oral (42 CFR pt. 73), just received by mail through the kindness of Dr. Roderick Murray, to determine if they appear to be possible and practicable. The decision to produce the Sabin vaccine on a commercial scale is impossible until we know what final standards our production must meet, and if it is possible to meet these standards.

To meet the newly issued additional standards we need to determine:

(1) If the NIH strains (Sabin strains) are sufficiently stable to yield reproducibly uniform lots of vaccine from batch to batch. This has never been demonstrated to our knowledge, and the requirement concerning consistency of manufacture requiring that pools meet the criteria of neurovirulence be consecutive pools may be unreasonable or impossible.

(2) If vaccine free from adventitious agents can be obtained from lot to lot under production conditions that are economical.

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(3) If these strains will uniformly produce vaccine capable of eliciting the required titer of specific neutralizing antibodies in "80 percent or more of susceptibles when administered orally in a single dose or in excess of 90 percent when administered in a series of doses"; to our knowledge no scientific papers have been published that have furnished proof as to such efficacy. If the antigenicity results to qualify for license must truly be met on "five consecutive lots" of each type, this may technically be an impossibility.

(4) If one or more of these strains have a potential for producing viremia in man, in view of the previous proposed recommendations, it should be clarified whether this will or will not be an issue. Since this subject has been previously discussed extensively, it becomes of vital importance to us in our developmental as well as our production plans.

(5) If the strains are stable genetically on passage in man; certain reports indicate the NIH type III (Sabin type III) may show a tendency to acquire some increased neurovirulence after passage in man. This information should be considered and a ruling on acceptability of the strain for licensing made.

(6) If the requirements as regards dating, that "no more than 7 days from the date of issue if issued as a liquid and provided it is maintained at a temperature no higher than 10° C." be adhered to the technical aspects of manufacture, distribution, and administration of a live virus vaccine may be medically impractical and commercially impossible. This requirement is so foreign to our past experience in developing biological products that have been useful to the medical profession that development work is essential to render these products stable under practicable conditions.

Even though we are well underway on our development program, it is extremely difficult to answer your second question, which requests us to estimate when commercial vaccine will be available. There are so many uncertainties at the moment, some of which have been touched on and some of which I will outline below, that the best estimate I can make at this time is not before the fall of 1961.

The NIH recommended requirements for licensing specify that consistency of production must be demonstrated by producing 5 consecutive lots of each strain in regular production facilities, or a total of 15 separate lots. They further require that, in addition to complete laboratory testing, their antigenic potency must be demonstrated by administration to a "statistically adequate" number of susceptible people.

At the best, it will have taken several months to produce these 15 separate lots. After production is completed the laboratory tests which are specified take approximately another 3 months. As the laboratory tests are completed, each of the 15 lots will be available for clinical testing.

For the clinical evaluations of antigenicity, blood and stool stamples must be taken before the vaccine is administered. After administration, a period of 30 to 45 days must elapse before the second blood is taken for testing to determine whether or not the required number of susceptibles have developed specific antibodies. This process will have to be repeated 15 times and will inevitably take several months at least.

In the event of a break in the five consecutive lots of the initial production or if any of the lots of any type fail to produce the required immunogenic response, then all of the tests will have to be reported on another series of five consecutive lots.

As you may know, the Health Department of Monroe County, under the auspices of the State Health Department, New York, is just completing the feeding of the three strains supplied by Dr. Sabin to more than 100,000 people in Rochester and surrounding areas. Types I and III were fed last June and feeding of type II has just been completed. We made a grant and assisted with arrangements to have several hundred "pre" and "post" blood taken and tested in an independent laboratory. This should provide a sufficiently large sample on which to base an opinion as to the antigenic response which can be expected.

Your third question involves the factors which should be clarified or resolved in order to expedite production of the vaccine.

The most important would be for the Division of Biologic Standards to firm up and public officially the additional standards for a live poliovirus vaccine in the Federal Register. This means prompt finalization of the additional standards (42 CFR pt. 73), in as realistic a light as possible.

You mentioned in your letter that Dr. Hiatt, of the U.S. Public Health Service, developed a method for differential inactivation of certain simian agents

which might be one way to meet the present requirement regarding such contaminants. Recognizing that the presence of vacuolating agent involves a severe production problem, discussions were held with the Division of Biologic Standards on the feasibility of using this method to inactivate any such virus present in each production batch as a routine step in the process.

The matter was left that any help the NIH could provide in resolving this question would be of greatest aid to potential manufacturers. This is a matter of great importance in expediting production, as lack of a method for inactivating such virus will involve the rejection of many lots of vaccine.

Your fourth question asks for our suggestions on what the Public Health Service can do to facilitate having this product at the earliest possible date. Its most important service, of course, would be the immediate clarification of the questions set forth above.

These are our principal recommendations. As requested, we will submit officially to you in writing data, views and arguments on the additional standards; poliovirus vaccine, live, oral, within the effective 30-day period after day of appearance of these standards in the Federal Register. In spite of this, I felt it important at this early date to stress the above issues in view of the importance of the overall subject, as a means of answering the questions raised in your letter.

Very truly yours,

L. C. DUNCAN, *General Manager.*

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ATTACHMENT B

PRODUCTION OF ORAL POLIO VACCINE

The production requirements established for the manufacture of an oral polio vaccine are unprecedented in the history of medicine. Many of these requirements involve scientific problems which have never before been encountered, let alone solved.

The solution of these complex problems, plus the absence of any final or official production regulations from the Government, have been major factors in the delay in making the Sabin vaccine available to the Nation.

Lederle Laboratories has invested 14 years of research and nearly $13 million in the oral vaccine field. Despite this experience and although we have marshaled all our resources behind the project, it has taken more time to solve all the problems attendant to the vaccine's manufacture and testing than we had anticipated. For those reasons the vaccine will not be available for the 1961 polio season.

MONKEY VIRUSES

The prime problem to date has been the detection and elimination of several monkey viruses from the vaccine. Since the tentative regulations read that no extraneous agents may be present in the final product, such contaminating viruses as the vacuolating and foamy agents must be proved absent from the monkey's kidney tissue or it may not be used. Research by the NIH which has shown that some 70 percent of all Macaca rhesus monkeys are contaminated with the vacuolating agent, helps place the problem in proper perspective. In addition Lederle has to date found that only 25 percent of the monkeys procured and housed under the best conditions did not harbor foamy virus.

The vaccine's manufacturing process as outlined by the NIH regulations, requires a minimum of 160 days for the completion of each batch. Approximately three-fourths of this time is devoted to testing procedures. Fortunately, many of the time-consuming, but necessary, tests can be run concurrently which helps accelerate the production cycle.

In order to obtain a license for the general manufacture and distribution of an oral vaccine, Lederle and other prospective manufacturers must submit 15 consecutive monovalent batches, 5 for each type of polio, to the Government for evaluation. It is impossible to estimate how long Government clearance will take.

In addition, Lederle must conduct tightly controlled clinical studies among susceptible individuals with each of the 15 consecutive batches of vaccine to determine its immunizing power as well as to help establish the dosage. These

dosage data are extremely important since published experimental information on the Sabin strains provide conflicting evidence of immunizing levels. Such testing will require at least 2 months for each batch. Results of these studies must also be sent to Washington as part of the license application.

### PREPARATION OF STANDARDS

The preparation of these standards represents somewhat of a departure from the methods successfully utilized for many years prior to the advent of the Salk vaccine. Formerly, regulations for producing a vaccine were worked out between the Government and the technical production people of the prospective manufacturer on a step-by-step basis. This had the value of balancing theoretical requirements with the practical techniques necessary to bring about and adequately control large-scale production. Thus, mutually satisfactory conditions, designed to get the vaccine to the public as soon as practical, could be evolved.

The present oral polio production standards represent the views of outside experts who have had little or no contact with the problems of mass producing vaccines, as well as Government officials. Such a procedure must prove wasteful in terms of the scale-up process necessary for mass production.

### PRODUCTION PROBLEMS

To help explain the complexity of the situation, the following is a brief account of Lederle's efforts to overcome some of the production problems.

Lederle received the seed virus from Dr. Sabin on September 1, 1960. But before any experimental production could be initiated, Lederle had to grow additional virus for its seed bank. This task was complicated by the fact that the Sabin seed strains were already contaminated with vacuolating agent, whose presence is expressly prohibited by the NIH regulations.

To obtain its own pure seed virus, Lederle was forced to neutralize the vacuolating agent found in the original Sabin seed. This was done by using a vacuolating agent antiserum produced in rabbits. Lederle received the antiserum from Dr. M. Hilleman who had isolated the virus. Therefore, it was not until late November 1960 that experimental production of even one Sabin strain could get underway.

### MORE ABOUT MONKEYS

The most important source of these contaminating viruses, however, is the rhesus monkeys themselves which are used in production. It was Dr. Caspar Hiatt, of the National Institutes of Health, who determined that 70 percent of the monkeys examined in his laboratory were infected with vacuolating agent. This means that under present circumstances they couldn't be used in production. Further, Dr. Hiatt reports that 100 percent of all the tissue culture pools (i.e., tissue from several animals) that he has evaluated were contaminated.

The proposed Government regulations specifically call for Maccaca monkeys, "or a species found to be equally acceptable" to the Government, to be used in vaccine production. It is quite possible that other species of monkeys might not be infected with these two contaminating viruses. However, another variety of monkey could conceivably harbor some other viruses not encountered in the rhesus.

In any event U.S. companies looking toward production of the new vaccine in the United States of America have had no choice but to work with the type of monkey specified. The time and effort which would possibly be required to obtain and test hundreds of monkeys of the many other types and proving their acceptability to the NIH could be indfinitely more time-consuming than our present efforts to solve the problems posed by the proposed regulations.

The vacuolating agent and foamy virus are not harmful to the monkey. And the probable presence of these agents in much of the oral vaccine fed to some 80 million persons throughout the world in the past few years has apparently not caused any adverse effect in humans. However, in the absence of scientific proof that these simian viruses are not harmful to man, the NIH has ruled out their presence in any vaccine produced for commercial use.

Some scientists have indicated that if these standards for a live virus vaccine had been in existence previously, such vaccines as smallpox and yellow fever, which have been successfully administered to millions of people would probably not have been approved. Under present regulations for their manufacture, extraneous agents are not excluded.

### MISSION TO INDIA

As a possible solution to this monkey problem, Lederle dispatched one of its veterinarians, Dr. James Vickers, to India's Uttar Pradesh Province for 8 weeks. His assignment was to go into the jungle and capture rhesus monkeys, place them in individual cages, and rush them back to Pearl River by air. In this way, Lederle hoped to avoid any cross-contamination which could take place in the previously used gang cages which held as many as 25 monkeys each. The individual handling technique doubles the cost of each monkey, the company estimates.

Dr. Vickers shipped home about 200 monkeys in this fashion. While the initial results of this venture have been somewhat encouraging, it does not appear to be the final solution. For these animals are probably the most complex raw material production people have ever encountered.

Lederle researchers have also been trying to devise laboratory procedures which would detect the viruses in the monkeys before production gets underway. This work is being done under the direction of Dr. Victor Cabasso. Such a technique would permit scientists to cull out any animals proved to harbor the viruses and would literally save weeks of effort. At present it is not until after a 6-week quarantine period, sacrifice of the monkey, and the preparation of kidney tissue cultpre plates that available tests can detect the virus.

This has meant that Lederle is now intimately involved in monkey medicine, an area which researchers have only begun to explore. A concerted effort is now underway at Lederle to study the life cycle of these agents in an attempt to learn the most effective method of controlling them. Resolution of this problem might be an important step in producing the vaccine.

### SELECTIVE INACTIVATION

Several investigators have suggested the possibility of selective inactivation of unwanted or contaminating viruses which may be present in the harvested vaccine. Among the methods proposed is the treatment of the vaccine with a blue dye coupled with exposure to high intensity light. Dr. Hiatt has achieved some success with this procedure. Other suggestions include the use of bile salts and a chloroform-ether mixture to kill the extraneous agents.

Lederle scientists, leaving no possibility unexplored, have had a SIPU unit (selective inactivation photodynamic unit) constructed and installed.

### PRODUCTION FACILITIES

In anticipating the production of the oral vaccine, Lederle has, over the past 2 years, constructed two new buildings and completely revamped three others at a cost of nearly $3 million. The two new buildings are an air-conditioned monkey house and a quality control facility. The buildings which were redesigned include a tissue culture preparation area, the actual vaccine production unit, and a $500,000 sterile filling area.

The monkey house which cost $650,000 was constructed after long consultation with Government officials. A subsequent change in regulations has necessitated the installation of 50,000 dollars' worth of new cages.

Lederle has also made certain that all personnel and equipment involved in polio production do not come in contact with other manufacturing areas. All production personnel are immunized against smallpox and tetanus as well as with the Sabin vaccine. No street clothes may be worn in production areas.

### START OF PRODUCTION

The production of the oral vaccine begins in the monkey house. Once the animals arrive at Pearl River, each is given a complete medical examination and a test for tuberculosis. Each production monkey is housed in an individual steel enclosed cage for at least 6 weeks. If more than 5 percent of the animals in any

one group of cages die due to an infection during that period, the entire 6-week quarantine is started over again among the survivors.

At the conclusion of the quarantine period, the monkeys are again carefully examined by a qualified veterinarian for any signs of ill health. The regulations state that if there are any such signs, the animals cannot be used for production.

Under aseptic operating room conditions, the healthy monkeys are anesthetized and sacrificed to obtain their kidneys. The kidneys are then minced, chemically treated to disperse individual cells, and centrifuged. The next step is to place approximately 30 million living kidney cells in a Povitsky bottle containing 300 milliliters of a nutrient medium contaning vitamins, amino acids, and salts.

After the bottles are incubated for 8 days at 37° C. to promote cell growth, each bottle is examined microscopically for any possible deterioration in the cell layer. If such is noted, the bottle is discarded.

An additional precaution calls for 25 percent of the tissue culture bottles to be set aside as controls, and to be microscopically examined for another 2 weeks. Also, the nutrient fluid in these bottles is tested at various intervals during the 2-week period to detect extraneous viruses.

### TISSUE CULTURE TESTS

After the 8-day incubation period, the fluid from the rest of the culture bottles is drained and tested in four separate tissue culture systems for the absence of microbial agents. Each sample is tested in tissue cultures prepared from rhesus and "green" monkey kidney cells, rabbit kidney cells, and human cells. These cultures are also observed for 14 days. It is only at this point that the presence of vacuolating agent or foamy virus can now be detected. The finding of any extraneous agent rules out the use of the cultures in vaccine production.

Those bottles which pass the microscopic inspection on the eighth day are inoculated with the seed virus. The seed virus itself, according to the regulations, must be tested periodically by injection in 25 monkeys to assure that its neurovirulence has not changed.

The seeded cultures are then placed in an incubator at temperatures no higher than 35° C. for 4 days. During that time the attenuated polioviruses invade the monkey kidney cells and multiply. This forms the crude vaccine. At least 1,000 cubic centimeters of this undiluted material is then quick frozen and held for tests.

### ANIMAL TESTS

From this point on, the safety of the vaccine is evaluated in laboratory animals. The first test is to determine the absence of Simian B and other viral agents. A minimum of 100 milliliters of each monovalent vaccine lot is injected into at least 10 healthy rabbits which are then observed for 3 weeks. Only if at least 80 percent of the rabbits survive the test and only if an autopsy of the survivors fails to reveal nerve damage at the site of inoculation or the presence of any viral infection, may the vaccine be used.

A similar test to demonstrate the absence of lymphocytic choriomeningitis is conducted in at least 20 adult mice who are also observed for 3 weeks. Tissue from any mouse that expires after the first 24 hours of inoculation is then injected into five more mice which are observed for another 21 days.

Another 20 mice, each of which is less than 24 hours old, must be inoculated to demonstrate the absence of Coxsackie virus. Each animal is observed daily for 2 weeks. Once again, any animal that dies after the first 24 hours is autopsied and a suspension of its tissue inoculated into five more mice which are observed daily for 14 days. The regulations read that 80 percent of the original suckling mice must survive and also call for an additional 14-day test to be carried out with their emulsified tissue.

### TB TEST

A 42-day test is also conducted among at least five guinea pigs to eliminate the possibility of tuberculosis contamination and the presence of lymphocytic choriomeningitis virus. This test also requires that rectal temperatures be taken daily for 3 weeks on each guinea pig. The issue of any animal that dies after the first 24 hours is examined microscopically and in tissue culture for evidence of the TB bacillus and is then injected into at least three other guinea pigs. The 80-percent survival rule also holds for these animals or the vaccine lot must be thrown out.

The next step is to take at least 500 human doses of undiluted vaccine and neutralize the polio virus by means of antiserum. The resulting material is then tested in rhesus and "green" monkey kidney tissue cultures to once again preclude the presence of simian viruses. Human cell cultures are also used at this point to make sure no measles virus is in the vaccine. If it is, the vaccine is not usable.

Similarly, if a test with another 500 cubic centimeters of vaccine in rabbit kidney tissue culture detects the presence of B virus, the vaccine cannot be used. If the vaccine passes all these tests, it is considered a candidate for filtration as a final monovalent pool.

MONKEY NEUROVIRULENCE

After filtration a highly critical test involving the intracerebral and intraspinal inoculation of monkeys, which have demonstrated a lack of polio antibodies, is carried out to establish whether there is any nerve damage. The intracerebral test calls for 20 monkeys to be inoculated with the test vaccine. Another 25 monkeys are also inoculated intraspinally with various dilutions of each batch of the vaccine. The regulations indicate that from time to time the NIH reference strains should be similarly injected into monkeys as a control factor.

DISTRIBUTION COMPLICATIONS

The proposed regulations currently indicate that if the vaccine is issued in a frozen state, it must be used within a year of issuance. On the other hand, if the vaccine is issued as a liquid and kept at a temperature of no higher than 10° C., then the regulations state that the vaccine can be used for only 7 days after the date of issuance. This establishes additional problems from the standpoint of large-scale distribution and administration.

These regulations have been in the formulation stage for over a year. Initially they were described as "idealized" and open to scientific negotiation. If anything, the regulations now appear more formidable than the tentative standards issued in 1959.

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[Letters from Merck & Co., Rahway, N.J., supplied at request of subcommittee]

NOVEMBER 25, 1959.

Dr. LEROY E. BURNEY,
*Surgeon General,*
*Department of Health, Education, and Welfare,*
*Washington, D.C.*

DEAR DR. BURNEY: I want to thank you for the opportunity I had recently in Bethesda to discuss briefly with you our research programs in virology, and particularly how these programs have influenced our decision to discontinue our work on oral polio vaccine. As we discussed, I had hoped to be able to discuss this subject with you further in Washington. Since I understand, however, that you'll be out of the country until the end of December I thought I'd send this letter along so that your associates may be aware of our plans. We'll be glad to discuss the situation with you or your Public Health Service or NIH associates at any time you or they designate.

As you know, we have assisted Dr. Albert Sabin of the University of Cincinnati in his studies by producing quantities of Sabin oral poilo vaccine. This material has been used in some of the field studies in the United States and other countries, and is also serving as seed for further production here and abroad. We have given financial support to studies in Mexico arranged by Dr. Sabin. Our collaboration with him stemmed from our desire to further the oral vaccine program and to be in a position to produce the material if studies indicated that it would be useful. We have kept in close touch with his programs, and until recently it has been our intention to develop the Sabin vaccine and to be ready to produce it for sale.

However, a recent review of our efforts in virology shows that our research and development programs in new fields, which are progressing well, would need to be delayed or stopped if we now proceed with a full-scale effort to undertake the development of the Sabin vaccine. Among the important and promising programs that would be so affected are a purified Salk vaccine, a measles vaccine, and a vaccine designed for the respiratory diseases.

I am sure you know that we have developed a relatively simple method for isolating the viruses which make up the Salk vaccine and during the past 3 years have spent considerable effort in developing a purified vaccine using these isolation procedures. This means that for the first time we shall be able to control with certainty the quantity of each antigen in the finished product, and that we can regulate the quantity of each antigen to assure a much higher conversion rate than is obtainable with the present vaccine. Our clinical data indicate that more than 90 percent of our subjects have high antibodies after two inoculations with this new product. A vaccine with such performance may find use in epidemic areas since the two injections are given a month apart. Although the development of the purified Salk vaccine has been difficult and time consuming, we now believe we shall have a product ready for distribution during the spring of 1960.

Our measles vaccine program has also been making good progress. We have developed a killed measles vaccine which produces antibodies in human subjects and which shows promise in preventing the disease. Endeavors are underway to increase the antigen content, since the antibody response is not as high as we would like. We are also developing the Enders live vaccine, since we feel that the ideal treatment would consist of inoculation with the killed vaccine followed at a later time by a live vaccine. From the public health viewpoint, the control of measles is, of course, most important.

We have an intensive program in the field of respiratory viruses. It is based upon an extensive epidemiological study, in collaboration with a number of hospitals and institutes, of the viruses responsible for most of the respiratory diseases. It is our intention to isolate the new causative agents and to determine which adenoviruses and HA viruses play major roles in the respiratory infections. We believe that such data are essential if one is to develop a safe and effective respiratory disease vaccine.

I think you will agree with us that the above three programs are highly important and deserve all the effort we can muster to bring them to successful conclusions. Each would be a major contribution to public health.

We have gained the impression that Pfizer, Pitman-Moore, and Wyeth are proceeding with development of live polio vaccine, although for many good reasons we have not discussed the matter directly with these firms. We are, of course, also aware of the published reports that Lederle has applied to the NIH for license for its Cox vaccine, which is also an oral live polio vaccine. It is our understanding that the needs of the country would easily be filled by the production programs of even a couple of these four potential producers because a little of the oral vaccine goes such a long way. Furthermore, the extensive Russian production plans, as well as production in England, Canada, and other countries, presumably will be able to handle a good part, if not all, of the foreign country requirements.

If our present assumptions do not materialize, and experience shows that current and expected efforts to develop and produce oral vaccine are inadequate, we would want to reexamine our decision. Since we are not able, under the antitrust laws, to check our assumptions regarding the plans of the above competitive companies directly with them, I would greatly appreciate having the benefit of any advice or suggestions you may care to give us on this matter.

If we adhere to our decision on the Sabin vaccine, we would nevertheless watch the developments of the next few months very carefully and be prepared to reenter the Sabin vaccine development at any time it seems to us essential to assure adequate supplies.

Sincerely yours,

JOHN T. CONNOR.

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DECEMBER 16, 1960.

LEROY BURNEY, M.D.,
*Surgeon General,*
*U.S. Public Health Service,*
*Department of Health, Education, and Welfare,*
*Washington, D.C.*

DEAR DR. BURNEY: This is in response to your recent letter addressed to Dr. Knoppers, inquiring as to our present plans for production of live polio vaccine. As we wrote to you at the time, we discontinued our research program on live polio vaccine in November 1959, to concentrate our research efforts else-

where in the field of virology, and particularly in the development of a more effective vaccine of the killed virus type. It is our belief that this decision has proved to be in the public interest since we were able to develop and make available to the medical profession last July a new, highly purified killed virus vaccine.

We have, however, once again reviewed our decision in the light of your letter and of the standards for live poliovirus vaccine published in the Federal Register. Our scientific staff have emphasized to us that there are a number of serious scientific and technical problems which must be solved before we could engage in large-scale production of live polio-virus vaccine. Most important among these is the problem of extraneous contaminating simian viruses which may be extremely difficult to eliminate and which may be difficult if not impossible to detect at the present stage of the technology. Additionally, our scientific staff called to our attention that there is still controversy within the scientific community regarding safety and efficacy of the Sabin vaccine. Important in this connection are the appraisal of significance of viremia in man following feeding of type II virus, the high rate of reversion to monkey neurovirulence of type III virus following passage in the human gut, and the safety for the nonimmune human adult who comes in contact with fed individuals. There is also the nagging problem of reliability and acceptance of the Soviet surveillance data together with the lack, to the present, of a large-scale trial of the Sabin vaccine in the United States.

We feel that many or all of these problems would have to be clearly resolved in the scientific community before we could market a vaccine with our usual assurance of safety. These scientific problems also raise serious questions as to whether the product liability risks which will accompany the marketing of live virus polio vaccine are ones which can reasonably be borne by a private company.

In view of the magnitude of the effort that would be required we have again concluded that undertaking a research and production program on live virus vaccine would seriously interfere with our existing effort in the field of virology, which, in addition to our polio vaccine program, contains the other important projects we described in our letter to you of November 25, 1959. We, therefore, believe that we can best serve the public health by continuing our current research program and concentrating our efforts in the further improvement of killed poliovirus vaccine and in the development of live and killed vaccines against other diseases. We do not plan to manufacture a live poliovirus vaccine.

We are, of course, ready at any time to discuss with you any work by us that you feel to be necessary in the interest of public health.

Sincerely yours,

JOHN T. CONNOR.

(Whereupon, at 4 p.m., the hearing was closed.)

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# APPENDIXES

(The Public Health Service later submitted the following documents which are printed as appendixes for the information of the committee.)

## Appendix A

### Live Attenuated Poliomyelitis Vaccine

(Statement by Leroy E. Burney, M.D., Surgeon General, Public Health Service)

For many years, the possible use of a live attenuated poliomyelitis vaccine, that is, a virus which has been grown in animals or eggs until it has lost its disease-producing potential without losing its immunizing ability, has been discussed. For more than 7 years, the problem has been under serious investigation.

The Salk vaccine, now in use and giving good results in protecting against paralytic poliomyelitis, is made from killed virus.

The main advantages visualized for a vaccine made from live attenuated virus are: (*a*) longer lasting immunity—although the Salk vaccine is believed to provide protection for some time, the actual duration of immunity is not yet known because it has been in use for such a short time; (*b*) ease of administration, with the live virus given orally instead of by injection; and (*c*) presumably lower costs of production.

At the present time three sets of strains are under investigation. These are most readily identified by the names of their developers, the Sabin, Lederle, and Koprowski strains, named respectively for Dr. Albert Sabin of the University of Cincinnati, Lederle Laboratories, and Dr. Hilary Koprowski of Wistar Institute of Philadelphia. The name of Dr. Herald Cox, of the Lederle Laboratories, is also associated with the Lederle strains.

Each set consists of three type strains. These sets of strains have now been administered to large numbers of persons in an attempt to determine: (*a*) their ability to produce adequate and durable levels of antibody, and (*b*) their safety in general use.

No untoward results have been reported in relation to these studies. Stated in this way, the facts appear impressive. It must be remembered, however, that the data these studies were designed to collect have not yet been fully assembled, analyzed, or made public.

The Public Health Service is following these developments closely. Our Division of Biologics Standards of the National Institutes of Health, for example, is conducting laboratory investigations aimed at characterizing the type strains. These investigations are of importance because the Service may be asked some day to license the products.

I also have appointed an ad hoc committee composed of outstanding experts in this field to keep me advised of developments with respect to live attenuated poliomyelitis vaccines. This committee consists of Dr. Roderick Murray, Chairman, director of the Division of Biologics Standards, National Institutes of Health; Dr. David Bodian, Johns Hopkins University; Dr. William McD. Hammon, University of Pittsburgh School of Public Health; Dr. Alexander Langmuir, Public Health Service, Communicable Disease Center, Atlanta, Ga.; Dr. Joseph Melnick, Baylor University, and Dr. John R. Paul, Yale University Medical School.

This committee has met twice and considered all information now available on these vaccines. The committee finds a number of important issues remain to be answered or resolved before the live attenuated poliomyelitis vaccines can be considered other than in the experimental stage.

These issues cover such points as: apparent differences in the ability of the different strains to invade the nervous systems of experimental animals; trans-

mission of virus from vaccinated persons to others; feasibility of feeding the three type strains simultaneously; effect of viruses in the intestinal tract, other than polioviruses, on the development of immunity to poliomyelitis; validity of surveillance of populations inoculated to date.

The committee has felt some concern because some of the trials of live attenuated poliomyelitis vaccine have not followed the recommendations of the World Health Organization Expert Committee on Poliomyelitis. It also has been concerned by apparent differences in the virulence for the nervous system of some of the virus strains being used. This aspect of the problem needs further study.

The experience thus far indicates that encouragement should be given to carefully conducted, small-scale studies designed in such a way that the laboratory and epidemiological surveillance could produce results upon which a judgment could be made.

Large-scale trials of live attenuated poliomyelitis vaccine in the United States are considered unproductive because so large a proportion of the population already has been immunized with killed vaccine.

The decision to permit such trials in other nations is, of course, one for their health and medical authorities. However, because the experimental vaccines are made in the United States and because our ad hoc committee has been studying reports on them, I feel that such information as we have should be made public so that not only our people but the peoples of other nations can have all current available information as exists on which to form their opinions and base their decisions.

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## Appendix B

### First Report of the Public Health Service Ad Hoc Committee on Live Poliovirus Vaccine

The Ad Hoc Committee on Live Poliovirus Vaccine was organized by the Surgeon General of the U.S. Public Health Service on June 30, 1958. The Public Health Service was concerned with the creation and maintenance of a group of experts who would remain abreast of developments in the field of live attenuated poliovirus vaccines. The ultimate objective of the group is to assist in the selection of strains of virus for inclusion in a live attenuated poliomyelitis vaccine which might be licensed and used in the United States, if and when scientific experience indicates that such materials are safe and effective in man and readily susceptible to adequate biological control in the laboratory. In part, the initial task of the ad hoc committee was to assist the Public Helath Service in answering inquiries of the Conference of State and Territorial Health Officers regarding criteria for undertaking controlled studies with attenuated poliovirus vaccines within their own administrative areas. This report summarizes the opinions of the ad hoc committee concerning the present status of attenuated poliovirus vaccines, based upon a review of the available information as of May 1959.

In its considerations of this matter the committee has been cognizant of previous recommendations dealing with live poliovirus vaccination which appeared in the second report of the WHO's Expert Committee on Poliomyelitis—a report drafted in July 1957.[1] These 1957 WHO recommendations called for trials in man on a larger scale than had hitherto been attempted, with emphasis on the desirability of having such trials carried out in the near future within certain specified population groups and areas, under the most careful supervision of individuals who have adequate laboratory facilities and who are experienced in investigations involving polioviruses. The WHO report further specified that the poliovirus strains used should fulfill specific criteria for safety and effectiveness.

During the past 2 years, a number of large-scale trials involving the use of several strains of live, attenuated poliovirus have been carried out or are in progress—most of them outside the United States. In the light of new information available to the commitee, strains of attenuated poliovirus have been used in some of these trials which have shown degrees of virulence in monkeys exceeding the threshold implied in the recommendations of the WHO report.

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[1] Expert Committee on Poliomyelitis, second report, World Health Organization Technical Report Series, No. 145, Geneva, 1958.
See excerpts of this WHO report in appendix.

The ad hoc committee has noted that no strains of poliovirus are known which have failed to produce paralysis by the intraspinal route in monkeys when inoculated at a dose necessary consistently to infect human beings by the oral route, and that the degree of genetic stability of attenuated poliovirus on passage in human populations remains to be established.

Examination by committee members of sections of spinal cord of monkeys inoculated with strains being used in field trials clearly indicated to the committee that in the case of many of these strains intraspinally inoculated virus is capable of producing poliomyelitis lesions morphologically as severe as are found after inoculation with virulent strains, with spread to cervical spinal cord and brain stem.

Some of the small-scale trials have been backed up by careful surveillance and many completed laboratory tests, and thus have already yielded important information essential to an understanding of the potentialities of this proposed method of immunizing against poliomyelitis. It is a matter of concern that the degree of surveillance and concurrent laboratory support of some trials has not been made public.

The committee understands that the various live virus vaccination programs which have been carried out recently are part of an effort to find better and cheaper ways to immunize against poliomyelitis, particularly as it has been claimed in some part of the world that the local use of the inactivated poliomyelitis vaccine, as now administered, is impractical. The committee is also aware of the difficulties to be overcome by any group which wishes to meet all the criteria proposed, and of the fact that delays until adequate laboratory tests are completed are proverbial. However, the fact must be faced that practice has run ahead of scientific evidence and that the experimental, attenuated poliovirus vaccines are being used in public health programs for "control" of disease rather than for field studies of experimental vaccines.

One of the major problems that must be resolved before licensing of live poliovirus vaccines for sale and general use can be considered is the establishment of adequate laboratory controls for safety and potency. At the present time various laboratories are reporting divergent findings regarding the neurovirulence of some of the candidate strains following intracerebral and intraspinal inoculation of monkeys. The relationship of such laboratory findings to potential pathogenicity for human beings after oral administration is not clear but must be resolved before live poliovirus vaccines can be accepted as safe and standardized public health procedures or licensing of particular strains can be recommended.

The committee wishes to express its concern on the following points:

(1) Strains of poliovirus have been used in some of these trials which fail to meet the criteria of attenuation accepted by the WHO Expert Committee.

(2) Epidemiologic investigation of cases of poliomyelitis and of conditions resembling poliomyelitis which may occur in the vaccines and the local population does not appear to have been adequate in some studies.

(3) Reports on the degree to which laboratory tests have been completed on the specimens from vaccinees and their contacts are either lagging in publication or the information is unknown.

Thus there has been extension of studies to new groups and populations in the absence of published evidence of the safety factors involved and of the relative infection and immunization rates among each population group to which the vaccine was previously administered.

(4) In relatively few instances has the virulence of samples of human-passage, attenuated poliovirus strains, recovered from vaccinees and their contacts been measured and compared with that of the strains fed.

In fact, information on this point is sparse and reports of such increases in virulence on these so-called human-passage strains have not been satisfactorily or adequately explained.

## RECOMMENDATIONS

The committee agrees with the intent of the WHO recommendations mentioned above as regards the use of attenuated polioviruses in carefully evaluated field studies, and believes that if this intent is to be carried out emphasis should be placed on the following points:

(1) The committee urges the continuation of relatively small, carefully supervised investigations on the capacity of these strains to produce antibody in man, either as primary immunizing agents or as a supplement to the inactivated polio-

myelitis vaccine. Knowledge in this field has not yet progressed to such a state that large uncontrolled programs appear justified; therefore the committee urges that for the time being these trials be limited to number of vaccines small enough to make careful clinical surveillance and laboratory studies feasible so that, when completed, an analysis of results can serve as a basis for future action. Such types of surveillance should include (*a*) a prevaccinal antibody level survey of a representative sample of the population to be vaccinated; (*b*) a similar survey for the prevalence of enterovirus infections currently existent in the population; (*c*) adequate sampling measurements of the degree to which the vaccinated and unvaccinated population actually becomes infected with orally administered, attenuated polioviruses; (*d*) sampling measurements of antibody responses to the administered agents; (*e*) measurements of the CNS virulence in monkeys of the strains recovered from a sample of the vaccinees, as well as from some of their immediate contacts; and (*f*) careful clinical and laboratory diagnostic studies performed currently on all cases of poliomyelitis, suspected poliomyelitis, and other acute neurological diseases which may arise within the general population under study. It appears that the latter could be accomplished only with difficulty in any large area where a previously established and well-operated disease-reporting system did not exist.

(2) Until further information is available, no poliomyelitis strain should be regarded as adequate for such trials unless it has been shown by one or more independent laboratories that its virulence for the monkey does not exceed that of other known strains which are considered to have the lowest levels of virulence and yet are capable of producing inapparent alimentary infections in serologically susceptible persons. Other things being equal, the strains of poliovirus of choice are obviously those which are regarded as having the lowest virulence.

(3) Tests for virulence on the attenuated poliovirus strains which are to be used for oral administration and tests on strains recovered from the vaccinees and their contacts should be carried out by standard methods to be agreed upon. The fact that serious disagreement exists among competent investigators who have tested the same strains indicates that users and recipients of a particular experimental vaccine may be assuming unwittingly a greater than anticipated risk. The committee is unanimous in urging that tests for neurovirulence in monkeys should be carried out by the most sensitive quantitative procedures known, in order to be able to discriminate between strains of low virulence.

(4) Since one of the methods of estimating the infectivity and virulence of attenuated poliovirus strains is based on epidemiologic observations made in the field, it is strongly recommended that there be adequate and accurate documentation and study of events which take place in the field when a given strain is used in a vaccination trial. It is also recommended that criteria for such observations of field trials be agreed upon in advance of the trial, particularly as regards the type of epidemiologic surveillance of the population. It is further recommended that the laboratory which is to test specimens collected in the course of the trial be so organized that it will be able to produce the desired information in a relatively short period of time. This applies especially to studies on any cases of paralytic poliomyelitis or poliomyelitis-like disease which might arise within the vaccinated population and its vicinity; such cases should be thoroughly investigated at once with recording of pertinent clinical, laboratory, and epidemiologic data, including identification of viral agents isolated and comparisons with the strains used for oral immunization.

Respectfully submitted by the Ad Hoc Committee on Live Poliovirus Vaccine.

DAVID BODIAN.
W. MCD. HAMMON.
ALEXANDER D. LANGMUIR.
JOSEPH L. MELNICK.
RODERICK MURRAY, *Chairman*.
JOHN R. PAUL.

JUNE 1, 1959.

[From World Health Organization Technical Report Series, No. 145]

EXPERT COMMITTEE ON POLIOMYELITIS—SECOND REPORT

(Pp. 26 and 28, 1958)

Criteria which should be fulfilled in the design of carefully controlled field trials which the committee has in mind are as follows:

(1) Such trials should be under the supervision of an individual who is experienced in investigations involving polioviruses, who has adequate laboratory facilities, to whom the assistance and facilities of consulting virologists may be available, and who can devote an appreciable amount of time and direction to the project.

(2) The strains which are recommended for use in these trials should be selected with great care; this should be a most important part of the program. At the present, those strains should be used which have been purified by the plaque method and which have already been fed to various small groups of adults and children and whose behavior under these circumstances is well documented and appears to be satisfactory. A more detailed list of criteria is as follows:

(*a*) Progeny of triply purified plaques.

(*b*) Complete lack of paralytogenic activity on intracerebral inoculation of maximal doses (in excess of $10^7$ $TCD_{50}$) in rheus or cynomologus monkeys and only minimal residual neurotropism by spinal inoculation in monkeys—of maximal doses (in excess of $10^7$ $TCD_{50}$) in rheus or cynomologus monkeys receiving doses of $10^6$ $TCD_{50}$ or more, and no "zone phenomenon" in which monkeys inoculated with smaller doses of virus develop paralysis more frequently than those inoculated with larger doses.

(*c*) Adequate and regular multiplication in the alimentary tract of nonimmune human beings should have been demonstrated with doses in the range of $10^5$ $TCD_{50}$ or less and these infections should be accompanied by antibody response. Viraemia should be either absent or rare and if virus is present it should be in minimal concentration.

(*d*) The strains used should have been tested extensively for any increase in the neurotropism of the virus excreted in the stools of human beings after varying periods of multiplication in the alimentary tract. The virus excreted in the stools and that derived from it in the first tissue culture passage should still exhibit distinct evidence of attenuation as determined by intracerebral inoculation of monkeys.

(*e*) The lots of virus to be used should be large enough to permit test feedings of at least 1 million individuals and these lots should have been produced under conditions comparable to those that might ultimately be used in the manufacture of still larger quantities. Each lot should not only fulfill the requirements for neurotropic activity mentioned above (tested in at least 25 monkeys) but should also have been shown to be free of other viruses and bacteria as indicated by tests in tissue cultures, animals, and bacterial culture media.

(*f*) Absence of harmful reactions in small groups of human beings should be demonstrated before a lot is used in increasingly larger numbers.

(3) It is suggested that the properties of these attenuated strains, which can be tested in the laboratory, be measured in a number of different laboratories so that there can be more than one opinion as to their pathogenicity or the lack of it.

(4) It is recommended that in all such trials the administration of the agents be done on a voluntary basis. It is also essential that such trials have the approval of local health authorities.

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## Appendix C

### Second Report of the Public Health Service Committee on Live Poliovirus Vaccine

At its fourth and fifth meetings held in New York City on July 8 and in Bethesda on August 6 and 7, 1959, the committee reviewed the data on the rapid progress in the development and field testing of live poliovirus vaccines which had become available since the preparation of the first report. Particular attention was directed to the extensive new data reported at the Pan American Health Organization sponsored conference in Washington, June 22–26.

The committee has continued to be concerned with the potentialities of live poliovirus vaccines with particular attention to their safety and effectiveness.

In view of these recent developments, early requests for licensing of live poliovirus vaccines can be anticipated. Therefore, immediate steps should be

taken to prepare for such an eventuality. It is obvious, however, that many complex technical problems will require solution before detailed licensing requirements can be specified.

In this, the second report of the committee, the status of the problems of strain selection and licensing as visualized by the committee is summarized briefly and some of the major questions are discussed in broad outline. Somewhat idealized provisional specifications are presented here as a desirable first step toward defining the essential issues in the manufacture of live poliovirus vaccine. It is realized that some of these specifications may not be attainable in practice, but the committee believes that a statement of an ideal goal makes a good starting point in the effort to establish final licensing requirements. Furthermore, such proposals at this time should assist prospective manufacturers in planning for production and testing.

Individual sponsors of the several groups of attenuated poliovirus strains, prospective manufacturers, and others with scientific interest or responsibilities in this field may wish to comment. Such comments, both as to the broad outline and the detailed specifications, are solicited and will be welcomed by the committee.

As was emphasized in the summary report of the recent WHO–PAHO meeting on live poliovirus vaccines,[1] the use of this product represents a radical departure from present practice in human preventive medicine in that the virus spreads beyond those originally vaccinated. In other words, the administration of the vaccine to individuals, or a group of individuals, does not represent a medical procedure confined to those individuals alone, but can potentially create a spread of virus hopefully due to avirulent poliomyelitis virus. In the Soviet Union and elsewhere, an announced plan is to use these vaccines on large groups of people simultaneously, thereby blanketing entire areas with the attenuated strain in question. This presents quite a different situation from that which would pertain were these products now licensed for sale in the United States. With the patient-physician relationship which we have, individual patients would be given vaccine at different times thereby permitting wider spread through the community and possibly entail a greater number of serial passages. Thus, were there any reversion toward virulence, it would be more apt to reveal itself in the United States than in the programs visualized for other countries. Apart from the medical and epidemiological aspects of the administration of such vaccines, we also have the situation of involuntary vaccination due to spread of the virus, which imposes special responsibility in relation to the control of genetic stability of the poliovirus strains used.

### A. SUMMARY OF PRESENT STATUS

(1) Three sets of attenuated poliovirus strains have been proposed for use as oral vaccines. The Sabin strains have had extensive field trials in Eastern Europe, Mexico, and one type in Singapore; the Lederle-Cox strains have been widely used in Latin America; and the Koprowski type I strain has been used in a large trial in the Belgian Congo. However, no significant amount of field information is available concerning the Koprowski type II strain, and only limited information is available in relation to his type III component.

(2) There is considerable difference in the neurovirulence for monkeys among the three sets of strains as determined by intrathalamic and intraspinal inoculation. On this basis, the Sabin group has an advantage over the others, but none of these strains is completely avirulent when inoculated into monkeys by the intraspinal route.

(3) No evidence has been reported to indicate that any of these vaccines produced any harm to those individuals to whom they were administered. The degree of thoroughness with which the observations were made has varied in different studies.

(4) In some studies the ability of these strains to multiply within the human body and thus produce antibodies is less than could be expected on theoretical grounds. Apparently a number of factors operate under field conditions which may prevent alimentary infection and the subsequent development of immunity.

(5) A number of workers have reported that virus excreted by vaccinated

[1] World Health Organization-Pan American Health Organization joint meeting held in Washington, D.C., June 22–26, 1959, under the title "Conference on Live Poliovirus Vaccine."

individuals had shown increased neurovirulence for monkeys. There is considerable disagreement among investigators as to the significance of these reversions in virulence.

(6) Field experience with any strain to date cannot be interpreted as affording reasonable proof that the community of nonvaccinated persons will be free of danger from possible reversion of virulence in excreted virus under a great variety of readily anticipated circumstances. This is one of the most important unresolved problems.

(7) There is evidence which indicates that under some circumstances the simultaneous administration of all three types of virus may be effective.

### B. PROVISIONAL CRITERIA FOR ACCEPTABILITY OF STRAINS

To be considered for licensing, full documentation must be submitted for each strain. This must include history of its origin, laboratory manipulations during development and attenuation, and final characteristics regarding safety, potency, and effectiveness, including the field trial findings on which these are based. Broad outline of these criteria is listed below. More detailed provisional specifications are given in the appendix.

*1. Safety*

(*a*) Tests for neurovirulence:
Minimal neurovirulence for monkeys (app. 1).

(*b*) Viremia in man:
Absence of capacity to produce viremia in man after oral feeding (app. 2).

(*c*) Genetic stability:
Absence of capacity to revert to greater neurovirulence after passage in man. Consistency in maintaining genetic markers (d, MS, t) with repeated human passage (app. 3).

(*d*) Field tests among susceptibles:
Freedom from harmul effects upon administration to an adequate number of "triple negative" individuals under circumstances where adequate epidemiological surveillance of neurological illness has been maintained. (Many would feel that 100,000 is an adequate number.)

*2. Potency and effectiveness:*

(*a*) Antigenicity:[2]
The consistent production of specific antibodies in 90 percent or more of inoculated "triple negative" susceptibles (app. 4).

(*b*) Effectiveness:
It is now generally agreed that the production of specific antibodies is a presumptive indication of immunity. The need is paramount for an adequate carefully designed plan to serve as a direct demonstration of effectiveness in the field in large inoculated populations (app. 5).

### C. PROVISIONAL SPECIFICATIONS APPLICABLE TO MANUFACTURE

(1) Establishment of a seed virus system. The virus in the final product shall represent no more than three tissue culture passages from the seed strain which has met the criteria of acceptability (see B above), or whose immediate progeny have met these criteria.

(2) Proper isolation, housing, and conditioning of monkeys used in vaccine virus production (app. 6).

(3) Only primary monkey kidney tissue cultures to be used (app. 7).

(4) Processing shall be conducted in such a manner as to minimize the possibility of contamination with various infectious agents.

(5) Tissue culture production vessels shall at no time be maintained at a temperature above 36° C. during the course of virus propagation.

(6) Live poliovirus vaccines shall be extensively tested for the absence of adventitious infectious agents including *Mycobacterium tuberculosis*, Pox viruses, Lymphocytic Choriomeningitis Virus, ECHO Viruses, Coxsackie Viruses, B-virus and simian agents (app. 8).

(7) All personnel entering or working in live vaccine production areas shall be rigidly controlled (app. 9).

(8) Live poliovirus vaccine shall be manufactured in separate facilities (app. 10).

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[2] It has been suggested that a term such as "capacity to take" would be more appropriate.

### D. ADDITIONAL REQUIREMENTS FOR LICENSING

A demonstration shall be made of consistency of production for five consecutive lots using production facilities (see C(8) above) in their preparation. The testing of each of these five lots shall include—

(1) Tests for monkey neurovirulence;

(2) Characterization of each lot by means of tissue culture markers; and

(3) Determination of antigenic potency for human subjects (app. 4).

Item (3) may be omitted for subsequent lots with the same strain after the initial demonstration of consistency but should be applied periodically thereafter.

### E. RECOMMENDATIONS

(1) Evaluation of present new data: It is recommended that a small staff group be assigned the responsibility of consolidating and evaluating all of the available published data, and that which will become available as a result of the PAHO Conference, and that which will result from studies in progress during the poliomyelitis season of 1959. This evaluation would be oriented in direct relation to the above specifications. Travel to areas where field programs and other studies are in progress might be indicated as opportunities present themselves.

(2) Conduct of new studies: The PHS should encourage additional studies of live poliovirus vaccines directed toward obtaining answers to problems reflected in this report.

Respectfully submitted by the Public Health Service Committee on Live Poliovirus Vaccine.

DAVID BODIAN.
WILLIAM McD. HAMMON.
ALEXANDER D. LANGMUIR.
JOSEPH L. MELNICK.
RODERICK MURRAY, *Chairman.*
JOHN R. PAUL.

AUGUST 12, 1959.

## APPENDIX 1

### TESTS FOR NEUROVIRULENCE BY INTRACEREBRAL AND INTRASPINAL INOCULATION OF MONKEYS

At least five monkeys per dilution should be inoculated intraspinally and 10 per dilution intrathalamically in parallel with similar groups inoculated with a selected reference attenuated virus. Undiluted material and material diluted through $10^{-4}$ should be used for the intraspinal inoculations, and undiluted and $10^{-1}$ diluted material should be used for the intrathalamic inoculations. The inoculation dilutions should be spaced at tenfold intervals and the undiluted material should have a titer of at least $10^{7.0}$ $TCD_{50}$ per milliliter. Only monkeys which show gross evidence of inoculation into the thalamus or microscopic evidence of inoculation into the gray matter of the lumbar cord will be considered valid. No virus shall be considered satisfactory unless its neurovirulence is no greater than that shown by the selected reference strain.

Histopathologic examination shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, and mesencephalon.

Evidence of degree of neurovirulence shall be determined by the number of animals at each dilution showing lesions, by the severity of the lesions seen, and by the rate of occurrence of paralysis not attributable to the mechanical injury of inoculation procedures.

This test shall be carried out on (*a*) the seed virus, and (*b*) a sample of each lot of the final product.

It is realized that lesions in the brains and cords of monkeys may be caused by agents other than poliovirus. However, since it may be impossible to determine whether these agents are in the material tested, it is felt that any monkeys showing lesions shall be considered positive. In animals inoculated by the thalamic route, it is also desirable to ascertain, if possible, whether the distribution and histological nature of the lesions are characteristic of poliovirus infection.

In addition, samples of the final product should be examined and compared with the seed virus for the established in vitro markers of virulence and other distinguishable characteristics of the substrains. Seed virus and final products should be identical in all such respects.

## Appendix 2

### Absence of Viremia in Man

Failure to give rise to viremia is a characteristic which is generally accepted as being a necessary indication of safety.

This characteristic should be tested in at least 10 triply negative human subjects who are shown to become infected after virus feeding, and who should be bled daily on the 3d to 10th days after feeding. Undiluted blood serum specimens should each be tested in 10 sensitive tissue culture units, using 0.5 milliliter of serum. As a control for the sensitivity of cultures, 10 tissue culture preparations should be inoculated with reference virus using 5 culture doses.

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## Appendix 3

### Genetic Stability, Markers

#### A. genetic stability

The important criterion of stability of attenuated poliovirus strains demands that, during the course of an induced alimentary infection in man, the infected poliovirus strain shall not revert to a virulent form, and this same degree of stability should continue to be retained by the strains after several human passages.

Demonstration of stability calls for the consecutive isolation of the infecting strains of attenuated poliovirus from the intestinal tract of the vaccinees at approximately weekly intervals for a period of 1 month. A series of tests should be set up to compare the characteristics of the strain fed to that of the strains recovered. The tests shall be done on the original fecal specimen, if possible, and on the first or second (M.K.) tissue culture material and should include: The use of markers designed to detect avirulence (d, MS and t markers) as well as discriminatory neurovirulence tests to be carried out in monkeys inoculated intracerebrally and intraspinally (app. 1). Any strain which appears to have reverted to an unusual degree of increased virulence shall be considered as failing to meet this test.

The same procedure is required for the testing of each candidate strain in later human passages. The demonstration of actual cross-infection from a vaccinee to a susceptible contact is required for the second passage and, in turn, the infected contact may pass along his infection to produce a third passage. The strain of attenuated polioviruses from these infected individuals should be recovered during the second week of these alimentary infections, if possible.

If it is necessary to carry out human passage trials under experimental conditions, samples of positive human feces should be given in a suitable dose to a susceptible subject and passage virus again recovered in testing.

The demonstration of stability of an attenuated poliovirus for use in a vaccine is only warranted when at least 10 recovered strains from vaccinees and 10 from second to fourth human oral passages have been shown either to retain their original character of avirulence or have not deviated to an unusual degree in increased neurovirulence for the monkey. Similar criteria shall obtain for the other genetic markers.

#### B. definition of markers, including the d, MS, and t tissue culture markers

Strains positive for these characters are generally neurovirulent.

In all tissue culture tests it is essential that reference NIH attenuated and virulent strains be included as controls in order to establish the validity of each test. The results are calculated by indicating the degree of "attenuation" as measured against the reference NIH attenuated strain.

*d marker*

Strains which grow readily at low concentrations of bicarbonate under agar are classified as d+ in contrast to the d— strains which exhibit delayed growth under the same conditions. The test may be run in plates in a $CO_2$ incubator (Vogt, Dulbecco, and Wenner) or in stoppered bottles in an ordinary incubator (Hsiung and Melnick).

*MS marker*

Strains which grow more readily on MS cells are classified as MS+ in contrast to the MS— strains. The test may be run in tube cultures or in bottle cultures under agar (Kanda and Melnick).

*t marker*

Strains which grow readily at 40° C. are classified as t+ in contrast to the t— strains which fail to grow at this temperature. The test may be run in tube cultures (Lwoff) or in bottles.

*Serological marker (not a test for genetic stability)*

In addition to the standard tests for determining type specificity, each strain should have its serological K value determined (McBride). This test is based on the rate at which a strain is neutralized by antiserum. It is not a measure of neurovirulence; for attenuated and virulent sublines of the same strain possess the same K value. However, it may be a useful label for following a strain through human passages regardless of any potential increases in neurovirulence which may be revealed by other methods.

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## Appendix 4

### Antigenicity

Some attenuated poliovirus strains have lost their ability to infect man by oral administration. Accordingly, there should be a demonstration in the case of each of the first five batches of the product for the virus to multiply in the alimentary tract and thus to produce type specific neutralizing antibody in 90 percent or more of susceptibles when administered orally in the recommended dose.

The size of the group of subjects recommended for the testing of each poliovirus type should be statistically adequate.

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## Appendix 5

### Effectiveness

Live poliovirus vaccines present a serious problem to the investigator who wishes to conduct a controlled field trial. The capacity of such viruses to spread among contacts means that some uninoculated control subjects will become infected and thus presumably immunized. Furthermore, the size of the population that must be planned in a controlled study would seem to be unrealistically large.

The design of an adequate field trial is still one of the most urgent points for investigation. In such an evaluation of effectiveness it will be necessary to resort to mass immunization of large population groups and depend upon the demonstration of consistently low attack rates of paralytic poliomyelitis in contrast to expectancy based on careful epidemiological estimates of past experience. In most areas the normal variation of incidences from year to year is such that reliable estimates of expectancy can only be projected over a number of years. Therefore, adequate measures of effectiveness may take a long time to be demonstrated. Other measures of effectiveness such as change in the age selection of paralytic poliomyelitis and change in the ratio of paralytic to nonparalytic cases may also have a place in the demonstration of effectiveness.

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## Appendix 6

### Housing and Handling of Monkeys

Monkeys to be used for the production of live poliovirus vaccine shall be isolated in individual cages for at least 6 weeks prior to use in the manufacture of the vaccine. Such monkeys shall be negative to tuberculin prior to this period. The death rate, excluding accidental deaths, shall not exceed 5 percent for any group during this period.

## Appendix 7

### Types of Tissue Culture Preparation Permissible

Only primary monkey kidney tissue cultures may be used in the preparation of live poliovirus vaccine. The use of continuous line cells is specifically prohibited. Introduction of continuous line cells into production areas is likewise prohibited.

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## Appendix 8

### Presence of Adventitious Agents Derived From Monkey Kidneys

The presence of adventitious agents derived from monkey kidneys represents a potentially serious matter in the manufacture and testing of live poliomyelitis vaccine. Over 40 simian agents, including B-virus have been encountered in the routine testing of killed poliomyelitis vaccine. These have shown up in trypsinized monkey kidney tissue culture preparations. In the testing of killed poliovirus vaccine, the assumption is made that the adventitious viruses detected are potentially present in the vaccine itself unless it can be shown that they were undoubtedly originally present in the tissue culture test system. Proof that they are contaminants in the test system rests upon (1) previous experience with the agent, (2) demonstration that the agent occurred in uninoculated control tissue culture bottles or tubes, (3) demonstration that the agent is much more readily inactivated than the polioviruses so that its presence in living form in the final vaccine is improbable. In this connection it should be noted that while formaldehyde at 37° C. requires approximately 72 hours to decrease the titer of poliovirus from $10^{-6}$ to $10^{0}$, this is accomplished in the case of most of the simian agents encountered (including B-virus) in approximately 20 hours or less.

Little is known of the pathogenicity of any of these agents for man except in the case of B-virus and even here the minimum infecting dose is not known. Most of the human cases of B-virus infection have occurred as a result of exposure to the presumably infected monkeys. However, there is one authenticated case in which the individual was not exposed to monkey and is believed to have developed his infection from monkey kidney tissue culture preparations which he was handling.

In addition to the recognized tests for tubercle bacilli, LCM virus and B-virus (by inoculation of rabbits) it is suggested that the following be taken into consideration in developing standards for the presence or absence of such agents.

(1) The monkeys used should be indivdually isolated and housed for at least 6 weeks prior to use for the manufacture of live poliomyelitis vaccine. At the time of sacrifice they should be thoroughly examined by a competent veterinarian having experience with diseases of monkeys for the presence of signs or symptoms indicative of ill health particularly for the presence of herpeslike lesions, eruptions or plaques in and around the mouth, in the buccal cavity or on the gums, or signs of conjunctivitis.

(2) Kidneys from individual monkeys should be trypsinized and processed separately.

(3) Tissue culture growth bottles should be observed for evidence of degeneration for at least 3 days prior to inoculation with the seed virus.

(4) Twenty-five percent of the bottles should be control bottles and held for a period of 3 weeks.

(5) Virus fluids should be passed through bacteria-excluding filters after harvesting. Samples for testing by inoculation into rabbits, adult mice, suckling mice, guinea pigs, and for testing by tissue culture methods, should be removed immediately after harvesting and prior to further processing. The required tests should be conducted without delay.

(6) The virus fluids should then be kept at 37° C. for 24 hours.

(7) At least 500 milliliters of undiluted virus should be tested in monkey kidney tissue culture preparations after neutralization of polioviruses by high titer specific nonmonkey sera. The immunizing antigens used for the preparation of such sera should be grown in a human cell line to minimize the presence of simian virus antibodies in the neutralizing antisera.

(8) At least 500 milliliters of undiluted virus should be tested in dog tissue culture preparations for the presence of measles virus.

(9) At least 500 milliliters of undiluted virus shall be tested in rabbit tissue culture preparations for the presence of B-virus.

APPENDIX 9

PERSONNEL IN LIVE POLIOVIRUS VACCINE PRODUCTION AREAS

Personnel while working in live poliovirus vaccine manufacturing area may not work with other infectious agents at any time in any laboratory. All personnel shall have been vaccinated against poliomyelitis. Only personnel actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine manufacturing areas during the interval when active work is in progress. Casual visitors shall be excluded from such units at all times. Street clothing, including shoes, shall be replaced by suitable laboratory clothing before entering a live virus manufacturing unit.

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APPENDIX 10

SEPARATION OF PRODUCTION FACILITIES

Specific space shall be set aside for work with live poliovirus vaccine. To minimize the hazard of contamination such space shall be isolated either in a separate building, or in a separate wing of a building, or in quarters at the blind end of a corridor so situated as to be an independent unit. Such a separate unit is defined as the space for vaccine preparation including culture methods, media, incubation, filling into containers, media production, cleaning and sterilization of glassware. Test procedures which potentially involve the presence of micro-organisms, including viruses other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, may not be carried out in live poliovirus vaccine production areas.

APPENDIX D

[From Public Health Reports, November 1959]

LIVE POLIOMYELITIS VACCINE STATUS

(Statement by Leroy E. Burney, Surgeon General, Public Health Service, August 28, 1959)

The present status of attenuated live poliovirus vaccines has been reported by the Public Health Service's Committee on Live Poliovirus Vaccine, headed by Dr. Roderick Murray, Chief of the Service's Division of Biologics Standards.

The committee has reviewed the rapidly accumulating data on the development and field use of attenuated live poliovirus vaccines and has considered the initial problems involved in the preparation of provisional specification for their production. It has been given responsibility for evaluating all available information, for determining what additional information is needed, and, where necessary, for initiating studies to supply the answers to questions that must be resolved before licensing can be recommended.

If energetic efforts are continued to find answers to the remaining technical questions concerning safety, effectiveness, and manufacturing procedures, one or more of the three vaccines now being proposed may be under production within 1 to 2 years. Meanwhile, in the Salk vaccine there already is at hand at potent weapon whose value and effectiveness have been proved. I continue to urge all persons, particularly those under 40 years of age, to complete their series of Salk injections so that no one will remain unprotected at the time of the next poliomyelitis season.

The status of live poliovirus vaccine as reviewed by the committee follows:

1. Three sets of attenuated poliovirus strains have been proposed for use as oral vaccines. The Sabin strains (Dr. Albert Sabin, University of Cincinnati) have all had extensive field trials in Eastern Europe, Mexico, and Singapore. The Lederle strains (Dr. Herald Cox, Lederle Laboratories) have been widely used in Latin America. The Koprowski type 1 strain (Dr. Hilary Koprowski, Wistar Institutes, Philadelphia) has been used in a large trial in the Belgian Congo. However, no significant amount of field information is available concerning Koprowski's type 2 strain, and only limited information is available in relation to his type 3 component.

2. There is considerable difference in the neurovirulence or damaging effect on nerve cells for monkeys of the three sets of strains as determined by intrathaeamic and intraspinal inoculation. On this basis, the Sabin group has an advan-

tage over the others, but none of these strains is completely nonvirulent when inoculated into monkeys by the intraspinal route.

3. No evidence has been reported to indicate that any of these vaccines produced any harm to the individuals to whom they were administered. The thoroughness with which the observations were made has varied in different studies.

4. In some studies the ability of these strains to multiply and thus produce antibodies is less than could be expected on theoretical grounds. Apparently a number of factors operate in the field which may prevent alimentary infection and the subsequent development of immunity.

5. A number of workers have reported that virus excreted by vaccinated individuals has shown increased neurovirulence for monkeys. There is considerable disagreement among investigators as to the significance of these reversions in virulence.

6. Field experience with any strain to date cannot be interpreted as affording reasonable proof that the community of nonvaccinated persons will be free of danger from possible reversion of virulence in excreted virus under a great variety of readily anticipated circumstances. This is one of the most important unresolved problems.

7. There is evidence which indicates that under some circumstances the simultaneous administration of all three types of virus may be effective.

The committee reported the following major problems which remain to be solved before definitive decisions can be made regarding licensing:

1. The significance of increased neurovirulence for monkeys of virus excreted by vaccinated individuals.

2. The demonstration of adequate measures of effectiveness of live poliovirus vaccines in field trials which, to be definitive, must involve large population groups. The capacity of the virus to spread among contacts means that in such a controlled field trial some nonvaccinated controls will become infected and thus presumably become immune—a complicating factor in such a study.

3. The development of standards to determine the possible presence or absence of stray agents in the vaccine. More than 40 simian agents, including B-virus, have been encountered in the routine testing of killed poliovirus vaccine. These are derived from the monkey tissues used. Little is known of their pathogenicity for man except B-virus, and even for this the minimum infecting dose is not known.

4. The establishment of carefully designed and evaluated studies to demonstrate the production of specific antibodies in 90 percent or more of inoculated susceptibles in order to assure the potency of such vaccines.

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## Appendix E

### Recommendations Relating to the Manufacture of Live Poliovirus Vaccine

#### A. CRITERIA FOR ACCEPTABILITY OF STRAINS

Full documentation must be submitted for each strain. This must include: history of its origin, laboratory manipulations during development and attenuation, and full characteristics regarding safety, potency, and effectiveness, including the field trial findings on which these are based.

*1. Safety*

(*a*) *Tests for neurovirulence by intracerebral and intraspinal inoculation of monkeys.*—At least 5 monkeys per dilution should be inoculated intraspinally and 10 per dilution intrathalamically in parallel with similar groups inoculated with a selected reference attenuated virus. Undiluted material and material diluted through $10^{-4}$ should be used for the intraspinal inoculations, and undiluted and $10^{-3}$ diluted material should be used for the intrathalamic inoculations. The inoculation dilutions should be spaced at tenfold intervals and the undiluted material should have a titer of at least $10^{7.0}$ $TCD_{50}$ per milliliter when titered in comparison with the NIH standard polio vaccine preparation. Only monkeys which show gross evidence of inoculation into the thalamus or microscopic evidence of inoculation into the gray matter of the lumbar cord will be considered valid.

No virus shall be considered satisfactory unless its neurovirulence is no greater than that shown by the selected reference strain.

Histopathologic examination shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, and mesencephalon.

Evidence of degree of neurovirulence shall be determined by the number of animals at each dilution showing lesions, by the severity of the lesions seen, and by the rate of occurrence of paralysis not attributable to the mechanical injury of inoculation procedures.

This test shall be carried out on (*a*) the seed virus, and (*b*) a sample of each lot of the final product.

Any monkeys showing lesions other than those attributable to a sterile inoculum shall be considered positive. In animals inoculated by the thalamic route, it is desirable to ascertain whether the distribution and histological nature of the lesions are characteristic of poliovirus infection.

(*b*) *Viremia in man.*—This characteristic should be tested separately for each strain in at least 30 triply negative human subjects who are shown to become infected after virus feeding, and who should be bled daily on the 3d to 10th days after feeding. Undiluted blood serum specimens should each be tested in 10 sensitive tissue culture units, using 0.5 milliliter of serum. As a control for the sensitivity of cultures, 10 tissue culture preparations should be inoculated with reference virus using 5 culture doses. Not more than one of the subjects should show viremia.

(*c*) *Genetic stability.*—Strains must show absence of capacity to revert to significant neurovirulence after passage in man.

(*d*) *Field tests among susceptibles.*—Freedom from harmful effects upon administration to approximately 100,000 "triple-negative" individuals under circumstances where adequate epidemiological surveillance of neurological illness has been maintained.

*2. Potency and effectiveness*

(*a*) *Antigenicity (or capacity to take).*—There should be a demonstration in the case of each of the first five batches of the product for the virus to multiply in the alimentary tract and thus to produce type specific neutralizing antibody in 90 percent or more of susceptibles when administered orally in the recommended dose.

The size of the group of subjects recommended for the testing of each polio virus type should be statistically adequate.

(*b*) *Effectiveness.*—The production of specific antibodies is accepted as a presumptive indication of immunity.

### B. SPECIFICATIONS APPLICABLE TO MANUFACTURE

The following requirements shall apply to each lot of vaccine produced.

*1. Establishment of a seed virus system*

The virus in the final product shall represent no more than three tissue culture passages from the seed strain which has met the criteria of acceptability, or whose immediate progeny have met these criteria.

*2. Housing, handling, and conditioning of monkeys*

Monkeys to be used for the production of live poliovirus vaccine shall be isolated in individual cages closed on all sides except the front for at least 6 weeks prior to use in the manufacture of the vaccine. Such monkeys shall be negative to tuberculin prior to this period. The death rate, excluding accidental deaths, shall not exceed 5 percent per month for any selected group during this period.

*3. Types of tissue culture preparation permissible*

Only monkey kidney tissue cultures may be used in the preparation of live poliovirus vaccine. The use of continuous line cells is specifically prohibited. Introduction of continuous line cells into production areas is likewise prohibited.

*4. Possibility of contamination during processing to be minimized*

Processing shall be conducted in such a manner as to minimize the possibility of contamination with various infectious agents.

*5. Temperature of incubation*

Tissue culture production vessels shall at no time be maintained at a temperature above 36° C. during the course of virus propagation.

*6. Presence of adventitious agents derived from monkey kidneys*

Live poliovirus vaccines shall be extensively tested for the absence of adventitious infectious agents including *Mycobacterium tuberculosis*, pox viruses, lymphocytic choriomeningitis virus, ECHO viruses, Coxsackie viruses, B-virus, and other simian agents.

In addition to the recognized tests for tubercle bacilli, LCM virus, and B-virus (by inoculation of rabbits), the following procedures and tests will be followed:

(*a*) At the time of sacrifice, monkeys should be thoroughly examined by a competent veterinarian having experience with diseases of monkeys for the presence of signs or symptoms indicative of ill health, particularly for evidence of tuberculosis and for the presence of herpeslike lesions, eruptions or plaques in and around the mouth, in the buccal cavity or on the gums, or signs of conjunctivitis.

(*b*) Kidneys from individual monkeys should be trypsinized and processed separately.

(*c*) Tissue culture growth bottles should be observed for evidence of degeneration for not less than 3 days prior to inoculation with the seed virus. The fluid changes should be tested in monkey kidney cells, human cells, and in rabbit kidney cells.

(*d*) Twenty-five percent of the bottles should be control bottles and held and examined for a period of 3 weeks. At the end of the period, the fluids should be tested in the same way as the fluids in (*c*) above. The tissue culture bottles shall be examined for the presence of hemadsorption viruses by the addition of guinea pig red blood cells.

(*e*) After harvesting, virus fluids should be passed through filters having a porosity of Seitz ST–1. Samples for testing by inoculation into rabbits, adult mice, suckling mice, guinea pigs, and for testing by tissue culture methods, should be removed immediately after harvesting and prior to filtration and further processing, except that materials frozen a few minutes after harvesting may be tested on thawing. The required tests should be conducted without delay.

(*f*) At least 500 milliliters[1] of undiluted virus should be tested in monkey tissue culture preparations after neutralization of poliovirus by high titer specific nonmonkey sera. The immunizing antigens used for the preparation of such sera should be grown in a human cell line to minimize the presence of simian virus antibodies in the neutralizing antisera.

(*g*) At least 500 milliliters[1] of undiluted virus should be tested in dog tissue culture preparations for the presence of measles virus. In the absense of sensitive dog kidney cells the required volume of material neutralized with high titer poliovirus antibody may be tested in human cells.

(*h*) At least 500 milliliters[1] of undiluted virus shall be tested in rabbit tissue culture preparations for the presense of B-virus.

*7. Neurovirulence in monkeys*

Each lot shall be tested for neurovirulence in monkeys as set forth in A(1)(a).

*8. Genetic markers*

Each lot shall be tested for genetic markers in parallel with the seed virus.

(*a*) *d marker.*—Strains which grow readily at low concentrations of bicarbonate under agar are classified as d+ in contrast to the d— strains which exhibit delayed growth under the same conditions. The test may be run in plates in a $CO_2$ incubator (Vogt, Dulbecco, and Wenner) or in stoppered bottles in an ordinary incubator (Hsiung and Melnick).

(*b*) *MS marker.*— Strains which grow more readily on MS cells are classified as MS+ in contrast to the MS— strains. The test may be run in tube cultures or in bottle cultures under agar (Kanda and Melnick).

(*c*) *t marker.*—Strains which grow readily at 40° C. are classified at t+ in contrast to the t— strains which fail to grow at this temperature. The test may be run in tube cultures (Lwoff) or in bottles.

In all tissue culture tests it is essential that reference NIH attenuated and virulent strains be included as controls in order to establish the validity of each test. The results are calculated by indicating the degree of "attenuation" as measured against the reference NIH attenuated strain.

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[1] Either as a single amount of the total pool or the sum of the tests proportionately done on individual harvests or subpools.

*9. Personnel in live poliovirus vaccine production areas*

Personnel while working in live poliovirus vaccine manufacturing areas may not work with other infectious agents in any other laboratory during the same 24-hour period. All personnel shall have been vaccinated against poliomyelitis. Only personnel actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine manufacturing areas during the interval when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall only be admitted under supervision. Street clothing, including shoes, shall be replaced by suitable laboratory clothing before entering a live virus manufacturing unit.

*10. Separation of production facilities*

Specific space which may be individual or multiple units shall be set aside for work with live poliovirus vaccine. To minimize the hazard of contamination, work space shall be isolated either in a separate building or buildings in a separate wing of a building, or in quarters at the blind end of a corridor so situated as to be an independent unit. Such a separate unit is defined as the space for vaccine preparation including culture methods, tissue culture production, incubation, and filling into containers. Test procedures which potentially involve the presence of micro-organisms including viruses other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, may not be carried out in live poliovirus vaccine production areas.

C. ADDITIONAL REQUIREMENTS FOR LICENSING

A demonstration shall be made of consistency of production for five consecutive lots using production facilities in their preparation. The testing of each of these five lot shall include:

(1) Tests for monkey neurovirulence as set forth in A(1)(a).

(2) Characterization of each lot by means of tissue culture markers as set for in 8.

(3) Determination of antigenic potency for human subjects as set forth in A(2)(a).

RODERICK MURRAY, M.D.,
*Director, Division of Biologics Standards.*

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APPENDIX F

The following article by Dr. Leroy E. Burney, Surgeon General of the Public Health Service, reproduced as it appears in the December 18 issue of the Journal of the American Medical Association, summarizes the Public Health Service's observations on the current status of the live polio virus vaccine:

"CURRENT STATUS OF LIVE POLIO VIRUS VACCINE

"A considerable fund of information has been accumulating on the properties of live-virus poliomyelitis vaccines and on the use of these vaccines in human beings. The recent publication of the proceedings of the conference on live polio virus vaccines, held in Washington, D.C., June 22–26, 1959, under the auspices of the World Health Organization and the Pan American Health Organization, provides a good opportunity to review the current state of knowledge.

"The proceedings contain progress reports on field studies of these vaccines now underway in countries in Europe, Asia, and South America. Great numbers of people have been vaccinated in the U.S.S.R. and elsewhere. In general, the reports indicate a good record of safety for the vaccines under trial, although the extent of surveillance and followup study is somewhat unclear.

"The attenuated live viruses used in these vaccines have lost the power to produce disease through a process of selective cultivation in the laboratory. They can, however, be transmitted by persons who have ingested them to others through natural means. On this point, the conference report noted, 'The use of a product that spreads beyond those originally vaccinated represents a radical departure from present practice in human preventive medicine.'

"It has been maintained that this might be a useful characteristic under certain circumstances, i.e., if there were assurance that the virus would remain in an attenuated state after passage through the human intestinal tract. A

number of reports presented at the conference, however, including those of Melnick, Verlinde, Smorodintsev, and Stuart-Harris, indicated a potential in at least some of the vaccine viruses under consideration for reversion to virulence. This suggests a strong need for further study of the vaccines before they can be recommended for general use. The problem of reversion to virulence has been highlighted again in a recent report by Melnick and coworkers(2).

"The principal problem, therefore, in evaluating the ultimate safety of live polio virus vaccines is the possibility of the spread of virus, coupled with its potentiality for reversion to virulence.

"In June 1958, the Public Health Service established a committee on live polio virus vaccines, composed of experts in the fields of virology and immunology from within and outside the Government. This committee has been closely following developments relating to live-virus vaccines, both in the laboratory and in field trials in various parts of the world. The group recently drafted recommendations(3) pertaining to the problems which must be solved before licensing of a commercially produced vaccine can be considered.

"In addition to providing satisfactory results of field trials, a vaccine designed for general use must meet certain laboratory tests. Such tests represent the only experimental criteria available for the continued control of individual lots of vaccine as they are produced by the manufacturers.

"One criterion is based on the vaccine's degree of neurovirulence for monkeys. As the recent conference report disclosed, results obtained by different investigators have varied considerably. In order to obtain comparative information on the three sets of strains (Sabin, Cox, and Koprowski) in the experimental vaccines, the Division of Biologics Standards, which administers the Public Health Service's responsibilities in the field of biologicals control, carried out studies of these strains under standardized conditions. The data showed that there is considerable difference among the three sets of strains, from the point of view of their neurovirulence in monkeys, as determined by histological lesions and paralysis occurring after intracerebral and intraspinal inoculation(1). These results are also in agreement with those of Melnick and coworkers(2).

"The committee on live poliovirus vaccines therefore recommended that a virus strain be considered satisfactory only if its neurovirulence as tested by the recommended procedures is low. In addition, the committee agreed that live-virus vaccine strains must also demonstrate inability to revert to significant neurovirulence after passage in human beings.

"Each lot of vaccine produced must be shown to possess the same genetic markers as the seed virus. These genetic markers are inherent properties of a virus strain. If the markers of an individual lot of vaccine differ from those of the seed, that lot should not be used for immunizing human beings. A number of the markers are determined by studying characteristics of virus strains in tissue culture. One such characteristic, called the temperature (t) marker involves the growth of the virus at higher temperatures, such as 40° C. (104° F.). The virulent virus generally grows well at this temperature while the avirulent virus grows poorly, thus providing an element of discrimination. Another characteristic is the ability of the virus to grow when only a small amount of sodium bicarbonate is present in the tissue culture medium. A third characteristic is the MS (monkey-stable) marker, involving cultivation on a stable, continuous, tissue-culture cell line derived from monkey kidney.

"The determination of a number of these, and perhaps other, markers is essential in order to differentiate between the attenuated and the virulent or wild strains.

"A realistic consideration of these and other problems makes it difficult to predict when a live polio virus vaccine could be licensed for commercial production. The Division of Biologics Standards has met with the vaccine developers and with interested manufacturers as a step in establishing standards for safety and for production of such vaccines. The Public Health Service cannot recommend the licensing of such a biological product until the manufacturer has demonstrated not only the safety and potency characteristics of the vaccine strains but also his ability to meet established standards for successive production lots of vaccine.

"SUMMARY

"The Public Health Service has a considerable interest in the development of live polio virus vaccine. This interest arises both from its concern with preventive measures and from its legal responsibilities for the licensing of biological

products. A continuing review of progress has been made by the PHS committee on live polio virus vaccine. This review indicates important progress toward the development of a safe and effective poliomyelitis vaccine for oral use. Some important safeguards will need to be developed before there can be full assurance concerning the safety and potency of these products for general use by the physician.

"When the scientists and public health physicians of the United States and other countries have provided evidence of safety and of lack of significant reversion to virulence of the vaccine strains, on the basis of both laboratory and field experience, and when proper manufacturing safeguards have been satisfactorily established by the vaccine manufacturers the Public Health Service will act on applications for the licensing of live polio virus vaccine. In the meantime, there should be no abatement of full use of the demonstratedly effective Salk vaccine."

REFERENCES

(1) Murray, R.; Kirschstein, R.; Van Hoosier, G., Jr.; and Baron, S.: "Comparative Virulence for Rhesus Monkeys of Poliovirus Strains Used for Oral Administration," Proceedings of the World Health Organization-Pan American Health Organization Conference on Live Poliovirus Vaccines, Washington, D.C., June 22–26, 1959.

(2) Melnick, J. L.; Benyesh-Melnick, M.; and Brennan, J. C.: "Studies on Live Poliovirus Vaccine: Its Neurotropic Activity in Monkeys and Its Increased Neurovirulence After Multiplication in Vaccinated Children," J.A.M.A. 171: 1165–1172. (Oct. 31), 1959.

(3) "Second Report of Public Health Service Committee on Live Poliovirus Vaccine," Aug. 12, 1959; cited in Government Services, J.A.M.A. 171: 1127 (Oct. 24), 1959.

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APPENDIX G

A joint Russian-United States report on the polio meeting held in Moscow, May 12–16, was made public today by Dr. David E. Price, Assistant Surgeon General of the Public Health Service and Chief of the U.S. delegation. Dr. Price was the personnel representative of Surg. Gen. Leroy E. Burney.

Attended by 13 United States and 15 Russian physicians, the meeting was concerned chiefly with technical discussion of research, production, and testing of live polio vaccines.

The Russians reported successful use of the live polio vaccine developed by Dr. Albert Sabin, director of research at Children's Hospital, Cincinnati. Pieces of candy containing Russian-produced Sabin vaccine have been given to 60 million Russians, aged 2 months to 20 years. Russian physicians said that they were encouraged to hope that this method would completely control the disease in Russia within the next year or two. They agreed, however, that further studies of the effectiveness and duration of effectiveness were needed.

The Americans described U.S. experience with the Salk killed vaccine, which has now been used by over 90 million Americans, and with field trials of live vaccines. In these trials, the live vaccines of two other American scientists, Dr. Herald Cox, of Lederle Laboratories, and Dr. Hilary Koprowski, of the Wistar Institute, as well as the Sabin vaccine are being studied.

There are differences in the Russian- and U.S.-proposed standards for producing and testing live vaccines. It was agreed that further exchange of information and comparative studies is desirable and that such information be provided to the World Health Organization with a view to the ultimate development of international recommendations.

Use of live vaccines in the United States at present is limited to carefully controlled field studies. Dr. Leroy E. Burney, Surgeon General of the Public Health Service, announced on November 16, 1959, that such studies were being evaluated and that the vaccines would be licensed for commercial production and general public use whenever certain remaining technical problems were solved. No data presented at the Moscow meeting, Dr. Price said, would justify changing this policy.

In addition to Drs. Price, Sabin, and Koprowski, Americans who attended the Moscow meeting were:

Dr. M. Benyesh-Melnick and Dr. Joseph E. Melnick, Baylor University School of Medicine, Houston, Tex.; Dr. Theodore Boyd, National Foundation, New York

City; Dr. Victor Cabasso, Lederle Laboratories, Pearl River, N.Y.; Dr. Eugene Flipse, University of Miami School of Medicine, Miami, Fla.; Dr. John P. Fox, Institute for Public Health Research, New York City; Dr. Thomas Francis, University of Michigan, Ann Arbor, Mich.; Dr. Herman Kleinman, Minnesota Health Department, Minneapolis, Minn.; Dr. Alexander Langmuir, Communicable Disease Center of the Public Health Service, Atlanta, Ga.; and Dr. Roderick Murray, National Institutes of Health of the Public Health Service, Bethesda, Md.

The Russian delegation was headed by Dr. V. M. Zhdanov, secretary of the Academy of Medical Sciences of the U.S.S.R. Dr. M. P. Chumakov, director of the Institute for Poliomyelitis Research in Moscow, and other virologists, epidemiologists, and research scientists comprised the Russian delegation.

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APPENDIX H

Dr. Leroy E. Burney, Surgeon General of the Public Health Service, today issued the following statement on the recently concluded World Health Conference (June 26) on Live Virus Polio Vaccine held at Georgetown University under the sponsorship of the Pan American Health Organization:

"The Conference has been a valuable one. It has provided an opportunity for scientists to exchange information and views with one another and has brought together a mass of data about the use of the live vaccine in many areas of the world, including Latin America, Africa, Poland, Czechoslovakia, Russia, Singapore, the Netherlands, and Great Britain.

"It is apparent from reports that have come to me from the Conference that much favorable progress is being made with these attenuated vaccines, bringing closer to reality the possibility of a safe and effective vaccine of this type. The summary report issued by the Conference makes this clear.

"The report states: 'The very difficult problems in the development, control, and evaluation of the safety and effectiveness of experimental live attenuated polio virus vaccines were the main concerns of the Conference. The solution of many of these problems remains to be found.'

"The trials which have been undertaken to date and which have involved large numbers of persons have gone forward mostly in the developing nations. Children in these nations, unlike those in the United States and in other more developed nations, normally develop immunity at an early age because of the widespread occurrence of the polio virus.

"Accordingly, there is need for controlled studies in which, prior to inoculation, persons can be tested for antibody levels, immunized, retested, and the results evaluated on a scientific basis. Mass programs of immunization have provided encouraging but not as yet complete scientific data on which to base a real judgment as to the effectiveness of these live vaccines.

"To the degree that these mass immunization programs have possibly prevented polio in nations where they have been used, the effort has been very worthwhile.

"The Public Health Service will continue to follow the present studies and encourage others with interest and the hope that the result will be a vaccine which is easier to administer, since it is an oral vaccine; one which may provide longer lasting immunity; and one which, presumably, could be produced at lower cost. The Public Health Service Technical Advisory Committee on Live Poliovirus. Vaccine, made up of distinguished scientists in the field of infectious diseases, is undertaking an evaluation of the mass of data presented at the Conference and I shall make this report available as soon as it is received.

"It must be emphasized, however, that much remains to be done in the development of commercial production methods in terms of the safety, purity and potency of such products before their licensing for commercial sale can become a reality.

"To date, the Public Health Service has received no applications for licensing an attenuated vaccine. Should an application be received, the Public Health Service's Division of Biologic Standards will exercise its responsibility for insuring that the product is safe, potent, and capable of commercial production.

"In the Salk vaccine we already have a weapon of tremendous value and proved effectiveness. While noting the very gratifying and hopeful progress being made toward development of a live virus vaccine, I would urge that we go full speed ahead in using what we already have.

"Members of the Technical Advisory Committee are: Dr. Roderick Murray, Chairman, Director of the Division of Biologic Standards, National Institutes of Health; Dr. David Bodian, of Johns Hopkins University; Dr. William McD. Hammon, of the University of Pittsburgh School of Public Health; Dr. Alexander Langmuir, of the Public Health Service's Communicable Disease Center, Atlanta, Ga.; Dr. Joseph Melnick, of Baylor University, and Dr. John R. Paul, of the Yale University Medical School."

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## APPENDIX I

### STATEMENT BY L. E. BURNEY, M.D., SURGEON GENERAL, PUBLIC HEALTH SERVICE, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

During recent months, a number of conferences have been held at which progress in the field of immunization with live poliovirus vaccines was reported. These conferences include the meeting held in Moscow in May, the joint Pan American Health Organization-World Health Organization Conference held in Washington in June, and the Fifth International Congress on Poliomyelitis held in Copenhagen in late July. The staff of the Public Health Service and its Advisory Committee on Live Poliovirus Vaccine has given careful consideration to the information available from these meetings—indeed, some members have actively participated in these meetings.

It may be recalled that about a year ago recommendations relating to the manufacture and testing of live poliovirus vaccines were issued to facilitate the entry of interested manufacturers into this complex field. Last week, the Committee met with the manufacturers and other interested persons in order to review these recommendaions.

Revisions to these earlier recommendations, which will serve as the basis for adoption of regulations for manufacture and testing of the vaccine, have been agreed on by the Committee. These include the virus strains to be used, the general processes of manufacture to be followed, tests to be applied during manufacture, and factors relating to the continued safety, purity, and potency of the vaccine.

The Service's Division of Biologics Standards is moving with all speed to complete technical details of the final regulations while the manufacturers proceed with preliminary steps toward meeting these requirements. These details will be available in the near future.

In addition, I have received a general short report from the Committee, a copy which is attached. On the basis of these recommendations, it is considered that live poliovirus vaccine is suitable for use in the United States. It is now possible to visualize the licensing of the establishments for manufacture and sale of these products when the manufacturers have individually demonstrated the necessary experience and ability to produce material which conforms with the requirements.

It is not anticipated that the vaccine will be available in any quantity for a number of months and it is doubtful whether substantial supplies will be available before mid-1961. In any case, I consider it important to note the Committee's recommendation for the integrated use of the live polio vaccine with the presently available vaccine and for the rather special requirements concerning use of live poliovirus vaccine in the American population. I shall take up certain of the problems raised by the Committee regarding the optimal use of live poliovirus vaccine in the United States with appropriate advisory groups, such as the State and territorial health officers and representatives of the medical and health professions and of the voluntary health agencies.

### RECOMMENDATIONS OF THE PUBLIC HEALTH SERVICE COMMITTEE ON LIVE POLIOVIRUS VACCINE

AUGUST 24, 1960.

The Committee considers that field studies of oral poliovirus vaccines have advanced our knowledge to a stage where recommendations relating to its manufacture can now be written.

The Committee also has considered the need for careful analysis of the problems associated with adapting such vaccines to immunization programs in this country and made recommendations thereon.

### VACCINE CHARACTERISTICS AND STRAIN SELECTION

In line with its efforts to further the progress of immunization against poliomyelitis, the Committee met on August 19, 1960, with technical representatives of potential manufacturers, with other interested persons, and with the staff of DBS, for the purpose of reviewing the proposed requirements for the manufacture and testing of live poliovirus vaccine. The amended requirements which outline the manufacturing and testing objectives will become available shortly from the DBS and should be helpful in assisting those manufacturers who wish to enter into production. It is hoped that manufacturers can proceed without delay to develop the necessary experience for the mass production of live oral poliovirus vaccine.

The Committee feels that three factors when considered together make possible its recommendation regarding strain selection. These factors are: (1) Neurovirulence in monkeys, (2) viremia in man, and (3) field experience with all candidate strains. The Committee again emphasizes the need for definitive information on the question of viremia in man.

The Committee considers that of the strains available for preparing live oral poliovirus vaccine the Sabin type I and type II strains possess the most favorable laboratory and field characteristics and recommends their use. The Committee also recommends the use of the Sabin type III strain which is satisfactory from the point of view of neurovirulence although it has less than optimum immunogenic capacity and shows a tendency to change its neurovirulence characteristics after passage in man. The Committee urges the continued search for a superior type III strain. All candidate strains other than those of Sabin which have been studied extensively are of greater neurovirulence for monkeys than the selected reference.

The Committee expresses the view that neurovirulence for monkeys is the most important laboratory criterion available. This criterion was used for selecting candidate strains and is still the only measurable laboratory property which can be assumed to be correlated with neurovirulence in man. On the basis of the information available, the Committee recommends that the intrathalamic test in monkeys be adopted as the criterion for neurovirulence and that in order to be suitable for vaccine manufacture strains should exhibit little or no evidence of neurovirulence when inoculated in this manner into monkeys. The Committee considers that any strain which shows neurovirulence for monkeys by causing paralysis when administered by the intramuscular route is unsuitable. The Committee recommended that the intraspinal test be retained mainly as a measure of the susceptibility of the monkeys used. It recommends that the Sabin type I strain be used as a reference in the conduct of these tests.

The Committee took cognizance of the great contributions of Dr. Cox and of Dr. Koprowski, who with their colleagues promulgated the concept of live oral poliomyelitis vaccine and using their own attenuated strains, provided much of the crucial information which advanced the development of this new vaccine.

The Committee concludes that the field data now available indicate that while good levels of immunity can be obtained under certain conditions such levels can only be assured by repeated doses. Schedules of administration will depend upon local conditions since capacity "to take" or "immunogenic effectiveness" of these vaccines is influenced by a number of factors, the most important of which is the prevalence of other enteroviruses in the community being immunized. The Committee does not believe that the capacity to immunize of any strain is such that the neurovirulence requirements should be compromised.

### NEED FOR PLANNED USE OF LIVE VACCINE

In view of the fact that the nationwide programs with killed virus vaccine failed to achieve the hoped-for elimination of all epidemics of paralytic poliomyelitis, the Committee emphasizes the need for critical assessment of the place of live poliovirus vaccines in the overall picture of poliomyelitis prevention in the United States. The uncoordinated use of live poliovirus vaccine is unlikly to accomplish more than has been achieved with inactivated poliomyelitis vaccine as presently employed. It appears probable that only a unified national program which utilizes each of the available types of vaccine to its best advantage can accomplish the total prevention of outbreaks.

The Committee must also emphasize that when live poliovirus vaccine becomes available generally in this country, its use will be more appropriate on

a community than on an individual basis. This will depend upon a number of factors, and special recommendations will be necessary for the guidance of physicians, public health officials, and others who will be engaged in such programs. Attention should be given to such matters as administration to special groups; e.g., very young children, pregnant women, susceptible adults, and others, and even more important is the planned continuation of this program as long as necessary to achieve and maintain the required results.

The Committee supports the view that the Public Health Service has a function to perform, extending beyond its regulatory responsibilities, to the end that a satisfactory live poliovirus vaccine my not only be made available at an early date, but may be properly integrated into the total pattern of infectious disease prevention in the United States.

Because of the unique nature of live poliovirus vaccine, with its capacity to spread the virus in a limited manner to nonvaccinated persons, the Committee cannot make recommendations for manufacture without expressing concern about the manner in which it may be used. The seriousness of this responsibility can be illustrated, for example, by the known potentiality of reversion to virulence of live poliovirus vaccine strains, and the possible importance of this feature in the community if the vaccine is improperly used.

For example, the vaccine has been employed largely in mass administrations where most of the susceptibles were simultaneously given the vaccine, thus permitting little opportunity for serial human transmission; or it has been administered during a season of the year when wild strains have usually shown limited capacity for spread. This experience should provide the basis for developing usable practices for the United States.

Respectfully submitted by the Committee on Live Poliovirus Vaccine.

RODERICK MURRAY, M.D., *Chairman.*
DAVID BODIAN, M.D.
WILLIAM MCD. HAMMON, M.D.
ALEXANDER D. LANGMUIR, M. D.
JOSEPH L. MELNICK, PH. D.
JOHN R. PAUL, M.D.

PUBLIC HEALTH SERVICE COMMITTEE ON LIVE POLIOVIRUS VACCINES

Authority: Established administratively by the Surgeon General in June 1958.

Structure: Consists of six members appointed by the Surgeon General who are experts in the fields of virology with particular competence in epidemiology and immunology. The Director, Division of Biologics Standards, serves as Chairman. effectiveness. Makes broad general recommendations regarding provisional vaccine on the basis of data available from field and laboratory studies. Summarizes such evaluations for the Surgeon General and advises concerning the potentialities of these vaccines with particular attention to their safety and effectiveness. Makes broad general recommendations regarding provisional criteria for acceptability of strains and requirements for licensing.

Meetings: Meetings are called by the Surgeon General when necessary.

Member, organization, address:

Murray, Dr. Roderick (Chairman), National Institutes of Health, Bethesda, Md.

Bodian, Dr. David, Johns Hopkins University, 710 North Washington Street Baltimore, Md.

Hammon, Dr. Wm. McD., University of Pittsburgh, Pittsburgh, Pa.

Langmuir, Dr. Alexander D., Communicable Disease Center, PHS, Atlanta, Ga.

Melnick, Dr. Joseph L., Baylor University, Houston, Tex.

Paul, Dr. John R., Yale University, 333 Cedar Street, New Haven, Conn.

AUGUST 24, 1960.

SUMMARY BY L. E. BURNEY, M.D., SURGEON GENERAL, PUBLIC HEALTH SERVICE, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Sufficient progress has been made so that we can, with some assurance, predict a schedule of events which will take place between now and the time when appreciable quantities of live polio vaccine will be available in the United States. The schedule is as follows:

(1) The final draft of the proposed requirements will be completed during the next week, and will be made available immediately to potential manufacturers and to the press. These proposed requirements will serve as the

basis for the preparation of the legal regulations covering the manufacturers and licensing of live poliovirus vaccine.

(2) The legal regulations will be published for the first time in the Federal Register on or about November 1.

(3) The regulations will again appear in the Federal Register a few weeks later, and we expect that they will be adopted in the last part of this year.

In the meantime, the potential manufacturers working with the technical details contained in the proposed requirements will be able to get underway with the assurance that no serious changes will be made in the technical procedures for manufacturing and testing.

In all our procedures with the live poliovirus vaccine, we have been most careful and conservative because we feel that the licensing of a product is a grave responsibility. I want to point out also that we already have a satisfactory vaccine against poliomyelitis, and that we have in this country a level of immunization that is relatively high in comparison with other areas of the world.

In our best judgment, the live vaccine will not replace the Salk vaccine. There is need for both and they will complement each other.

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APPENDIX J

The Public Health Service announced today the formation of a Surgeon General's Committee on Poliomyelitis Control to be made up of representatives of the medical and health professions and the general public.

Invitations are going forward to the heads of 23 organizations asking them to designate members to serve on the Committee, according to the announcement.

The organizations are as follows: American Academy of Pediatrics, American Academy of General Practice, American College of Preventive Medicine, American Hospital Association, American Medical Association, American Nurses Association, American Pharmaceutical Association, American Public Health Association, AFL–CIO, Association of State and Territorial Health Officers, Association of State and Territorial Public Health Educators, Association of State and Territorial Public Health Laboratory Directors, Children's Bureau, Conference of State and Territorial Epidemiologists, Council of State Governments, Department of Defense, General Federation of Women's Clubs, National Congress of Colored Parents and Teachers Association, National Congress of Parents and Teachers Association, National Foundation, National Health Council, National Medical Association, Inc., and Pharmaceutical Manufacturers' Association.

In a press conference on August 24, the Surgeon General made public the recommendations of the Public Health Service Committee on Live Poliovirus Vaccine on the basis of which the Service considers that the vaccine is suitable for use in the United States.

Dr. Porterfield, Acting Surgeon General in Dr. Burney's absence from the city, said that the Surgeon General was also appointing an agenda committee, made up of representatives of the medical and public health professions, which will meet at the Public Health Service's Communicable Disease Center in Atlanta on October 11 and 12. This agenda committee will consider both the technical and administrative problems and develop the basic agenda for the first meeting of the Committee on Poliomyelitis Control. Members of the agenda committee are as follows: American Academy of Pediatrics, American Academy of General Practice, American Medical Association, Association of State and Territorial Health Officers, Children's Bureau, and the National Foundation.

The Surgeon General has invited a number of experts in the field of polio vaccines to serve as consultants to the agenda committee and the Committee on Poliomyelitis Control. The Public Health Service is seeking to obtain the fullest range of technical information on the oral vaccine available today. No date has been set for the initial meeting of the Control Committee. However, it is expected that it will hold its first session in December or January.

A the time of his news conference, the Surgeon General took special note of a recommendation by the Committee on Live Poliovirus Vaccine that use of the live polio vaccine should be integrated with the presently available Salk vaccine. Dr. Burney also pointed out that the use of live virus vaccine in the American population posed a number of special problems which would require careful consideration. Among them is the Committee's suggestion that the administration of the live virus vaccine will be more appropriate on a community than on an individual basis according to the Service announcement.

The Committee on Poliomyelitis Control will consider these and other questions developed by the agenda committee at its midwinter meeting.

Production of the oral vaccine is not anticipated before mid-1961 and the Service will continue its efforts to promote the widest possible use of the Salk vaccine in the interim period, the Public Health Service announcement said.

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APPENDIX K

## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

### PUBLIC HEALTH SERVICE

[42 CFR PART 73]

### BIOLOGIC PRODUCTS

ADDITIONAL STANDARDS: POLIOVIRUS VACCINE, LIVE, ORAL

NOTICE OF PROPOSED RULEMAKING

Notice is hereby given of proposed rulemaking pursuant to section 351 of the Public Health Service Act, as amended (58 Stat. 702; 42 U.S.C. 262), providing regulatory standards for the manufacture of poliovirus vaccine.

Notice is also given that it is proposed to make any amendments that are adopted effective 30 days after the date of publication in the Federa lRegister.

Inquiries may be addressed, and data, views and arguments may be presented by interested parties, in writing, in triplicate, to the Surgeon General, Public Health Service, Washington 25, D.C. All relevant material received not later than 30 days after publication of this notice in the Federal Register will be considered.

1. Redesignate sections 73.110, 73.111, 73.112, 73.113, 73.114, and 73.115 as sections 73.130, 73.131, 73.132, 73.133, 73.134, 73.135, respectively.

2. In section 73.130(b) as redesignated, substitute the numerals "73.132" and "73.133" for the numerals "73.112" and "73.113".

3. In section 73.130(c) as redesignated, substitute the numerals "73.132" and "73.133" for the numerals "73.112" and "73.113".

4. In section 73.131(d) as redesignated, substitute the numeral "73.132" for the numeral "73.112" in the three places where it appears.

5. In section 73.132(b) as redesignated, substitute the numeral "73.131" for the numeral "73.111".

6. In section 73.135 as redesignated, substitute the numerals "73.130" and "73.134" for the numerals "73.110" and "73.114", respectively.

7. Insert the following immediately after § 73.105:

ADDITIONAL STANDARDS: POLIOVIRUS VACCINE, LIVE, ORAL

Section 73.110 *The Product.*

(a) *Proper name and definition.* For the purpose of section 351(a)(2) of the Act and section 73.1(k), the proper name of this product shall be "Poliovirus Vaccine, Live, Oral", followed by a designation of the form in which the vaccine is dispensed. The vaccine shall be a preparation of one or more live, attenuated polioviruses grown in monkey kidney cell cultures, prepared in a compatible vehicle for oral administration.

(b) *Criteria for acceptable strains.*

(1) Strains of attenuated poliovirus types 1, 2, and 3 used in the manufacture of the vaccine shall be identified by: (i) historical records including origin and techniques of attenuation, (ii) antigenic properties, (iii) neurovirulence for monkeys, (iv) pathogenicity for other animals and tissue cultures of various cell types, and (v) established virus market including rct/40, d, MS.

(2) Poliovirus strains shall not be used in the manufacture of Poliovirus Vaccine, Live, Oral, unless, (i) data are submitted to the Surgeon General which establish that each such strain is free of harmful effects upon administration in the recommended dosage to at least 100,000 people susceptible to poliomyelitis, under circumstances where adequate epidemiological surveillance of neurological illness has been maintained, and, (ii) each such strain produces a vaccine meeting the safety and potency requirements of sections 73.114(b),

73.115 and 73.117 of the regulations of this part. Susceptibility shall be demonstrated by blood tests, stool examinations, and other appropriate methods.

(3) The seed material for each strain shall be demonstrated to be free of extraneous microbial agents.

(4) No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the NIH Reference Attenuated Poliovirus. The neurovirulence of the seed virus shall be demonstrated by the following tests to be performed by the manufacturer: (i) The test prescribed in § 73.114(b)(1) using seed virus as test material in place of monovalent virus pool material and (ii) the following comparative intramuscular neurovirulence test: Each of at least 10 monkeys shall be injected in either the gluteus or the gastrocnemius muscle with no more than 5 milliliters of the seed virus under test. A similar injection shall be made in another group of 10 monkeys using the NIH Reference Attenuated Poliovirus. Each monkey shall be injected intramuscularly with no less than $10^{7.7}TCD_{50}$ of viral inoculum.

(5) Subsequent and identical neurovirulence tests shall be performed in monkeys whenever there is evidence of a change in the neurovirulence of the production virus and upon introduction of a new production seed lot and as often as necessary otherwise to establish to the satisfaction of the Surgeon General that the seed virus strains for vaccine manufacture have maintained their neurovirulence properties as set forth in section 73.114(b)(1).

(6) The Surgeon General may, from time to time, prohibit the use of a specified strain whenever he finds it is practicable to use another strain of the same type which is potentially less pathogenic for man, and that it will produce a vaccine of equivalent and potency.

Section 73.111 *NIH reference strains.* The following NIH reference viruses shall be obtained from the Division of Biologics Standards.

NIH Reference Poliovirus, Live Attenuated, type 1, for correlation of virus titers in tissue cultures.

NIH Reference Poliovirus, Live Attenuated, type 2, for correlation of virus titers in tissue cultures.

NIH Reference Poliovirus, Live Attenuated, type 3, for correlation of virus titers in tissue cultures.

NIH Reference Attenuated Poliovirus, type 1, for correlation in monkey neurovirulence tests.

Section 73,112 *Animal conditioning, personnel, and facilities.*

(a) *Monkey conditioning, housing, and handling.*

(1) Only Macaca monkeys, or a species found by the Director, Division of Biologics Standards, to be equally suitable, in overt good health, that have reacted negatively to tuberculin 6 weeks prior to use, shall be used as the source of kidney tissue for the manufacture of poliovirus vaccine.

(2) Monkeys that have been used previously for experimental purposes shall not be used as a source of kidney tissue in the manufacture of vaccine.

(3) Monkeys to be used as a source of kidney tissue in virus manufacture shall be maintained for at least 6 weeks prior to use in cages closed on all sides with solid materials except the front, which shall be screened. Not more than two monkeys shall be housed in one cage, and cage mates shall not be interchanged.

(4) Excluding deaths from accidents or causes not due to infectious diseases, the death rate of any group of animals being conditioned in accordance with subparagraph 3 above, shall not exceed 5 percent per month.

(5) Each animal at necropsy shall be examined under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for the presence of signs or symptoms of ill health, particularly for (1) evidence of tuberculosis, (2) presence of herpeslike lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (3) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the kidneys shall not be used in the manufacture of vaccine.

(b) *Personnel.* All possible steps shall be taken to insure that personnel are immune to poliovirus in order to minimize the possibility that they may become excretors of poliovirus.

(c) *Facilities.* The space set aside for work with live poliovirus vaccine shall not be used for any other purpose during the vaccine manufacturing period. All areas used for live poliovirus vaccine manufacturing shall be decontaminated prior to the initiation of such manufacturing. Such separate unit is

defined as the space for vaccine manufacture including tissue culture production, virus production, and related storage. Test procedures which potentially involve the presence of micro-organisms including viruses other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in live poliovirus vaccine manufacturing areas.

Section 73.113. *Manufacture of Poliovirus Vaccine, Live, Oral.*

(a) *Primary cell cultures.* Only primary monkey kidney tissue cultures may be used in the manufacture of poliovirus vaccine. Continuous line cells shall not be introduced or propagated in vaccine manufacturing areas.

(b) *Virus passages.* Virus in the final product shall represent no more than three tissue culture passages from the seed strain, all of which shall have met the criteria of acceptability prescribed in section 73.110(b).

(c) *Identification of trypsinized kidneys.* The kidneys from each monkey shall be trypsinized and processed and the viral fluid resulting therefrom shall be identified as a separate harvest and kept separately from other harvests until the testing procedures relating to that pair of kidneys have been satisfactorily completed as prescribed in the following paragraph.

(d) *Monkey kidney tissue production vessels prior to virus inoculation.* Prior to inoculation with the seed virus, the tissue culture growth in vessels representing each pair of kidneys shall be examined microscopically for evidence of cell degeneration for no less than 3 days after complete formation of the tissue sheet. If such evidence is observed, the tissue from that pair of kidneys shall not be used for poliovirus vaccine manufacture. To test the tissues found free of cell degeneration for freedom from demonstrable viable microbial agents, the fluid shall be removed from the cell cultures immediately prior to virus inoculation and tested in each of four culture systems: (1) Macaca monkey kidney cells, (2) Cercopithecus monkey kidney cells, (3) primary rabbit kidney cells, and (4) human cells (from one of the systems described in § 73.114 (a)(6)), in the following manner: aliquots of fluid from each vessel shall be pooled and at least ten ml. of the pool inoculated into each system, with ratios of inoculum to medium being approximately 1:1 to 1:3 and the area of the surface growth of cells being at least three square centimeters per milliliter of test inoculum. The cultures shall be observed for at least 14 days. If these tests indicate the presence in the tissue culture preparation of any viable microbial agent the tissue cultures so implicated shall not be used for poliovirus vaccine manufacture.

(e) *Control vessels.* Before inoculation with seed virus, sufficient tissue culture vessels to represent at least 25 percent of the cell suspension from each pair of kidneys shall be set aside as controls. The control vessel shall be examined microscopically for cell degeneration for an additional 2-week period. The cell fluids from such control vessels shall be tested, both at the time of virus harvest and at the end of the additional observation period, by the same method prescribed for testing of fluids in the preceding paragraph (d). In addition the cell sheet in each control vessel shall be examined for presence of hemadsorption viruses by the addition of guinea pig red blood cells. At least 80 percent of the control vessels shall successfully complete the additional 14-day observation period without microscopic evidence of cell degeneration of the tissue sheets. If less than 80 percent of the control vessels fail to complete satisfactorily the observation period, no tissue from the kidneys implicated shall be used for poliovirus vaccine manufacture.

(f) *Control vessels—Interpretation of results.* If the results indicate the presence of any extraneous agent in the control vessels at the time of virus harvest from the inoculated vessels, the entire virus harvest from that tissue culture preparation shall not be used for poliovirus vaccine manufacture. If there is evidence of the presence in the tissue culture preparation of any human pathogen, as demonstrated by any of the tests or observations described in paragraphs (d) or (e), the virus grown in such tissue culture preparation shall not be used for poliovirus vaccine manufacture.

(g) *Kidney tissue production vessels after virus inoculation—Temperature.* After virus inoculation, production vessels shall be maintained at a temperature not to exceed 35.0° C. during the course of virus propagation.

(h) *Kidney tissue virus harvests.* Virus harvested from vessels containing the kidney tissue from one monkey may constitute a monovalent pool and be tested separately, or viral harvests from more than one pair of kidneys may be combined, identified and tested as a monovalent pool. Each pool shall be mixed thoroughly and samples withdrawn for testing as prescribed in section 73.114

(a). The samples shall be withdrawn immediately after harvesting and prior to further processing, except that materials frozen immediately after harvesting and maintained at —60° C. or below, may be tested upon thawing, provided no more than one freeze-thaw cycle is employed.

(i) *Filtration.* After harvesting and removal of samples for the safety tests described in section 73.114(a), the pool shall be passed through sterile filters having a sufficiently small porosity to assure bacteriologically sterile filtrates.

Section 73,114 *Test for Safety.*

(a) *Tests prior to filteration.* Monovalent vaccine pools shall contain no demonstrable viable microbial agent other than the attenuated live polioviruses intended. The vaccine shall be tested for the absence of adventitious and other infectious agents including polioviruses of other types or strains, simian agents, Mycobacterium tuberculosis, Pox viruses, Lymphocytic Choriomeningitis virus, ECHO viruses, Coxsackie viruses, and B-virus. Testing of each monovalent pool shall include but is not limited to the following procedures.

(1) *Inoculation of rabbits.* A minimum of 100 milliliters of each monovalent virus pool shall be tested by inoculation into at least 10 healthy rabbits, each weighing 1,500–2,500 grams. Each rabbit shall be injected intradermally in multiple sites, with a total of 1 milliliter, and subcutaneously with 9 milliliters, of the viral pool, and the animals observed for at least 3 weeks. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool may be used for poliovirus vaccine only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of B-virus or any other viral infection.

(2) *Inoculation of adult mice.* Each of at least 20 adult mice each weighing 15–20 grams shall be inoculated intraperitoneally with 0.5 milliliter and intracerebrally with 0.03 milliliter of each monovalent virus pool to be tested. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied, the brain removed and examined for evidence of viral infection. The examination shall include subinoculation of appropriate tissue into at least five additional mice and observed for 21 days. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of lymphocytic choriomeningitis virus or other viral infection.

(3) *Inoculation of suckling mice.* Each of at least 20 suckling mice less than 24 hours old, shall be inoculated intracerebrally with 0.01 milliliter and intraperitoneally with 0.1 milliliter of the monovalent pool to be tested. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness shall be necropsied and all areas examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by the intracerebral and intraperitoneal routes and daily observed for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14-day test. The virus fluid under test is satisfactory for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of Coxsackie or other viral infection.

(4) *Inoculation of guinea pigs.* Each of at least five guinea pigs, each weighing 350–450 grams, shall be inoculated intracerebrally with 0.1 milliliter and intraperitoneally with 5 milliliters of the monovalent pool to be tested. The animals shall be observed for at least 42 days and daily rectal temperatures recorded for the last 3 weeks of the test. Each animal that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied. The tissues shall be examined both microscopically and culturally for evidence of tubercle bacilli, and by passage of tissue suspensions into at least three other guinea pigs by the intracerebral and intraperitoneal routes of inoculation for evidence of viral infection. If clinical symptoms suggest infection with lymphocytic choriomeningitis virus, serological tests shall be performed on blood samples of the test guinea pigs. Animals that die or are sacrificed during the first 3 weeks after inoculation with poliovirus shall be examined for infection with lymphocytic choriomeningitis virus. Animals that die in the final 3 weeks shall be examined both microscopically and culturally for *M. Tuberculosis.* The monovalent virus pool is satisfactory for poliovirus vaccine only if at least 80 percent

of all animals remain healthy and survive the observation period and only if all the animals used in the test fail to show evidence of infection with *M. Tuberculosis*, or any viral infection.

(5) *Inoculation of monkey kidney tissue cultures.* At least 500 doses or 50 milliliters, whichever represents a greater volume of virus, of each undiluted monovalent virus pool or in equal proportions from individual harvests or subpools, shall be tested for simian viruses in Macaca and Cercopithecus monkey kidney tissue culture preparations after neutralization of the poliovirus by high titer type specific nonsimian antisera. The immunizing antigens used for the preparation of antisera shall be grown in a human tissue culture cell line. The monovalent virus pool is satisfactory for poliovirus vaccine only if all the animals fail to show evidence of the presence of simian viruses.

(6) *Inoculation of human cell cultures.* At least 500 doses or 50 milliliters, whichever represents a greater volume of virus, from one or more monovalent pools in equal proportions, shall be tested for the presence of measles virus in either (a) primary human amnion cells, (b) primary human kidney cells, or (c) any other cell system of comparable susceptibility to unmodified measles virus. The test material shall be neutralized with poliovirus antiserum of nonsimian derivation if the tissue culture cell system used is susceptible to poliovirus. The monovalent pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of measles virus.

(7) *Inoculation of rabbit kidney tissue cultures.* At least 500 milliliters of virus fluid, taken from either a single monovalent pool or in equal proportions from individual harvests or subpools, shall be tested in primary rabbit kidney tissue culture preparations for evidence of B-virus. The monovalent pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of B-virus.

(b) *Tests after filtration.* The following tests relating to safety shall be performed after the filtration process, on each monovalent pool or on each multiple thereof (monovalent lot):

(1) *Neurovirulence in monkeys.* Each monovalent pool or monovalent lot shall be tested in comparison with the NIH Reference Attenuated Poliovirus for neurovirulence in monkeys by both the intrathalamic and intraspinal routes of injection. A preinjection serum sample obtained from each monkey must be shown to contain no neutralizing antibody in a dilution of 1:4 when tested against no more than 1,000 $TCD_{50}$ of each of the three types of poliovirus. The neurovirulence tests are not valid unless the sample contains at least $10^{7.0}$ $TCD_{50}$ per milliliter when titrated in comparison with the NIH Reference Poliovirus, Live, Attenuated, of the appropriate type. All monkeys shall be observed for 17 to 19 days, under the supervision of a qualified pathologist, physician, or veterinarian, and any evidence of physical abnormalities indicative of poliomyelitis or other viral infections shall be recorded.

(i) *Intrathalamic inoculation.* Each of at least 10 monkeys shall be injected intrathalamically with 1.0 milliliter of undiluted virus and each of at least 10 additional monkeys shall be injected intrathalamically with 1.0 milliliter of virus diluted $10^{-1}$. Similar infections shall be made in each of two similar groups of monkeys with the NIH Reference Attenuated Poliovirus. Comparative tests and evaluations shall be made with the virus under test and the NIH reference. Only monkeys that show evidence of inoculation into the thalamus shall be considered as having been injected satisfactorily.

(ii) *Intraspinal inoculation.* Each of a group of at least five monkeys shall be injected intraspinally with 0.2 milliliter of undiluted virus and each monkey in four additional groups of at least five monkeys, shall be injected intraspinally with 0.2 milliliter of virus diluted $10^{-1}$, $10^{-2}$, $10^{-3}$, and $10^{-4}$, respectively. Similar injections of the NIH Reference Attenuated Poliovirus shall be made in each of five similar groups of monkeys. Comparative tests and evaluations shall be made with the virus under test and the NIH reference. The injections are satisfactory only if each monkey shows microscopic evidence of inoculation in the gray matter of the lumbar cord.

(iii) *Determination of neurovirulence.* At the conclusion of the observation period comparative histopathological examinations shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla and mesencephalon of each monkey in the groups injected with vaccine under test and those injected with the NIH reference virus, except that for animals dying during the test period, these examinations shall be made immediately after death. The animals shall be examined to ascertain whether the distribution and histological nature of the

lesions are characteristic of poliovirus infection. A comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the NIH Reference Attenuated Poliovirus with respect to (1) the number of animals in each dilution showing lesions characteristic of poliovirus infection, (2) the number of animals in each dilution showing lesions other than those characteristic of poliovirus infection, (3) the severity of the lesions, (4) the degree of dissemination of the lesions, and (5) the rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. The virus under test is satisfactory for poliovirus vaccine manufacture only if at least 80 percent of the animals in each group survive the observation period and if a comparative analysis of the test results demonstrates that the neurovirulence of the test vaccine does not exceed that of the NIH Reference Attenuated Poliovirus.

(2) *Test for virus titer.* The concentration of living virus in each monovalent pool or lot shall be determined, using the NIH Reference Poliovirus, Live, Attenuated of the same type as a control. The titration shall be performed with either groups of 10 tubes at 1-log dilution steps or groups of 5 tubes of 0.5-log dilution steps and the 50 percent ($TCD_{50}$) titration end point calculated.

(3) *Tests for invitro markers.* Two tests shall be performed with each monovalent pool, or each monovalent lot resulting therefrom, and with the NIH Reference Poliovirus, Live, Attenuated, of the same type. The tests shall be performed on the vaccine and on the NIH Reference Poliovirus as closely together in time as possible, using the rct/40 market and at least one of the other marker methods described below. The validity of all tissue culture tests shall be confirmed by including appropriate postive and homotypic negative strains of attenuated poliovirus as controls. The results of the tests shall demonstrate that the marker characteristic of the virus being tested does not differ significantly from that of the NIH Reference Poliovirus, Live, Attenuated of the same type.

(i) *rct/40 marker.* Attenuated strains which grow readily at 40° C. (±.5° C.) are classified as rct/40 positive (+) in contrast to the rct/40 negative (—) strains which show an increased growth of at least 100,000 fold at 36° C. over that obtained at 40° C. Comparative determinations shall be made in either tube or bottle cultures.

(ii) *d marker.* Attenuated strains which grow readily at low concentrations of bicarbonate under agar are classified as d positive (+) in contrast to the d negative (—) strains which exhibit delayed growth under the same conditions. The cultures shall be grown in a 36° C. incubator either in stoppered bottles or in plates in an environment of 5 percent $CO_2$ in air.

(iii) *MS markers.* Attenuated strains which grow more readily on monkey stable (MS) cells are classified as MS positive (+) in contrast to the MS negative (—) strains. Comparative determinations shall be made in either tube cultures or in bottle cultures under agar.

(4) *Test for sterility.* Each monovalent pool or each monovalent lot resulting therefrom shall be tested for sterility by the procedure prescribed in section 73.73.

Section 73.115 *Potency test.*

The concentration of living virus expressed as TCD of each type in the vaccine shall constitute the measure of its potency. The accuracy of the titration to determine the concentration of live virus shall be confirmed by using the NIH Reference Poliovirus, Live, Attenuated of the appropriate type as a control on the titration technique. The concentration of living virus (per milliliter) of each type contained in the lot under test shall be equal (± 0.5 log) to the average of the concentrations of virus (per milliliter) in the five lots of vaccine used in the clinical trials which qualified the vaccine for license.

Section 73.116 *General Requirements.*

(a) *Final container tests.* Tests shall be made on final containers for identity, safety, and sterility in accordance with sections 73.72 and 73.73.

(b) *Consistency of manufacture.* No lot of vaccine shall be released unless each monovalent pool contained therein is one of a series of five consecutive pools of the same type, each pool having been manufactured by the same procedures, and each having met the criteria of neurovirulence for monkeys prescribed in section 73.114(b)(1), and of in vitro markers as prescribed in section 73.114-(b)(3).

(c) *Dose.* The individual human dose of live poliovirus vaccine and the dosage schedule recommended on the label shall be the same as that used in the clinical trials which qualified the vaccine for license.

(d) *Labeling.* Labeling shall comply with the requirements of sections 73.50 to 73.55, inclusive. In addition, the label or a package enclosure shall include the identification and source of the virus or viruses contained in the vaccine, the tissue medium on which the virus or viruses were propagated, stabilizers and preservatives, if any, and the type and amount of antibiotics.

(e) *Dating.* (1) The expiration date in no event shall be more than 2 years after the date of manufacture as defined in section 73.82(a) provided the product is maintained in the frozen state, (2) the expiration date shall be no more than 1 year from the date of issue provided that the product is maintained in the frozen state, and (3) the expiration date shall be no more than 7 days from the date of issue if issued as a liquid and provided it is maintained at a temperature no higher than 10° C.

(f) *Samples and reports.* For each lot of vaccine, the following materials shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda 14, Md.:

(1) All protocols relating to the history of manufacture of each lot of vaccine, and the results of all tests performed.

(2) A 1-liter bulk sample of each monovalent pool used for the test described in section 73.114(b).

(3) A total of no less than a 200-milliliter sample of the vaccine in final labeled containers.

Section 73.117 *Clinical trials to qualify for license.* To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design, by oral administration of the product. Such clinical trials shall be conducted with five consecutive lots of poliovirus vaccine which have been manufactured by the same methods, each of which has shown satisfactory results in all prescribed tests. Type specific neutralizing antibody (from less than 1:4 before vaccine treatment, to 1:16 or greater after treatment) shall be induced in 80 percent or more of susceptibles when administered orally as a single dose or in excess of 90 percent of susceptibles when administered orally after a series of doses. A separate clinical trial shall have been conducted for each monovalent and each polyvalent vaccine for which license application is made.

Section 73.118. *Equivalent methods.* Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Poliovirus Vaccine, Live, Oral, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Surgeon General so finds and makes such finding a matter of official record.

(Sec. 215, 58 Stat. 690, as amended; 42 U.S.C. 216. Interpret or apply sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262.)

Dated:

_____,
*Surgeon General.*

Approved:

_____,
*Secretary.*

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