CHAPTER 13

Prelude to the Salk Vaccine

But my purpose here is to doo theym good that haue moste nede, that is to saye, children: and to shewe the remedies that god hath created for the vse of man. . . .

Thomas Phaire, *The Boke of Chyldren*, 1545

Q: Dr. Rivers, on January 23, 1953 the Committee on Immunization of the National Foundation held a special meeting at Hershey, Pennsylvania, to examine the reports made by two young scientists. One of these was Dr. Jerome Syverton, the other was Dr. Jonas Salk.[1]

Rivers: I have told you something about Jerry Syverton before. For now, let me say that when Dr. Enders and his associates succeeded in propagating poliovirus in nonnervous tissue in 1949, Dr. Syverton set himself the task of trying to extend that work by developing pure strains of human and monkey extraneural cells *in vitro*. In the beginning he had little success. However, after about two or three years of experimentation, he and an associate, Dr. William Scherer, succeeded in propagating all three known types of poliovirus in morphologically pure cultures of monkey testicular fibroblasts maintained in a series. A short time later they succeeded in repeating this work with a strain of human malignant epithelial cells called HeLa cells.

These are very interesting cells, and perhaps I ought to take a minute or two to tell you how they were found, because they have since become important to people engaged in cancer research. Originally HeLa cells were discovered in the tissue of a Negro woman who was

[1] Minutes of the Meeting of the Committee on Immunization, The National Foundation for Infantile Paralysis, January 23, 1953.

operated on for a cancer of the cervix sometime during World War II. Later, they were named in honor of this patient. So far as I know, the initial biochemical and cytological studies of HeLa cells were done by Dr. George Gey of the Johns Hopkins Medical School, and it was he who supplied Dr. Syverton with his first strain. The achievement of Syverton and his coworkers rested on the fact that they discovered that HeLa cells could be used effectively for the detection and quantitation of poliovirus as well as its cultivation.

Syverton's work was beautifully done and created a great impression on the Immunization Committee, but there was serious doubt on the part of many virologists that it would be feasible to use HeLa cells to produce virus for a potential vaccine. John Enders best expressed that doubt when he said that he wouldn't want to use cancer cells as the basis for any vaccine, on the grounds that, since investigators at that time didn't know the cause of cancer, it was extremely unwise to inject any elements cultivated in HeLa cells into people until such answers were forthcoming. Later Joe Smadel and I talked about Syverton's work at great length and came to the same conclusion, although for different reasons. Unlike Dr. Enders, we felt that if the proper precautions were taken to filter the HeLa cells from the tissue cultures before the virus was used in a vaccine, it would be perfectly safe to use such virus. However, we didn't believe that the public would take a polio vaccine if it discovered that such a vaccine was made from viruses cultivated in tissue cultures of malignant cells. We believed that such a public attitude would not only be natural, it would also be right. Hell, if I was completely ignorant of what went on in science, I wouldn't take such a vaccine. In spite of this I don't want you to make any mistake about the importance of Dr. Syverton's work. Although investigators couldn't use HeLa cells for the production and harvesting of poliovirus, they could use such cells immediately and profitably in the laboratory for diagnostic purposes.

Q: Dr. Rivers, how much of a problem was it in 1953 to produce poliovirus in sufficient quantity to make a polio vaccine?

would go so far as to say that, by the time Dr. Syverton had reported
Rivers: I don't believe that it was much of a problem in 1953. I

his first success in 1952, Raymond Parker at the Connaught Laboratories in Toronto had already taken an important step in solving the problem of producing poliovirus in large quantities in tissue cultures. I have known Dr. Parker for a long time. He is a Canadian by birth and received a good deal of his scientific training at Yale and at the Kaiser Wilhelm Institute in Berlin. I first met him during the early thirties when he was associated with Alexis Carrel at the Rockefeller Institute. I don't know how much the latter association contributed to his knowledge of tissue culture work, but there can be no doubting that he was expert in this area. In 1951 Dr. Parker and some of his associates at the Connaught Laboratories devised a synthetic medium, know as mixture 199, as a nutrient for tissue cultures. It was soon discovered that, when this medium was substituted for the traditional Hanks solution and ox serum filtrate as a nutrient in tissue cultures used to cultivate polioviruses, such cultures could also produce large amounts of poliovirus without the presence of foreign serum. That work caught Harry Weaver's attention, and in 1952 the National Foundation gave the Connaught Laboratories a special grant to see if they could adapt tissue-culture techniques to the production of polioviruses in large quantities. Dr. Andrew Rhodes carried that pilot study through very successfully, and when the Salk vaccine came to be produced commercially the Connaught Laboratories were initially chosen to grow poliovirus for American pharmaceutical houses.

Q: Dr. Rivers, before we begin to talk about Dr. Salk's work, I wonder if you would tell me when you first met him.

Rivers: I first met Jonas Salk in 1940 when he was an interne at the Mt. Sinai Hospital in New York. At the time he and Tom Francis, who had been his professor of bacteriology at the New York University Medical School, had come to the Rockefeller Institute as guest investigators to study the use of ultraviolet light in inactivating influenza virus. I remember that they received much help in this project from Dr. George Lavin. However, I myself saw little of them at this time. I only met Dr. Salk casually and knew little about him save that he was a bright youngster who worked with Dr. Francis. You may remember that, when Dr. Francis was appointed professor of epi-

demiology at the School of Public Health at Michigan, in addition to his research he also undertook the obligation of developing a training program for young virologists.

In 1942, after Dr. Salk had finished his interneship, he took advantage of this program, and under a fellowship established by the National Foundation resumed his virus studies with Dr. Francis.[2] I would like to emphasize here that although Francis's laboratory spent a good deal of its time studying poliomyelitis, in the beginning Salk did not work with poliovirus. Instead, Dr. Francis put him to work on influenza and, in particular, purifying and concentrating the various strains of influenza virus for future use in a vaccine.[3] That work absorbed Salk and was later continued under the auspices of the Influenza Commission of the Armed Forces Epidemiological Board. In 1951 it culminated in his development of an inactivated vaccine, prepared with adjuvants, against both Influenza A and Influenza B strains of virus. I was a member of the Armed Forces Epidemiological Board, and I can tell you that the vaccine that Salk prepared with adjuvants was a damned good vaccine. It was by no means the first inactivated influenza vaccine ever to be developed—Frank Horsfall, for example, had developed a heat-inactivated vaccine against influenza several years before—but it was one of those that pointed the way to establishing immunization against influenza with an inactivated vaccine as a valid procedure in military medicine.[4] I would like to add

[2] Technically, Salk's grant was made by the National Research Council, but the funds for the grant program were supplied by The National Foundation for Infantile Paralysis.

[3] Dr. Francis notes, "The work I 'put' Dr. Salk on was at first his own fellowship request regarding local antibody formation. The influenza work had always been supported by the Commission on Influenza. The purifying and concentrating work was not an assignment but was done in conjunction with my own vaccine objectives and commitments" (private communication).

[4] Dr. Rivers here has telescoped a series of separate events relating to the making of vaccines against influenza. In 1942 Dr. Francis and his staff at the University of Michigan helped perfect an inactivated vaccine against influenza. Subsequently that vaccine was tested in a well-designed study in the ASTP units of a number of universities by a large group of investigators affiliated through the Commission on Influenza. This study confirmed the high effectiveness of the vaccine, and in 1945 it was used throughout the U.S. Army. Dr. Salk took part in this study. When Dr. Salk later moved to the University of Pittsburgh he continued his work on influenza and in 1951 prepared an adjuvant vaccine against influenza. This vaccine is the one that Dr. Rivers has reference to. See Members of the Commission on Influenza, Army Epidemiological Board, "A clinical evaluation of vaccination against influenza," *J. Amer. Med. Assoc.* vol. 124:982 (1944); J. E. Salk, H. E. Pearson, P. H. Brown, and T. Francis, Jr., "Protective effect of vaccination

that the problem that Salk faced—in providing an inactivated vaccine to evoke a high level of antibody and to maintain an antibody titer above the critical level required for immunity against influenza was strikingly similar to the problem he later faced in preparing an inactivated vaccine against polio.

I actually came to know Dr. Salk better after his laboratory at the University of Pittsburgh agreed to participate in the National Foundation's program for typing poliovirus. Harry Weaver, who played a key role in organizing that program for the Foundation, was very much impressed with Salk and communicated his enthusiasm about his work to the Virus Research Committee. I know that on more than one occasion he sang his praises to me. It was because of his work typing polioviruses that Salk began to turn up at the conferences held by the Foundation on problems of immunization. I must say that although Dr. Salk was respectful of his elders—which one might expect of a youngster—he nevertheless gave a good account of himself in the give-and-take that distinguished these affairs. As a matter of fact, if you had a thin skin it was not a good idea to attend these conferences because no one was ever spared. Hell, if you presented a paper or got up to talk, you had to be prepared to be ripped apart. It didn't matter who you were: if you got up to talk you were a fair target. That was the function of these meetings—it was to examine results and test ideas. Why should anybody be sacred?

In 1950, when a number of refinements in typing poliovirus made it feasible to cut back the number of laboratories exclusively working

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against induced influenza B," *Proc. Soc. Exptl. Biol. Med.*, vol. 55:106 (1944); J. E. Salk, M. L. Bailey, and A. Laurent, "A safe immunologic adjuvant for enhancing the height and persistence of antibody response to influenza virus vaccines in man," *J. Clin. Invest.*, vol. 30:669 (1951). Although Dr. Rivers is correct when he credits Dr. F. L. Horsfall, Jr., with being among the first to produce an inactivated vaccine against influenza, Horsfall was by no means the first to work on problems of a vaccine against influenza and was preceded by several years in this activity by a number of American and British investigators. For further details, see A. Chenoweth, et al., "Active immunization with the viruses of human and swine influenza," *Amer. J. Diseases Children*, vol. 52:757 (1936); J. Stokes, Jr., et al., "Vaccination against epidemic influenza with active virus of human influenza," *Amer. J. Med. Sci.*, vol. 194:757 (1937); C. H. Andrewes, and W. Smith, "Influenza: Further experiments on the active immunization of mice," *Brit. J. Exptl. Pathol.*, vol. 18:43 (1937); F. L. Horsfall, Jr., et al., "Studies on the efficacy of a complex vaccine against influenza A," *Public Health Rept.*, vol. 56: 1863 (1941). The problem of influenza is superbly reviewed by R. E. Shope, "Influenza, history, epidemiology and speculation," *Public Health Rept.*, vol. 73:165 (1958).

on typing problems, Harry Weaver encouraged Dr. Salk—whose laboratory you may remember was one of four engaged in typing work—to submit an application to the Foundation for developing a new research program in immunization for his laboratory. He didn't have to prod too hard, because within a very short period of time, Salk submitted a first rate program to the Virus Research Committee for consideration. The interesting thing about this application is that if you examine it, you will find that Salk initially was far more concerned in searching for nonpathogenic live-virus strains of polio that could induce immunity than he was in an inactivated vaccine. I would go so far as to say that one of Salk's secondary projects in passive immunization—one that involved the oral administration of antibody derived from the yolk of eggs laid by hens previously immunized with all three types of poliovirus—probably absorbed him more in the beginning than working on an inactivated vaccine.[5]

Within a year after starting his new program, Dr. Salk shifted the focus of his attention to study the effect of formalin-inactivated vaccines. I think that the impetus for the shift came from two sources. The first was his success in preparing an inactivated vaccine with adjuvants against influenza, and the second was the rapid development of tissue-culture work in his laboratory. The latter development not only allowed him to cultivate polioviruses for his vaccines but also allowed him to undertake quantitative estimations of virus and antibody. It's easy in the saying, but actually Dr. Salk had to surmount a great many technical problems in order to prepare an inactivated vaccine against polio. For instance, although it was known how much formalin was necessary to destroy the infectious nature of poliovirus, no one at that time knew how much in excess of that amount poliovirus could tolerate and still be antigenic. Another typical problem was the necessity of studying the extent to which a virus suspension could be diluted and still induce antibody formation when mixed with adjuvants. Within a year, however, Salk and his associates solved these and other problems.

Perhaps one of Dr. Salk's most significant technical achievements during this period was his extension of techniques for cultivating all

[5] Jonas Salk, Grant Application to The National Foundation for Infantile Paralysis, July 20, 1950 (CRBS #105, University of Pittsburgh, 1950, National Foundation Archives).

three types of poliovirus in roller-tube cultures of monkey testicular and kidney tissue. I say this because in the end it was these techniques which supplied him with the material of high antigenic content—especially when combined with an adjuvant—which he needed for his inactivated vaccine. No scientist works alone, and I would like to stress here that some of Dr. Salk's success in the area of cultivating poliovirus owes much to Dr. Syverton and his team at the University of Minnesota, and to Dr. Charles A. Evans and his associates at the University of Washington for their pioneer efforts in growing neurotropic viruses in extraneural animal tissues. Be that as it may—by the end of 1951 Dr. Salk was able to demonstrate that he could successfully immunize monkeys against polio by inoculating them intramuscularly with tissue-culture fluids treated with formalin and emulsified with mineral oils. In fact, it was this success which encouraged him in the spring of 1952 to test the effect of his inactivated preparations on a limited group of children at the D. T. Watson Home for Crippled Children just outside Pittsburgh and at the Polk State School at Polk, Pennsylvania.

I think that I should take a moment to tell you something about these tests. First, all of the children who were inoculated at the D. T. Watson Home were paralytic victims of recent polio epidemics. With the exception of one small group, all of these children were inoculated intradermally with formalin-inactivated tissue culture fluids, in aqueous solution, containing the virus responsible for their original infection. The purpose of this test was to learn whether inoculation of such material would act as a booster. The second test was different both in purpose and in the nature of the children tested. The children at the Polk State School were mental defectives who previously, as far as was known, had not had paralytic polio. Those children were inoculated intramuscularly with small amounts of formalin-treated tissue-culture fluids containing all three immunologic types of poliovirus emulsified with mineral oils. The purpose of this test was to see if such a vaccine could in fact induce antibody formation in humans.

I must say that the initial results of these limited human tests carried a great deal of promise. For instance, the children at the Polk State School who received small doses of inactivated preparations with adjuvants demonstrated antibody formation for all three immuno-

logic types of poliovirus, while the children of the D. T. Watson Home, who were inoculated with inactivated preparations without an adjuvant, showed antibody formation to type 2 polio. In either case, the data for the level and persistence of antibody fortified the conviction that it was possible to approximate the immunologic effect of the natural disease with an inactivated vaccine. Actually, one of the purposes of the Conference on Immunization in January 1953—which you mentioned earlier—was to give virologists a chance to examine the early results of Dr. Salk's tests.

Q: What was the reaction of those present at the conference to Dr. Salk's report?

Rivers: Unfortunately, I can't answer that question firsthand, because I was unable to attend that particular conference. What I know of it comes from a subsequent reading of the minutes of the conference. However, I will say that you can't read the minutes without feeling that those present were impressed with Dr. Salk's achievement. This doesn't mean that they accepted everything he said, lock, stock, and barrel—not by a long shot—and I can tell you that they put Jonas through his paces. Some of those present were doubtful that immunization with formalinized vaccines would give antibody levels higher than that produced by a natural infection. Others were skeptical of the use of adjuvants. Many adjuvants at that time were produced commercially and had toxic components that caused rather severe local reactions when given intradermally. Still other virologists were worried about the possibility of organ damage caused by inoculating people with material derived from monkey kidney tissue. They examined Jonas closely—that's not surprising—these boys would have questioned their own mothers if they were foolhardy enough to give a paper at a conference.

When the problem of whether Dr. Salk's results warranted his carrying out a field trial later that spring was brought up, a wide variety of opinion was expressed. Dr. Smadel got up and asked, "When are you going to do your Provo test?" Dr. Smadel was bold and at this point, I would say, was even out in front of Harry Weaver. From the January meeting forward, Dr. Smadel consistently preached "to get

going and hold a field trial." Dr. Tommy Turner of Johns Hopkins was another who felt that, if an inactivated vaccine could be produced under rigid standards of safety, an early field trial was warranted. Dr. Sabin on the other hand, counseled against holding a field trial. Like some others at the conference, he too was concerned about the use of adjuvants and the organ damage that might be caused through the use of monkey kidney material. He particularly urged that more work be done with animals and even suggested that antibody surveys be made in representative communities. Albert not only looked directly at the question, he looked around it and examined every possible facet, including a few theoretical facets that didn't occur to others. A number of other virologists, while impressed with Dr. Salk's results, were at that time simply against the idea of holding a field trial of the nature of the Provo, Utah, gamma globulin tests. These recommended that Dr. Salk extend his clinical studies on a more limited basis than that suggested by a field trial. Dr. John Enders fell into this category. I think that it might be helpful if I quoted some of the remarks he made at that time.

I am afraid that I can't quite agree with Dr. Turner if he uses the term "Provo experiment." I don't think that we are ready for it. I think, if we do such a thing, it would mean that we would go off half cocked.

What I have heard here makes me think that, first of all, we haven't decided on the strain of virus that is most suitable to use yet. Dr. Salk is not quite satisfied with his test for safety in respect to the virus. Further work should be done on that, and careful work. The mode of vaccination, the route and type of vaccination, adjuvant or no adjuvant, intradermal against intramuscular—we haven't enough data to decide which to use on a scale of this magnitude.

Those are a few of the points that it seems to me we have made a lot of progress on with respect to solving them, but we haven't got the answer yet, and I don't think that a large scale experiment should be undertaken until those things have been worked out on smaller groups such as Dr. Salk has already used.

I would suggest more experimentation along the same lines that he is doing so admirably at the moment, and not enter into a large experiment which will inevitably he connected with a lot of publicity and may jeopardize the entire program. I don't see that we are prepared to go into it in the time that we have at our disposal. I would be very strongly against any thing of the Provo sort this year.[6]

[6] Minutes of the Meeting of the Committee on Immunization, The National Foun dation for Infantile Paralysis, January 23, 1953, pp. 237–238.

I would like to add here that at no time during the conference did Dr. Salk push for a field trial. As a matter of fact, like Dr. Enders, he too spoke of extending his clinical studies, rather than doing a field trial on the order of Provo. He was very cautious. After this canvas of opinion—and believe me when I say that everybody spoke his mind —the conference adjourned. As far as I know, at no time did the conference take a formal vote on whether to do a field trial or not. That was not its purpose. Several days after this conference, Harry Weaver met with me to discuss further the pros and cons of doing a field trial later that spring. It was not an easy matter. The dilemma that we faced is perhaps best expressed in a memorandum that Harry Weaver prepared for Mr. O'Connor following our meeting. I would like to quote a part of it here:

During the past several months very considerable progress has been made toward the development of a safe and effective vaccine for poliomyelitis. In fact, one of our grantees has developed a vaccine which, when injected intramuscularly, stimulates production of all three poliomyelitis antibodies in amounts that should be adequate to protect against the paralytic consequences of an infection with the virus. This vaccine already has been injected into 161 individuals without any untoward effects that were discernible.

The practice of medicine is based on calculated risk. Where the risk is known, the physician elects to follow the course that provides the greatest benefit with the least risk of incurring any untoward effects.

It is impossible at this stage of development to predict the degree of efficacy on the one hand, and the degree of safety, on the other, of the poliomyelitis vaccine that has been developed. These questions can only be determined after injecting relatively large numbers of human beings.

There is no question of the facts that with additional research: (1) A still more effective poliomyelitis vaccine could be produced; (2) We would be better informed as to the kind and frequency of untoward effects that might result from the use of the vaccine; and (3) We would be better informed with respect to the best route of inoculation, and the best time for administration, of the vaccine to obtain maximal protection against paralytic disease. . . .

If such research is carried out, a very considerable amount of time will elapse before a poliomyelitis vaccine is made available for widespread use; with the result that, in the interim, large numbers of human beings will develop poliomyelitis who might have been prevented from doing so had the vaccine been made available at an earlier date.

It seems to many of us that we have come to a stage where the future course of our work must be governed by both scientific and sociological considerations. At the request of Dr. Thomas M. Rivers, Director of the Hospital of the Rockefeller Institute for Medical Research, I am calling a meeting of leaders in both these fields. During this meeting we will review the status of the poliomyelitis vaccine as of the day of the meeting; attempt to weigh the consequences of moving into the field too rapidly on one hand, as contrasted with postponing field work on the other; and to give the investigator the benefit of our thinking regarding the future course of action he should follow.[7]

I would like to underscore here our purpose in broadening the base of the new conference to include participants other than virologists. At that time the problem of human experimentation was in the public eye for a wide variety of reasons. For instance, in September 1952, Pope Pius XII had given a speech at the First International Congress on the Histopathology of the Nervous System in which he outlined the Roman Catholic Church's position on the moral limits of human experimentation for purposes of medical research. That speech had a very broad impact on medical scientists both here and abroad.[8] At the very same time, the American Medical Association was also trying to sketch principles to guide scientists on the use of human subjects in medical experimental work. This particular attempt was made in response to the death of three prisoners from infectious hepatitis following a series of experiments in a federal penitentiary designed to discover a method for making whole blood and plasma safely.

Well, how would you weigh those deaths? Would you have stopped the experiments, or would you have continued them? I feel free to ask you these questions, because I was faced with them as a member of the Armed Forces Epidemiological Board. I can tell you now that they weren't easy to decide. For one thing, there was no settled code or standard to which one could refer regarding such experiments. To be sure, a number of statements on human experimentation had been made at the Nuremberg War Crimes trials. Unfortunately, however, these statements were not clearcut and in some in-

[7] Memorandum, Harry Weaver to Basil O'Connor, January 30, 1953 (Folder, Vaccine, Polio, Salk: Development and Promotion, 1952, National Foundation Archives).

[8] Dr. Rivers had been much impressed with Pope Pius's speech, "The Moral Limits of Medical Research and Treatment," and later sent his annotated copy to Basil O'Connor (see T. M. Rivers to Basil O'Connor, January 29, 1953, folder, personal correspondence, 1953, Rivers papers).

stances were even contradictory. I will say this, that in the end the Armed Forces Epidemiological Board voted to continue with the whole blood and plasma experiments in spite of their hazardous nature, because at that time thousands of people were dying annually of infectious hepatitis following blood transfusions and the injection of plasma. I don't mean by this to compare the dangers of those experiments with tests of Dr. Salk's polio vaccine—I only want to stress that the general question of human experimentation was one of the key questions that had to be considered in extending Dr. Salk's tests on the scale of a field trial. Another important reason for broadening the base of the conference was to share the responsibility with Dr. Salk for conducting a field trial if a decision to go ahead was finally reached.

Q: Dr. Rivers, I would like to pursue with you the problem of sharing responsibility with Dr. Salk.

Rivers: Before I answer your question I would like to emphasize once more that Dr. Salk was very cautious about extending his clinical tests to field-trial status during the spring of 1953. I think that his attitude was nowhere more apparent than in the comments he made during the special February meeting called by the Foundation. For instance, at one point a discussion that Dr. Salk began on safety tests became so bogged down in detail that it got Dr. Smadel sore. "Look," Joe said, "if we've got something good enough to work on, let's quit fooling around with minutiae and get down to work. If every vaccine that was ever used on humans was put through half of this, we never would have had any preventive measures at all, because no one would have bothered with them." I felt like Joe. I was sure that Jonas had an inactivated vaccine that was safe for children. If I didn't think that, I never would have allowed the Foundation to use my name to call the February meeting. I can tell you that if I had a kid I wouldn't have hesitated for one minute to inoculate him at that time with Salk's vaccine. Damn it, do you know that at this meeting, Salk wouldn't even call his vaccine a vaccine; he kept calling it an inactivated preparation. Now, what I have just said doesn't mean that I was ready to run off half-cocked for a field trial in the spring. It simply means that,

like Samuel Johnson, I realized that nothing would ever be accomplished if we waited to overcome all possible objections.

The basic problem that I and others at the February meeting faced was to decide what measures were necessary to test the safety and efficacy of Dr. Salk's vaccine. Now that sounds more complicated than it actually was, because at that particular point the problem of safety was paramount, all other problems such as efficacy were actually secondary. Believe me, when you deal with a vaccine, the first question that you ask is, "Is it safe?" and if it isn't you stop right there; you don't even bother to ask any other questions. In the end we decided that it wasn't feasible or necessary to hold a field trial that spring to establish the safety of Salk's vaccine. Instead we recommended that between five and six hundred children in Alleghany County, Pennsylvania—the site of Dr. Salk's laboratory—be inoculated with the vaccine well before the onset of the polio season. The limitation on time was important and was made because we wanted to avoid the vaccine's being blamed for incidents of polio that had nothing to do with the vaccine. You know, occasionally a person will drop dead if you only stick him with a sterile needle. We just wanted to avoid as many untoward, accidental incidents as was humanly possible. It was felt that these inoculations, plus the 161 children that Dr. Salk had previously inoculated at the D. T. Watson Home and the Polk State School, would furnish important evidence about the safety of the vaccine in humans. It was contemplated, moreover, that after the polio season—the late fall and winter—such inoculations would be continued in a sufficient number of communities to furnish more data which later might be helpful in evaluating the safety and effectiveness of the vaccine before large-scale trials were undertaken in 1954. These recommendations marked the first step taken for sharing responsibility with Dr. Salk.[9] The second involved sending a letter to the *Journal of the American Medical Association*. The circumstances were these.

Before the February meeting, it was known that Dr. Salk had submitted an article to the *Journal of the American Medical Association* describing the initial results of the early tests of his vaccine on chil-

[9] See also Minutes of Meeting of The National Foundation for Infantile Paralysis, February 26, 1953.

dren. That article was scheduled for publication late in March of 1953.[10] The great fear that existed at the Foundation and elsewhere was that the appearance of the article would create a public demand for the vaccine, and that great pressure would subsequently be brought to bear on both Dr. Salk and the Foundation for the immediate release of the vaccine. To counter that anticipated pressure, I suggested that the meeting join with me in writing a letter to the *Journal* embodying the recommendations we had earlier made to Dr. Salk for the development of procedures for testing the safety of his vaccines, and in particular to explain the need for such procedures. A long letter was drafted and, after some changes of phraseology, was signed by all those present at the meeting and sent off to the *Journal.* It was a good letter, but frankly I don't think that it would have amounted to a hill of beans if the people present at the meeting hadn't agreed to join with me in signing it. These people were eminent in the world of science, government, and education—their names meant something and afforded protection, because people would stop and listen to them. Believe me when I say that no one in the wide, wide world would have paid any attention to that letter if I had signed it alone.

Q: Dr. Rivers, what was the reaction of the American Medical Association to the letter?

Rivers: As far as I know, there was no reaction at all, except that the *Journal* published the letter in the issue following the publication of Dr. Salk's article. Dr. Thomas P. Murdock, who was a member of the Board of Trustees of the American Medical Association, and Dr. Austin Smith, who was then serving as editor-in-chief of the *Journal,* had a great deal of sympathy for the problems involved in developing a vaccine against polio, and they saw to it that the letter was published. In all fairness, I should add that the *Journal* also published an editorial underlining the purpose of the letter.[11] However, the AMA

[10] Dr. Rivers' reference here is to J. E. Salk, "Studies in human subjects on active immunization against poliomyelitis. A preliminary report of experiments in progress," *J. Amer. Med. Assoc.,* vol. 151:1081 (1953).

[11] Editorial: "Research on a vaccine for the prevention of poliomyelitis;" *J. Amer. Med. Assoc.,* Vol. 151:1194 (1953). The letter signed by Dr. Rivers and others appeared in the same issue, on p. 1224.

itself did nothing more. They certainly didn't do what they later did for Albert Sabin. Recently, as you know, the House of Delegates of the AMA endorsed the use of the Sabin live-virus vaccines.[12] That decision, by the way, marked the first time that the AMA has taken such action, and I can assure you that they didn't do anything comparable for Jonas Salk. They published his paper, sure, but if the vaccine had turned out badly I believe that the *Journal* would have turned around and said, "There was no evidence from the paper we received that the vaccine was dangerous—the fault resides with the author of the article." That is a set policy. The AMA never takes any blame—and they shouldn't—for articles published in their *Journal.*

Q: Dr. Rivers, in May of 1953 the National Foundation organized a special Vaccine Advisory Committee to advise the Foundation with respect to the field trials of the Salk vaccine. Why was this necessary when the Foundation already had in being a special Immunization Committee composed of the leading virologists in the country? [13]

Rivers: The Immunization Committee, as you say, was made up of distinguished virologists. I would like to add that many—although not all—were also grantees of the Foundation, and each of these in one way or another had a special stake in the polio research then in progress. As is natural, each man's opinion was a bit biased in favor of what he was doing, especially when it came to a question between his work and that of another. Now as far as the work of the Immunization Committee went, that bias didn't matter one whit, because the basic function of the Immunization Committee was to discuss and examine the research that was then in progress. The committeemen presented papers, listened to one another, or fought with one another.

[12] Dr. Rivers here has reference to the report, *The Present Status of Poliomyelitis Vaccination in the United States,* which was approved by the House of Delegates of the American Medical Association on June 28, 1961.

[13] The Vaccine Advisory Committee was formed on May 25, 1953. The Immunization Committee of The National Foundation for Infantile Paralysis was created in April 1951 and met for the first time on May 17, 1951. Its original members were David Bodian, John Enders, Thomas Francis, Jr., William McD. Hammon, Howard Howe, John R. Paul, Andrew J. Rhodes, Albert Sabin, Jonas E. Salk, Joseph Smadel, Thomas Turner, and Antonio Ciocco. At various times other experts were invited to join with the Immunization Committee in its conferences and meetings.

They were frequently called together so that they and the Foundation could learn what was going on, but they were never an executive committee, and they never had any power to act one way or another.

I know that what I have just said is not exactly the view that many members of the Immunization Committee had of their functions, and some would strongly disagree with my interpretation. Some members always thought that their responsibilities transcended mere discussion, and when the Vaccine Advisory Committee was formed they felt that they were being bilked out of making decisions on the Salk vaccine. I tell you this because I want it clearly understood that some members of the Immunization Committee resented the organization of the Vaccine Advisory Committee. They didn't keep their feelings secret; as a matter of fact, they were pretty vocal about it. I would like to add that this resentment was not limited to decisions about the Salk vaccine and was revived from time to time, especially when executive decisions had to be reached about live-virus vaccines and orphan viruses.

Now I will tell you why Mr. O'Connor created the Vaccine Advisory Committee and the reason why I agreed with him. Mr. O'Connor designed the Vaccine Advisory Committee as a small executive committee whose duty it was to inform the Foundation what was going on, scientifically speaking, and to devise a program for action in developing a vaccine. We didn't think that it would be proper for anybody who had a personal stake in immunization research—whether it was Salk, Sabin, or anybody else for that matter—to be allowed to vote for anything. We thought that such decisions were best arrived at by disinterested people who were not necessarily virologists. The committee that was eventually organized met those requirements. It was made up of Dr. David Price, Dr. Thomas Murdock, Dr. Ernest Stebbins, Dr. Thomas Turner, Dr. Norman Topping, Dr. Joseph Smadel and myself. Some of these names are already familiar to you —I have previously spoken of Smadel and Stebbins and Turner— but I will say something of the others. David Price was then the Assistant Surgeon General of the United States, Thomas Murdock was a practicing physician and a member of the Board of Trustees of the American Medical Association, and Norman Topping, who was then Vice President of Medical Affairs of the University of

Pennsylvania, had previously had a long and distinguished career in the U.S. Public Health Service.

Q: Dr. Rivers, most of the members of the committee that you have described seem to have had a larger experience in public health than in virology. As far as I can see, only Dr. Smadel and yourself had previously done laboratory work with viruses.

Rivers: That's true; however, I think that you ought to keep two things in mind. First, as I indicated before, the problems of the Salk vaccine involved matters of public policy and were not restricted to problems of virus research. Second, people like Price, Turner, Stebbins and Topping were trained public health men and previously had been closely associated in research involving the epidemiology of polio. More important, they were people who were accustomed to examining and weighing scientific evidence. They didn't have to be virologists to reach a judgment about the Salk vaccine—hell, if they needed a virological viewpoint, Joe Smadel and I were fully capable of supplying a disinterested opinion. I can tell you quite frankly that I would not have served on a committee where some of the members were people who had a personal interest in either an inactivated or a live-virus vaccine. I have always had the conviction that Mr. O'Connor was right in organizing the Vaccine Advisory Committee—if he hadn't, I probably would have tried to persuade him to form such a committee.

Q: Dr. Rivers, were there any changes in the personnel of the Vaccine Advisory Committee during the consideration of the Salk vaccine?

Rivers: There were two changes. In the fall of 1954, a little over a year after the committee was first organized, Dr. Murdock resigned. Tom Murdock was one of the nicest and fairest men I ever met. He didn't know anything about viruses particularly, but he could listen to evidence and reach a decision. He didn't always vote the way I voted, but that made no difference. Plenty of people didn't think the way I thought. I should make it clear here that this resignation had nothing

to do with policy. During the summer of 1954, Tom began to have terrible pains in his chest, and upon examination it was discovered that he had an aneurysm of the thoracic aorta. The pain became so bad that his doctor finally advised an operation and it was then that he resigned from the committee. The operation was successful and Dr. Murdock lived for some years afterward. However, although he still took a keen interest in Foundation matters, he could never carry on as actively as he had before the operation.

The second person to resign from the Vaccine Advisory Committee was Joe Smadel. Again, the resignation had nothing to do with policy. Joe, in addition to his regular work as chief of the Virus and Rickettsial Laboratories of the Army, was asked in the winter of 1954 to undertake a special assignment by the government, and he discovered that he just didn't have enough time to meet all of his obligations, so he resigned from the committee. However, as you will see, he still continued to play an active role in working on problems relating to the production of the Salk vaccine. I hated to lose Joe, but fortunately we got an excellent replacement in Dick Shope.

Q: Dr. Rivers, wasn't Dr. Shope's experience mainly in animal pathology?

Rivers: The first thing to remember about Dick Shope is that he is an M.D., and the second is that there are few people in the country who can match his general knowledge of virology. It is true that Dick interests himself in veterinary problems, but it would be a mistake to assume that because of this he has less reverence for human life. Pigs or men, Dick Shope has a reverence for life. I can tell you that when he prepared his influenza vaccine for hogs he wasn't ready to lose one hog. Safety was ingrained in him. Oh, I know that you have heard some people say that Dick Shope likes his hogs better than he likes some human beings—hell, I can't say that I blame him for that.

Q: Dr. Rivers, previously you described Dr. Weaver's role in developing the Salk vaccine. Did he play any part in planning the field trials to evaluate the vaccine?

Rivers: I would like you to bear in mind that the Vaccine Advisory Committee did not at any time have any administrative responsibilities for carrying out the field trial. Those responsibilities were Foundation responsibilities and in the beginning they fell on Harry Weaver's shoulders. I must say that Dr. Weaver never shirked these responsibilities. On the contrary, I think that he embraced them. Long before the Vaccine Advisory Committee ever met, he set about to develop plans for a field trial. For instance, almost the first thing he did was to reorganize the Medical Research Division of the Foundation so that it could become the instrument for holding the trials. As a part of that reorganization, he persuaded Dr. Joseph Bell of the U.S. Public Health Service to take a leave of absence and come to the Foundation to help him develop epidemiological programs for evaluating the vaccine. I believe that Dr. Weaver planned for Dr. Bell to eventually be the scientific director of the field trial under his immediate jurisdiction. I don't know the full ins and outs of subsequent developments, as I wasn't an employee of the Foundation at the time, but I do know that, just about this time, Weaver got into one hell of an administrative hassle with Hart Van Riper, who was medical director of the Foundation and Weaver's boss.

It's no secret that the two men didn't get along very well together. They had fought before this on a variety of issues. Dr. Van Riper was a good pediatrician, but that was about the end of it. Research was just outside of his ken. Dr. Weaver, on the other hand, was a smart, aggressive hombre who knew a great deal about research and the Salk vaccine in particular, and, as I say, wasn't loathe to push his ideas and assume responsibility for the trial. When Weaver began to reorganize his department, the two clashed. Van Riper claimed that Weaver was going over his head in getting things done, and Weaver claimed that Van Riper was thwarting his plans for the trial. When Melvin Glasser, who had previously worked very closely with Mr. O'Connor in the International Red Cross, was hired by the Foundation as assistant administrative director, to coordinate the work of the field trial and other departments of the Foundation, Weaver looked upon the appointment as an expression of a lack of confidence in his ability to plan and carry out the trial and soon afterward resigned.[14] I will

[14] Dr. Weaver resigned his post on August 29, 1953.

say this. I personally hated to see Weaver leave, and so for that matter did Mr. O'Connor. Mr. O'Connor was always very fond of Weaver, and his resignation didn't affect Mr. O'Connor's opinion of him one bit. They are friends to this day. The moral should be plain: if you have occasion to fight with your boss, you must also be prepared to leave your job.

Q: Dr. Rivers, how did Dr. Weaver's resignation affect the development of the field trial?

Rivers: If you mean, did it slow things up, the answer is no. Henry Kumm, who had joined the Research Division of the Foundation a year or two before Weaver's resignation, was appointed director of research in his place. Dr. Kumm was very knowledgeable about research and particularly well trained in public health, having served for many years as a field officer for the International Health Board of the Rockefeller Foundation in Central and South America. I would go so far as to say that Weaver's resignation did not immediately affect Dr. Bell either. As a matter of fact, after Weaver left, Bell was formally appointed scientific director of the field trial, and as such was charged with formulating and administering policies and plans for all aspects of the field trial. To help him in this work, Dr. Thomas Dublin, who was actually hired by Weaver, was appointed as Bell's deputy.

Q: Dr. Rivers, one of the keys to understanding the subsequent development of the vaccine field trials are the plans that Dr. Bell initially developed for the trial.[15] Before we discuss these plans, I wonder if you could tell me something about Dr. Bell.

Rivers: At the time that Dr. Bell was hired by Harry Weaver, he was chief of the Epidemiological Unit of the Microbiological Insti-

[15] Joseph Bell, Outline of Considerations and Tentative General Plans for an Epidemiological Field Trial of a Poliomyelitis Vaccine, September 8, 1953 (folder, Vaccine, Polio, Salk: Development and Promotion, September 1953, National Foundation Archives); Summary of a Proposed Plan for a Field Trial, October 1, 1953 (folder, Vaccine, Polio, Salk: Development and Promotion, October 1953, National Foundation Archives).

tute of the National Institutes of Health. He had had a long-time interest in preventive medicine and was widely known as an expert in the epidemiology and prevention of childhood diseases. More particularly, he knew a great deal about vaccines. For instance, Bell was the first to show that alum-precipitated pertussis vaccine gave real protection against clinical whooping cough in children. In the area of epidemiology, it was his study of an outbreak of Q fever in Los Angeles which led the way to the prevention of that disease by demonstrating that the fever was practically confined to the consumers of raw milk from infected cows or to people who lived or worked near infected dairies. Just before coming to the Foundation, Bell also made an important contribution to understanding the epidemiological aspect of Coxsackie viruses in human disease. I tell you all this to underline that Dr. Bell was a good choice for the job that Harry Weaver had in mind. He subsequently proved his worth to the Foundation in a number of ways. To my mind, one of the very early important contributions that he made to the design of the field trials involved the use of adjuvants in the Salk vaccine.

You may remember that, when Dr. Salk carried out his early tests in 1952 and 1953, several groups of children were inoculated with a vaccine that was emulsified in mineral oils for the specific purpose of enhancing their antibody titers. These tests were very successful, and initially Salk believed that one dose of an adjuvant vaccine would be sufficient to immunize children. While it is true that many adjuvants were known to be irritating, Salk's experience—he had participated in inoculating soldiers with an inactivated influenza vaccine emulsified in mineral oil without undesirable reactions—fortified his conviction that it was possible to remove the reactive impurities of commercially produced adjuvants. As a matter of fact, he spent a good deal of time during the summer of 1953 looking for better adjuvants.

I believe that the Vaccine Advisory Committee would have gone along with a vaccine prepared with adjuvants, if it hadn't been for Dr. Bell. Bell had discovered that, when the influenza vaccine prepared with adjuvants was given to children, they showed a reaction that was quite different from that manifested by adult soldiers. In the case of children, such vaccine proved to be irritating, and a substantial number of children developed swollen painful arms and running abscesses that took months to heal. When the Vaccine Advisory Committee

received Bell's report, we decided against using an adjuvant vaccine. I remember that when we later asked Salk whether he could do without an adjuvant, he replied that he could and intimated that two or more doses of an inactivated saline vaccine would probably give the same result as one dose of an adjuvant vaccine. However, no one at that time actually knew how those injections should be spaced, and Salk himself suggested that studies be instituted to discover the required interval for optimal effect in giving such a vaccine. I think that it is fair to say that the decision to use multiple inoculations of a saline-inactivated vaccine in the field trials in part stems from Bell's report.

Looking back, I would have to admit that I still don't know whether an adjuvant in Salk's vaccine would have caused the trouble that Bell described. I say this, because the Salk polio vaccine is not as irritating a vaccine as the influenza vaccine, and to this day I wish we had inoculated several thousand kids with an adjuvant vaccine to test Dr. Bell's contention. I can only say that at that time the Vaccine Advisory Committee was primarily interested in being bloody-well certain that the vaccine that the children got in the trial was as safe and nonirritating as could possibly be made.

Q: Dr. Rivers, didn't Dr. Bell make other recommendations?

Rivers: Indeed he did, and I certainly didn't mean to imply by this short review that Dr. Bell's recommendations concerning the use of an adjuvant vaccine were the only recommendations he made. Actually, when Bell first came to the Foundation he developed a very detailed model for holding the field trials. At the time he drew up this model, he was particularly concerned with determining whether the Salk vaccine—which was then a laboratory prepared product—could be consistently and uniformly reproduced by pharmaceutical houses on a scale suitable for mass immunization. As a good epidemiologist, he also wanted to know whether the vaccine impaired the natural spread of polio infection, and whether the neutralizing antibodies induced by the vaccine protected children against naturally occurring paralytic disease. I would say that these questions constituted Bell's major objectives.

To achieve these objectives he recommended that two strictly com-

parable groups of children of school age be chosen and that one group be inoculated with Dr. Salk's vaccine and that a second control group be inoculated with inactivated influenza vaccine. If I am not mistaken, he originally suggested that both the polio and control influenza vaccine be given to children in the first and second grades, that no vaccines be given to third and fourth grades, and that both vaccines be given to fifth and sixth grade children. He further suggested that, before the field trials actually began, Dr. Salk institute limited trials with commercially prepared vaccines in about 5000 children in Alleghany County as a precautionary safety test.

No one had any quarrel with Dr. Bell's suggestions for limited safety tests with commercially prepared vaccines, but one hell of a fight developed over the question of using an injected control group, and in particular over using influenza vaccine as a placebo. The Vaccine Advisory Committee, for example, thought that the placebo should be a normal saline solution. That didn't suit Bell. He claimed that it would be more ethical to give the control group influenza vaccine because it would do them some good while the saline solution would do no good at all. I don't really know how far Bell was actually concerned with ethics; I think that it would be closer to the mark to say that as a public health man he saw the field trials as an opportunity to collect data about the effect of influenza vaccine in children, without too much extra effort and expense. In other words, he saw a chance of killing two birds with one stone.

Dr. Salk on the other hand was very unhappy with Dr. Bell's recommendations, so unhappy that a week or two after the Vaccine Advisory Committee first discussed Bell's recommendations he presented the committee with an alternative proposal for carrying out the field trial. The nub of Salk's proposal was that a narrow age band of the child population in specific communities—children in the second grade—be inoculated with the test vaccine, and that, instead of inoculating a control group with influenza vaccine, uninoculated children in the first and third grades of these same communities act as observed controls. Salk's proposal found favor with many people in the Foundation, because the use of nonvaccinated controls seemed to confer substantial administrative benefits in running the field trial. For one, under the Salk plan the manpower and time available for

vaccination would be concentrated on giving the vaccine and not be divided between giving the vaccine and the control substance. Second and perhaps even more important, the plan seemed to point a path that would avoid the difficulties that many feared would arise in ensuring that three identical injections of either the test or control vaccines would be given to the same individuals. Further, many felt that, by avoiding control injections, the localization of paralysis-provoking effect that sometimes occurred by the mere act of inoculation could be avoided.

The question of injected versus observed controls was argued before the Vaccine Advisory Committee not once but many times throughout the fall of 1953. It was never a tea party argument and the fur flew more than once. Dr. Bell was a good fighter and he was not a dumbbell. It's true that he was a hard guy to get along with, but, by the same token, some of the people at the Foundation were also hard to get along with. In the midst of these arguments Bell decided that he had had enough and resigned and went back to his old post at NIH.[16] In case you are wondering, I can tell you right now that Bell's resignation did not end the debates over the design of the field trials. Although the Vaccine Advisory Committee did not go along with all of Bell's recommendations, it did favor his orthodox plan for an injected control over Salk's plan for an observed control. I remember that several weeks after Bell left the Foundation the Vaccine Advisory Committee met in a special session to discuss this problem once more.

At that time, commercial production of the vaccine was lagging and it seemed highly doubtful whether it would be administratively possible to put on a controlled trial of the size that the Vaccine Advisory Committee had originally deemed necessary. The committee faced an unhappy dilemma. With the production of the vaccine lagging, if the Foundation ran a limited controlled trial, it also ran the risk of coming up with answers that would not be useful. We all believed that the Foundation had to put on a field trial in the spring of 1954; if it didn't, the lid would be off and the following year everybody and his aunt would be trying out their own vaccines unless the Public Health Service could put a muzzle on them. It was nothing we

[16] Dr. Bell resigned on October 31, 1953.

could count on, and in the circumstances we thought it might be more feasible to go along with the alternative plan developed by Dr. Salk.[17] I think it is fair to say that, from the middle of November 1953, the Foundation was prepared to run the field trials under Salk's plan and had even started the ball rolling in that direction. However, early in December, not more than two or three weeks later, everything stopped as the Foundation reexamined once more whether it was proper for it to conduct the field trial under its own auspices. At that time it was decided that the evaluation of the vaccine had best be done by a scientist outside the Foundation, and Tom Francis at the University of Michigan was chosen to do the job. That choice, I might add, changed the design of the field trial once more.

Q: Dr. Rivers, before we discuss Dr. Francis and the new design of the field trial, I would like to ask you whether the government played any role in planning the field trials.

Rivers: I don't know that I can answer that question in a clean-cut way. If you mean did the government know what was going on, the answer is yes. Dr. David Price, who was then the Assistant Surgeon General of the United States, and Joseph Smadel, who was then Chief of the Department of Virus and Rickettsial Diseases at the Walter Reed Army Center, were both members of the Vaccine Advisory Committee and participated in the various discussions and decisions made by the committee. One of the early decisions that we made directly involved NIH in the field trials. Initially, the Vaccine Advisory Committee was concerned about the safety of commercially produced vaccine and decided that, before such vaccine was passed for use in the field trials, it would have to pass safety tests in three different laboratories—the producer's laboratory, Dr. Salk's laboratory, and the Division of Biological Control at NIH. Later the Foundation signed a formal agreement with NIH that the Division of Biological Control would independently test all batches of Salk vaccine prior to the field trials for safety, potency, and sterility. As a matter of fact, the Foundation even agreed to supply monkeys to NIH for such safety tests.

[17] Dr. Rivers has reference to a special meeting held of the Vaccine Advisory Committee on November 13, 1953 in New York.

Designating three different laboratories to do safety testing did not end the problem, because the Vaccine Advisory Committee soon discovered that it was quite a problem to achieve uniformity in safety testing commercially produced vaccine. It was a problem because the previous direct experience of these laboratories with poliovirus varied. For example, prior to this time the Division of Biological Control at NIH had very little experience with the clinical manifestations and histopathology of polio in monkeys. I will give you an example of what I mean. In the beginning of safety testing commercially produced Salk vaccine, a certain batch of vaccine which had passed the safety tests at Parke-Davis was sent to NIH for further testing. It didn't take long before the Division of Biological Control informed the Vaccine Advisory Committee that that particular batch of vaccine was causing polio in monkeys. In the circumstances, I hurried down to Washington with David Bodian. I invited Dr. Bodian to come along because he probably knows more about what takes place in man and monkeys when they are infected with poliovirus than any other person in the United States. Polio, like yellow fever and other virus diseases that attack the central nervous system, leaves a rather characteristic distribution of lesions following infection. Dr. Bodian examined the sections of the spinal cords of monkeys that NIH claimed had come down with polio and discovered that the so-called polio lesions were in fact old dengue-virus lesions. The monkeys, which had come from the Philippines, had apparently been previously infected with dengue virus and had recovered. I tell this story not to cast any reflection on the Division of Biological Control. The people who worked in that divison were first rate. I just want to underscore that at that particular time they lacked experience in the histopathology of polio. Subsequently, Dr. Bodian, as well as other grantees of the Foundation who were well versed in this area of polio research, educated the personnel at NIH, as well as the personnel at the laboratories of pharmaceutical houses, so that they could cope with the clinical and histopathological problems of polio that came up during safety testing.

Q: Dr. Rivers, if developing uniform testing procedures was a problem, how much of a problem was it to get pharmaceutical houses to produce the vaccine commercially in a uniform manner? Did the

Vaccine Advisory Committee have any function in overseeing the production of the vaccine?

Rivers: Most of the poliovirus that was originally used in the vaccines for the field trial was initially grown in the Connaught Laboratories in Canada and then shipped by truck to Parke-Davis and Company in Detroit to be inactivated and prepared as a vaccine. There was a great deal of red tape in getting such virus into the United States because it was infectious material, and special passes had to be obtained from Quarantine Control of NIH to carry the virus over the border. Later, Dr. Salk's laboratory at the University of Pittsburgh also undertook to grow poliovirus, and other pharmaceutical houses such as Eli Lilly, Cutter, Wyeth, and Pitman-Moore, joined Parke-Davis in preparing the vaccine. All the firms charged with producing the vaccine were guided in that production by a detailed set of requirements and specifications. These covered production of the virus, safety tests in animals and tissue culture, potency tests, and even included such general things as methods of labeling and dating the vaccine. Let me emphasize that the key to uniformity in commercial production as well as safety testing of the vaccine were these requirements and specifications. Their preparation was the work of several hands.

When the decision to hold a field trial was reached, Dr. Salk undertook to revise the original specifications he had used in producing the vaccine in his laboratory for large-scale commercial production. In the summer of 1953 he gave the Vaccine Advisory Committee his revision.[18] However, as the commercial production and safety testing of the vaccine developed that fall, the revised requirements and specifications were further modified. We waited a while and then asked Jonas to put the new modifications down in a more permanent form. He was working in the laboratory continually during this period, and he just never got around to doing what we asked. As the fall wore on we began to badger him.

I would like to explain that writing such specifications was not a little chore. You don't write up specifications for a vaccine in a para-

[18] See J. Salk, Specifications and Minimal Requirements for an Experimental Poliomyelitis Vaccine August 26, 1953 (folder, CRBS #105, University of Pittsburgh, July 1953, National Foundation Archives).

graph or a page. You have to spell out everything and you can take nothing for granted, because if anything later goes wrong you can't turn around and say to the commercial producer, "Why, any damn fool knows that you should have done thus and so." Everything has to be put down, the *i*'s dotted and *t*'s crossed. We kept pushing Jonas until, at one Advisory Committee meeting held in Pittsburgh, Joe Smadel climbed his back and insisted that there had to be a cut-off point if the requirements and specifications were ever going to be written. Joe was so annoyed that before he realized what he was saying he about half-way volunteered to do the job himself. The committee didn't give him a chance to reflect and accepted then and there. Later, Salk sent Smadel a copy of the requirements and specifications that he had worked out, and during Christmas week of 1953 Smadel and Dr. William Workman of the Division of Biological Control at NIH rewrote and revised them to the satisfaction of the Vaccine Advisory Committee. From time to time in 1954, Salk, in collaboration with Workman, added a number of amendments and appendices, but basically the redrafted specifications and requirements which Smadel and Workman set down guided the commercial production and testing of the Salk vaccine.[19]

You asked whether the Vaccine Advisory Committee was ever burdened with overseeing the production of the vaccine. The answer to that is no. Although the committee was concerned about how the vaccine should be made and tested, it was never directly responsible for guiding and overseeing the actual process of production. The person in the Foundation with that responsibility was Dr. G. Foard McGinnes. I have spoken of McGinnes before with reference to the gamma globulin program. Let me add here that originally McGinnes had been trained in public health at the Johns Hopkins School of Public Health, and, before coming to the Foundation, had had a very wide experience in public health administration, including service in the Tennessee State Department of Health, and as national medical director of the American Red Cross. In the latter post, McGinnes had

[19] See J. Salk, Specifications and Minimal Requirements for an Experimental Poliomyelitis Vaccine. Working draft of first revision, November 25, 1953; and especially Joseph Smadel to T. M. Rivers, December 28, 1953; T. M. Rivers to Joseph Smadel, December 30, 1953; and Joseph Smadel to T. M. Rivers, January 26, 1954 (folder, personal correspondence, 1953–1954, Rivers papers).

worked for a time under Mr. O'Connor and they got to know and like one another—so much so that, when Mr. O'Connor later left the Red Cross, he persuaded McGinnes to become a consultant for the National Foundation on problems of patient care. In this position he actually served as a liaison man between the Foundation, the U.S. Public Health Service, and various medical organizations and pharmaceutical houses. He maintained an office in Washington and just about knew and worked with everyone. I would say that Foard was an A No. 1 politician, and I don't mean to use the word in a derogatory sense—I just mean that he was able to get things done.

When the Foundation began to plan the field trials, Mr. O'Connor decided to make McGinnes responsible for getting the vaccine into production. He hit the nail on the head, because McGinnes again proved wonderfully adept in getting the various people and companies associated with making the vaccine to work together. If that job had been left up to me, it probably would never have been done. I'll tell you why. I am a rough fellow and I didn't give a damn how pharmaceutical companies were going to meet the requirements for producing vaccine so long as they met them. Can you imagine what would have happened if I had done the telling instead of Foard McGinnes? Foard had a way of telling people what to do without getting them mad. If I had told them, they would have gotten mad and closed up shop. Don't ask me how he did it, because I don't know. I do know this, I wouldn't have had his job if you had paid me.

Q: Dr. Rivers, did you ever have occasion to tell people off about the Salk vaccine? I raise the question because in one sense the Vaccine Advisory Committee seems to have been designed for meeting and coping with criticism made of the vaccine.

Rivers: That, of course, was not the immediate or specific purpose of the Vaccine Committee, but I will admit that on several occasions we did answer criticisms made of the vaccine both before and during the field trials. Actually, several months before the field trials were held, some members of the medical profession began sniping at the vaccine. I'll tell you of one such incident because it involved me personally. Sometime early in the fall of 1953, Dr. Salk gave an address

at the annual meeting of the American Academy of Pediatrics on his vaccine. His talk was well received and later during the course of the meetings, the Academy adopted a special resolution supporting the projected field trials. I think that it might be helpful if I quote that resolution here.

When and as it becomes possible to extend studies on immunization of children against polio by means of killed vaccine, the American Academy of Pediatrics wishes to extend to the National Foundation and its cooperating investigators the professional support and cooperation of its entire membership.

I was a member of the Academy of Pediatrics and, although I didn't attend this particular meeting, I thoroughly approved the resolution. However, not all members felt the same way. About a month after that meeting, Dr. C. Henry Kempe, who was then an assistant professor of pediatrics at the University of California Medical School, wrote a very hot letter to Aims McGuinness, Chairman of the Committee on Immunization and Therapeutic Procedures of the Academy, urging that the Academy withdraw its endorsement of the field trials. In Dr. Kempe's view the Salk vaccine at that time was potentially unsafe and of undetermined potency, and as far as he was concerned had been insufficiently tested for a mass field trial. He seemed to believe that there was a reluctance on the part of virologists to go on record against the field trial plans of the Foundation, and he urged Dr. McGuinness to canvass leading virologists for their opinions in this matter. Dr. McGuinness then sent that letter to me and to several other virologists and asked us if we cared to make any comment.[20]

I can't say that I thought much of Kempe's letter. Mind you, he was no slouch, and although he was still a youngster, he did have a reputation for knowing a good deal about smallpox and the reaction of children to smallpox inoculations. Don't ask me why he wrote that particular letter because I don't know. The only thing that comes to mind is that he might have been impressed with reports that Albert Milzer and Sidney Levinson of Chicago had made that they couldn't

[20] C. Henry Kempe to Aims McGuinness, November 27, 1953; Aims McGuinness to T. M. Rivers, December 26, 1953; T. M. Rivers to Aims McGuinness, December 29, 1953 (folder, personal correspondence 1953, Rivers papers).

inactivate poliovirus using Salk's methods of inactivation with formalin. Those charges created a great furor, because both Dr. Milzer and Dr. Levinson were highly respected workers. I remember that Dr. Hart Van Riper was so upset that he went to the trouble of asking Dr. Salk to prepare a rebuttal. It never bothered me, first, because other laboratories which followed Salk's instructions carefully succeeded in inactivating poliovirus, and, second, because I always believed that Dr. Milzer and Dr. Levinson's private interest in inactivating poliovirus by irradiation blinded them to the usefulness or efficacy of using other techniques for purposes of inactivation.[21]

Several weeks before I received Dr. Kempe's letter from Dr. McGuinness a special meeting of the Vaccine Advisory Committee was called to advise Mr. O'Connor whether the Salk vaccine at that time was safe and ready for the field trial. I remember this particular meeting very vividly because Mr. O'Connor invited a special group of leading pediatricians and virologists—people like Rusty McIntosh, Horace Hodes, and Theodore Senn—to aid the committee in its deliberations.[22] Mr. O'Connor often acted like that when he was about to take an important step, because he always wanted to be doubly sure that the ground he was going to walk on was firm. At that meeting the committee reviewed with Dr. Salk all of the protocols and procedures for producing and inactivating poliovirus in preparation for making a vaccine, and came to the conclusion that he had in fact provided exacting safeguards for the safety of the vaccine. Later, we formally expressed these views in a letter to Mr. O'Connor.[23] I tell you this because, when the question of Dr. Kempe's letter came up, Mr. O'Connor did not depend on the letter we had sent him earlier, but

[21] This debate broke out following the presentation of a paper by Milzer at a meeting of the American Public Health Association in Chicago on November 10, 1953. Later Milzer retracted a portion of his statement; however, the paper itself was subsequently published. A. Milzer, S. O. Levinson, H. J. Shaughnessy, et al. "Immunogenicity studies in human subjects of trivalent tissue culture poliomyelitis vaccines inactivated by ultraviolet irradiation," *Amer. J. Public Health*, vol. 44:26 (1954). For the furor caused initially by the paper see *The New York Times*, November 11, 1953, and *The New York Herald Tribune*, November 11, 1953.

[22] Rivers once again has reference to the special meeting of the Vaccine Advisory Committee held on November 13, 1953, in New York.

[23] Vaccine Advisory Committee to Basil O'Connor, December 3, 1953 (folder, Vaccine, Polio, Salk: Development and Promotion, December 1953, National Foundation Archives).

instead convened the Vaccine Advisory Committee in a special meeting for the express purpose of answering Dr. Kempe's criticism. I have the letter that the committee finally sent to Dr. McGuinness, and I would like to read it here because it answers in a detailed way many of the criticisms which were made of the Salk vaccine before the field trials.

February 4, 1954

Dear Doctor McGuinness:

The undersigned Committee on Vaccination which was chosen to advise The National Foundation for Infantile Paralysis regarding the field trials this coming summer has received a copy of Doctor Kempe's letter from you. The Committee members have individually considered this letter, and have jointly prepared this reply following a full discussion of its contents at a meeting of the entire Committee which was held in New York City on February 1, 1954.

Doctor Kempe points out in his letter that other organizations, such as the American Public Health Association, have not passed resolutions comparable to those passed by the American Academy of Pediatrics. A member of this Committee who is also a member of the Executive Board of the American Public Health Association assures us that the failure of the Executive Board of the American Public Health Association to enact such a resolution was based not on any question of the validity or safety of the proposed vaccine field trials, but upon an established policy of that Association not to enter into active endorsement of any specific study of this nature.

Taking up the questions as Doctor Kempe lists them, the Committee would like to state that vaccine used in the field trials has been and is being prepared in accordance with procedures acceptable to this Committee and acceptable as minimal requirements by the Laboratory of Biologics Control of the National Institutes of Health, United States Public Health Service. It is the opinion of the Committee that the methods of preparation and testing provide adequate safeguards as to the non-infectivity of the vaccine insofar as animal and other laboratory studies of a practical nature can be expected to safeguard such procedures. The Committee has satisfied itself that every reasonable safeguard possible has been incorporated in these standards. A copy of these standards is attached.

Prior to the initiation of the larger field trial an initial group of 5000 children will have received the vaccine, 2500 the vaccine produced in Doctor Salk's laboratory, 2500 the vaccine produced commercially. In addition to the tests as set forth in the minimal requirements, for each lot of vac-

cine a group of children will be inoculated and serological studies made to establish antigenic effectiveness of each batch.

The second question raised by Doctor Kempe concerning the evidence of antigenicity of the aqueous vaccine is also of importance. He has suggested that available published data concerning the number of children who have received the aqueous vaccine and whose sera have been titrated for antibody levels is limited. However, additional unpublished information has been made available to this Committee as to the consistency of the antigenic response to aqueous vaccine, and other extensive work is in progress to confirm this point. We have assurance that the sera of a minimum of 100 from each of the two groups referred to above in the trial run will be titrated for antibody to establish the comparability of the mass produced vaccine with that produced in Doctor Salk's laboratory. Animal tests already demonstrate that both products are equally antigenic.

The minimum standards for production of the vaccine require that there be no more than two periods of incubation with formalin in a concentration of 1:4000. There is no appreciable change in antigenic activity during this limited period of formalinization. To assure antigenic potency of the final product the minimum standards require that the vaccine elicit an antibody titer of at least 1:8 when tested in monkeys, and it must also show an antigenic response in human beings.

Treatment of the virus with formalin 1:4000 is carried out in the range pH 6.9 to 7.1. Experience has demonstrated no difficulty in maintaining the pH within this range. However, should any circumstance prevent proper inactivation of the virus, the rigorous safety tests which the finished vaccine is required to meet, would detect residual living virus.

Although it might be feasible to concentrate the virus particles of the finished vaccine to increase the sensitivity of a test for residual living virus, the Committee believes the procedure as indicated in the attached standards by which inactivation time is carried beyond the point of disappearance of live virus, provides an adequate margin of safety.

The method of inactivation of the virus as set forth in the attached minimum standards has been duplicated by at least three commercial manufacturers of biologicals. Members of the Committee have, in addition, communicated with a number of laboratories experienced in the field and with one single exception have been advised that it is possible to reproduce Doctor Salk's methods. The single exception referred to above was reported at the annual meeting of the American Public Health Association in New York on November 10, 1953, and received wide publicity through the press. Those who made that report have since indicated that they had not carried out Doctor Salk's techniques in detail and they have retracted their statement that the techniques could not be successfully duplicated.

With reference to the total nitrogen, according to the minimal requirements for the finished vaccine the batch of filtered tissue culture fluid will

be considered suitable for further processing if it contains less than 0.35 mgm. per ml. of total nitrogen, 0.20 mgm. per ml. of amino nitrogen and 0.02 mgm. per ml. of protein nitrogen. It may be noted that synthetic nutrient fluid mixture 199 itself (without kidney cells or virus) contains approximately 0.25 mgm. per ml. of total nitrogen and 0.12 mgm. per ml. of amino nitrogen.

The important practical question, however, is whether the minimal amounts of monkey kidney protein present in the vaccine is in fact harmful to the persons receiving the vaccine. Evidence indicating that it is not harmful is derived from the observations in over 700 persons thus far vaccinated by Doctor Salk, in whom no ill effects attributable to kidney damage have been observed.

In addition, intensive studies are being made on the serological responses of human beings to this vaccine from the standpoint of the possible development of antirenal substances. The results thus far indicate that antirenal substances are not evoked by the vaccine which, in turn, suggests either that monkey kidney material is present in very small amounts, or that which is present is not highly antigenic. The Committee and Doctor Salk are fully cognizant of this problem and if any untoward effects are subsequently noted they can be relied upon to take appropriate steps.

The vaccine in terms of antigenic capacity has been tested and has been found to be stable for many months. Animal potency tests have been developed and are being employed so that one batch of vaccine can be compared with other batches. Such tests will be made before the vaccine is released for mass trial. For such tests sera from monkeys receiving three doses of vaccine at weekly intervals must have neutralizing titers of at least 1 to 8 when drawn one week after the third dose of vaccine. In addition, tests for antigenic potency of each lot will be made in human beings.

It is true that the early available data, March, 1953, were based on the adjuvant type vaccine. The report in *Pediatrics*, November 1953, was based upon experience with both adjuvant and aqueous vaccine. Since then, information has become available to the Committee on antibody response to aqueous vaccine in children as well as certain animals. Of course, the animals had had no previous experience with the antigen, as was true with many of the children. The response in both was entirely satisfactory and these data will be published soon.

The mass field trials as recommended by the Committee will now consist primarily of studies with injected controls and with an adequate sampling of children for pre- and postvaccination antibody titers.

In addition to answering the quesions specifically raised by Doctor Kempe, there is enclosed a statement made by the Vaccine Committee which will be sent to a number of scientific and medical publications, along with a copy of the minimum requirements.

The Vaccine Committee sincerely hopes that the answers given in this

communication will be found satisfactory by the Immunization Committee of the American Academy of Pediatrics.

Sincerely yours,

THOMAS M. RIVERS, M.D., *Chairman*

Committee Members
THOMAS P. MURDOCK, M.D.
DAVID E. PRICE, M.D.
JOSEPH E. SMADEL, M.D.
ERNEST L. STEBBINS, M.D.
NORMAN H. TOPPING, M.D.
THOMAS B. TURNER, M.D.

Q: Dr. Rivers, this might be a good place to discuss in greater detail some of the problems that came up in producing the Salk vaccine. For instance, wasn't there a substantial problem in choosing the various strains of poliovirus used in the vaccine?

Rivers: It is true that that was an important problem, but in the main it was restricted to making a choice of the type 1 strain that we were going to use; making a choice of the type 2 and type 3 strains was not too difficult. All of the strains picked for the vaccine were originally chosen by Dr. Salk. That shouldn't be too surprising. Remember, through his participation in the poliovirus typing program, Salk had acquired a rather unique and substantial knowledge of the quality and characteristics of the various polio strains isolated in the United States. He knew what each and every one could do, and initially he chose the Mahoney as his type 1 strain, the MEF[1] as his type 2 strain, and the Saukett as his type 3 strain. I should add here that the three strains as finally used in the vaccine were monkey kidney tissue-culture adapted strains.

Now, not all polio strains within a given type are alike, and virologists have known for a long time that some are certainly more antigenic than others. We don't know why this is so; we only know that it is so. For instance, although the Mahoney strain is a very virulent type 1 strain, it is nevertheless one of the best type 1 strains for making antibodies. The Parker strain, which is a less virulent type 1 strain and does produce antibodies fairly well, still cannot make antibodies

as well as the Mahoney strain. From the beginning, a number of virologists opposed using the Mahoney strain in the vaccine, and for a long time the Vaccine Advisory Committee held off in giving final approval to the use of the Mahoney strain. It got so that almost every letter I received from Joe Smadel during the fall of 1953 would ask, "When are you going to pick the goddamn strain?" Joe was anxious to standardize the strains so that various laboratories could plan their serum neutralization tests and other necessary diagnostic procedures. In the end we wound up okaying the Mahoney strain in spite of the fact that it was virulent. We chose it because it had excellent antigenic qualities. Most of the polio at that time was type 1 polio and the Vaccine Advisory Committee wanted a vaccine with a good antigenic type 1 strain in it. I think that we did the right thing, although not everybody at the time agreed with that choice.[24] Since then, any number of virologists have from time to time wondered out loud whether we should keep the Mahoney strain in the vaccine. The British, for example, use an attenuated Brunhilde strain developed by John Enders and his associates in their inactivated vaccine. However, in the United States most producers, with the exception of Merck, Sharpe, and Dohme, who use the Parker strain, still make the Salk vaccine with the Mahoney strain. They haven't switched to other strains because the evidence from the field is that the Mahoney strain has excellent antigenic qualities, and I expect that they will never give it up.

Q: Dr. Rivers, when Dr. Salk presented the results of his early tests with his vaccine to the Immunization Committee in January 1953, Dr. Smadel and Dr. Sabin both raised the question whether the vaccine would cause damage to human kidney tissue.[25]

Rivers: That was an important question and Dr. Smadel and Dr. Sabin—and there were others too—had every right to raise it, and I

[24] David Bodian of the Johns Hopkins Medical School to this day believes that a serious error was made by the Vaccine Advisory Committee in selecting type 1 Mahoney strain for the Salk vaccine. He maintains that this choice did more to antagonize the Committee on Immunization than any other action taken in the making of Salk vaccine (private communication).

[25] Minutes of the Meeting of the Committee on Immunization, *op. cit.*, pp. 197–198.

will tell you why. The polioviruses from which the Salk vaccine was made was cultivated in tissue-culture media made up of minced monkey kidney tissue suspended in Raymond Parker's solution 199. Sometime during the early thirties a Japanese investigator named Masugi took rabbits and ducks and immunized them with rat kidney material. Subsequently, he bled those animals and when he put their serum into rats he discovered that the rats showed marked change in the output and character of their urine, developed ascites and had other symptoms of nephritis. Some years later, Dr. Smadel and Dr. Farr at the Rockefeller Institute repeated Dr. Masugi's work with great care, and produced beautiful examples of nephrotoxic nephrosis in laboratory animals. The members of the Immunization Committee and the Vaccine Advisory Committee were well aware of this work and its implications, although nobody at that time had been able to produce lesions in the kidneys by injecting kidney tissue directly into laboratory animals.

In his early tests, Dr. Salk had not elicited any evidence of monkey-kidney-protein sensitivity in the children he had vaccinated, but to be doubly sure the Vaccine Advisory Committee asked Manfred Mayer, an immunochemist at the Johns Hopkins Medical School to study the problem independently. The results of Dr. Mayer's study were equivocal. Although he found that children who were vaccinated with Salk vaccine had an absence of complement-fixing antibody to monkey-kidney antigen, he couldn't actually tell us whether the children formed such antibody, because there was a very remote possibility that the antibody might have become fixed in their kidneys and thus screened from their blood streams.

To exclude this remaining small possibility, the Vaccine Advisory Committee asked Dr. Salk to do kidney function tests on the children then being inoculated in Alleghany County preliminary to the field trials. It was not a simple matter. First, this particular test required a control group, because there was always a possibility that when you inoculated several thousand kids, one or two might come down with a glomerulonephritis or other things that had nothing to do with the vaccine. Second, all of the children had to be looked at clinically and their bloods and urines carefully examined. At the very least, it was time consuming. To help Salk, the Vaccine Advisory Committee

asked Dr. Robert Korns of the New York State Department of Health, who was then acting as a deputy to Dr. Francis in setting up the field trials, to go to Pittsburgh to supervise the clinical examination of all children who were absent from school for three or more days following vaccination with the Salk vaccine. Those tests were carried out meticulously and in the end proved that any fears we might have had about monkey-kidney-protein sensitivity were groundless.[26]

Q: Dr. Rivers, early in 1954 workers at the Connaught Laboratories in Toronto discovered B virus in some lots of monkey kidney tissue, and some investigators in that laboratory became quite concerned about the implication of that discovery for the production and use of Salk vaccine.[27]

Rivers: It agitated some of them all right, although for the life of me I don't know why. I am not saying that B virus wasn't a dangerous virus. I have known about B virus since Albert Sabin isolated and named it following the death of Dr. William Brebner from a monkey bite back in 1932. I am saying that it didn't constitute a very great hazard in the production and use of polio vaccine. For one, B virus is very easily demonstrated by injecting material into rabbits. Rabbits are very susceptible to the virus and even a very small amount will bring a rabbit down. For another, as a rule B virus is much more susceptible to formalin than poliovirus and it is easily inactivated. I knew that and other virologists knew that, and it has always been my feeling that the people at the Connaught Laboratories should have known that. To be perfectly fair, not everybody at the Connaught Laboratories was upset by the discovery of B virus. Dr. Robert DeFries, who was then director of the laboratory, took the discovery in stride. If it had been left to him, I seriously doubt whether any fuss would have been made at all.

The person who really agitated the question was Dr. Clennel E. Van Rooyen. Dr. Van Rooyen was a Canadian by birth who before World War II had achieved an international reputation as a virologist

[26] The tests were carried out from December 1953 through April 1954.

[27] Robert DeFries to Hart Van Riper, February 8, 1954 (folder, CRBS Appr. #19, Connaught Laboratories, 1954, National Foundation Archives).

by publishing a large, compendious textbook called *Virus Diseases of Man* in collaboration with Dr. Andrew J. Rhodes, one of his colleagues at the University of Edinburgh. After World War II, Van Rooyen returned to Canada and took a post as director of research at the Dufferin division of the Connaught Laboratories. Van Rooyen's opinions carried great weight in Toronto, and when he began to voice his concern about the discovery of B virus in monkey-kidney tissue there were repercussions in New York, and Mr. O'Connor decided that it would be wise to call a special meeting to discuss the problem.

Mr. O'Connor's action in calling the meeting is understandable. The Connaught Laboratories was a key to the production of poliovirus and any problem that affected that production would, of course, have had serious repercussions on the field trial which was then just about ready to get under way. A meeting was arranged [28] and a special delegation composed of Dr. DeFries, Dr. Van Rooyen, Dr. Rhodes, Dr. Fraser, and a lawyer from the University of Toronto came to New York on behalf of the Connaught Laboratories. Mr. O'Connor, Henry Kumm, Hart Van Riper, and I appeared on behalf of the Foundation. In this particular instance I told Mr. O'Connor that it would be unnecessary to convene the Vaccine Advisory Committee. The meeting, as I remember it, went very smoothly. Van Rooyen raised his questions and I tried to answer them. In substance I said what I told you earlier. I don't think that I had much trouble convincing DeFries, Fraser and Rhodes that B virus wasn't a grave problem, but it did take me the better part of a day to do it. Later I believe the Connaught people sent the B virus they had isolated to John Enders so that he could compare it with some unknown monkey viruses that Dr. Robert Rustigian had earlier isolated in Chicago. In the course of that work Dr. Enders confirmed my contention that B virus was easily inactivated by formalin. To sum up, I would say that B virus never really interfered with the production and use of Salk vaccine. At best, it was a tempest in a teapot.

There were any number of such troublesome incidents before the field trials got under way. One that I remember very well was brought about by a report made by Dr. Fred Stimpert, who was director of microbiological research at Parke-Davis and the man who had the responsibility for producing Salk vaccine for that company. In brief,

[28] This meeting was held on February 10, 1954.

Dr. Stimpert reported that during the course of some safety tests, he inoculated some tuberculin-sensitive guinea pigs with material from a recently produced lot of Salk vaccine and discovered that the animals had developed positive reactions. He interpreted these reactions to mean that that particular lot of vaccine either had tuberculin in it or had a substance which was biologically indistinguishable from tuberculin. It was a grave report and when it reached the Foundation it just about set everybody off. Mr. O'Connor was so upset that he came to my office at the Rockefeller Hospital to discuss the report. It was one of the few times in my long association with Mr. O'Connor that he made that trip. There was no doubt that the matter had to be cleared up. If that report had ever become public before the Foundation had an answer, there would have been the devil to pay. A number of investigators who had been called on the telephone suggested that there was a possibility of a nonspecific false positive result. Others thought there might have been a contamination in the laboratory. They were certainly reasonable suppositions, but they had to be tracked down and nailed. What we needed was somebody who knew about the tuberculin reaction in guinea pigs. Luckily, such a person worked at the Rockefeller Institute. I am speaking here of Merrill Chase. Early in his career Dr. Chase had worked with Karl Landsteiner, and it is not hyperbole to say that Merrill Chase probably knows more about hypersensitivity reactions in guinea pigs and other laboratory animals than anybody else in the United States or, for that matter, the world. I asked Merrill to check Dr. Stimpert's findings, and he got right down to work. He is much like Landsteiner when it comes to investigation—he is all business. In a little under two days, he demonstrated that Stimpert's results were incorrect and that the so-called tuberculin reactions occurred in control animals as well as in tuberculin-sensitive animals. He eventually traced the reaction to merthiolate, a mercury containing compound which was used as a preservative in the vaccine. That settled the matter, but I can tell you that before Dr. Chase's report was made, a hell of a lot of people were unsettled.

Q: Dr. Rivers, material in the National Foundation files indicate that in 1954 you heard a rumor that Dr. Sven Gard of Sweden was cultivating poliovirus in human embryonic tissue preparatory to mak-

ing a vaccine against polio. I raise the issue because the news apparently upset you.[29]

Rivers: You are damn right, I was upset. I wasn't upset at the fact that Dr. Gard was undertaking to make a vaccine; I was upset because he was cultivating the virus for that vaccine in human embryonic tissue. I believed that by doing that he had a good chance of picking up hepatitis virus. This, by the way, is one of the reasons why nobody in this country will approve a vaccine made by such techniques. Sven Gard is a first-rate investigator and, while I have no doubt that he was concerned about hepatitis virus, I do not believe that he was as impressed with the harmful effects of the virus as investigators in this country. We had that attitude because we had quite a big mouthful of hepatitis during World War II. Hepatitis is a disease that doctors used to call catarrhal jaundice, and at one time it was believed that the disease was caused by mucus blocking the main bile duct of the liver. However, early in World War II we learned that the disease was really caused by a virus, when a hell of a lot of boys in the service came down with hepatitis following inoculation with yellow fever vaccine that had human serum in it. Many died. That experience had a profound effect on me, and since then I have always balked at anyone's taking a chance on having human serum or human tissues in a polio vaccine, period.

Since we are talking about hepatitis, I would like to talk about another aspect of the hepatitis problem, because it later became important in the administration of the vaccine during the field trials. After World War II there was a serious outbreak of hepatitis among soldiers stationed in Germany, and John Paul was sent by the army to investigate the epidemic. He soon discovered that this particular epidemic had its origin in the fact that needles of hypodermics were not properly sterilized following routine inoculations. Dr. Paul's experience alerted the Vaccine Advisory Committee to still another hepatitis hazard, that of inadvertently transmitting the virus during routine inoculation with polio vaccine. I don't mind telling you that before the field trials were put on, I was more concerned that children

[29] News release on Gard vaccine, April 9, 1954 (folder, Sven Gard, Public Relations Files, National Foundation Archives); T. M. Rivers to Fritz Buchtal, February 11, 1955 (folder, personal correspondence, 1955, Rivers papers).

might come down with hepatitis than I was with the possibility of their coming down with polio because of live virus in the vaccine. I'll tell you why. When a doctor injects anyone with formalinized material, he is always afraid that he might put it directly into the vein causing convulsions and other complications. To avoid such a possibility, he usually pulls back on his needle to see if he is going to get any blood. Nine-hundred-and-ninety-nine times out of a thousand, he doesn't get any blood and he continues giving his injection. However, when he pulls back, he sometimes also pulls back a little juice from the subcutaneous and muscular tissues, and on occasion even a little blood from a small blood vessel. If the person being injected has hepatitis virus, there is an excellent chance that this procedure has contaminated the needle, syringe, and contents of the syringe with hepatitis virus. You must bear in mind that even an infinitesimal amount of hepatitis virus from such juice or blood will suffice to contaminate, and if the proper precautions are not taken the next person inoculated with these materials can become infected with hepatitis.

Before the field trials, the Vaccine Advisory Committee worried a great deal about this hazard until Henry Kumm reminded us that, when yellow fever vaccine was given in South America, hepatitis never became a problem because the physicians giving the vaccine were instructed not to pull back on the needle. Later, when the Foundation prepared a handbook of instructions for those participating in the field trials, similar directions were given to physicians, and a special point was made of instructing personnel to autoclave all needles and syringes for a period of at least twenty minutes following their use in inoculating children.

Q: Dr. Rivers, you just mentioned that you had no great fears that live virus would turn up in the Salk vaccine. Yet just before the field trials got under way Dr. Hart Van Riper, the medical director of the National Foundation, made a public announcement that four batches of commercially produced Salk vaccine had to be discarded because of the discovery of live virus in these batches. Could you tell me the procedures which the Vaccine Advisory Committee followed before they released the Salk vaccine for use in the field trials? [30]

[30] Hart Van Riper, News release, April 5, 1954 (folder, Vaccine, Polio, Salk: Development and Promotion, April 1954, National Foundation Archives).

Rivers: Although it is true that live virus was found in four batches of commercially produced vaccine, in each case the Vaccine Advisory Committee found that the companies involved had not followed the procedures for inactivating the virus as carefully as they should have. In each instance the live virus was discovered in the safety testing. As I mentioned earlier, all batches of commercially produced Salk vaccine were tested independently in three laboratories—the producer's laboratory, the laboratory of the Division of Biological Control of the National Institutes of Health, and Dr. Salk's laboratory. These tests were uniform for all laboratories and set out in detail in the minimum requirements and specifications for making the vaccine. I would like to quote a portion of the specifications for safety testing in monkeys here verbatim.

Final Vaccine Test for Active Virus in Monkeys: A formaldehyde neutralized sample of the final vaccine without added preservative is inoculated intracerebrally in 1.0-ml amounts into each of 12 rhesus or cynomolgous monkeys and intramuscularly in 10-ml amounts into 6 healthy cynomolgous monkeys. The intracerebral inoculation consists of 0.5 ml into the thalamic region of each hemisphere and the intramuscular inoculation of 2.5 ml bilaterally into the gastrocnemius-soleus and the biceps muscles. The monkeys are observed for 28 to 33 days and symptoms suggestive of poliomyelitis are recorded. At least 8 of the intracerebral test monkeys and at least 4 of the intramuscular test monkeys must survive the test period. Histopathologic examination is made of all monkeys which die or survive the test period.

The lot of vaccine is considered satisfactory if no lesions suggestive of poliomyelitis are present.

If minimal inflammatory lesions of questionable significance are present in one or more monkeys an enlarged sample of sections from these animals may be examined, but the lot of vaccine is not considered satisfactory unless the enlarged sample permits reclassification into the negative category of no lesions suggestive of poliomyelitis.[31]

I read this specification to you, because I think it is fair to say that in the beginning not all virologists were satisfied with safety tests in monkeys alone and some requested additional tests in chimpanzees. I remember that at one point, when the requirements were being discussed at a meeting of the Immunization Committee, Howard Howe

[31] From Minimum Requirements, Poliomyelitis Vaccine. First revision, April 12, 1955, p. 3 (folder, Salk Vaccine Requirements, Rivers papers).

of Johns Hopkins suggested that the vaccine be safety-tested by inoculating chimpanzees intraspinally. The Vaccine Advisory Committee did not accept that particular suggestion not only because it would have taken the U.S. Mint to conduct such tests, but also because the committee believed that chimpanzees like men were less susceptible to poliovirus than monkeys. In other words, while it is easy to bring a monkey down with an intraspinal inoculation of poliovirus, it is more difficult to bring a chimpanzee down by such a technique, because chimpanzees are more resistant to poliovirus than monkeys are. The committee felt that in dealing with an inactivated vaccine an intracerebral inoculation of poliovirus in monkeys was a severe enough test. I do not believe that that particular safety requirement for the Salk vaccine was ever modified, although it is true that other safety tests were later added to the original requirements.

Q: Dr. Rivers, I take it that when the Salk vaccine passed the safety tests in all the laboratories it was released for use in the field trials.

Rivers: No indeed. After a particular batch of vaccine passed the safety tests in all three laboratories, all the protocols of production and safety testing were sent to Dr. Theodore Boyd in the Division of Research at the National Foundation. Dr. Boyd then checked all the production records—the amount of protein, pH, temperatures, and so forth—against the minimum requirements and specifications and very carefully noted if there were any differences between the two. The pharmaceutical houses, as near as I can make out, put down their findings honestly and scrupulously. When Dr. Boyd completed his analysis he would send me all the records and his notes for final approval. By ad hoc agreement with NIH, I would only release vaccine for use when a certain number of consecutive batches of vaccine from a particular producer met all of the production safety and potency requirements. I forget now the exact number of consecutive batches that had to be passed but the important thing to remember is that they had to be consecutive batches. I would not release a single batch on its own. There was quite a hassle about this, so keep it in mind. I will say this, the vaccine that I finally approved might have a little more protein than the specifications allowed, or the pH might be 7.1

instead of 7.2, or the temperature for inactivation might have varied and not been just so. My final decision to pass the vaccine always hinged on whether the safety tests in all three laboratories showed that no live virus was present. I could always depend on Dr. Boyd to bring to my attention any factor that didn't quite hit the mark.

Q: Dr. Rivers, was Dr. Boyd a virologist?

Rivers: No. Theo Boyd is a physiologist—and a damn good one. He studied physiology with old Ajax Carlson at the University of Chicago. I don't know what he did immediately after he got his degree, but I do know that before he came to the National Foundation he was a professor of physiology at the Loyola University Medical School in Chicago. Boyd is an extremely unusual person, and I suspect that the only reason he hasn't reached a pinnacle in science is that he is one of those rare people who is not concerned about himself. There are not many like that around, you know. Although Boyd has never worked with viruses in the laboratory, he is probably one of the best informed men about virology in the country, and to my mind knows a great deal more virology than a lot of so-called virologists. Not only is his knowledge accurate, he uses it in an accurate manner. One of the best measures that I know of Boyd's scholarliness is a review that he wrote on immunization against polio. That review was so good that the *Bacteriological Reviews* published it as a special supplement to one of its numbers.[32] To my knowledge, the Society of American Bacteriologists had never before or since accorded such an honor to a physiologist. I think you can see from what I have said why I could depend on Theo Boyd. Hell, I still depend on him. Today he is director of the Division of Research at the Foundation.

Q: Dr. Rivers, what was the attitude of NIH to the field trials, given the discovery of live virus in several batches of commercially produced vaccine?

Rivers: Just before the Vaccine Advisory Committee gave its final approval to the use of the vaccine in the field trials, we held a meeting

[32] T. Boyd, "Immunization against poliomyelitis," *Bacteriol. Rev.*, vol. 17:339 (1953), also later issued as a special supplement.

in Washington with NIH to review the protocols of all the vaccine produced up to that time.[33] I will tell you plainly that Dr. James Shannon and Dr. Victor Haas of the U.S. Public Health Service at that time were against passing the vaccine. As a matter of fact, Dr. Haas said that in his view the vaccine was dangerous and that he would not give it to his own children. When Dr. Shannon presented statistics to prove that commercially produced vaccine was unsafe, I just about hit the ceiling. It was apparent to me and other members of the Vaccine Advisory Committee that the batches of vaccine that contained live virus were due to faulty production techniques, and that, if the producers followed the requirements and specifications which were laid down, a perfectly safe vaccine could be and was made.

Let me give you an example of what I mean. During the process of inactivation in one of the companies—I am not going to tell you its name—live virus was passed from one tank connected on its underside with a pipe and pitcock to another tank. The virus was inactivated in the second tank and when inactivation was completed passed through the pipe back to the original tank. The only trouble with that procedure was that nobody had bothered to clean the pipe or the first tank after the live virus had been siphoned off to be inactivated. No wonder there were batches of vaccine with live virus.

Here Jim Shannon was counting statistics, and statistics had nothing to do with the case. I got madder than hell. Luckily, Dave Bodian was there and he came to my rescue. Dave in his quiet manner polished off everybody pretty thoroughly, but the meeting dragged on until we finally agreed that other people ought to be brought in the next day to join the deliberations.[34] After the meeting, Mr. O'Connor took me aside and said, "Tom, I want you to go back to New York

[33] The meeting was held on April 24 and 25, 1954, in Washington. An agreement between the National Foundation and NIH was signed on April 25, 1954 (folder, personal correspondence, 1954, Rivers papers).

[34] Dr. Bodian points out: "Rivers is less than fair to Shannon here, since Shannon's statistical point became the basis for the requirement that a given number of consecutive lots must be clean before any one of them can be passed. Earlier Rivers emphasizes this as one of his major requirements in accepting batches for the field trial, but the device was Shannon's. My only accomplishments at this meeting, which I attended as consultant for the National Foundation, were to dispel the unwarranted fear of nonspecific brain lesions in monkeys, and to support Shannon's idea for certifying batches of vaccines" (personal communication).

tonight and cool off. Forget the meeting tomorrow, come back tomorrow night." I was hot under the collar, but I took his advice and went back to New York, and I suppose that I did cool off a little bit. The next day the new people who were brought in suggested that producers had to submit a certain number of consecutive batches of vaccine that passed all the safety tests before any one batch would be passed for use in the field trial. After that meeting Mr. O'Connor, anticipating that the Vaccine Advisory Committee would now approve the vaccine for use in the field trials, drew up a series of recommendations signifying that approval. When I returned to Washington that evening, he showed me the recommendations that he had drafted and then made me sit down with him to polish and rephrase them. The next morning the Vaccine Advisory Committee met, and after reviewing the discussions held at NIH approved the use of the vaccine for the field trials. When everybody had signified approval of the vaccine, Mr. O'Connor produced the recommendations that we had worked on the night before. I sat back and watched. You know how people are—they made several changes,—nothing important, and then everybody signed. Later, these signed recommendations were sent over to NIH and they issued a statement that our recommendations were sound and that the National Foundation was justified in holding the field trial.

Q: Dr. Rivers, earlier you mentioned the selection of Dr. Thomas Francis as director of the field trial. Can you tell me how he came to be chosen?

Rivers: As I told you before, originally, the Foundation planned to evaluate the vaccine under its own auspices. However, when Joseph Bell resigned his post as scientific director of the field trial, the Vaccine Advisory Committee and a number of state health officers took the opportunity to urge the Foundation to reconsider its original plan. We all felt that it would be wiser to have the evaluation of the vaccine made by a scientist outside the Foundation and preferably one connected with a university. Although I cannot now pinpoint the exact date when the Foundation began to look for such a scientist, I do remember that I consulted a number of times with Hart Van

Riper about such a person late in November and early December of 1953. My first recommendation was that the Foundation try to get Dr. Francis Schwentker then a professor of pediatrics at Johns Hopkins and a very smart fellow to do the job. Van Riper took my advice and made him an offer but he turned it down. Thank God that he did. If he had accepted, I think that the trials might have ended disastrously. I say this because at the time the offer was made Dr. Schwentker was seriously ill—I didn't know about it—and a short time later he committed suicide.

After Schwentker's refusal a number of other names were thrown in the hopper. I can't honestly say now who first mentioned Tommy Francis's name. I do know that, once his name was mentioned, Dr. Van Riper made immediate overtures to him. It wasn't easy. At the time Francis was on a sabbatical leave in Europe and it took more than one cablegram to bring him back to this country. When he returned he spoke to Van Riper and then came to see me at the Rockefeller Institute. Francis must have spent about a half a day pacing up and down my office discussing the various aspects of the offer that Van Riper had made to him. I have known Tommy Francis for over twenty-five years. He is an extraordinarily intelligent man, but he does have a hell of a time making up his mind. He certainly had qualms about taking on this job. First, although evaluation of the vaccine fitted in with his interests in epidemiology and study of disease control, he didn't consider it research. I think that in part his fear here was that, if he undertook to do the evaluation, it might result in the Foundation's discontinuing its support of the research grants he was then working under. There was, of course, no such jeopardy, but he thought of it all the same.

I don't know if I have made myself clear. The thing I would like to emphasize is that Dr. Francis wanted assurances from the Foundation that this new job would not in any way jeopardize or interfere, even for a brief period, with the continuity of his research interests. Perhaps his greatest qualm, when he spoke to me, related to the then-announced design of the field trial. Briefly, Francis had serious reservations about doing an evaluation based on observed controls alone. He firmly believed that the most effective procedure for measuring the effect of the vaccine was through studies based on an injected

control. While he was willing for the evaluation to be based in part on an observed control, he was adamant that the integral and major part of the field trials had to be based on an injected control. Actually, this was not as much of a problem as Francis thought it would be, because by the time he was approached to evaluate the vaccine a substantial number of state health officers had indicated to the Foundation that they preferred injected control studies to be made in their states. That battle was won even before Dr. Francis stated his position.[35]

Many scientists, when they receive a grant or undertake a job for a foundation or government, are very sensitive about what freedom they will have in carrying out their work. Dr. Francis was no different. He wanted assurances that a special evaluation center would be set up at the University of Michigan and that he and the center would have complete control over all the collected data, codes, and rights of publication. I was amused by this, because I didn't think that the Foundation wanted it any other way. I was, of course, right. In the end, the Foundation agreed to all his demands and an open-end grant was made to the University of Michigan to establish a special evaluation center to carry out the study.

Q: Dr. Rivers, signing an agreement is one thing, living with it is quite another. Was there any conflict between Dr. Francis and the Foundation in carrying out the field trials?

Rivers: If you mean, did the Foundation bother Dr. Francis in the running of the field trials, the answer is no. On the contrary, there was a good deal of cooperation between the two. For instance, when it came to choosing those areas best suited for holding the trials, Gabriel Stickle of the Foundation's statistical department helped Dr. Francis and his associates choose the counties most likely to experi-

[35] Although Dr. Rivers is correct in saying that many state health officials preferred injected control studies, his belief that the battle was won before Dr. Francis stated his position is incorrect. Dr. Francis engaged in negotiations on this and other points with the Foundation for almost a month before accepting responsibility for the trials. See Hart Van Riper to Thomas Francis, Jr., December 10, 1953; Hart Van Riper to Basil O'Connor, January 13, 1954; Thomas Francis, Jr., to Basil O'Connor, January 25, 1954 (folder CRBS Appr. #19, University of Michigan, 1953, National Foundation Archives).

ence epidemic conditions during the trial with a great deal of accuracy. The intricate reporting forms used in gathering statistics for the evaluation was in part the work of still another Foundation staff member, Dr. Thomas Dublin.[36] Actually, I can't begin to detail the hundreds of ways in which the Foundation cooperated with Francis, save to say that such cooperation ranged from sending him detailed reports of polio admissions in hospitals throughout the country to recruiting professional personnel to do muscle evaluations. In my view, one of the Foundation's most important contributions prior to the holding of the trials was to call a series of conferences with its grantees so that they could discuss with Francis the problems involved in taking blood samples and standardizing laboratory procedures for virus recovery, preparing antisera, and doing serum neutralization tests. Come to think of it, it is wrong merely to stress the cooperation between the Foundation and Francis. Most of the virus laboratories in the country cooperated as well. They knew that one man and one laboratory couldn't do the work alone and they willingly took on the many laboratory burdens that had to be done. John Paul and Joe Melnick at Yale, Herbert Wenner at the University of Kansas, Edwin Lennette at the University of California, Howard Shaughnessy at the State Health Department of Illinois, Dave Bodian and Howard Howe at Johns Hopkins, John Enders at Harvard, Morris Schaeffer at the government laboratories in Montgomery, Alabama—and there were others—all did their share and more. You can take it from me if these boys had not cooperated there wouldn't have been a successful field trial.

[36] Rivers' statement on the role of Gabriel Stickle and Thomas Dublin, Jr., in the preparation of the Salk vaccine field trials should be amended. Although Stickle helped in the selection of the counties used in the field trials, his work was adjunct to that of the Vaccine Evaluation Center at the University of Michigan. Again, although both Mr. Stickle and Dr. Dublin helped in the preparation of some of the reporting forms later used in the field trials, these forms were drafted to specifications drawn up by Dr. Francis. Later they were revised and modified by Francis. The final decision as to use was at all times the responsibility of Francis and his associates at the Vaccine Evaluation Center at the University of Michigan.

CHAPTER 14

Salk Vaccine and Sabin Vaccine—1954-1958

Thirty years ago Franklin D. Roosevelt had a tremendous dream—a dream that the public could and would participate with scientists in lifting a fear from the minds of mothers and fathers and children, not only in the United States of America, but all over the world. If we think of the solution of the problem of paralytic poliomyelitis in terms of eliminating one fear besetting the people of the entire world, the activity we have conducted takes on even greater significance.

Basil O'Connor, *An Address on the Occasion of the Presentation of the Francis Report,* April 12, 1955

Q: Dr. Rivers, what impact did the development of the Salk vaccine and the field trials have on the other research that the National Foundation was then supporting?

Rivers: That support went on. The Virus Research Committee and Mr. O'Connor always understood the necessity for maintaining continuity in polio research, just as they always understood the need for supporting basic research in virology. If you will examine the grants approved by the Virus Research Committee during this period, you will find that more than half were devoted to basic virus research. For instance, during this period Barry Commoner received several grants to develop his investigations of the biochemical mechanisms which govern the synthesis and reduplication of tobacco mosaic virus. Linus Pauling received support to investigate by means of x-ray diffraction the structure and molecular composition of plant and animal viruses. Earl Evans was given several grants to continue his investigation of