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

the biochemistry of bacteriophage. There were, of course, many other grants of a similar nature. I only cite these as typical examples. Now, I am not saying that investigators weren't worried about their support —they were. Hell, I received letters every other day in 1954 and 1955 asking me whether the Foundation would continue to support this or that work. There were trepidations, and I will admit that on several occasions during this period not everybody got the exact sum of money they put in for, but in most cases support was generous and full.

Let me reemphasize: although the Salk vaccine had been developed and was then being tested, if an investigator had an important lead about the fundamental nature of poliovirus and needed support to continue his research—vaccine or no vaccine—he was supported. Let me give you an example of what I mean. Sometime in 1954, Gregory Schwartzman, an investigator at the Mt. Sinai Hospital in New York, discovered that when he injected poliovirus into hibernating hamsters, the virus located itself in brown fat but did not penetrate the central nervous system. Initially, Dr. Schwartzman wondered whether poliovirus remained in the brown fat of the hamsters in a latent state.[1] Later, when brown fat was discovered in humans, he thought the persistence of poliovirus in the brown fat of a person who had been infected and had recovered might well be a source of spreading the virus at a later time. It was an interesting finding, and when Dr. Schwartzman asked us to support his investigations we did so. Nothing of any great significance came out of this research, but that doesn't mean that it wasn't worthwhile. Today the problem of brown fat is being pursued by Dr. George Dempster of the University of Saskatchewan and something may come out of it yet.

Q: Dr. Rivers, I would like to pursue the question of research on another level. What, for example, was the attitude of the Foundation at this time toward supporting the development of other vaccines?

Rivers: I take it that you want to speak about Dr. Sabin.

[1] G. Schwartzman, "New aspects of pathogenesis of experimental poliomyelitis," *J. Mt. Sinai Hosp.*, vol. 21:3 (1954).

Q: Yes. Dr. Rivers, when did the Virus Research Committee become aware that Dr. Sabin was on the point of developing a live-virus vaccine?

Rivers: It is difficult to say. My own impression is that I and other members of the Virus Research Committee became aware of Dr. Sabin's progress along these lines sometime during the fall of 1953. At that time, Sabin reported to the Foundation that he had succeeded in transforming all three types of poliovirus to avirulent variants by making repeated passage of large amounts of poliovirus in tissue cultures. Initially, these tissue cultures contained virulent as well as avirulent strains. However, Sabin indicated that by utilizing terminal dilution techniques, he was able to segregate relatively stable variants. Later, when he inoculated monkeys intracerebrally with these variants, he found that they did not cause any lesions or paralysis. Dr. Sabin's report dovetailed very nicely with what other investigators had found. In 1952, for example, John Enders and his associates at Harvard had produced an avirulent Brunhilde type 1 poliovirus by passage in nonnervous tissue culture.[2] If I am not mistaken, Enders even sent this attenuated strain to Sabin for experimental purposes. In 1953, Joe Melnick at Yale, in an effort to extend the work of the Enders group—using techniques similar to those used by Dr. Sabin—independently, and I would say almost simultaneously with Sabin, also succeeded in developing polio strains with a decreased virulence.[3] In the circumstances, I think you can appreciate why I and others thought that Sabin's work was promising. You would do well, however, to keep in mind that much was then still unknown. For example, Sabin at that time didn't know anything about the genetic stability of the variant strains he had developed. He didn't know the conditions under which poliovirus could be regularly cultivated in an avirulent form. Nor did he know whether there existed in nature avirulent strains that were better than those he had produced in the laboratory.

[2] J. F. Enders, T. H. Weller, and F. C. Robbins, "Alteration in pathogenicity for monkeys of Brunhilde strain of poliomyelitis virus following cultivation in human tissue," *Fed. Proc.*, vol. 11:462 (1952).

[3] J. L. Melnick, "Variation in poliomyelitis virus on serial passage through tissue culture," *Cold Spring Harbor Symp. Quant. Biol.*, vol. 18:278 (1953).

During the winter of 1953 Dr. Sabin made a special trip to New York to ask Henry Kumm and myself whether the Foundation would allow him to change the research program he had originally proposed for his grant so that he could develop his new leads. I can tell you that he didn't have to twist my arm or Henry Kumm's. The Virus Research Committee very readily agreed to the change, and I saw to it that he was given a special supplementary grant so that he could continue his new research without any delays.

Q: Dr. Rivers, how rapidly did Dr. Sabin's research develop?

Rivers: I would say, very rapidly. Dr. Sabin, you know, has never been a slouch in exploiting a promising lead. In the spring of 1954, just when the Salk vaccine field trials were about ready to get under way, Sabin discovered that there was considerable variation in the immune response of both monkeys and chimpanzees to his new mutant viruses. He found, for example, that when he inoculated monkeys intracerebrally with these mutants he could not produce any paralysis or lesions in the central nervous system. On the other hand, if he inoculated monkeys intraspinally with these same viruses he could produce a paralysis. Sabin called these mutants "spinal variants." The interesting thing about these "variants" was that they seemed to possess an affinity for certain neurones, and, for some reason, in the process of multiplication they only seemed to produce a small number of infectious particles having neurotropic properties. Sabin soon discovered that when these "variants" were inoculated intraspinally in chimpanzees none of his animals would come down with paralysis. Chimpanzees like men are less susceptible to poliovirus than monkeys, and these results fortified Sabin's conviction that he had finally isolated mutant strains of poliovirus which could be candidates for experimental tests in man.[4]

[4] A. B. Sabin, W. A. Hennessen, and J. Winsser, "Studies on variants of poliomyelitis virus. Experimental segregation and properties of avirulent variants of three immunologic types," *J. Exp. Med.*, vol. 99:551 (1954); A. B. Sabin, "Characteristics and genetic potentialities of experimentally produced and naturally occurring variants of poliomyelitis virus," *Ann. N.Y. Acad. Sci.*, vol. 61:924 (1955). For an excellent review of the process of Sabin's research during this period, see also A. B. Sabin, *Immunity in Poliomyelitis, with Special Reference to Vaccination.* World Health Organization Monograph Series, No. 26, pp. 297–334 (1955).

Late in March 1954 Dr. Sabin approached the Foundation for permission to test these mutants in children. The request was passed on to the Vaccine Advisory Committee, and we postponed action on it until we had a chance to talk to him personally. We had a lot of questions to ask, particularly about the possibility of reversion to virulence of these mutants, and just didn't feel that it would be wise to extend his experiments at that time. When he learned our decision, he just about went up like a skyrocket. He came to see me in New York and after some discussion I finally persuaded him to postpone his request until the fall. He agreed but I don't want anybody to think that he was happy. He wasn't. I don't think that he was particularly angry with me then, but very shortly thereafter he got sore as hell at me. I'll tell you why.

A few weeks after the Vaccine Advisory Committee had tabled his request to extend his experiments to human subjects, Dr. Sabin asked the Foundation for 1000 monkeys to push his animal experiments forward. I don't remember now just how many monkeys Sabin used in his experiments during the spring of 1954, but it was well over 1000. When Dr. Kumm brought me a request for another thousand monkeys, I put my foot down and said no. I said other things too. I just didn't think that he needed that many monkeys, and I felt that he could accomplish what he wanted to do with a smaller number.

I would like to take a moment here to say a word or two about monkeys, because they constituted quite a problem at that time. As I mentioned earlier, getting monkeys from India and elsewhere was so difficult that in 1952 the Foundation opened a monkey farm at Okatie, South Carolina, for the specific purpose of supplying grantees with enough healthy monkeys to carry on their research. The monkeys that were captured in India were frequently in poor shape; if they weren't in poor shape when they were caught, they soon deteriorated because of crowded quarters and poor feeding. If one monkey came down with diarrhea, it wasn't too long before the rest would come down as well. The same held true for TB. Although the farm at Okatie made particular effort to condition the monkeys in their care, it was not unusual for the Foundation to receive complaints from laboratories that the monkeys they had received had to be discarded because of illness. During the Salk vaccine field trials, the Foundation

had the added burden of supplying monkeys to commercial firms producing Salk vaccine and to the government laboratories testing the vaccine. The supply of monkeys became so tight at the time of the trials that vaccine producers began to complain that they didn't have enough monkey kidney tissue to cultivate poliovirus. Luckily, Dr. Melnick later rescued us from that difficulty by devising a method to increase the number of cultures which could be made from a given amount of monkey kidney tissue. What he did was to take a monkey kidney, snip it into small pieces and suspend it in a solution containing trypsin in a large Ehrlenmeyer flask. The trypsin had a disintegrating effect on the bits of kidney tissue and they soon separated into individual cells. When they reached this state, Melnick siphoned them from the flask, plated them on the surface of another flask, and covered them with a nutrient medium. Under these new conditions, monkey kidney cells multiplied very rapidly and were easily harvested. Many commercial houses later adopted this method for growing poliovirus.[5]

I tell you about the monkey problem in this detail because I want you to understand why I turned down Dr. Sabin's request for a thousand monkeys. The fact that I turned him down did not mean that I wasn't enthusiastic about his work. I was, and I said so privately and publicly. This is not a story. If you examine the paper that I gave on the progress of immunization at the Third International Poliomyelitis Conference in Rome in September 1954, you will find that I devoted a good part of my talk to summarizing Sabin's research to that date. I certainly didn't mind telling an international audience at that time, "This work is exciting and should be continued vigorously but with caution." I tacked on the word caution, because I felt that a lot of questions still remained to be answered. I was particularly concerned at that time with the stability of the mutant strains that Sabin had developed.

[5] G. L. Morann and J. L. Melnick, "Poliomyelitis virus in tissue culture. VI: Use of kidney epithelium grown on glass," *Proc. Soc. Exptl. Biol. Med.*, vol. 84:558 (1953). The technique of trypsinization was initially developed by Dr. Peyton Rous at the Rockefeller Institute in 1916. Simultaneously with Dr. Melnick, Dr. A. W. Frisch developed a similar technique, using monkey testicular tissue. See A. W. Frisch and V. Jentoft, "Use of trypsin in preparing subcultures of monkey testicular tissue," *Proc. Soc. Exptl. Biol. Med.*, vol. 82:322 (1953).

Q: Dr. Rivers, there is evidence that, during the summer and fall of 1954, Dr. Sabin felt so frustrated that he contemplated going to other foundations for support of his research.[6] Given his feelings, I can't understand why he came before the Virus Research Committee in the fall of 1954 to ask for permission to conduct limited trials with his live viruses among the prisoners at the Federal Penitentiary at Chillicothe, Ohio.[7] Was it in any way necessary for him to obtain such permission from the Virus Research Committee?

Rivers: The truth is that Dr. Sabin never needed any outside support. He was getting all the damn support he needed and more from the National Foundation. He was impatient and, as far as I am concerned, that was his major problem. I remember that in the fall of 1954 he submitted an application for a supplementary grant to the Foundation and asked for immediate action. When Henry Kumm brought the application to my attention, I tabled it for about three months. The Virus Research Committee did not have a formal meeting scheduled at the time I received the application, and getting immediate action would have meant submitting it to a mail vote. On that voting it always took a unanimous vote to pass. One vote could have stopped that application, and believe me when I say that there were always one or two guys on the committee who were willing to throw a monkey wrench into the works. Why risk a refusal? In this particular instance, I arranged for a reallocation of the balance of funds in Sabin's original grant so that he could use it as a temporary source of credit. All Sabin could see was that he wasn't getting what he had asked for.

As for the second part of your question, I think that Dr. Sabin was just acting wisely when he asked the Virus Research Committee for permission to conduct tests with the prisoners at Chillicothe. Although it is true that he could have asked the prison authorities for such permission on his own, he knew that he didn't stand a chance of getting it without our help, because the authorities would have turned around and asked him what we thought. They knew of our existence. Why should they stick their necks out and make an impor-

[6] See, particularly, Memorandum from Henry Kumm, April 19, 1954 (Kumm memoranda, 1954, National Foundation Archives).

[7] Albert Sabin to H. M. Janney, medical director, Federal Bureau of Prisons, November 19, 1954 (copy in folder, Personal correspondence, 1954, Rivers papers).

tant decision like that without having it protected by the advice of a committee of scientists who had long worked in the field? By asking us first, Sabin was saving time. We didn't hold him up. Actually, he wasn't going to do a hell of a lot. If I remember correctly, he initially planned to test his strains in about thirty prisoners. Previously he had fed his strains to a few people in Cincinnati with very good results. The committee knew that his mutant strains were far less virulent than those one would ordinarily meet in nature. We also knew that even if he took a type 1 Mahoney strain and fed it to thirty prisoners, he could probably get away with it.

Q: Dr. Rivers, had Dr. Sabin himself taken his viruses at this time?

Rivers: Oh, yes. Most scientists in his position would have done the same. Dr. Salk, for example, took his own vaccine and inoculated his wife and children with it long before the field trials. It's not that one expects to learn a lot by taking such material—one guy or his family proves nothing. But in the circumstances, someone was bound to ask him, "Dr. Sabin, have you taken your vaccine?" I know that if anyone ever came up to me and asked me to take an untried vaccine, I'd ask, "Have you taken it?" and, by God, if that person said No, I'd tell him to go to hell. This would be the reaction of most anybody, I think. Since the question of this early trial has come up, let me say that in the winter of 1954–55, Dr. Sabin fed his mutant viruses to the prisoners at Chillicothe with great success. All the prisoners developed immunizing alimentary tract infections, no viremias were discovered, and no clinical illness resulted.

Q: Dr. Rivers, I would like to change our focus at this point and turn to an examination of the Salk vaccine during this same period—the winter of 1954. Isn't it true that some months after the Salk vaccine field trials were held the government and several commercial producers discovered that several batches of Salk vaccine which were in storage were losing their potency? [8]

[8] See, especially, telegram, Jonas Salk to Basil O'Connor, November 8, 1954; memorandum from Jonas Salk, November 12, 1954; William G. Workman to Basil O'Connor, November 23, 1954; Thomas Rivers to William Workman, November 23, 1954 (folder, Vaccine, Polio, Salk: Development and Promotion, November 1954, National Foundation Archives).

Rivers: That's true and it involved the Foundation and Dr. Salk in quite a hassle with NIH.

Let me begin by saying that the government has long required commercial producers to put preservatives in the vaccines they manufacture. These preservatives are not made to kill anything, because they are not strong enough to kill; they are merely added as a way of preventing bacteria or molds, which may have gotten into the vaccine during manufacturing or storage, from multiplying. Merthiolate was added to the Salk vaccine as just such a preservative. When the Salk vaccine was originally prepared for the field trials, it was used so promptly that little if any of it was ever stored. However, once the trials were over, surplus vaccine was stored for future use, and it was these batches of vaccine which were later discovered to have lost their potency. Examination very quickly revealed that the merthiolate was responsible and, in the circumstances, there was nothing to do but to get rid of it. It was at this point that the trouble began.

The government took the position that since the Salk vaccine used in the field trials contained merthiolate, they would in the future be unable to license Salk vaccine without merthiolate unless they had additional evidence of the safety of such a modified product. That position got me sore as hell, and I'll tell you why. First, when the merthiolate was added to the vaccine, it was added as a preservative and never as a factor in relation to the safety of the vaccine. Second, the safety tests of the vaccine were determined long before the addition of merthiolate as a preservative. The Vaccine Advisory Committee was certain that the elimination of merthiolate would have no effect on the safety of the vaccine and wrote a letter to that effect to Dr. Sebrell and Dr. Workman at NIH. They, however, remained adamant. In part, I think they were caught by their own rules of procedure.

The government has always required commercial producers to submit clinical evidence of the safety of their products. For example, when a commercial house makes vaccinia virus to protect human beings against smallpox, they have to test every batch in a certain number of unvaccinated children and nearly all, if I am not mistaken, have to have primary takes. In this instance, Dr. Workman wrote back to the Vaccine Advisory Committee and said that he wanted

each of the producers to submit clinical evidence of the safety of the Salk vaccine they produced without merthiolate in at least 2000 individuals. For six commercial firms at that point to conduct safety tests on their own in 12,000 individuals would have been well nigh impossible without disrupting production. Everybody got sore—me, the Foundation, Dr. Salk, Dr. Workman, and Dr. Sebrell. We had a hot correspondence for a while. However, in the end we got together and worked out a compromise plan. Since the Foundation had contracted for nine million doses of Salk vaccine from the commercial producers, NIH agreed that Dr. Salk would be allowed to safety test representative batches of vaccine made without merthiolate from each of the producers in from 5000 to 8000 children so as to satisfy the clinical evidence that NIH required.

Q: Dr. Rivers, during the winter of 1954 and the early spring of 1955, a number of articles appeared in newspapers and magazines on Dr. Francis's evaluation of the Salk vaccine.

Rivers: I never bothered about such reports. Whenever there is anything important going on, you always see such reports in the newspapers. They are called leaks. There are honest-to-God leaks and there are just plain manufactured leaks. Both kinds went on here.[9] To this day, I don't know which was which, because I never paid any attention to them. I didn't ask Dr. Francis if they were so, because I didn't want to embarrass him. Heck, if he was to tell me that a statement was correct or incorrect he would in effect be giving me information that I had no right to have. Why bother him? I knew that when Francis got through with his work he would give us answers and that would be that. Personally, I had every reason to believe that his report would be favorable. I had watched the development of the vaccine from its inception. I was sure that it was safe, and I also believed that it was effective; the only thing I didn't know was how effective.

Q: Dr. Rivers, did you or the Vaccine Advisory Committee play any part in planning where and when the Francis report was to be given?

[9] Dr. Francis takes exception to this statement by Dr. Rivers and points out that there were no leaks from the Vaccine Evaluation Center nor was any information given to anyone (private communication). The same point is made in a contemporary news report in *The New York Times,* April 1, 1955, p. 19, column 1.

Rivers: I had nothing to do with that kind of planning, and I can tell you that it was never a function of the Vaccine Advisory Committee. I do know that early in February 1955 Dr. Francis told Mr. O'Connor that he expected to finish writing his report by the end of March. In the beginning, Mr. O'Connor thought it would be nice if the report could be made public at the National Academy of Sciences in Washington. However, Dr. Bronk, who was then the president of the Academy, indicated that, since the National Academy had never before participated in such a function, it was unlikely that the members of the Academy would approve of such a step. It was then decided that, since the evaluation had been carried out under the auspices of the University of Michigan, the report should be made public from Ann Arbor. The final choice of a date was fortuitous. Originally, Francis had expected to finish writing the report by the end of March; later, however, he informed the Foundation that he couldn't have the report before April 8th or 9th. At that point, the suggestion was made that the report be given on April 12th, the anniversary of President Roosevelt's death. There could be no quarrel with that decision. What if the report was delayed for three or four days? President Roosevelt had been the founder of the National Foundation; Mr. O'Connor had been one of his closest friends—hell, they started everything—without them there would have been no Foundation and I dare say no vaccine. Why shouldn't the report be given on that day? It was fitting.[10]

Q: Dr. Rivers, do you remember going out to Ann Arbor?

Rivers: Yes. I started out alone, but when I boarded the Wolverine to Detroit I met Harry Weaver. Mr. O'Connor had invited him to

[10] On the choice of date for presenting the Francis report, Dr. Francis makes this observation:

The choice was made by my staff and me with no knowledge that any political significance attached to the date. The decision was made at Ann Arbor in a conference that we had with university public relations personnel, and members of the Evaluation Center. It was made only because we couldn't get finished as earlier expected. The only angle was that the public relations people thought Tuesdays were to be preferred. The statement that a suggestion was made that it be done on the anniversary of President Roosevelt's death is not correct. We didn't know the relationship until after the decision was made (private communication).

the meeting, and we had a nice time together on the train reminiscing. It was only when we arrived in Detroit that I realized that a lot of other people were going to the same place. I don't mind telling you that there were a few things about the meeting that I didn't like, and that I am sure the University of Michigan didn't like. In a word, the newspaper people and photographers created a madhouse. I don't know when I have seen such wild people. Talk about putting frosting on the cake, these boys and girls put Christmas trees on with the frosting. It is true that never before had there been a scientific trial of the scope of the vaccine field trials of 1954. It can also be said that the report that Dr. Francis gave of the results of that trial deserved the attention it got, but it always rubs me the wrong way when something like the madhouse at Ann Arbor happens. Newspaper people say that if it wasn't for public support there wouldn't be any scientists and that the public have a right to know what's going on. I can't argue with them too much if they want to tell the people what scientists are doing, except that I wish that they would put it on a little bit thinner, and not quite so thick.

I don't think that there is any need for me here to recapitulate all of Dr. Francis's findings save to say that he reported that the vaccine as used in the field trials was 60 to 70 per cent effective in preventing type 1 virus positive paralytic cases, and 90 per cent and more effective in preventing paralytic cases of type 2 and type 3 polio. If anyone is interested in all of the details and figures, they can always turn to the final report which Francis published in 1957.

After Dr. Francis gave his presentation he turned the report over to me and I made an appropriate little say-so. Then came the speeches. Mr. O'Connor made a speech, Alan Gregg made a speech, Dave Bodian made a speech, and Bill Workman made a speech. Then late in the afternoon Jonas Salk made a speech, and that speech got me sore. When the field trials were put on, children were given three doses of vaccine several weeks apart. The Vaccine Advisory Committee suspected that it could probably get better results if the inoculations were spaced differently but, unfortunately, it had not time to experiment. The field trials did not begin before April and in some parts of the country like the South and Southern California, polio frequently made its appearance long before the summer. As a result

we did the next best thing—we decided to get an optimum amount of vaccine into the kids before the polio season began and asked Dr. Francis to give the inoculations several weeks apart. I am not saying that, when Dr. Salk reported at Ann Arbor that he got a higher antibody titer when he gave the first two doses a few weeks apart and the third dose seven months later, he was wrong. On the contrary, he was right. I am saying that he should not have made that particular speech on that occasion. To my mind, it was an implied criticism of the way Francis had run the field trials, and nothing should have detracted from the kudos that Tommy received that day. Dr. Francis's evaluation of the Salk vaccine was a superb achievement.[11]

Q: Dr. Rivers, had you or the Vaccine Advisory Committee decided before the report what effectiveness would be acceptable?

Rivers: I think that I can honestly say that I and the other boys had not made up our minds one way or the other. However, Mr. O'Connor had made up his mind a long time before. I know because, while plans were being made for the Third International Conference on Poliomyelitis during the summer of 1954, Mr. O'Connor indicated to me that if the vaccine only proved 25 per cent effective, he still would advise everyone to take it. He felt that anything that would prevent even a small number of paralytic cases was worth while. I could understand that; I think that anyone who has ever seen a paralyzed kid could understand that. The figures that Francis later presented on the effectiveness of the vaccine were, of course, eminently acceptable to the Vaccine Advisory Committee. Actually, Francis initially underestimated the effectiveness of the vaccine, because some of the batches of vaccine which were used in the trials were for one reason or another not as good as they might have been.

As soon as Dr. Francis finished giving his report, a special commit-

[11] The schedule of inoculations of vaccine during the field trials were at 0, 1, and 5 weeks or at 0, 7, and 35 days. The decision as to the schedule of administration of the vaccine was made by the Vaccine Advisory Committee of The National Foundation for Infantile Paralysis in collaboration with Dr. Jonas Salk and Dr. Francis and his associates in the Vaccine Evaluation Center. See T. Francis et al., *Evaluation of the 1954 Field Trial of Poliomyelitis Vaccine: Final Report*. Poliomyelitis Evaluation Center, Department of Epidemiology, School of Public Health, University of Michigan, April 1957, pp. 36–38.

tee met in Ann Arbor and recommended that the Secretary of Health, Education, and Welfare, Mrs. Oveta Culp Hobby, license the manufacture of Salk vaccine. She did. However, certain details remained to be taken care of—one of these related to the potency-titer requirement. Several days after the Ann Arbor meeting, a special committee, of which I was a member, met with officials of NIH in Washington and agreed to lower the original potency titer required for the manufacture of Salk vaccine. If we hadn't done this, I doubt whether we would have had a vaccine. Some people have since questioned our good sense in doing this, but the fact remains that the original potency-titer requirement was too high for commercial houses to meet and still have a vaccine that would be available at a price that the public could stand. There are times when you can set too high a standard. I think that since the standard that we set holds to this day, we perhaps did the right thing to lower it a little bit.[12]

Q: Dr. Rivers, soon after the acceptance of the Francis report and the government's licensing of commercial producers, the production and distribution of the Salk vaccine seemed to degenerate into a state of chaos. How involved was the Foundation in these matters?

Rivers: While the field trials were being held, Mr. O'Connor and I frequently talked about what the Foundation should do about the vaccine after the Francis report was made. These were not formal talks in any way and took place at odd moments in the backs of automobiles and in airplanes while we were traveling together. I can't even tell you now how often we spoke about this problem, but I can tell you that we finally reached the conclusion that, when and if the vaccine was licensed, the production and distribution of the vaccine should become the government's business and the Foundation should wash its hands of these particular problems. After all, the Foundation had helped develop the vaccine, had helped lay down the rules and regulations for safe and effective commercial production, and had in fact done everything possible to get the government to like what was done. At this point it could do little more.

[12] Dr. Bodian points out that the potency requirements were subsequently raised, but that this was not known except in the "trade" (private communication).

Q: Dr. Rivers, in the period following licensing, did the government call on the Vaccine Advisory Committee for advice or help?

Rivers: No. Actually, there was no reason for it to do so. When the government licensed commercial production, NIH appointed its own committees of experts, and when problems came up it went to them rather than to a committee originally organized by the Foundation.

Q: I raise the question because, a scant two weeks after the presentation of the Francis report, a number of cases of paralytic polio occurred among children inoculated with vaccine produced by the Cutter Laboratories. I wonder if you would speak with me about the Cutter incident.[13]

Rivers: I don't think that it's proper for me at this time to discuss the Cutter incident, because, as you know, several suits which were later brought against the company are still being adjudicated. But I will say this: when I first learned about the Cutter cases, I was extremely disturbed, because I believed that if the vaccine was made and tested as had been done before and during the field trials, it was perfectly safe. I still believe that.

Q: Dr. Rivers, it is a matter of public record that, following the first reported cases of polio among children who had been inoculated with batches of vaccine produced by Cutter, Dr. Leonard Scheele, then the Surgeon General of the United States, withdrew the Cutter vaccine from the market and temporarily suspended all inoculations with commercially produced vaccine, pending retesting. He also called meetings with nongovernmental virologists. Did you take part in any of these meetings?

Rivers: I attended only one such meeting. However, I do not now remember exactly when it took place.[14] It's strange that I don't re-

[13] For a contemporaneous analysis of the polio cases that arose as a result of the administration of Salk vaccine between April 22 and May 27, see Public Health Service, Technical Report on Salk Poliomyelitis Vaccine. Washington, D.C., June 1955 (mimeographed).

[14] Following the Cutter incident, Surgeon General Leonard A. Scheele called a meeting of scientific experts on April 29–30, 1955 to discuss the Salk vaccine. This group

member that, because several things occurred at that meeting that still stand out in my memory. The first was the testimony of Herdis von Magnus. Dr. von Magnus was a member of the Serum Institute of Copenhagen and was specially flown to the United States from Denmark so that she could tell the meeting about the Danish experience in manufacturing and using Salk vaccine. I should perhaps explain that at that time the Serum Institute, under the direction of Dr. Prebend von Magnus (Herdis von Magnus's husband), was making Salk vaccine for the Danish vaccination program against polio.[15] Dr. von Magnus told us that the Serum Institute followed all the specifications and requirements which guided commercial producers in the United States, save that they used Brunhilde instead of Mahoney poliovirus as the type 1 strain in their vaccine. However, she was adamant that when the vaccine was made according to specifications, it was perfectly safe, and that to her knowledge no cases of paralytic polio had occurred in Denmark as a result of inoculation with the vaccine.

That testimony was to the point. I can't say the same for the fight I

initially contained eleven members: David Bodian, John Enders, Thomas Francis, William Hammon, Edwin Lennette, Foard McGinnes, Howard Shaughnessy, John Paul, Albert Sabin, Jonas Salk, and Joseph Smadel. Later the Surgeon General organized this group into several small Technical Advisory Committees. The first Technical Advisory Committee was composed of David Bodian, John Enders, Howard Shaughnessy, Jonas Salk, and Joseph Smadel. Richard E. Shope of the Rockefeller Institute and Carl Larson of the National Institutes of Health were later added to some of the Technical Advisory Committees. It is difficult to pinpoint the meeting that Dr. Rivers refers to, since he did not serve on any of these committees. It is possible, however, that he was asked to join a meeting for purposes of discussion. It is equally possible that the meeting that Rivers refers to was held under the auspices of a special committee to investigate the Salk Vaccine, which was headed by Dr. Chester A. Keefer, a special assistant to the Secretary for Health and Medical Affairs. I have found no documentary evidence of the meeting, as the papers of the National Institutes of Health on the Salk Vaccine are as yet unavailable for purposes of research.

[15] At the time of the Salk vaccine trials, Dr. J. Ørskov was director of the Statens Serum Institute in Copenhagen; it wasn't until some years later that Prebend von Magnus became director. Dr. Prebend von Magnus, however, did play a role in the polio vaccination studies in Denmark. For information on this program, see H. von Magnus, P. von Magnus, I. Petersen, A. Godtfredsen, and M. Rønkjaer, "Polio vaccination in Denmark: The production of formalinized polio vaccine and preliminary results," *Danish Med. Bull.*, vol. 2:226 (1955); S. Tulinius and E. J. Henningsen, "Polio vaccination in Denmark April–June 1955. II. Organization and procedure for the school vaccination," *Danish Med. Bull.*, vol. 2:233 (1955); P. von Magnus, K. B. Petersen, V. Bech, I. Petersen, and H. von Magnus, "Tissue cultures of trypsinized kidney cells from different monkey species," *Danish Med. Bull.*, vol. 2:236 (1955).

later had at that meeting with Dr. Alex Langmuir of the U.S. Public Health Service. I remember that we were talking about the implications of the cases that had occurred in California and Idaho, when Alex went on record as saying that he was convinced that these cases were going to trigger a horrible epidemic of paralytic polio in the United States. Everybody sat up—Alex is no dumbbell—and I thought I had better say something. "Alex," I said—although not in these words "you are just a damn fool. Nothing like that is going to happen. I don't care if ten kids have polio or a hundred kids have polio. There has never been a man-made epidemic among humans, and I don't think there is going to be one this time." Well, we argued the point and I suppose that we finally generated more heat than light. You know how it is when two bulls lock horns—each bull thinks that he has won. My guess is that Alex to this day still believes that such an epidemic was a distinct possibility. He is one of those fellows you have a hell of a time convincing. For the record, we never had that epidemic that Alex was so afraid of.

Q: Dr. Rivers, did this meeting make any particular recommendations to the Surgeon General?

Rivers: I don't remember whether we did or not. I do know that the Surgeon General did not depend on this one meeting alone for advice. I would say that he depended more on a special committee of experts that he called together soon after the Cutter incident occurred. I wasn't on that committee but it was quite a committee, and I don't know where he could have gotten better advice. John Enders, Dave Bodian, Albert Sabin, Jonas Salk, Tommy Francis, Joe Smadel, Edwin Lennette and Howard Shaughnessy were all members. Most of the action that the Surgeon General took after the Cutter incident was based on the recommendations of this committee.[16] Earlier you mentioned that the Surgeon General withdrew all Cutter vaccine from the market and ordered the retesting of all existing batches of commercially produced vaccine. I would like to add that other things were done as well. For instance, the U.S. Public Health Service instituted a very careful reexamination of the manufacturing process at

[16] This is the committee listed in note 14.

the Cutter Laboratories, and a number of important amendments were also added to the existing safety requirements for producing Salk vaccine.[17] To my mind, however, the best and most important thing that was done was the organization of a special surveillance unit at the Communicable Disease Center in Atlanta, to keep track of all cases of paralytic polio among vaccinated and nonvaccinated children in the United States. Alex Langmuir was made the boss of this unit, and I must say that from the beginning he has done a first rate job. People have often asked me, "Did anything good come out of the Cutter incident?" My answer is always, "Yes, the Polio Surveillance Unit at the Communicable Disease Center in Atlanta." [18] I don't know of anyone in the past six years who works in the field of polio research who hasn't in one way or another been indebted to them.

Q: Dr. Rivers, in addition to the meetings called by the Surgeon General, several congressional committees also held hearings with reference to the Salk vaccine. I raise this point because at one of the hearings held by the Committee on Interstate and Foreign Commerce, on June 22 and 23, 1955, you and several other scientists testified on the safety and effectiveness of the Salk vaccine. Do you remember what you said at that time? [19]

Rivers: I didn't say very much. In essence, all I said was that I believed that, when the vaccine was made according to the specifications which were laid down, and was produced by a commercial house that knew its business in making a vaccine of this kind, it was safe. I didn't call anybody any names. I went on to say that since I was certain that the Salk vaccine, if properly made, would do a great deal for the children of the United States, I thought it would be a great pity if the Congress or anybody else stopped the production and use of the vaccine at that time. I felt very strongly that if the program was halted it would create a doubt in the minds of the public and that it

[17] The early actions taken by the Surgeon General are summarized in Public Health Service, *op. cit.*, pp. 87–93.

[18] The Special Poliomyelitis Surveillance Unit in the Communicable Disease Center in Atlanta, Georgia, was organized on April 28, 1955.

[19] House of Representatives: Interstate and Foreign Commerce Committee, 84th Congress 1st Session. *Hearings on Poliomyelitis Vaccine,* June 22–23, 1955.

would take a number of years before the vaccine was produced and used again. In the meantime a lot of children would needlessly contract paralytic polio and a number would even die.[20]

That was my position, but not everybody at the hearings agreed with it. Dr. Wendell Stanley, for example, said some very harsh things about the safety of the vaccine, particularly about the reliability of the process of inactivation with formaldehyde. He was joined by Dr. Sabin, who further argued that it was dangerous to proceed with a vaccine made with Mahoney poliovirus and urged that the vaccination program be postponed until a satisfactory type 1 attenuated strain could be substituted in its place. John Enders supported Sabin, as did Bill Hammon who, although not present at the hearings, sent a special memorandum to the committee asking that the vaccination program be discontinued. I would like to quote here a portion of the testimony that Dr. Enders gave at the hearings because I think that it summarizes in a succinct way most of the important reasons given by virologists for opposing use of the Salk vaccine after the Cutter incident.

Dr. Enders. Since Mr. Wolverton has asked for an opinion, I will say that I agree, I think, with everything—practically—that Dr. Sabin has said. I think the great point that he made was that we could not predict with regularity that another incident such as we have had would happen on any information that we are now in the possession of.

In view of that situation, I might perhaps review the facts again that he mentioned for the sake of clarity.

1. There has been some doubt cast on the process of inactivation of the virus. We do not know absolutely whether it works according to theory, as Dr. Shannon has pointed out.

2. The safety test may not be sensitive enough to detect the amount of virus that is sufficient to infect a few human beings who are unusually sensitive.

3. We do know that somehow—I think it is fair to say we do know now—somehow in the Cutter case, that in spite of the processing, in spite of the safety tests, live virus did get through and was inoculated, with the production of disease.

Now, new safety tests may take care of that. They have not been tried so far as I know. There are certainly additional improvements that could be made along the lines that Dr. Shannon has mentioned—in particular, the

[20] *Ibid.*, pp. 173–174.

suggestion of the use of an avirulent strain. Indeed, I don't think that, until that is done, I would advise going ahead. I believe I so recommended at a meeting on May 7 in the National Institutes of Health.

I think that within a reasonable time we will undoubtedly have a safe and effective product. In view of the facts that have been brought out here this afternoon, it seems to me the better part of wisdom to wait a little while until we have it.[21]

Q: Dr. Rivers, would it be fair to say that the other virologists present at the hearings supported your views?

Rivers: No, it would not be fair to say that. Dr. Manfred Mayer of Johns Hopkins was another who was against using the vaccine. John Paul, who served as chairman, spent most of his time performing his duty as an impartial chairman and as far as I remember did not make any plea either for or against the vaccine. Even the boys who later went along with the notion of continuing the vaccination program didn't completely agree with everything I said. Actually, one of the most cogent presentations for continuing the vaccinations was made by Dr. Francis, and I think his argument was far more representative of the feelings of those who finally voted to go ahead than my own. I'll quote some of what he said here, so you can get the flavor of his thinking at that time:

Dr. Francis. Mr. Priest, gentlemen, I too agree that there are advantages to be gained in the substitution of strains which have less virulence for immunization, provided they are otherwise effective. But I think that this also introduces several other questions. The first of them has been referred to by Dr. Horsfall—that not only must these strains be shown to be effective under laboratory conditions, but they must also be suitable for mass production and use, and they must be stable under those conditions.

Secondly, the fact that an attenuated strain is used does not ensure that there will be no risk if there is still active virus in the vaccine. The procedures which would be employed to prevent infection by strains such as Mahoney would also have to be applied to these other strains, because, while any of the Mahoney strain that slips through may produce damage directly, active attenuated strains may also change if they are allowed to be present. So it is not simply a matter of relaxing your guard and reducing

[21] *Ibid.*, p. 180. The editor has taken the liberty of editing the remarks of Dr. Enders and the later remarks of Dr. Francis, because the printed versions of the hearings are garbled in places.

the requirements for production and safety by saying that, if they are in there, they should be attenuated. It makes little difference if attenuated strains are used, because the risk is still there that they may change and become virulent.

Finally, I think that the safety tests and the improved safety testing that have been developed are of such a nature as to give a very high degree of confidence that active virus should not occur. As Dr. Shannon says, and I think we would all agree, there is nothing that can give you absolute guarantee under all conditions that no active virus could be present in the preparation.

. . . The suggestion is made that this can all be done in six months. If one were to stop the present program, the result would be to remove a product that has been proved safe and effective, and substitute for it an unknown —an idea which, at the present time, is still experimental. You would then be substituting for a proven product something that is yet to be tested, which Dr. Sabin thinks might be better, but for which the proof is not yet available and would not be available until the tests were done. . . .

In view of all these considerations, I would certainly be opposed to stopping the present program until that other work has been done. I think the suggestions which have been made are there, for anyone to work on. There is nothing in the world to hinder anyone from developing different kinds of vaccines and different procedures, and there is no hindrance to their being accepted, when the evidence is in that they are satisfactory.

Dr. Paul. Dr. Francis, would you feel that you have said all you want to say on the substitution of strains, in terms of an opinion for or against?

Dr. Francis. On the substitution of strains, I would agree, provided they are satisfactory. I think one might point out, no matter what else is said, that the presence of the Mahoney strain and the fact that it was used in vaccine and produced disease was of itself a significant fact for educational purposes at least. Had that not happened, I think a number of the deficiencies and perhaps inadequacies in the type of reporting that was done on production of material might not have been detected until some other kind of accident showed up.[22]

There was some surprise testimony at that hearing and the most surprising as far as I personally was concerned was the testimony given by Jim Shannon of NIH. I didn't quite know what to expect from Jim Shannon before the hearings. As I indicated earlier, I had had a run-in with him on the question of safety just before the Vaccine Advisory Committee finally approved the vaccine for the field trials in 1954. I

[22] *Ibid.*, pp. 198–199.

want to tell you that I was pleasantly surprised when I heard him make a plea for continuing the vaccination program. I hadn't prepared anything when I came down to testify—I spoke off-the-cuff—but Jim came loaded with charts, statistics, and a lot of other evidence, all beautifully prepared. It has always been my feeling that Dr. Shannon's presentation helped carry the day at these hearings because it was so beautifully done that it made it easier for Dr. Horsfall, Dr. MacLeod, Dr. Hodes, and Dr. Francis to go along.[23] In the end, when the committee asked us to vote on whether to continue the vaccination program we voted 8 to 3 to go ahead.

Q: Dr. Rivers, at least five of those who voted in the affirmative can be said to have been your boys. Dr. Horsfall, Dr. MacLeod, Dr. Francis and Dr. Smadel were all previously closely associated with you at the Rockefeller Institute, and during the war Dr. Hodes served under you in NAMRU 2.

Rivers: I'll admit that I could be pretty sure how the fellows I had been associated with would react. When you work with people for several years you begin to know how they think. Joe Smadel and I probably knew more about the vaccine as vaccine than anybody else who was present because we had served together on the Vaccine Advisory Committee. After the field trials nobody had to tell Tommy Francis anything about the vaccine. I believe that Horsfall, MacLeod, and Hodes would have voted the way they finally did if they hadn't come to Washington. They didn't hear anything in Washington that they hadn't heard before. None of these fellows are dummies. Let me tell you, if any of them thought that I had pulled a boner, they would have turned me in as fast as a cop turns in a robber. I wouldn't admit that they were my boys if they weren't that kind of folks. The people that I like and have a high regard for are people who are honest and would turn in their own mothers if they did something crooked or wrong. I never expect Smadel, Horsfall, MacLeod, or any of my boys ever to protect me. If they think that I am wrong, they say so and they don't pull their punches.

[23] *Ibid.*, pp. 162–166.

Q: Dr. Rivers, you indicated that the final vote was 8 to 3 to continue with the vaccination program. Unless I am mistaken, more than three people opposed the vaccine at the hearings.

Rivers: Not everybody who spoke against the vaccine voted against it. Dr. Stanley and Dr. Mayer, who had plenty to say against the vaccine, refrained from voting on the grounds that they were only Ph.D.'s and not physicians. I was dumbfounded, because I had never heard such a statement before. I have known a great many Ph.D.'s in my time, and I can tell you that they just love to vote. Did you ever try stopping one from voting? I won't say anything about Stanley's and Mayer's reasoning—I will say that another Ph.D. was present at those meetings who wasn't bothered about being a Ph.D. John Enders got up and voted loud and clear against using the vaccine at that time. That was perfectly all right. I have always had the firm belief that every man has the right to vote the way he believes. You know, even if Stanley and Mayer had voted, it wouldn't have changed the final result: the ayes would have still won.

Q: Dr. Rivers, from evidence that I have seen, it is apparent that, even after the Congressional hearings of the spring of 1955, some of the pharmaceutical firms making Salk vaccine had difficulty from time to time in inactivating poliovirus.

Rivers: There was such difficulty, and during the summer and fall of 1955 Henry Kumm and I visited the laboratories of all the commercial producers making Salk vaccine for the express purpose of looking into the matter. Not all of the producers at that time would admit to having such a problem. However, the Parke-Davis people were frank enough to tell me that on several occasions they had had trouble inactivating poliovirus. A short time later, when I visited the Connaught Laboratories, I heard of similar difficulties. It has always been my belief that whether they admitted it or not, all of the producers making Salk vaccine at that time discovered occasional batches of vaccine in which the virus was not inactivated. No one in the pharmaceutical firms knew why this was happening. That, of course, is nothing against them. As a matter of fact, many virologists outside

the commercial laboratories didn't know either. Sometime later that fall [1955] Dr. Salk and a number of other investigators began to supply evidence that the trouble might in part lie in the storage of virus fluids.[24]

During the field trials the vaccine was used so rapidly that virus fluids used in preparing the vaccine very rarely got a chance to stand or be stored. After the field trials, however, the picture changed, and pharmaceutical houses began to store their virus fluids in five and ten gallon demijohns until they accumulated large enough batches of virus to be inactivated. In some instances such virus fluids remained untouched for months. For example, Dr. Salk later showed that, although such stored virus looked normal, when the jars in which they were kept were shaken, a precipitate or cloudy sediment would rise from the bottom of the jar. He maintained that this precipitate was in fact a conglomeration of a number of virus particles and could not be inactivated with the same concentration of formalin, temperature and pH used to inactivate single poliovirus particles. To cope with the conglomerations he suggested that the commercial houses filter their stored virus fluids before undertaking final inactivation. Such extra

[24] Dr. David Bodian observes here:

Dr. Rivers attributes to Dr. Salk an analysis of the problem that was actually made by Dr. Richard Shope, who visited all the manufacturers and studied their details of processing of vaccine fluids, as subcommittee chairman for the NIH Technical Committee on Poliomyelitis Vaccine. The Technical Committee studied a great deal of manufacturer's data in detail for many weeks before recommending new filtration procedures (private communication).

Dr. Bodian's additional information points up the problems of depending on memory in history. The special Technical Advisory Committee on Poliomyelitis Vaccine, which the Surgeon General had organized, contained, among others, James Shannon, David Bodian, Thomas Francis, Jr., Jonas E. Salk, Richard Shope, and Joseph Smadel. There is no doubt that Dr. Shope, as Dr. Bodian intimates, examined the problem of processing vaccine fluids. Dr. Salk, however, was no less concerned, and carried out examinations of his own. He later discussed these at length with Dr. James Shannon in a letter dated October 5, 1955. Dr. Rivers was undoubtedly privy to this letter, because a copy was found in his correspondence files. The incident that Dr. Rivers recounted above about Dr. Salk and the demijohns of poliovirus fluid actually happened and was recounted to Dr. Rivers by Dr. Henry Kumm who visited Dr. Salk's laboratory on October 26, 1955. See also memorandum from Henry Kumm, October 26, 1955; and especially memorandum of November 1, 1955, in which Kumm notes that he has spoken to Dr. Rivers about his observations in Dr. Salk's laboratory (Kumm memoranda, 1955, National Foundation Archives). Both Dr. Rivers and Dr. Bodian are here telling "the truth" as they know it.

filtrations were later written into the requirements and specifications and went a long way toward clearing up the problem of inactivation.

Q: Dr. Rivers, earlier you mentioned the Danish experience in manufacturing and using Salk vaccine, yet not all countries at that time were equally enthusiastic about adopting and using Salk vaccine.

Rivers: When we were about to begin the vaccine field trials in 1954, any number of foreign governments wrote the Foundation and offered facilities for holding the trials in their countries. The Canadians and Danes later vaccinated their populations with Salk vaccine of their own manufacture, but it is true as you suggest that this didn't happen everywhere. Dr. Pierre Lépine at the Pasteur Institute made his own polio vaccine for the French, and the British certainly were very reluctant to begin a vaccination program with the Salk vaccine. I honestly don't know how to explain the British attitude. It certainly has nothing to do with the quality of their virologists. You will have to go a long way before you can find people of the caliber and quality of Sir Christopher Andrewes or Alick Isaacs. I hate to blame it on British conservatism—heck, vaccination as a procedure is a British medical innovation. The only thing I know was that it was difficult to convince them. Early in 1955, Sir Weldon Dalrymple-Champneys of the British Ministry of Health visited the Foundation for the express purpose of learning about the Salk vaccine. I thought he was won over to the vaccine, but after the Cutter incident he gave a paper in which I thought he was unduly conservative about its prospects. I didn't say anything to him at the time; however, early in 1956, when I learned that the British were about to undertake a limited field trial with Salk vaccine, I wrote to him to ask about the trials and the reasons for the delay. I would like to quote his reply to me here, because it expresses the British attitude very clearly and incidentally casts some light on modifications which the British later introduced in the manufacture and safety testing of Salk vaccine.

25th January, 1956

Dear Rivers,

Thank you for your letter of 20th January.

I am sorry that you found my optimism with regard to vaccination against poliomyelitis unduly restrained, but I believe that it is useful to err,

if anything, on this side when trying to make people understand the problems involved in a matter of this sort. This does not mean that I do not regard the great trial of the Salk vaccine as a very remarkable achievement, which is bound to have a profound influence on the history of poliomyelitis control, even if the vaccine eventually used may be different in type.

In this regard, I am very interested to read your opinion of the probable attitude of your people to a live virus vaccine, though I should have thought that the success of other attenuated live vaccines would give some encouragement to those trying to devise one for this disease.

The news items about the use of poliomyelitis vaccine of the Salk type is quite correct and I send you herewith some papers which will show you just what we are doing. The first step is described in these papers, and it is only necessary to add that vaccination will, according to present plans, begin again in November after the poliomyelitis season, when much larger quantities of the vaccine are expected to become available. It is very difficult to tell what the acceptance rate will be, but we expect to get many more children registered for vaccination in the next few months than we can provide vaccine for.

You will also see that, though there is no intention to carry out a real "trial" like yours, we do hope to get some valuable information out of our procedure, especially with regard to children under 6 years old.

As regards the vaccines which will be used, that of one manufacturer contains Type I Enders modification of Brunhilde; Type II MEF [1]; Type III Saukett. The vaccine of the other manufacturer will contain Type I Enders' modification of Brunhilde (as with other manufacturer); Type II SK; Type III Leon.

Regarding safety tests, we have adopted those laid down in the latest U.S. Minimum Requirements, up to and including Amendment 4 of 11th November 1955, but have introduced the following modifications:

1. In the monkey tests cortisone will be given in divided doses, with an initial dose of 125 mg 2 days before the vaccine is injected, followed by 5 doses of 25 mg given every second day.
2. The vaccine to be tested is injected intra-cerebrally and intra-spinally. The intra-spinal test of vaccine given to monkeys will be 0.2 ml directly into the lumbar enlargement and 0.3 ml into the subarachnoid space around the cauda equina.

All monkeys will be observed for a period of 28 days. In the final monkey test, intra-muscular injection has been omitted as it might cause antibody production and interfere with the results.

Yours sincerely,

WELDON DALRYMPLE-CHAMPNEYS [25]

[25] Weldon Dalrymple-Champneys to Thomas Rivers, January 25, 1956 (folder, Personal correspondence, 1956, Rivers papers).

Q: Dr. Rivers, what effect did the progress of the Salk vaccination program in 1955 have on the development of Dr. Sabin's research?

Rivers: I would be inclined to say that it had little or no effect for the simple reason that Dr. Sabin didn't work by keeping one eye cocked on what was happening with the Salk vaccine. The rate of his progress and development was determined by what he was able to do in his own laboratory. My impression is that throughout 1955 his research developed very rapidly, and unless my memory plays me false, by the end of that year he was concentrating his efforts on studying the pathogenicity of viruses recovered from the stools of human subjects whom he had vaccinated on a limited basis. If Sabin had any difficulty at that time, it was in choosing stable and effective nonpathogenic strains for his vaccine. For example, although none of the nonpathogenic strains which Sabin recovered from his vaccinated subjects proved to be as pathogenic as the original strains before they were attenuated, the truth is that some of them still retained the ability to cause paralysis in monkeys upon intracerebral inoculation. I would go so far as to say that these findings convinced Sabin to discard the early type 1 and type 2 variants he had developed and to try working instead with the nonneurotropic Mahoney strain that Dr. C. P. Li and Dr. Morris Schaeffer had developed by passage in monkey testes cultures in mice,[26] and a type 2 virus that he isolated from the stools of healthy children sent to him by Dr. John Fox from New Orleans.[27] I believe that, if you had asked Sabin in the fall of 1955 whether it was possible to get completely nonneurotropic strains of poliovirus, he would have said that it was impossible.

I would like to take a moment to say something about the Li-

[26] C. P. Li and M. Schaeffer, "Adaptation of type I poliomyelitis virus to mice," *Proc. Soc. Exptl. Biol. Med.*, vol. 82:477 (1953).

[27] The origin of this virus is recounted by Dr. Sabin in a special note to Dr. Henry Kumm on the copy of a letter sent originally to Dr. Harry Eagle at the National Institutes of Health, on August 30, 1956.

Dear Henry,

I appreciate your note about the origin of "P712" virus. What I received from Dr. Gelfand was not a virus but a stool specimen. This specimen actually contained two viruses, one polio and one not polio. I have designated my derivatives from this in different ways, always referring to "P712" as the source. I think it matters little what the derivative is called, but rather what it does and how it was obtained (folder, CRBS #139, University of Cincinnati, 1956, National Foundation Archives).

Schaeffer strain. You know, I take a great deal of pride in the development of that strain. Some people might call that pride odd—I know that Dr. Li would—because the fact is, about thirty years ago I fired Dr. Li, who was then a young man working in my laboratory, for carrying on a sitdown strike against a work program that I had mapped out for him. Twenty years later he was able to rub my nose in that mistake. I don't mind telling you that Dr. Li and Dr. Schaeffer demonstrated a great deal of patience and ingenuity in adapting the Mahoney strain to go in mice. It had never been done before, and I doubt that before they did their trick anybody even suspected that it could be done. I don't know why they tried to do this—perhaps it was to get a cheap laboratory animal for diagnostic purposes. If that was their purpose, they got that and more, because the strain they finally developed turned out to be a mutant that was avirulent for both mice and monkeys by all routes and later proved very useful to Sabin.[28]

Q: Dr. Rivers, what was the cause of Dr. Sabin's difficulties?

Rivers: Basically, I think it boiled down to the fact that the terminal dilution techniques that Dr. Sabin was then using for the selection of his strains was just not sufficient to do the job. I know that, at that time, I and several other members of the Vaccine Advisory Committee believed that the tissue-culture plaquing techniques that Dr. Dulbecco had developed would provide a far better means for selecting the genetically homogenous nonneurotropic strains that Sabin needed. I remember that when Sabin visited the Vaccine Advisory Committee in December 1955 we examined these possibilities with him. However, we reached no conclusions at that time and finally decided that it might be more profitable to hold a special meeting devoted to genetics so that he might have a chance to discuss his problems further with specialists working in this area.

Earlier you asked me what the National Foundation did for Dr. Sabin, and I told you that they supported his research. I would like to

[28] Dr. Sabin observes, "This mouse-adapted strain was tested by me in chimpanzees and was found to be unsatisfactory and was never used in tests on human beings" (private communication).

add here that probably one of the most important things they ever did for him was to call this conference on genetics.[29] Usually when Sabin attends a meeting or conference he does the telling, and more often than not it is worth while because Sabin is a very smart hombre. However, I will go on record as saying that this was probably the only conference that Sabin ever attended where somebody else did the telling. It was set up that way. I know, because I helped set it up. The Foundation invited a lot of heavy guns to this conference for the specific purpose of getting Sabin to listen—Sir MacFarlane Burnet, Edward Tatum, Joshua Lederburg, Renato Dulbecco, Max Delbrück, Barry Commoner, Salvador Luria, and nine or ten other people of similar caliber.

Actually, we didn't have to twist his arm that hard; nevertheless by the time the conference was over Sabin was ready to discard his terminal dilution techniques. As a matter of fact, a short time after the conference, Sabin and Dulbecco began to cooperate in studying the plaque characteristics of the three type strains which Dr. Sabin then believed were his optimum strains—that is, those strains which showed the lowest neurotropism for monkeys and the greatest stability after propagation in the human alimentary tract. These particular studies were most important, because they showed Sabin that the strains he previously believed to be homogenous in fact represented mixed populations of virus particles. I believe that at this point he decided that the homogenous nonneurotropic strains that he wanted could only be obtained from the progeny of single virus particles derived from his optimum strains by plaquing techniques, and in the months that followed he increasingly devoted himself to such studies. My remembrance is that these studies went on for approximately six or seven months. Sometime in the fall of 1956, Sabin succeeded in developing triple purified, plaqued, attenuated strains[30] of poliovirus that finally appeared to have the characteristics that he was looking for—that is, they were stable, they were not paralytogenic for monkeys on intraspinal inoculation, and, except in very large doses, they were immunogenic when fed to chimpanzees and human volunteers.

[29] See Proceedings of the Round-Table Conference on Genetic Aspects of Virus-Host Relationships, with Particular Reference to Polioviruses. February 23–24, 1956, National Foundation Archives.

[30] Dr. Sabin observes that he never called these strains (private communication).

Q: Dr. Rivers, what were the minimal requirements for a live polio vaccine?

Rivers: These were established very early and I must say that Dr. Sabin was always very explicit about them. First, the polio strains which were selected for the vaccine could not be paralytogenic for the most susceptible human being: second, they had to have the capacity to multiply in the human alimentary tract so that they could produce the infection necessary for immunity; and third, and perhaps most important, the virus strains finally selected had to be stable, that is, they had to have the ability to maintain their attenuated characteristics after propagation *in vitro* and multiplication *in vivo*. The first two requirements were easy enough to prove, the third one was the rough one.

Q: Dr. Rivers, when Dr. Sabin began to study the plaque characteristics of his optimum strains of poliovirus in the spring of 1956 he voluntarily suspended his experimental vaccination program at the Federal Penitentiary in Chillicothe, Ohio. Did the Vaccine Advisory Committee ever interpose any additional requirements for the resumption of these tests? [31]

Rivers: No. Later in the fall of 1956, after Dr. Sabin had developed his new attenuated strains, he asked the Vaccine Advisory Committee for permission to resume human testing of his vaccine on a limited experimental basis. Merck, Sharpe, and Dohme at that time had prepared about 60 liters of vaccine incorporating Sabin's new strains, and we agreed. The only limitation we put on him, as I recall, was that he restrict his new tests to adults and not do any tests with children unless they had previously been inoculated with Salk vaccine. It was not much of a restriction. I think it's fair to say that at that time —early in 1957—Sabin himself didn't want to do much more than establish the safety of his new attenuated strains and determine something of their behavior and activity in humans.

[31] Albert Sabin, Application for a Grant to The National Foundation for Infantile Paralysis, August 4, 1956. Section on Summary of Work to Date (folder CRBS #139, University of Cincinnati, 1956, National Foundation Archives).

I don't want to give the impression that Dr. Sabin was a shy violet in asking to do things—he wasn't—but I want it clearly understood that at no time did he try to go off on his own or circumvent the Vaccine Advisory Committee. For example, during the spring of 1957, a number of virologists in other countries asked Sabin for seed lots of his newly attenuated strains. Sabin forwarded each and every one of those requests to the Vaccine Advisory Committee, and the viruses were sent abroad only after the committee had given its permission. I'll admit that we weren't exactly enthusiastic about doing this. However, the only limitation that we finally placed on such foreign shipments was that the virus strains could only be sent to highly qualified virologists for experimental purposes, and that all experiments had to be undertaken by such investigators on their own responsibilities and in their own countries. As I remember it, shipments were later made to investigators in Russia, Holland, England, South Africa, and Mexico. I want to emphasize that these shipments were made for experimental purposes and not for field trials. The field trials came later.

Q: Dr. Rivers, why were the first field trials of the Sabin vaccine held in foreign countries and not in the United States?

Rivers: I would like to correct a misconception that you seem to have. It is true that initially Dr. Sabin's vaccine was more widely tested in foreign countries than in the United States; however, I think that you should not overlook the fact that, beginning in 1956, the Yale polio unit under the direction of John Paul and Dorothy Horstmann started to conduct limited trials of Sabin vaccine in several small communities in the United States.[32] While these trials were never done on the scale of those carried out in the Soviet Union, they

[32] Dr. Rivers undoubtedly has reference here to tests carried out in November 1956, March 1957, and November 1957 in a children's home, and in 1957–1958 in a village community in Southern Arizona. See, further, D. M. Horstmann, J. C. Niederman, and J. R. Paul, "Attenuated type I poliovirus vaccine: its capacity to infect and spread from 'vaccinees' within an institutional population," *J. Amer. Med. Assoc.*, vol. 170:1 (1959); D. M. Horstmann, J. C. Niederman, and J. R. Paul, "The trial use of Sabin's attenuated type I poliovirus vaccine in a village in southern Arizona," *Amer. J. Hyg.*, vol. 70:169 (1959).

were nevertheless some of the most meticulous and careful ever conducted with Sabin vaccine.

I don't know that there is one simple answer why the first mass trials of Sabin vaccine were held in foreign countries; there is certainly more than one reason why that happened. By the fall of 1957, a year before the first large-scale field trials took place abroad, a large proportion of the population in the United States had already received Salk vaccine. The Salk vaccine was by then established as a safe and effective immunizing agent, and Salk immunization programs were in progress throughout the United States. On the other hand, it is fair to say that in 1957 extensive tests were still needed to establish the safety of Sabin's vaccine. A mass trial of Sabin vaccine in the United States at that time would most certainly have disrupted the then current Salk immunization programs, and in the circumstances it would have been a very unwise move. I can tell you that as late as 1959, the Vaccine Advisory Committee still felt that it needed more laboratory information relative to the reversion of virulence of Sabin's attenuated strains before sanctioning a large field trial with Sabin vaccine in the United States. I know that at that time I personally argued against using the Sabin vaccine in such a program, because I was still not satisfied that his type 2 and type 3 attenuated strains would not cause viremias.

Abroad the situation was quite different. In many foreign countries, in 1957 and the years immediately thereafter, it was not feasible for economic and other reasons to undertake mass immunization programs with Salk vaccine. As a result, public health officers and virologists in such countries began to take a very lively interest in the development of live-virus vaccines, not only the Sabin vaccine but the Cox and Koprowski vaccines as well. One measure of that interest is to be found in the fact that immediately after the Fourth International Conference on Poliomyelitis—which was held in Geneva early in the summer of 1957—a special international committee of experts met under the auspices of the World Health Organization and recommended that field trials be held to test the value of the live-virus vaccines then being developed. The action taken by this committee was very important, because it also went on to set down the first ground rules for conducting such trials. I would like to insert here the major

portion of these rules, so you can get some notion of the criteria which later guided the field trials held in foreign countries (see Appendix E).

Q: Dr. Rivers, I wonder if you can give me an example of how countries were chosen for field trials with Sabin vaccine.

Rivers: No one chose the country. Generally, it was the public health officials or virologists of a given country that did the choosing, and usually for reasons of their own. For example, during the summer of 1958, Czechoslovakia through WHO asked Dr. Sabin to send them enough live-virus vaccine to inoculate approximately 200,000 children in a special field trial. What had happened was that a year or so before, all of the children under 12 in Czechoslovakia had been given three doses of Salk vaccine. However, not all of the children had developed neutralizing antibodies, and public health officials decided that in such circumstances it would be fruitful to determine the effects of giving 200,000 children in one part of the country a fourth inoculation with Salk vaccine and 200,000 children in another part of the country a dose of Sabin vaccine. That, of course, was not the sole purpose of the field trial, but it certainly was one of the major purposes.[33]

In the Soviet Union the situation was different. In 1957, Dr. Smorodintsev, one of the investigators who earlier had received seed lots of Sabin's attenuated strains for experimental purposes, inoculated some 3000 children in Leningrad with Sabin's vaccine on a limited test basis. The results of this particular test were so encouraging that the Russians, who earlier under Dr. M. P. Chumakov in Moscow had developed a program of inoculating their children with Salk vaccine, decided instead to concentrate their efforts on developing a mass immunization program with Sabin live-virus vaccine. In 1958, Dr. Smorodintsev and Dr. Chumakov asked Sabin for enough vaccine to inoculate 200,000 children in two widely separated areas in the Soviet Union. I would like to point out that the Russians later used some of

[33] For a report on this trial see V. Skovranek et al., "Field trial with Sabin's live polio virus vaccine in Czechoslovakia 1958–1959," in *Live Polio Virus Vaccines, First International Conference on Live Poliovirus Vaccines.* Pan American Sanitary Bureau, Washington, D.C., 1959, pp. 530–571.

the lots of this vaccine to produce secondary lots of Sabin vaccine in their own laboratories. In essence this marked the beginning of probably the largest live-poliovirus immunization program ever undertaken anywhere. If memory serves, by 1960 over 70,000,000 people had been vaccinated with Sabin vaccine in the Soviet Union and I might add by all accounts most successfully.

Q: Dr. Rivers, did you ever have occasion to meet any of the Russian virologists engaged in the Sabin immunization program?

Rivers: Oh yes. In February of 1956 a delegation of Russian virologists including Dr. Smorodintsev, Dr. Chumakov, and Dr. Marina Voroshilova visited the National Institutes of Health in Washington on some official business. They had some very formal discussions and meetings in Washington which I did not attend. Later the Russian delegation came to New York to visit the National Foundation and I met with them on that occasion. The meeting between the Russians and ourselves was informal and friendly. We gave them a lunch and we chatted. They were very much interested at that time in obtaining copies of papers which had been published under Foundation auspices and were equally anxious to get advice on the purchase of some laboratory equipment. However, at no time during this visit did we ever get down to any arguable discussion of either the Salk or Sabin vaccine. My suspicion is that they probably learned a great deal more about the Sabin vaccine when Dr. Sabin addressed a microbiological conference held in the Soviet Union in June of 1956 than they did when they visited the Foundation.[34]

This, by the way, was not the first time that I had met Russian virologists. During World War II I had met Dr. Smorodintsev and Dr. Soloviev in Washington when they were demonstrating a new method that the Russians had then devised for making typhus vac-

[34] Albert Sabin writes, "These Russian virologists spent three days in my laboratory during their visit to the USA and carefully went over my current work. Arrangements for collaborative studies were made then. My visit to the Soviet Union followed" (private communication). The microbiological conference referred to by Dr. Rivers was the 13th All-Union Congress of Epidemiologists, Microbiologists and Hygienists held in Leningrad, June 20–June 28, 1956. Albert Sabin to Henry Kumm, June 11, 1956 (folder CRBS #139, University of Cincinnati, 1956, National Foundation Archives).

cine. Both of these boys spoke English surprisingly well, and I was impressed by what they had to say, but for some reason or other I took a dislike to Smorodintsev. I don't know what it was, I just didn't like him. When he visited the United States in 1956, he rubbed me the wrong way again. I remember that we got into a discussion of tick-borne encephalitis, and he told me in rather glowing terms of a formalinized mouse-brain vaccine that the Russians had perfected for such infections. I'll be frank with you. I personally have never thought much of a mouse-brain antigen for an encephalitis vaccine; yet that isn't what really riled me. The thing that got my goat was that not once in that entire discussion did Smorodintsev ever show any concern about the possible danger of an allergic encephalitis.

Dr. Chumakov and Dr. Voroshilova were completely different. Also they indicated to me very early by their actions and the things that were said that they knew what they were talking about. Chumakov had done a great deal of work on Russian spring-summer encephalitis virus, and as a matter of fact had quite a memento of that research. When I met him he had a complete flaccid paralysis of his right arm, apparently the result of a previous infection with that virus. He was also very deaf, but I don't know whether the deafness was the result of the infection with spring-summer encephalitis virus or not. Dr. Voroshilova was equally impressive. Sometime later she translated and pirated my book on *Viral and Rickettsial Infections of Man*. The Russians, you know, do not belong to the Universal Copyright Convention and they pirate any damn book they want to. In due time I received a copy of my book in Russian and a nice note from Dr. Voroshilova thanking me for the use of the book. I didn't see any reason why she should thank me because she had used it without my knowing anything about it. The letter, while a nice gesture, was on the order of closing the barn door after the horse had been stolen. What bothered me about the whole affair was the possibility that Dr. Voroshilova had misquoted me and other contributors to the volume in translation. Russians on occasion are guilty of such slips, and sometimes they put down things that they think ought to have been said. I can't read Russian and eventually I sent my copy to Joe Smadel in Washington and asked him to have one of the Russian experts at NIH check the translation. They did, and Joe later informed

me that Dr. Voroshilova—who by the way speaks English as well as she does Russian—had done an excellent job of translation. My fears were for naught, because the boys in Washington told me that whenever Dr. Voroshilova disagreed with the text she put in a footnote to register that disagreement, so in the end everything turned out all right.

Now that I have told you how these people struck me, I want to reemphasize that they were all very competent virologists and certainly knew what was what about polio. Dr. Smorodintsev was chief of the Department of Virology at the Institute of Experimental Medicine in Leningrad, Dr. Chumakov was director of the Institute of Poliomyelitis Research in Moscow, and Dr. Voroshilova—who by the way was Dr. Chumakov's wife—was a senior worker in the same institute. Dr. Dorothy Horstmann of Yale, who visited the Soviet Union in 1959, later told me that she found Dr. Smorodintsev's and Dr. Chumakov's staffs were also very competent and that the standards of their laboratory work were very high.[35]

In the early summer of 1959, Dr. Smorodintsev, Dr. Chumakov, and Dr. Voroshilova visited the United States once again. This time they came to attend the First International Conference on Live Polio Virus Vaccines, which was held in Washington. It was a very important conference and I must say that they created quite a stir. During that conference Dr. Smorodintsev and Dr. Chumakov gave a number of papers which contained both experimental and epidemiological evidence that strongly supported the contention that the Sabin vaccine, as used in the Russian mass immunization program of 1958, was both effective and safe. Although the papers that the Russians gave were impressive, they did not wipe out all of the doubts which investigators here had about Sabin's vaccine. I think it is understandable that there were such doubts. At the time the First International Conference on Live Virus Vaccines was held, only a few months had elapsed following the 1958 Russian field trials. Not all of the results of those trials were then in, and a number of important follow-up studies still remained to be undertaken. Most important, the Russian

[35] See also D. M. Horstmann, Report on a Visit to the USSR, Poland, and Czechoslovakia to Review Work on Live Polio Virus Vaccine, August–October 1959. This trip was undertaken under the auspices of WHO (mimeograpred copy in Rivers papers).

field trials were not controlled, and that made it damned hard for investigators here to interpret with any precision the immunizing effectiveness of the Sabin vaccine which the Russians had used.[36] In regard to safety, as I mentioned earlier, in 1959 I and a number of other investigators were still concerned about the reversion to virulence of Sabin's attenuated strains and the ability of his type 2 and type 3 strains to cause viremias. I think that it would be a mistake to say that only the members of the Vaccine Advisory Committee of the National Foundation had such reservations. I know that members of the special Live Polio Virus Vaccine Committee appointed by the U.S. Public Health Service had similar reservations, and I can tell you that they gave Albert quite a time during the winter of 1959 when criteria for the commercial production of Sabin vaccine had to be set up.

Q: Dr. Rivers, I would like later to examine with you in detail the development of Dr. Sabin's research between 1958 and the present. Now I would like to turn back to the spring of 1955 and take up a matter that in one sense develops out of both the inactivated and live-virus vaccine research programs—that is, the discovery of a new group of viruses known as "orphan" viruses.

Rivers: Unless I am mistaken, the first so-called orphan virus was discovered by John Enders and his associates in 1950, when they first began to type polioviruses by tissue-culture methods. Later Albert Sabin, Joseph Melnick, Gilbert Dalldorf, and a number of other investigators also began to turn up other such viruses. By 1955, in a period of about five years, well over 600 strains had been isolated. All of these new agents seemed to have similar characteristics: all were cytopathogenic for cell cultures, all failed to induce disease in experimental animals, and none could be neutralized by poliomyelitis antisera. I think that originally Dr. Melnick was responsible for calling them orphan viruses. He called them that because he claimed that, like Pirandello's *Six Characters in Search of an Author,* these new viruses seemed to be in search of a disease. As a matter of fact, Melnick was the man who initially persuaded the National Founda-

[36] See *Live Polio Virus Vaccines, op. cit.*

tion to organize a special conference among its grantees for the purpose of learning more about these viruses.[37] It was a good move because, by the spring of 1955, it was becoming increasingly disconcerting for investigators to look in stools for poliovirus and to discover viral agents they knew nothing about.

Q: Dr. Rivers, did anyone ever confuse these new viruses with poliovirus?

Rivers: No, but I would like to tell you a story that I believe bears on the question that you ask. In 1950 there was a polio epidemic in Central Asia, and two Russian virologists, M. P. Chumakov and M. K. Voroshilova whom I mentioned earlier, isolated a virus from several patients that they claimed was a fourth type of polio. When that report reached the United States, it caused some furor, because we were convinced by then that there were only three types of poliovirus. Eventually we received the virus from the Russians, and upon testing we discovered that it did kill monkeys. However, when the pathological lesions left by this virus were later examined it was found that they were quite different from those caused by poliovirus. Still later it was discovered that the virus that the Russians had sent us was in fact similar to Coxsackie A^7 that Dr. Melnick had earlier isolated from a case of aseptic meningitis in Kentucky.[38] Basically, I don't believe that the discovery of these new viruses confused the polio picture. Virologists at that time knew that the new orphan viruses were different from Coxsackie viruses, and that both Coxsackie and orphans were in turn different from polioviruses. If there was any confusion, it was a confusion that arose from a duplication of work, especially with the ever increasing isolation of new strains of viruses throughout the early fifties. By 1955 most virologists were agreed that what was needed was a common nomenclature, standard pools of viruses, and standard antisera. In the fall of 1955, the National Foundation organized a small special committee made up of

[37] Proceedings of the Conference on Orphan Viruses, New York, May 19–20, 1955 (National Foundation Archives).

[38] Dr. Sabin notes here that Coxsackie A^7 caused transitory paralysis but did not kill. He adds that the identification of the virus took place in Sweden (private communication).

John Enders, Albert Sabin, Jerry Syverton, William Hammon, Joe Melnick, Gilbert Dalldorf, Henry Kumm, and Theo Boyd to deal with the problems created by orphan viruses. Appropriately, the committee was first called the "Orphan Virus Committee" but very soon it changed its name to ECHO Virus Committee.[39]

In the beginning practically every virologist had his own name for these new agents. As I mentioned earlier, Joe Melnick called them orphans in search of a disease; Albert Sabin called them human enteric viruses because they were found in the gut. Bill Hammon, in an effort to reconcile Melnick's and Sabin's observations, called them CEVDU's, which stood for cytopathogenic, enteric, virus disease unknown. Although they were descriptive, none of these names particularly hit the mark, and the search for a more suitable name might have gone on for a considerable time if it hadn't been for John Enders. At one of the early committee meetings, Enders suggested that the new viruses be called ECHO viruses, because they were enteric, cytopathogenic, human orphan viruses. It's funny, once he spilled the name, everybody immediately knew that it was just what we were looking for, and it was unanimously adopted. Today it's part of every virologist's lexicon. So you see, John is not only a genius in the laboratory but in other ways as well.

Q: Dr. Rivers, with the almost continuous discovery of more and more Coxsackie and ECHO viruses during the fifties, don't the edges of the illnesses caused by these viruses become indistinguishable from one another?

Rivers: Yes. I would go so far as to say that in some instances it even seems foolish to make any serious effort to separate them, except for diagnostic purposes. This is echoed—if you will forgive the pun—in fact that today we call all the polios, Coxsackies, and ECHOs, enteroviruses. The enteroviruses are not distinguished from one another by name but by number. For instance, enteroviruses 1, 2, and 3, correspond to polioviruses 1, 2, and 3; all enteroviruses from 4 to 30

[39] The Orphan Virus Typing Committee was initially organized on August 9, 1955. Its name was changed to the ECHO Virus Committee following a meeting on November 4, 1955. Minutes, Orphan Virus Typing Committee August 9, 1955; November 4, 1955 (National Foundation Archives).

are Coxsackies, and those above 30 and up to 60 are ECHOs. I believe that to date [1961] virologists have typed approximately 30 ECHO viruses. The order that that typing represents is one of the fruits of the work of the ECHO Virus Committee. In one sense it can even be said that the work of this committee was similar to the work undertaken during the late forties by the Poliovirus Typing Committee. Its problems certainly were.

I say this because Coxsackie and ECHO viruses, like the polioviruses, cannot be identified by type under the electron microscope or by clinical means. However, since they all differ immunologically, they can be differentiated from one another by type specific antisera. If each of the laboratories working with Coxsackie and ECHO viruses had been forced to prepare its own antisera, a great deal of confusion would undoubtedly have arisen through variation of potency and other qualities. To avoid such problems, the ECHO Virus Committee sponsored a special program to prepare standard pools of antisera. I don't mind telling you that as more and more new Coxsackies and ECHOs came to light, the problem of preparing antisera to match them became more and more complicated and expensive. I don't know if this program would have had the success it finally achieved if the committee didn't also have the good sense to choose Herb Wenner to carry the ball. Previously Dr. Wenner had prepared all of the antisera against the polioviruses. He had a number of research projects going when the committee asked him to produce antisera in monkeys against Coxsackies and ECHOs, and I think it was plain good luck that he agreed to take on this job as well. I'll tell you plainly, it was a hell of a job, and if it had been put up to me I wouldn't have done it, but Wenner did and what's more carried it out beautifully. Today the National Foundation is the only agency in the world that has standardly prepared antisera for all the enteroviruses. If a qualified virologist anywhere in the world needs any—and this goes for the government as well—all he has to do is to write to the Foundation and he gets it without charge. The only restriction is that requests can only be made for research purposes. The reason for this is that there is such a great demand for these antisera for diagnostic purposes that our stock would be depleted in no time at all if such a restriction didn't exist.

The Foundation has every right to be proud of the work of the ECHO Virus Committee. As a matter of fact, the National Institutes of Health thought so highly of the committee's work that about a year ago they asked the Foundation if they could take it over, lock, stock, and barrel. The Foundation agreed, and today the National Cancer Institute supports Dr. Wenner's production of antisera. I didn't mind the government taking over; about the only thing that miffed me was that when the National Institutes of Health announced their support of Dr. Wenner's work, nobody in Washington had the courtesy to say that the program they were so happy about was something that the National Foundation had originally helped to develop.

CHAPTER 15

Early Days of Retirement

Remembrance—all the joy that is left to us now; a poor joy, but our own.
Sean O'Casey, *Under a Greenwood Tree He Died*

Q: Dr. Rivers, did your service on the Virus Research Committee, the Immunization Committee, the Vaccine Advisory Committee, and the various other committees of the National Foundation ever interfere with your work at the Rockefeller Institute?

Rivers: It did not; there was never any reason for it to interfere. To be sure, I served on all of these committees, but I want you to keep clearly in mind that they were always part of my extracurricular activity. My full-time job was as director of the Rockefeller Hospital and a member of the Rockefeller Institute. I continued in those capacities until my retirement in November 1955.

Q: Dr. Rivers, your retirement and Dr. Gasser's retirement marked the end of a second generation of administrators at the Institute.

Rivers: It marked more than that. It marked the beginning of a complete change in the development of the Institute. Actually, Dr. Gasser retired two years before I did—at the end of June 1953. According to the rules of the Institute, he could have stayed on an extra year as director if he had so chosen, because his sixty-fifth birthday occurred after the end of the fiscal year in June; however, Dr. Gasser at the time was not as strong as he would have liked to be and was inclined to shed his administrative duties just as soon as he could, and the Board of Trustees permitted him to retire.