CHAPTER 12

Active and Passive Immunization against Poliomyelitis— 1949-1953

To witness with thine eyes what some perhaps
Contented with report hear only in heav'n.

John Milton, *Paradise Lost*

Q: Dr. Rivers, one of the most important breakthroughs in polio research occurred in 1949 when Dr. John Enders reported that he and two of his associates, Dr. Thomas Weller and Dr. Fred Robbins, had successfully cultivated Lansing type poliovirus in nonnervous tissue.[1] When, for example, did the National Foundation begin to support Dr. Enders' work?

Rivers: That is a difficult thing to say because, as I remember, the first grant which supported Dr. Enders' work was not directly made to him. It was made to the Bacteriology Department of the Harvard Medical School and specifically to Howard J. Mueller, who was then serving as chairman. As I indicated earlier, that department was originally Hans Zinsser's baby and had long had a considerable reputation in bacteriological and virus research. It had many fine investigators and, during Zinsser's tenure and later, had strong financial support from a wide variety of sources, including several private foundations,

[1] J. F. Enders, T. H. Weller, and F. C. Robbins, "Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues," *Science*, vol. 109:85 (1949).

the state, and the national government. Actually it wasn't until after World War II that Dr. Mueller first approached the National Foundation for a long-term grant to develop their virus studies. If you examine Dr. Mueller's application, you will find that the Harvard group was interested in exploring such problems as the relation of viruses to host-cell metabolism and the cultivation of viruses by tissue-culture techniques. I think it is fair to say that, at that time, they were more interested in investigating mumps and influenza virus than poliovirus. The Foundation, of course, had no doubt that the investigations they had in mind could also be applied to polio research, and they got their grant. I remember that one of the things that impressed me about the Harvard application was that almost half of their projected budget was set aside for animals and experimental supplies. In other applications at that time, it was more usual to find the major part of the budget allocated for salaries.

This was an unusual grant for still another reason. After the war, universities were beginning to discover that, when a member of their faculty received a large grant for scientific research, it did not necessarily follow that such a grant was a financial asset to the university. It was more likely to be a liability, since such grants rarely, if ever, made provision to cover the indirect costs incurred by the university in administering grant funds. The National Foundation was one of the first philanthropic organizations to recognize this problem as a threat to the development of the research programs they were supporting, and when the Harvard application was being considered Harry Weaver worked out a plan with Harvard President James Conant for the Foundation to give a special supplementary grant to Harvard to cover the indirect costs of administering the grant being made to Dr. Mueller. This plan not only made it possible for Dr. Mueller to accept a grant from the Foundation; it also provided a new model for making research grants. Today, for example, other foundations as well as the government follow this system in making research grants.

I was not intimate with John Enders during his early years at Harvard. At best, I think I may have met him several times, but I nevertheless knew a great deal about him, because Hans Zinsser, whom I did know well, always used to talk about him and tell me what great

ability he had. Very few people in those early years were particularly burnt up about Enders, because he was a quiet person and published modestly, but those who followed his work on panleucopenia, mumps, and vaccinia knew him, at the very least, to be a careful and ingenious investigator.

I don't remember the precise date, but sometime in 1946 Enders decided to leave the Department of Bacteriology at Harvard, and took a post as director of the Department of Infectious Diseases at the Children's Hospital in Boston. I don't know the inside story of that move, but I think that Enders had come to that point in his career where he wanted to devote his time to research and writing and to get out from under the teaching load he was carrying. In spite of his move, he continued to work under the terms of the grant originally made to Dr. Mueller and, if I remember correctly, devoted himself to such problems as isolating the etiologic agents of pleurodynia and chickenpox, searching for better methods of propagating viruses, and working on problems relating to vaccination against influenza. I mention this not only to show the kind of questions that were absorbing Enders in 1947 and 1948 but to demonstrate that he was not exclusively concerned with poliovirus at that time. I would go so far as to say that he wasn't originally specifically concerned with growing poliovirus in tissue culture. If I am not mistaken, he first tried propagating mumps virus in a tissue-culture setup that he and Tom Weller had devised, and it was only after this work had been successful that he attempted to grow Lansing virus in a similar tissue-culture setup. I want to tell you that, when Enders' early reports on this latter work came into the Foundation, it was like hearing a cannon go off.

Q: Dr. Rivers, I wonder if you would take a moment here to detail the nature of Dr. Enders' achievement.[2]

Rivers: Please bear in mind that, until 1949, most virologists believed that it was impossible to cultivate poliovirus in nonnervous tissue. I know that I believed that it couldn't be done, and I certainly

[2] Dr. Enders notes that the work in his laboratory was a true collaboration with Dr. Thomas Weller and Dr. Frederick Robbins, and that it is a mistake for the interviewer and Dr. Rivers to convey the impression that the achievements that came out of his laboratory were his alone (private communication).

wasn't alone; in 1936 Dr. Olitsky and Dr. Sabin proved that it couldn't be done. I watched that work and I believed it. There was, I might add, no reason to disbelieve it. Dr. Enders' achievement in 1949 lay in the fact that he and his coworkers proved the exact opposite when they successfully cultivated Lansing virus (a type 2 poliovirus) in a modified Maitland tissue-culture setup containing nonnervous tissue taken from the skin, connective tissue, muscles, and intestines of human embryos. Now if that wasn't shooting off a cannon, I don't know what is. I'll tell you one thing, that report sure as hell captured everybody's attention.

In the beginning Dr. Enders worked solely with Lansing virus. However, within a very brief period he succeeded in growing Brunhilde virus—a type 1 poliovirus—in a similar tissue-culture setup. Still later he grew both viruses in tissue cultures consisting of human prepuces or foreskins. I see you are smiling; perhaps I should take a minute to explain why Dr. Enders used foreskins in his cultures. Actually, it was difficult to get human tissues because there were just so many human embryos available, and doctors couldn't go around cutting the skin off people unless they had good reason to do so. Fortunately, babies as well as young boys were being circumcised routinely in Boston hospitals, and Dr. Enders had the foresight to make use of a source of human tissue that in the normal course of events would have been thrown away. It wasn't easy to use foreskins because they were not sterile and Dr. Enders had to go to a certain amount of trouble to utilize them in his tissue cultures. I would like to emphasize here that most of Dr. Enders' work propagating poliovirus in tissue cultures was done with human tissue. It took some years before virologists turned to animal tissues, and in particular monkey kidney tissues, for such work. Once it was discovered that poliovirus could be cultivated in such tissue, it was widely adopted. Monkey kidney tissue was not only more easily available than human tissue; it had the virtue of being free from bacteria, if the kidneys were removed aseptically. It is, of course, true that on occasion virologists ran into monkeys that had TB, but most investigators who used monkeys were aware of this problem and kept a sharp eye out for such infected animals. Still later, a number of investigators discovered that some monkey kidneys had simian viruses in them and this alerted polio

workers to still another problem that had to be faced in using these tissues.

There can be little doubt that one of the first people at the National Foundation to recognize the implications of Enders' work was Harry Weaver. Harry saw in Enders' reports the first possibility of a practical solution to the problem of producing the large quantities of virus which would be necessary in carrying out a vaccination program. When the Foundation later publicized this hope in a number of news releases, Albert Sabin came down like a ton of bricks on the Foundation and Dr. Weaver. Dr. Sabin believed that such publicity at that time—1950—held out an unwarranted hope for an early vaccine. Furthermore, he was still quite skeptical about the initial reports of Enders' work. There was good reason for such skepticism on Dr. Sabin's part. As I mentioned earlier, he and Dr. Olitsky were unable to propagate the Rockefeller Institute's MV poliovirus in nonnervous tissue. That work was very carefully done, and Dr. Sabin had every right to have faith in it. What he didn't know, and, of course, had no way of knowing, was that the MV virus had become neurotropic and could not be cultivated in nonnervous tissue. It wasn't until 1954 when he tried to reconcile his findings with Enders' reports that he discovered that the MV virus had mutated and had become neurotropic because of its long passage in monkey brains.[3] Still later, when Dr. Sabin was seeking to attenuate certain polio strains for his live-virus vaccine using Dulbecco's plaquing techniques, he once more discovered that on some occasions he would get a mutation that would be strictly neurotropic and would only grow on nervous tissue.

I would like to add here that, although the Foundation gave strong and prompt support to Dr. Enders, nobody told him what to do, and he certainly did not restrict his research merely to looking for ways of increasing the yield of poliovirus from tissue cultures. As a matter of fact, one of the interesting aspects of Dr. Enders' research at that time was how rapidly and in how many directions it proliferated, and in particular how quickly he applied it to problems of isolation, titration, and typing of poliovirus.

For example, within a year of reporting the growth of Lansing virus

[3] A. B. Sabin, "Noncytopathogenic variants of poliomyelitis viruses and resistance to superinfection in tissue cultures," *Science*, vol. 120:357 (1954).

on nonnervous tissue, Dr. Enders successfully isolated a number of strains of poliovirus by inoculating stool material directly into his tissue cultures. On another occasion, and again very early in his research, he noticed, following the inoculation of his tissue cultures with Lansing virus that there was not only an impairment of tissue metabolism but that his virus-infected cells also failed to exhibit the customary cell migration of normal cells in plasma hanging-drop cultures. Using these phenomena as indices of infection, Enders was soon able to titrate virus samples directly in tissue cultures.

Perhaps one of the most significant early observations that Dr. Enders made was that both Lansing and Brunhilde viruses produced degenerative changes in tissue culture, and that such cytopathogenic effects could be inhibited by use of type-specific immune serum. By this observation, Dr. Enders in effect created a more rapid and certainly less expensive way of typing viruses than was then available. I cite this work, and, by the way, it was by no means the totality of Dr. Enders' research at that time, to show that he was not exclusively concerned with such problems as increasing the yield of virus through tissue-culture techniques. I do not say that he didn't work on this problem. He did, and I might add, most successfully. The point I want to make is that he very quickly exploited the implications of his original research. Nobody told him. It came about because he followed his nose or put another way, because he pursued his own imagination and curiosity.

Q: Dr. Rivers, how quickly did other virologists adopt Dr. Enders' tissue-culture techniques for typing and titering poliovirus?

Rivers: In some instances almost immediately, and I don't think that one should be too surprised at such a development. Take the problem of typing poliovirus. Up until about 1950, all typing—except in the case of type 2 poliovirus—had to be done in monkeys. Now, when you begin to do neutralization tests in monkeys and have to use six or more monkeys for each test, the expense very quickly mounts. The tests moreover take some time. It didn't take virologists long to realize that tissue cultures would permit them to do such tests rapidly and at a reasonable price. Perhaps the expense of using monkeys

made them realize this sooner than they might have in ordinary circumstances. Now that I have made that point I should in fairness point out that not all virologists adopted Dr. Enders' tissue-culture techniques with equal fervor or rapidity. Strangely enough, one of the best laboratories in the country was the slowest to take hold and that was Dr. Bodian and Dr. Howe's laboratory at Johns Hopkins. I have never been able to quite figure out why they hesitated, but they did delay for almost a year. I know that Harry Weaver remonstrated with them about it, but he never made much headway. Finally, after just about everybody had adopted tissue cultures, Bodian and Howe joined the parade, but they were a little bit behind the crowd and it took them a while to catch up.

Q: Dr. Rivers, you mentioned the usefulness of Dr. Enders' tissue-culture work for typing polioviruses. Could you tell me what effect this had on the rather long search for more efficient *in vitro* diagnostic tests for poliomyelitis?

Rivers: It didn't stop the search for such tests, if that's what you mean and, as far as I know, investigators went right ahead trying to devise flocculation and complement-fixation tests for polio. You must remember that, for a long time, the only methods available to investigators for identifying and differentiating polioviruses from each other and from other viruses were expensive and laborious. For instance, in the old days if you wanted to identify a poliovirus, you would take a monkey which was known, let us say, to have recovered from a Lansing type infection, and you would inoculate it with the virus you wished to identify. If the monkey came down following inoculation, you concluded that the virus was different from the one which caused its original infection. If it didn't come down, you concluded that the viruses were alike. Another method was to take serum from a known immune monkey, mix it with the virus you wanted to identify, and then inoculate the mixture into a susceptible monkey. If the monkey did not come down, you assumed that the serum you mixed with the virus had neutralized it and made it harmless. If the monkey did come down, you prepared to test the virus with a half a dozen other preparations of immune sera and monkeys until you discovered an

immune serum that neutralized your virus. No matter which method you used, you needed a great deal of patience and a great many monkeys.

It was this state of affairs which encouraged the search for a good *in vitro* diagnostic test for poliomyelitis. I think that many virologists were excited by the possibilities of using John Enders' tissue-culture techniques for such testing, but it didn't necessarily follow that if they had been searching for an *in vitro* diagnostic test they would drop their own work because Dr. Enders had a promising lead. They kept on with what they were doing. For years, Dr. Eugene Roberts at the Hooper Foundation tried to get a good flocculation test for polio. He tried and tried and tried. I remember that in 1950, just about the time that John Enders was developing his own work. Dr. Roberts had developed an extraordinarily complicated procedure for preparing antigens so he could get certain specific precipitin reactions. Initially, I think he got some positive reactions, but then the work petered out.

I don't know how many workers over the years tried to devise a complement-fixation test for polio. They also tried and failed, but in 1950 Jordi Casals and Peter Olitsky at the Rockefeller Institute finally did develop a very successful complement-fixation test for type 2 and 3 poliovirus.[4] That work, by the way, was most ingenious. While working with various neurotropic viruses in Olitsky's laboratory, Casals had noticed that, if such viruses were propagated in the central nervous system of infant mice, they yielded complement-fixation antigens with a higher titer than those usually found in preparations made from the tissues of adult mice. Lansing virus (a type 2 poliovirus), as you know, is the only type which will go in mice. Casals and Olitsky soon discovered, as others had before them, notably Dr. Albert Sabin and Dr. Gilbert Dalldorf, that poliovirus unlike other viruses was nonpathogenic for infant mice, although it was disease-producing in adult mice. Fortunately, this didn't faze them, and with a great deal of patience they thereupon undertook to adapt in newborn mice the MEF[1] (type 2) poliovirus that Dr. Olitsky and his associates had previously isolated from tissues which I had given

[4] For an early report and discussion of this work, see Round-Table Conference on a Complement-Fixation Test for the Detection of Poliomyelitis Infection. Rockefeller Institute for Medical Research, New York, April 16, 1951.

him during World War II. By repeated passages from a newborn mouse to a newborn mouse by intracerebral inoculation of brain tissue, they finally succeeded and obtained the antigen with high titer that they were looking for. By doing this, Dr. Casals and Dr. Olitsky in effect gave virologists the one component necessary for a practical complement-fixation test.

Complement, as you know, is a substance that is found in all animal bloods which, when united with a specific antibody, has the capacity to lyse cells. If you took the antigen that Casals got from newborn mice and mixed it with an unknown immune serum and complement, two things might happen. First, if the immune serum was related to the antigen, they would unite and, in the process of uniting, would engage or fix the complement. However, if the antigen and immune serum had no relation to each other, the complement would remain unengaged. If you later added to your mixture of antigen, immune serum, and complement, some sheep cells and an antibody against sheep cells, you would find that in the first instance your sheep cells would not be hemolyzed. However, in the second instance, where your complement was not engaged, your complement would react with the antibody against sheep cells and hemolyze them.

I realize that all of this sounds very complex to you, but actually it was a very simple test and proved to be very helpful in identifying type 2 polio. I should add here that today complement-fixation tests are used very rarely if at all in routine identification tests for poliomyelitis. Virologists rely more on neutralization tests in tissue cultures. They are much cheaper and less time-consuming than complement fixation tests and, of course, work for all three types of polio as well as *ECHO*s and Coxsackies. The only time you turn to complement-fixation tests is if there is an absence of cytopathogenic effects in the tissue culture. Then you are kind-of up against it, but such occurrences are rare. If you think from what I have said that Casals' and Olitsky's work on complement fixation was wasted, you would be dead wrong. In recent years the complement-fixation test has become quite important in identifying many of the new queer arbor viruses that are turning up throughout the world. In many instances, it is the only way we have of identifying them. Casals, by the way, has made this new field in virology his very own.

Q: Dr. Rivers, when the National Foundation began its typing program in 1948, it appointed a special committee to meet and discuss the various problems that emerged as a result of this program. Many distinguished virologists served on this typing committee among them Dr. Bodian, Dr. Sabin, Dr. Salk, Dr. Francis, and others. Oddly enough, I don't find your name on this committee, although you served on practically every other committee organized by the Foundation on problems of immunization.[5]

Rivers: The answer to your question is simple. I just didn't let myself be drafted for this committee, because I looked upon their work as being of a routine nature. I don't mean by that that their work was unimportant; on the contrary, they performed a valuable and necessary function. Basically, they had to find ways of getting virologists to do their typing and other tests in a standard way, so that the results of one laboratory could be compared with the results of other laboratories. I just didn't see the necessity of my being on such a committee. Actually, I can give you one good reason why it was better that I was off of it. I have never been to any medical meeting where I didn't ask at least one or two irritating questions. The truth is, I might have slowed up this committee in its work by asking such questions, and instead of getting the boys to work together I probably would have driven them apart. The main purpose of the meetings held by this committee was to find ways of getting the boys to work together.

Q: Dr. Rivers, if one of the results of the typing program was the establishment of three basic immunologic types of poliovirus, certainly another result was a movement toward standardization—standardization of tissue culture methods, standardization on preparing prototype pools of viruses and prototype pools of antisera. How did virologists react toward this drive for standardization?

Rivers: If you mean did they like it, I can tell you that a large proportion of them didn't. You must remember that research people are always a little bit peculiar. They are that way or they wouldn't be re-

[5] The Typing Committee was organized on July 10, 1948, and had as members the following physicians: Charles Armstrong, David Bodian, Thomas Francis, Jr., Louis Gebhardt, John Kessel, Charles F. Pait, Albert Sabin, Jonas Salk, and Herbert Wenner.

search people. Their very life is dedicated to looking for new things or things to be done differently from the way they have been done previously. They are by their nature rebels against tradition or standardization. They were this way a century ago, 50 years ago, 25 years ago, and still are today. Now, if you need to compare the work done in one laboratory with the work done in another laboratory, and have that comparison have any meaning, you have just got to have some kind of standardization. It is a proposition that seems logical and clear on its face, but I want to tell you that it was and still is difficult to get across to researchers immersed in their work. They resent anybody coming into their laboratories telling them how to do their stuff. This was one of the key problems that the Committee on Typing and later the Committee on Standardization had to face. I don't believe that it ever became a very critical problem, but it sure as hell was an irritating one. There were a great many arguments; however, if you look at the record, I think that you will find that in the end the committees were very successful in getting the boys to work together the same way. They might not have been as successful if I had served with them.

Q: Dr. Rivers, with the development of tissue-culture techniques and the new complement-fixation tests, did a need arise for specially trained laboratory technicians? Where, for example, did laboratories get technicians to do tissue-culture work? Was there any competition for such help?

Rivers: Most laboratory technicians are trained in the laboratories in which they work. In my own laboratory I always had two kinds of technicians. The first were generally men with at least a high school education, who took care of my animals and did the heavy work which is sometimes required in a laboratory. The second were well-educated young ladies from either Smith College or Vassar, with a bachelor's degree in science, who had some knowledge of biology and chemistry and knew their way around a laboratory. I'll admit that at the Rockefeller Institute I never had any great difficulty recruiting such personnel, and that it probably was more difficult for a laboratory in a small college or the government to get technicians of like ability and background. As far as I know, the problem of getting well-

trained technicians for polio research did not become acute until we began to make efforts at standardizing laboratory procedures in the early fifties. I remember that at one of the Immunization Committee meetings held by the Foundation Joe Smadel made a statement that reflected that difficulty. I would like to quote it in part here.

> I see no reason in the world why one should use the same kind of test for all three strains of virus.
>
> I am thoroughly in favor of going over to tissue-culture method for the Brunhilde type and the Leon type, but with all due respect for the great advance which has been made in the tissue-culture neutralization technique, I certainly would not employ it if I could do a good simple mouse neutralization test. Any person can do the mouse neutralization. You have to have a well trained technician to do the tissue-culture work, so that I would think it is important to go ahead and get down a good common neutralization test which employs certain simple materials, simple animals that can be accepted as a reasonably good standard test for such work, as has been talked about. . . . The way to get a technique that is going to stand up is to start with a good technique that works well in one laboratory, then agree on certain modifications of that, and then give it to the young people who will work with it for awhile. After about a year, when you have found out all the mistakes that they make, then you have a real test: one that you can give to a PFC in the Army, and with one sergeant looking after him, you can get results of value, and I think that is what you want from this Lansing test—something like that.[6]

Joe certainly had a point. Any technician can do a mouse-neutralization test. Tissue-culture work always required a well-trained technician—I was even about to add a woman technician. Some women I know would just about jump down my throat for what I am about to say, but I will say it anyway. It's been my experience that women are better at tissue-culture work than men are. I think that it's for the same reason that women are better at taking care of a house or cooking. The truth is that women seem to be willing to do the same thing over every day. Men are not. Tissue-culture work, by God, can get to be pretty dismal, because you have to do the same God-damned thing over and over again, day after day. Unless you do it that way, your results just don't stand up. You have got to be patient, and it's been my experience that women have that quality more frequently than men.

[6] Proceedings of the Committee on Immunization, New York, December 4, 1951, pp. 16–17 (National Foundation Archives).

Q: Dr. Rivers, following the work of Dr. Enders and his associates in 1949 polio research developed at such a rapid pace that, in a period of approximately two years, the unspoken wish of 1949 to take steps to make a vaccine against polio becomes the stated subject of a round-table conference called by the National Foundation in March 1951, at Hershey, Pennsylvania. To refresh your memory of the purposes of this conference, I would like to quote some of the introductory remarks made by Dr. Kenneth Maxcy, who served as chairman.

This conference is an expression of our mutual interest in poliomyelitis, which goes back many years. As each year has passed, we have approached more and more closely to our ultimate goal, the prevention of paralytic poliomyelitis. As our knowledge of the epidemiology of the disease has developed, it has become increasingly apparent that there is no expectation of being able to prevent human exposure to the virus. Even the attempts to postpone exposure may be misdirected.

There is some reason to believe that exposure in early infancy is less likely to be followed by paralysis than exposure in the latter part of infancy or during childhood. There is also some reason to believe that paralytic attacks are somewhat more severe in adults than in children.

For the present, therefore, it would seem that efforts directed toward reducing or postponing exposure are not promising. If we grant that exposure to this virus is inevitable at some time during life, then our objective is to provide means whereby every individual may acquire immunity through subclinical infection or antigenic experience without the risk of paralysis and death.

As our knowledge of the immunity mechanism of poliomyelitis has grown during recent years, it begins to appear that this objective is feasible. Experimental work on animals has suggested that any one of a number of procedures might be effectively utilized to this end.

The possibilities presented are, briefly, inoculation of infants with poliomyelitis virus inactivated by some method with or without adjuvant, with or without gamma globulin; or with active virus as an avirulent strain or mutant of good antigenic potency, administered by mouth or peripherally, with or without adjuvant, under the protection of passive immunity confirmed by gamma globulin; or by passive immunization with gamma globulin during an epidemic period, when natural exposure to infection is frequent. Variations of these procedures could be amplified.

The time is fast approaching when important questions must be answered; sooner or later the answers to some of these questions can be obtained only through observations on human beings.

The purpose of this conference is to obtain a group judgment as to important considerations in this respect. Are we justified, on the basis of present-day knowledge, in undertaking limited and well defined experiments on human beings? If not, what further knowledge is needed before undertaking such experiments? [7]

It is apparent from Dr. Maxcy's remarks that both methods of active immunization—using inactivated vaccines and live-virus vaccines—and passive immunization were at that time under consideration by virologists. I would like to turn here to a consideration of some of the problems that existed in regard to active immunization in the spring of 1951.

Rivers: What I am going to say will be somewhat repetitious, but please bear with me. By 1951 Dr. Isabel Morgan had demonstrated beyond a shadow of a doubt that she had been able to immunize rhesus monkeys with formalin-inactivated viruses of all three basic immunologic types to a point where it was impossible to bring down such animals by the most sensitive routes. I need hardly repeat that, up until the time she did her work, most virologists believed that you couldn't immunize against poliomyelitis with a formalin-inactivated poliovirus. She converted us and that was quite a feat. Isabel, bless her soul, very cautiously refused to say that, because she got such results with monkeys, it could be taken that she would get equally good results with humans. As a matter of fact, she reminded one and all that it was almost impossible to translate her results quantitatively for human use. Now, that is a rule that an experimenter might well keep in mind, namely, if you want to find what something will do in human beings, you ultimately have to do the test in human beings. You can only go just so far with animal tests alone.

In 1950 Howard Howe extended some of Isabel Morgan's original observations when he tried to immunize chimpanzees and monkeys with both formalinized inactivated vaccines and live-virus vaccines against all three types of polio. He soon discovered that, while those animals which received formalinized inactivated vaccine could not be prevented from having an alimentary infection and putting out virus in their stools, they nevertheless resisted paralysis upon intracerebral

[7] Proceedings of Round-Table Conference on Immunization in Poliomyelitis, Hershey, Pennsylvania, March 15–17, 1951, p. 1.

and oral challenge. Even more interesting were his observations that the antibody responses to all three poliovirus types were within satisfactory limits, and that adjuvants were able to stimulate antibody responses to even very small amounts of formalin-treated material. Although Dr. Howe was aware at the time that little was known about the relative sensitivity of chimpanzees and humans, he thought that the chimpanzees' reactions were within a range where it might be feasible to administer formalinized material to children. About a year later, he inoculated between six and a dozen mentally defective children in a Maryland home with formalin-inactivated vaccines and was able to show that the children did develop antibodies against all three polio types. It was an important finding, but no one was in a hurry to give Dr. Howe's vaccines to all of the children in the United States and for a very good reason—they were made of monkey cord material.[8]

Q: Dr. Rivers, I have a host of questions to ask. How did virologists in 1951 know when an inactivated virus was truly inactive?

Rivers: Today, if you want to know whether a virus is inactivated, you test it in tissue culture. In 1951 if you wanted to know, you tested it by an intracerebral challenge in monkeys. There were, however, a number of pitfalls in this method. I remember that Dr. Hubert Loring, of the University of California, once inactivated some poliovirus with formalin and found that when he used this material in a dilute state that his monkeys were able to resist an intracerebral challenge. Later he concentrated this same material in an ultracentrifuge and, upon intracerebral challenge, all of his monkeys were brought down. It is plain that his original so-called inactivated virus must have contained some live virus particles.

There were still other pitfalls. Because some animals varied in their susceptibility to poliovirus, a virus that would be inactive in one species might very well be active in another species. Then again, some animals required much larger doses of virus to be brought down than

[8] H. A. Howe, D. Bodian, and I. M. Morgan, "Subclinical poliomyelitis in the chimpanzee and its relation to alimentary reinfection," *Amer. J. Hyg.*, vol. 51:85 (1950); H. A. Howe, "Antibody response of chimpanzees and human beings to formalin-inactivated trivalent poliomyelitis vaccine," *Amer. J. Hyg.*, vol. 56:265 (1952).

others, and in such cases a small amount of active virus particles might be present and still have no untoward effect on the test animal. In another test animal, such a small amount of live virus might well cause a paralysis. The point I want to make is that the terms "active" or "inactivated" virus in 1951 was only meaningful in relation to the animal in which it was tested and the manner in which the test was done. Put another way, if in 1951 you had told me that you were using an inactivated virus in immunizing human beings, you would have had to convince me that the virus was inactivated as far as human beings were concerned.

Q: Dr. Rivers, an examination of some of the papers presented at this round-table conference indicates that not all investigators were addicted to using formalin in inactivating viruses. For example, Dr. George W. A. Dick, then at Johns Hopkins University, tried preparing vaccines with viruses that had been inactivated by ultraviolet irradiation or by ultrashort high-speed electron bombardment. He found that the antigenic effectiveness of viruses inactivated by these means compared favorably with those inactivated by formalin. You may remember that I raised this same issue earlier in the context of the work done by Dr. Albert Milzer and Dr. Sidney Levinson of Chicago.[9]

Rivers: I will admit that in 1951, and even earlier, virologists were agreed that one could inactivate polioviruses by irradiation or by ultra short high-speed electron bombardment using a capacitron. Some virologists, like Dr. Carleton Schwerdt, of the virus laboratories at the University of California, even tried inactivating polioviruses with nitrogen and sulfur mustards. However, most polio workers were of the belief that they could test for inactivation more reliably if the virus was inactivated by formalin, because formalin had been used more frequently in the past in inactivating viruses and, therefore, they had that much more experience to draw upon. This attitude was not necessarily a mark against using irradiation or other techniques in inactivation. It simply meant that, when virologists were faced with the necessity of making up their minds about using something that in the long run would be a key factor in the production of a vaccine

[9] Proceedings of Round-Table Conference, *op. cit.*, pp. 12–16.

(that was going to be used on a very large number of humans), they chose to rely on experience. You might even say that they were being cautious.

Q: Dr. Rivers, during the course of a subsequent discussion on the inactivation of polioviruses at this conference Dr. Joseph Smadel made the following observation:

> . . . I would still like someone to get an answer to the simple question of how many virus particles it takes to produce obvious disease. If you told me that it took one, ten, or a hundred, then I would say that there is just no point in fooling around with the present material that you have as an inactive vaccine. If you told me that it took a hundred thousand or a million, then I would say that we are on the right track.[10]

Rivers: When Dr. Smadel made that point he was simply raising a question of the margin of safety in making an inactivated vaccine. He had every right to make it. Back in the thirties, when he and Dr. Bob Parker worked in my laboratory on vaccinia virus, they discovered that probably one purified elementary body vaccinia, if placed in contact with a susceptible cell in the skin of a rabbit, would infect that rabbit. You might say that Dr. Smadel had a special appreciation of what could be done quantitatively in determining the size of a dose necessary to infect. If one particle of poliovirus would cause disease in a human, and in the process of inactivation a particle or two of poliovirus escaped inactivation, such particles in an otherwise inactivated vaccine given to a human being would bring him down. If, on the other hand, it took 150,000 or 300,000 particles of poliovirus to bring a person down, one or two particles that escaped inactivation were not going to be very dangerous.

Q: Dr. Rivers, did virologists in 1951 know how many particles of poliovirus would bring down an animal?

Rivers: I am not sure that, when Dr. Smadel made his remarks, virologists actually knew very accurately how many particles of poliovirus would bring an animal down. They could say that a tenth of a cc or a thousandth of a cc of a particular mixture of poliovirus would

[10] *Ibid.*, p. 37.

bring down 50 per cent of their monkeys in a given experiment. But they could not tell you how many particles were actually contained in a tenth or a thousandth of a cc. A short time after Joe made his remarks, the development of plaquing techniques by Renato Dulbecco and his associates at the California Institute of Technology made it possible to count particles in tissue cultures. Dr. Dulbecco discovered that the highly destructive activity of poliovirus in cultures of monkey epithelial cells made little plaques in the culture, similar to those made by phage in bacterial cultures. Through dilution experiments, he soon estimated that each plaque was made by a single virus particle.[11] It was only after Dr. Dulbecco's work that it actually became possible for virologists to say with any degree of accuracy how many particles in a particular mixture of poliovirus would bring down their monkeys.

Q: Dr. Rivers, one of the interesting features of the Immunization Conference of March 1951 was that it was not solely concerned with inactivated vaccines. At least one paper, that given by Dr. Hilary Koprowski, devoted itself to the problems of live-virus vaccines. While the paper itself dealt in detail with rabies vaccines, Dr. Koprowski also spoke later of developing an attenuated nonpathogenic strain of poliovirus useful for immunization purposes.[12] After that presentation Dr. Howard Howe made the following comment:

> Dr. Koprowski has already started the ball off at a terrific clip with his presentation this morning, but I am going to have to take a position which is different from his in that I do not myself feel that active virus is the answer to our problem. I am expressing my opinion at this point, and I hope that others will feel free to express theirs as well. . . . It is very hard to show that it provides the extra margin of safety, which I think we must try to insure for all those who are being immunized against this disease. Natural exposure is producing immunity with a paralytic penalty of roughly one in a hundred, or one in a thousand infections, so that the vaccine has to be pretty safe in order to beat that. . . . It is my feeling that active virus,

[11] R. Dulbecco, "Production of plaques in monolayer tissue cultures by single particles of an animal virus," *Proc. Natl. Acad. Sci.*, vol. 38:747–752 (1952).

[12] The first of Dr. Koprowski's papers was titled "Immunization with modified living virus as exemplified by rabies," the second was called, "A preliminary report on feeding of children with live attenuated polio virus." See Proceedings of Round-Table Conference, *op. cit.*, pp. 87–98, 155–160.

even though it were possible to produce mutants of all three types which are now known, would be very difficult to justify on a large scale. For that reason, we have put most of our effort in trying to evaluate the results of vaccination with inactivated virus. I think that it is clear now, beyond any doubt that it is possible to immunize animals effectively with inactivated virus preparations.[13]

How typical was Dr. Howe's attitude on inactivated versus live-virus vaccines in 1951?

Rivers: I don't know how typical Dr. Howe's attitude was, but I do know that he was not the only virologist who thought that way. In 1951 quite a number of virologists, including myself, thought that the first effective vaccine against polio would be an inactivated vaccine. This does not mean that I or anybody else ruled out the possibility of a live-virus vaccine; after all, our experience with smallpox and yellow fever vaccines certainly pointed in that direction. But in 1951 it seemed to me and others that the quickest and safest way we were going to get a vaccine against polio would be to concentrate our efforts on developing an inactivated vaccine. It was not a unanimous opinion by any means. Some virologists believed that the antigenic power of polioviruses was affected when they were inactivated with formalin, while others thought that the immunity obtained by such inactivated vaccines would be too short-lived to be of any real use. Actually, in 1951 and in the years immediately following, there were any number of virologists who devoted themselves to developing a live-virus vaccine against polio. Herald Cox and Hilary Koprowski and

[13] *Ibid.*, pp. 222–224. The interviewer must add here that Dr. Koprowski's second paper had a marked effect on all those present and in particular Dr. Howe. It is noteworthy that the excerpt of Dr. Howe's remarks quoted in the interviewer's question ends in these words:

I am tremendously interested in Dr. Koprowski's report of this morning because, in feeding a Lansing-type virus to his unusual group of experimental subjects, he got roughly the same levels of antibody that we have obtained in feeding either the Lansing or the Wallingford strains to chimpanzees, all of which suggests, then, that the human is certainly not less—or shall I put it this way—that the human is at least as sensitive a reactor to the poliomyelitis antigen as is the chimpanzee.

I think we have also had a little suggestion here at this meeting that as one climbs the ladder of the susceptible animals from the mouse to the rat to the monkey to the chimpanzee, the degree or the facility of antigenic response increases, and that we could expect that the response of man would certainly not be any less than the last of these. I think that Dr. Koprowski's data are extremely valuable in giving us a bridge which up to now we have not really had.

their associates at the Lederle Laboratories in Pearl River, New York, were certainly among the first to take an active role in developing such an approach. I hesitate to call them the first, because I think that Max Theiler deserves a lot of credit for pointing the way. I have reference here not only to his work in developing a successful live-virus vaccine against yellow fever, but also to his work in developing an attenuated strain of Lansing virus that successfully immunized monkeys against type 2 polio. A lot of people have forgotten about that work, but I think that it is a good thing to remember it.[14]

Another virologist who worked on the development of a live-virus vaccine against polio was Herbert Wenner of the University of Kansas. As early as the spring of 1952, Dr. Wenner asked the National Foundation for a grant to study the effects of certain attenuated strains of types 1, 2, and 3 polio in human volunteers. As I mentioned earlier, Dr. Wenner was trained under John Paul at Yale and from 1948 played an important role in the Foundation's polio typing program along with Jonas Salk, John Kessel, and Louis Gebhardt. He is a quiet, modest individual who doesn't startle you in conversation; but let me tell you, when he reports a piece of work it generally stands

[14] There can be little doubt that Dr. Max Theiler was the first to immunize monkeys with an attenuated variant of Lansing type 2 poliovirus, as Rivers says above. There is, however, no evidence that Dr. Theiler ever extended those preliminary experiments to man. The first scientist to report the successful immunization of man against poliomyelitis with a live-virus vaccine was Dr. Hilary Koprowski, then at the Lederle Laboratories, and now director of the Wistar Institute. That work began in 1947 when Dr. Koprowski and two of his associates, Dr. T. W. Norton and Dr. W. McDermott, isolated a type 2 poliovirus from the blood of a poliomyelitis patient through inoculation of mice. This later gave them the idea of using mouse-adapted virus as a source of an attenuated agent for men. On February 27, 1950, after working out safety tests in monkeys, Koprowski inoculated a six-year-old boy with a live, attenuated type 2 virus. Within the next year, 19 more children were fed the same virus. On March 15, 1951, Koprowski made the first semipublic disclosure of the successful immunization of these children at a meeting on immunization against poliomyelitis at Hershey, Pennsylvania, that was organized by the National Foundation. The first printed account of Dr. Koprowski's work with a live-virus vaccine did not appear before January 1952. See H. Koprowski, T. W. Norton, and W. McDermott, "Isolation of poliomyelitis virus from human serum by direct inoculation into a laboratory mouse." *Public Health Rept.*, vol. 62:1467 (1947); H. Koprowski, T. W. Norton, and G. A. Jervis, "Studies on rodent-adapted poliomyelitis virus. I. Cerebral resistance induced in the rhesus monkey," presented at the 51st General Meeting of the Society of American Bacteriologists, Chicago, May 1951; abstract in *Bacteriol. Proc.* 1951, p. 92; H. Koprowski, G. A. Jervis and T. W. Norton, "Immune responses in human volunteers upon oral administration of a rodent-adapted strain of poliomyelitis virus." *Amer. J. Hyg.*, vol. 55:109 (1952).

up. In other words, he is a first-rate investigator. It should come as no surprise when I tell you that, when his application initially came before the Virus Research Committee at the Foundation, it was approved. A short time later, however, the Foundation's special Immunization Committee became skeptical of the nonpathogenic qualities of his strains, and support for that work was withdrawn. Dr. Wenner was undoubtedly disappointed by this action, but he wisely accepted it. A year later he got some new attenuated strains of poliovirus that John Enders had developed in tissue culture at Harvard. These were of excellent nonpathogenic quality, and the Foundation very quickly reactivated Wenner's original grant in this area. From that date to this a portion of Wenner's work has been devoted to the development of attenuated strains of poliovirus suitable for a live-virus vaccine.

Another laboratory which early devoted itself to the development of a live-virus vaccine was that of Dr. Albert Sabin. Unfortunately, I can't pinpoint the exact date when Dr. Sabin began to think about the possibilities of a live-virus vaccine against polio. He has always, for example, been a friend of Max Theiler's, and he certainly didn't need anyone to tell him about the implication of Max's work for such a vaccine. Nobody, for that matter, has ever had to draw Albert a picture of the implications of any virus research. He has always had a mind and imagination of his own. While Dr. Theiler's work may have prodded him to think along the lines of live-virus vaccine, I think in the final analysis, it was his own research with the cynomolgous monkey which prompted him to investigate the possibilities of oral immunization with modified strains of active poliovirus. I believe that he was fortified in this approach by two important observations. First, he had observed that, when poliovirus was grown in nonnervous human tissue, it showed a decreased pathogenicity for the central nervous system of monkeys. This led him to believe that, by propagating poliovirus in various nonnervous tissues of monkeys, it might be possible to develop strains of poliovirus with different pathogenic qualities. Second, and perhaps equally important, he had observed that not all polioviruses with a high intracerebral pathogenicity were capable of producing a paralysis or an inapparent infection when given to cynomolgous monkeys orally. As I say, I can't pinpoint the date when

he began to think along these lines. I do know, however, that he didn't ask the National Foundation to support his experiments with live-virus vaccines before the summer of 1952.

Q: Dr. Rivers, I wonder if you would take a moment here to tell me something of Dr. Koprowski's early work with live-virus vaccines.

Rivers: Again, I am afraid that I can't tell you when Dr. Koprowski actually began his work with live-virus vaccines. I only know of that work which began when he received some monkey cord containing a strain of Brockman poliovirus from John Kessel's laboratory in California. Koprowski took this strain and, with the aid of some of his associates at the Lederle Laboratories, attempted to adapt it to mice and cotton rats. After a number of passages through the brains of cotton rats, Koprowski isolated a strain which, when inoculated intracerebrally into monkeys, seemed to be devoid of pathogenic qualities. He called this mutant strain TN. It was a most interesting strain: not only did it have nonpathogenic qualities, but upon immunological testing it also turned out to be a Lansing type 2 variant. The Brockman strain is a type 1 polio. Well, I can't blame Koprowski for that mixup; in all probability, the strain originally got mixed up in Dr. Kessel's laboratory. The important thing to keep in mind is that the strain was nonpathogenic and was a type 2 variant. A short time later Koprowski gave the TN strain orally to chimpanzees, and when they didn't come down and showed a good titer of antibodies in the blood, he and some of his associates were encouraged to test the strain on themselves. I don't know how many people at the Lederle Laboratories actually took the strain, but again, when nobody came down and when it turned out that they too had antibodies in the blood, Koprowski wrote to the New York State Department of Health for permission to test the effectiveness of his mutant strain on some mentally defective children in a home in upstate New York.

The State Department of Health wrote me and asked what I thought of doing such a test, and I wrote back and told them I was opposed to it. First, I didn't think that the safety tests that Dr. Koprowski had done were anything to write home about, and, second, I personally did not approve of using mentally defective children for

such a test. To be sure, other scientists had used mentally defective children for similar tests with inactivated vaccines, and what Koprowski wanted to do was not unusual—you might even say that it was standard practice. Well, I didn't give a damn about what other scientists did. I would like to make it clear that my attitude had nothing to do with Koprowski. I had such an attitude long before the question of testing inactivated or live-virus polio vaccines ever came up.[15] For instance, about 20 years ago, some people at the Public Health Research Institute of New York wanted to test what was then a new typhus vaccine on some mentally defective children in Letchworth Village, and they found me bitterly opposed, and I use the word bitterly advisedly.

I think that if someone wants to use adults as volunteers to try out a new drug or vaccine, that is perfectly all right, provided that the adult has been told about the nature of the disease he is exposing himself to, has been completely informed about the nature of the

[15] Dr. Koprowski makes the following comments on Rivers' account:

Dr. Rivers presents a confused picture of the facts. He cannot be blamed for it because he had very little to do with the group which originally discovered the live-virus vaccine and therefore did not have the facts in hand. After they had fed the live virus to chimpanzees, Koprowski, Norton, and Jervis administered it to twenty children who had no antibodies against the type 2 strain. It was senseless to feed the virus to people with antibodies against type 2, since the results would be of very little value as far as the effectiveness of a vaccine immunization procedure was concerned. Therefore, only two or three people at the Lederle Laboratories actually took the strain after the first study was completed. It was only after the safety and effectiveness of the immunization procedure was established in a preliminary trial in twenty children that the New York State Department of Health was approached for permission to undertake trials in a state institute for the mentally defective. Officials of the New York State Department of Health advised that a visit to Dr. Rivers might expedite matters. During this visit, Dr. Rivers was generally enthusiastic about the original work which by then had already been reported at the Hershey conference, and he admired the courage of those who were able to take the first step in the right direction. He voiced no opposition to a new trial to be conducted in an institution for mentally defective children, and gave the general impression that he would support this trial wholeheartedly. It is impossible to know what he actually wrote to the officials of the New York State Department of Health, but the negotiations dragged on for such a long period of time that, following a meeting with Dr. Joseph Smadel and Dr. Karl Meyer at the Barbizon Plaza Hotel on January 26, 1952, live-virus vaccine trials were continued not in New York but in California (private communication).

ED. NOTE: For a report on Dr. Koprowski's test in California, see H. Koprowski, G. A. Jervis, T. W. Norton, and D. J. Nelson, "Further studies on oral administration of living poliomyelitis virus to human subjects," *Proc. Soc. Exptl. Biol. Med.*, vol. 82:277–280 (1953).

agent he is to receive, and has been told the chances for success or failure. If you examine human volunteers, I think that you will find that they generally fall into two classes: they are either prisoners in some state or federal institution, or they are scientists. I don't even know that you can actually call a prisoner a volunteer. I believe that, although prisoners are usually told that they will get nothing out of volunteering as guinea pigs, deep down they believe that they may get a commutation or reduction of their sentence. That's perfectly all right; the point is, prisoners are generally adults who can weigh the pros and cons of submitting to a test, and if they arrive at a decision to participate in a test, it's a decision or judgment that they have made. It's not made for them.

Scientists in their research generally try out material on themselves before they give it to other human beings. On at least two occasions I and people who worked with me in my laboratory took experimental inoculations of material we were working with. About thirty years ago, Bill Tillett and I took a cc of testicular emulsion from a rabbit that was infected with Virus III to see if human beings were susceptible to the virus. We thought that it was chickenpox virus. Fortunately, we never showed any ill effects from having taken that very sizable dose of Virus III. Bill Tillett and I were doctors, we knew what we were doing; he didn't have to do it unless he wanted to, and neither did I. The same thing later held true when I and some of my associates took psittacosis virus for purposes of immunization. Again, we knew the nature of the disease, and we had a pretty good idea of the chances of success or failure. An adult can do what he wants, but the same does not hold true for a mentally defective child. Many of these children did not have any mommas or papas, or if they did their mommas and papas didn't give a damn about them. Aside from their not being free agents, I wasn't sure that what Dr. Koprowski would find out about his live-virus vaccine in these children would be the same if it was tested in normal children. For instance, certain mentally retarded children—like mongolian idiots—are much more susceptible to infection than are other individuals. John Howland taught me this many years ago, and I believe that it still holds true.

My opposition to Dr. Koprowski's test proved to be ineffective, and in the end of the State of New York did give him permission to hold a

limited test. Approximately 20 mentally defective children received his vaccine. I must in all fairness say that none of these children ever came down with paralytic disease, and all showed a good titer of antibodies in their blood, but it was far from being a conclusive test. Several years later, when Dr. George Dick in Belfast, Ireland, tested Koprowski's TN strain and his SM strain, which was a type 1 variant, he discovered that Koprowski's attenuated strains had reverted to a relatively virulent state.[16]

Q: Dr. Rivers, I would like to pursue this point. When Dr. Koprowski originally gave his paper, no one at the immunization conference raised the question of back mutation, although at one point Dr. Koprowski himself raised such a point peripherally in his discussion of rabies vaccines.

Rivers: To be sure, nobody at the meeting said anything about it, but that didn't mean that they didn't think about it. I certainly thought about it, and I wasn't the only smart virologist around. As a matter of fact, by the time Dr. Koprowski gave his paper in 1951, a great many virologists were aware of at least one live-virus vaccine that had back mutated to a virulent state. At the beginning of World War II, a number of us were concerned that the Germans might try to introduce rinderpest virus and foot-and-mouth disease virus to our cattle. We did not have these two viruses in our country, and if they had ever been turned loose they would have worked havoc with our cattle. I don't have to draw a picture for you of what that would have meant for our supply of beef or milk or butter. It would have been a disaster. Early in the war, Dick Shope, who belonged to my Navy unit at the Rockefeller Institute, was given the job of trying to see whether a live-virus vaccine could be developed against rinderpest. Previously, at-

[16] See D. S. Dane, G. W. A. Dick, J. H. Connolly, O. D. Fischer, and F. McKeown, "Vaccination against poliomyelitis with live virus vaccines. 1. A trial of TN type II vaccine," *Brit. Med. J.*, vol. 1:59 (1957); "Vaccination against poliomyelitis with live virus vaccines. 2. A trial of SM type 1 attenuated poliomyelitis virus vaccine," *ibid.*, vol. 1:65 (1957). Dr. Koprowski adds the following observation, "While Dr. Dick's report was used as an argument at the time for or against a given strain of live virus, we now accept such a phenomenon as a matter of fact since all strains employed today, including those licensed by the U.S. Public Health Service, undergo the same change after passage through the human intestinal tract" (private communication).

tempts had been made to develop an inactivated vaccine, but they all more-or-less had ended in failure. By passing the virus through chick embryos, Dick finally did develop an attenuated rinderpest virus that could be given to calves. Upon inoculation, the calves would get a little rash and develop a slight temperature, but then they would recover and, when tested, show a marked immunity. It was awfully good, and if it had become necessary I believe we would have used it. But fairly soon after Dick had done his trick, it was shown that his attenuated virus had back-mutated.

The question of back mutation is in the picture with all live-virus vaccines. It bothered virologists when they considered Dr. Koprowski's vaccine, and it bothered them when they later considered Dr. Sabin's vaccine. I ought to explain that we were not fearful for the children that, let us say, took Dr. Sabin's vaccine in the first instance. Those children were probably one hundred per cent safe. We were concered for the children who would later come into contact with the mutant put out by the inoculated children. Now a lot of what I have said is in the realm of supposition. It is a possibility—however, a possibility that is small. For instance, to date the Russians have inoculated over 100,000,000 children with Sabin's vaccine and there is no evidence of any back mutation. If it did back-mutate, it certainly didn't cause any great catastrophe.

Q: Dr. Rivers, we have to this point talked about the various developments in active immunization against polio in the period 1949 to 1951. I would like to direct your attention now to the development of research programs in passive immunization during this same period —specifically the gamma globulin program developed by the National Foundation. I wonder if you can tell me how that program got under way?

Rivers: Properly speaking, the gamma globulin program did not begin with the National Foundation. In essence, it was initiated in the laboratories of Dr. Edwin J. Cohn at the Harvard Medical School. Edwin Cohn was the younger brother of Alfred Cohn who worked at the Rockefeller Institute. Unlike his brother who was an M.D. and a cardiologist, Edwin was a Ph.D. and a biochemist. They were unlike

in other ways. It is no secret that the brothers did not get along very well together. Alfred was an astute, cultured Jew who, in his actions toward other people, was just about the way he ought to have been. He was a gentleman. Edwin was just the opposite. He was cantankerous and a tough nut. I think that he liked to rough up the other fellow a little bit. I say this at second hand but it's essentially what Alfred used to tell me about him. No matter what his character was, there can be no doubt that he was also a superb biochemist.

Most of Edwin Cohn's work was concerned with the biochemistry of proteins, more specifically, the separation of proteins from the complex biological systems in which they occur in nature. When World War II began, there was not enough human blood available for blood transfusions, and Dr. Cohn was asked by the National Research Council to see if the plasma of animal bloods was suitable for human transfusions. Plasma, as you know, is the liquid remainder of unclotted blood after red cells and white cells and other formed bodies have been removed. It consists largely of proteins. Cohn got down to work and, with the aid of a brilliant group of colleagues, succeeded in developing a process for separating the proteins of plasma into various fractions like serum albumin, fibrinogens, and globulins of various sorts. Although the use of the plasma of animals for human transfusion turned out to be risky, Dr. Cohn's research proved to be extraordinarily important, in that it pointed the way for the fractionation of human blood. This fractionation, I might point out, had immediate medical application. The serum albumins, for example, proved useful in the treatment of shock, the fibrinogens and prothrombin in facilitating clotting and gamma globulin, one of several globulins which were finally obtained, in halting infections.[17]

One of the first investigators to grasp the importance of gamma globulin as an agent for possible use in immunization against poliomyelitis was David Kramer, who was then working in the laboratories of the State Department of Health of Michigan. I have mentioned Dr. Kramer several times before in other contexts, and I would like to take a moment here to speak of him again. I do this, because, by and large, Dr. Kramer has never really received the credit he has deserved

[17] For a detailed account of the history of blood fractionation, see E. J. Cohn, "The history of plasma fractionation," in C. E. Andrus et al. (eds.), *Advances in Military Medicine*. Vol. I. Little, Brown, Boston, 1948, pp. 364–443.

for his contributions to polio research. He was an imaginative investigator and a good experimenter, but somehow he was always on the edge of things and never quite in the center. I suppose that in part this was due to the fact that he never really had a post commensurate with his talents. During the twenties he worked very closely with Dr. Lloyd Aycock on the Harvard Infantile Paralysis Commission. When that job gave out, he moved on to the Long Island University Medical School in Brooklyn to continue his research in polio. His job there was just as tenuous, and after several years he moved on to the laboratories of the Michigan Department of Health. By the time he reached Michigan he had devoted the better part of twenty years to polio research. From the beginning of its existence the National Foundation supported a great deal of Dr. Kramer's research. As a matter of fact, when he first went to Michigan in 1940, the Foundation gave him several grants to develop a chemotherapeutic approach to the polio problem. I remember that in the course of this work he tested the effect of several hundred different chemical compounds on poliovirus with no success. I don't know whether he was disappointed by those uniformly negative results, but I do know that, at the same time, he was working on problems of chemotherapy, he began to reexamine the prophylactic value of human convalescent serum.

During the early thirties, a number of investigators, among them Dr. William Brebner of the New York City Health Department, and Dr. Joseph Stokes, Jr., of Philadelphia, had made claims that convalescent serum was useful in preventing polio. Unfortunately, however, their evidence was not conclusive. When Charles Armstrong succeeded in adapting Lansing virus to cotton rats in 1939, Kramer saw a chance of corroborating Dr. Brebner's and Dr. Stokes's claims in the laboratory and began to test the usefulness of human immune serum in preventing experimental infections in cotton rats and mice. As I mentioned earlier, his initial experiments were successful, but no one became excited by them. When Kramer learned of Edwin Cohn's work with fractions of plasma, he wangled a small supply of human immune globulin from him and began to test the effect on poliovirus. In a very brief time Kramer discovered that the globulin fractions which Cohn had sent him gave marked protection to both cotton rats and monkeys against an intracerebral inoculation of poliovirus. More

important, he learned that his globulin fractions possessed twenty-five times the amount of neutralizing substance originally found in the plasma from which it was taken. Kramer was so encouraged by his experimental findings in animals that in 1944 he asked the National Foundation if they would support him in running a small field trial so he could test whether gamma globulin had a prophylactic effect in humans as well.

I suspect that if it had been up to the Foundation alone Dr. Kramer would have been allowed to put on his field trial. At the time, other investigators were also beginning to get very suggestive results of the protective power of gamma globulin against polio infection in chimpanzees, and it seemed like a good thing to do. Indeed, if I remember correctly, the Foundation finally did approve Kramer's request for a field trial, but unfortunately neither Kramer nor the Foundation was able to persuade the Red Cross of the value of holding such a trial.

You must remember that, during the war, the American Red Cross had charge of collecting blood supplies, and since these supplies were the only source of plasma the Red Cross in effect also controlled the supplies of serum albumins, fibrinogens, and globulins obtained from plasma. Dr. Foard McGinnes, who was then in charge of the blood supply program of the American Red Cross, refused to release the necessary gamma globulin to Dr. Kramer, on the grounds that the projected field trial was not practical inasmuch as there weren't enough doctors and nurses available to do the necessary follow-up work required by such a trial. He was, however, willing to release a small amount of gamma globulin so that investigators could carry on further laboratory tests with chimpanzees. In retrospect, I would say that Dr. McGinnes was right. Wartime was a hell of a time to put on a field test even a small one. I don't think that he was being obstructive, because a year later, when an opportunity offered to put on a limited test during a polio epidemic in Freeport, Illinois, Foard sent Tommy Francis a supply of gamma globulin without too much protest.[18]

[18] It is of interest that Dr. Joseph Stokes, Jr., one of the early proponents of passive immunization in the United States, to this day maintains that it was Dr. Rivers' opposition to passive immunization that prevented an early field trial with gamma globulin.

Both Don Gudakunst and later Harry Weaver assured me that Tom would not lis-

After the war, the interest in gamma globulin continued not only among virologists but among medical practitioners as well. In 1948, for example, when a polio epidemic hit Houston, Texas, a number of pediatricians in that city gave children in their care a prophylactic inoculation of gamma globulin. I would like to emphasize that these inoculations weren't given as a test, Later, however, when this experi-

---

ten to my early pressure for studies on passive immunization in polio, and, since he was the chairman of the committee that decided on grants and no public health authority would move without the assurance of the National Foundation's approval, all of us, such as David Kramer, who felt that we could save a good many paralytics and a few lives had to wait. The waiting over seven or eight years seemed interminable since those of us in the clinical field saw many more children dying in respirators than did the workers in the laboratories. As later proved to be true, we felt a good many could have been saved, and the emotional reaction to this feeling also colored the urgency of our requests and perhaps therefore the stiffening of Tom Rivers' back. . . . Also . . . the fact that when he espoused a negative point of view he stuck to it with bulldog tenacity —even on numerous occasions contrary to mounting and solid evidence against him— made him often a frustrating experience for younger workers (private communication).

The sharpness of Dr. Stokes's comments on Dr. Rivers can perhaps best be understood when measured against the hopes he had for passive immunization. (See Appendix D, a confidential memorandum that Stokes presented to the Board of Managers of the Children's Hospital in Philadelphia on April 24, 1952.) Harry Weaver, the director of research of the National Foundation between 1946 and 1953, offers the following interpretation of the differences between Dr. Stokes and Dr. Rivers:

To understand the differing views of Drs. Stokes and Rivers on the possible usefulness of gamma globulin in poliomyelitis, it is important to realize that these differences arose during the early 1940's. In many ways, Stokes was "ahead of the times" when he first pressed for a test in man of the usefulness of gamma globulin in poliomyelitis.

Because knowledge of the pathogenesis of poliomyelitis was evolving so rapidly in the early 1940's, it is to be expected that serious differences existed on such important questions as the portal of entry of the virus; the significance—with respect to development of local and systematic immunity—of the virus in the gastrointestinal tract of both patients with the disease and apparently normal subjects; and the route by which the virus invaded the brain and spinal cord from the outside, and whether or not the virus at any time along this route became exposed to or in contact with poliomyelitis antibodies which may have been circulating in the blood. Also, opinion was divided as to the significance of the large quantities of poliomyelitis antibodies which were found circulating in the blood of patients who were in the early stages of the disease. And we did not know then how many different immunogenic types of the poliomyelitis virus existed, nor whether gamma globulin contained antibodies against each of the different types.

Then, too—people being what they are—whenever the suggestion was made to determine the usefulness of gamma globulin in preventing poliomyelitis or the paralytic consequences thereof, an adverse reaction was likely to result, because most investigators believed it was impractical to even think about controlling poliomyelitis through use of gamma globulin. The arguments in support of this view included the scarcity of gamma globulin, the short duration of protection that could be afforded by a single injection of this product, the enormous size and expense of the effort that would be

ence was analyzed, it seemed that the children who had been inoculated were afforded some protection. In 1950 Dr. William Hammon, who had long been working on immunological and serological responses to polio infections, gave a paper at a conference sponsored by the National Foundation in which he urged that the time had come to put on a field trial to test the effectiveness of gamma globulin as a prophylactic to polio infections.[19]

Q: Dr. Rivers, in 1950 there were not many virologists in the United States who were interested in passive immunization against poliomyelitis. What made Dr. Hammon interested in putting on a field trial to test gamma globulin?

---

required to give multiple injections of gamma globulin to each person each year, etc., etc., etc.

Perhaps Tom Rivers did have "feet of clay"—who of any substance does not? He may have been a bit slow in the early 1940's to support a test of the protective efficacy of gamma globulin in poliomyelitis, because he and most other people at that time did not really believe that a poliomyelitis vaccine was in the offing. Therefore, Doctor Rivers was inclined to view any proposal to test the efficacy of gamma globulin as a prelude to promoting this product for the control of poliomyelitis. He believed, and probably rightly so, that the demand for gamma globulin would vastly exceed its supply, and he objected to publicizing a preventive for poliomyelitis which could not be made freely available.

However, in the late 1940's, when it began to appear to some persons at least that a vaccine against poliomyelitis might be forthcoming, Doctor Rivers was quick to alter his former position and to support a test of the efficacy of gamma globulin, because he believed the answer to this question was a prerequisite to further work on a vaccine. In other words, by the late 1940's, Doctor Rivers was as desirous as anyone to learn if a susceptible person might be protected against the paralytic consequences of poliomyelitis by the presence of a small amount of antibody which was present prior to the subject's coming into contact with the virus. If so, the degree of protection afforded should be no less where antibody was induced by injections of vaccine (private communication).

Although it is true that Dr. Rivers was not an enthusiast for passive immunization, the weight of contemporary evidence is that the major opposition to Dr. Kramer's proposal for a gamma globulin field trial in 1944 lay with the American National Red Cross and not with Rivers. See, especially, *Proposal for a Field Study of the Value of Gamma Globulin as a Prophylactic Agent in Poliomyelitis*, July 25, 1944; Memorandum, Donald Gudakunst to Basil O'Connor, August 4, 1944; G. Foard McGinnes, Medical Director ARC, to Donald Gudakunst, August 21, 1944 (Research Immunization, Gamma Globulin Field Trials, General, 1944–1951, National Foundation Archives).

[19] While it is true that Dr. Hammon discussed gamma globulin in its relation to passive immunization at a Round-Table Conference on Gamma Globulin on February 3, 1950, that discussion cannot be construed as a proposal for a field trial.

Rivers: In part, the answer to that question lies in the personality of Dr. Hammon and, in part, with the development of gamma globulin research during the late forties. I have known Bill Hammon for well over twenty years, at least since the time he began to work with Karl Meyer on problems of encephalitis, and I can say that he is a virologist of distinction. He is also a rather unusual person. He was born of missionaries and to this day has that spirit that missionaries have of trying to sell something. They sell the gospel, he sells medical research. Once Bill Hammon latches on to an idea, he pursues it just as a missionary might pursue sin. Unfortunately, that attitude of mind sometimes makes it difficult to talk with him, and because of it my feelings about Dr. Hammon have gone up and down. Sometimes I think that he is great, and other times I get so sore at him I don't respect him at all. But if you push me to it, I will always have to tell you that Bill Hammon has done more than his share in developing virology in the United States.

In 1950 there was ample reason for Bill Hammon to become enthusiastic about gamma globulin. First, gamma globulin was made from pools of blood contributed by many people, and there was little doubt that it contained almost twenty times as much antibody as an equal volume of human serum. What made it even more attractive was the fact that David Bodian, while testing the polyvalent characteristics of polio antibody in gamma globulin in 1949, discovered that it contained antibody in equal titer to all three known types of polio. It had other features as well, perhaps the most important being its success against other virus diseases. Prior to 1950, gamma globulin had been used effectively by some investigators in the prevention of measles, and Dr. Joseph Stokes, Jr., had already clearly demonstrated that even a small amount of gamma globulin would give protection against infectious hepatitis. From the foregoing I think you can see why gamma globulin captured Dr. Hammon's imagination.[20]

[20] D. Bodian, "Neutralization of three immunological types of poliomyelitis virus by human gamma globulin," *Proc. Soc. Exptl. Biol. Med.*, vol. 72:259 (1949); J. Stokes, Jr., and J. R. Neefe, "The prevention and attenuation of infectious hepatitis by gamma globulin," *J. Amer. Med. Assoc.*, vol. 127:144 (1945); J. Stokes, Jr., et al. "Infectious hepatitis. Length of protection by immune serum globulin during epidemics," *J. Amer. Med. Assoc.*, vol. 147:714 (1951).

Q: That's the positive side of the ledger. Wasn't it also known that the immunity that gamma globulin might furnish would at best be transitory?

Rivers: That's true. But please remember that in 1950 there was no vaccine, and the idea of affording protection to humans for even a brief period during an epidemic was attractive.

Q: Dr. Rivers, how did the Foundation react to Dr. Hammon's proposals for a gamma globulin field trial?

Rivers: Negatively. Initially, most members of the Virus Research Committee were not very enthusiastic about Dr. Hammon's proposals, and it took the Foundation almost two years before it agreed to support a field trial. In the interim the Foundation held several round table conferences with leading virologists to discuss the wisdom of passive immunization. I can tell you that on more than one occasion the discussion at these meetings became very heated. Most polio investigators in 1950 and 1951—and this included some of our best workers, people like Albert Sabin, Howard Howe, and John Enders —just didn't think much of gamma globulin as a practical way of protecting against polio. I think that the basic reason for that attitude was that the boys in the know just did not believe that one could give enough gamma globulin to children to bring the antibody titer up to a level where it would be protective. You may remember that several years before Isabel Morgan had demonstrated that she had to get a high titer in the serum of monkeys before they could resist an intracerebral challenge of poliovirus. Although virologists by 1950 knew that poliovirus did not enter humans naturally in the way that Isabel challenged her monkeys, they nevertheless proceeded cautiously because, when they examined large groups of people who had antibodies against polio, they never found any antibody titers near the amount that Dr. Morgan pointed out was necessary for protection. I might add here that there were other findings which encouraged caution.

At one of the conferences held by the Foundation, Dr. Gaylord Anderson reported that an analysis of polio cases in Minnesota during the epidemic of 1946 revealed that a substantial number of paralytic

cases had occurred following the injection of an antigen, and that there was a high correlation between the site of the injection and the site of the paralysis. Even before Dr. Anderson gave his report, several British and Australian investigators had noticed that a number of their patients had contracted paralytic polio following inoculation against diphtheria and pertussis. This phenomenon was actually not new in 1950. I remember that as far back as 1935, during the Park-Brodie vaccine field trials, several children came down with paralysis of the arm in which the vaccine had been given and that that paralysis had occasioned a great deal of critical discussion. Dr. Anderson's paper, however, had the virtue of reminding us that inoculation of an antigen might induce a paralysis which in the natural course of events might not occur, and I can testify that it gave us pause. A short time later, these particular apprehensions were reinforced by Dr. Robert Korns of the New York State Department of Health. At a meeting of the American Epidemiological Society in 1951, Dr. Korns reported that an injection of penicillin or a hormone during the polio season was also capable of inducing paralytic polio, although it was an insoluble antigen. That finding threw us back on our heels, because it raised important questions relating to the design of Dr. Hammon's field trial, in particular, the method of carrying out controls.[21]

Many investigators, including Bill Hammon, felt that if you inoculated your trial group with gamma globulin, it was also necessary to inoculate your control group with a placebo that in appearance looked exactly like the gamma globulin. In ordinary circumstances, I don't think that anyone would have debated such a procedure. However, following the Anderson and Korns reports, a number of workers argued that if you inoculated your control group during the polio season, there was a good chance that some would come down with paralytic polio by the mere act of inoculation, and they urged instead that the placebo be given by mouth. Some went so far as to argue against using a control group at all. There was one hell of a debate. It was plain to me that once you distinguished the gamma globulin from

[21] G. W. Anderson, "Relation of antigenic injections to incidence and localization of paralysis," in Proceedings of Round-Table Conference on Immunization in Poliomyelitis, Hershey, Pennsylvania, March 15–17, 1951, pp. 190–210 (includes discussion); R. F. Korns, R. M. Albrecht, and F. B. Locke, "The association of parenteral injections with poliomyelitis," *Amer. J. Public Health,* vol. 42:153 (1952).

the placebo you were opening a Pandora's box. I could just see thousands of mommas and papas of those children who got the placebo descending on the Foundation asking why their children didn't get the gamma globulin. I also didn't know how anyone was going to prevent a local physician from giving gamma globulin on the q.t. to children who got the placebo. It would have balled up the field trial good and proper.

Q: Dr. Rivers, by your last statement you seem to be raising an ethical problem. How about the ethics of giving a placebo in the first place?

Rivers: The question you ask is not new and comes up every time a test is given. Essentially you are asking me, what right does an investigator have in withholding from some children something which he thinks might do some good. The answer is clear. If we were certain before the field trial that gamma globulin would be of help, then it is plain that we would have had no right to give any child a placebo. The point, however, is that we were not certain and, unless we ran a test with adequate controls, we would never know whether we were right or wrong. In the circumstances, I think that if we hadn't given a placebo we would have been unethical.

Q: Dr. Rivers, I don't want to disturb the trend of your thought, but I think that it might be helpful at this point if you could briefly outline the specific purpose of Dr. Hammon's field trial.

Rivers: I think that basically all Bill Hammon wanted to do was to put on a test whereby he could determine whether a given dose of gamma globulin could prevent paralytic polio before exposure to, or before the onset of, the illness. I do not believe that he was primarily concerned in these trials with discovering whether gamma globulin would interfere with inapparent or subclinical polio infections. I don't want to be misunderstood. I am not saying that he wasn't interested in this problem—actually he had to be because, if gamma globulin did interfere with subclinical infections, it might also have interfered with the process of subsequent active immunity. All I am trying to

say is that this problem was secondary to the original purpose of the field trial, which was to discover whether a given dose of gamma globulin would prevent paralytic polio. What that dose was, no one at that time knew. To be sure, there had been previous animal tests, but Dr. Hammon felt very strongly that it was almost impossible to extrapolate the amount of gamma globulin needed for man from the dosage per pound found necessary to protect a monkey against an intracerebral injection of virus. For one thing, the route of experimental infection in monkeys was not necessarily the route of natural infection in man; for another, the severity of the disease in monkeys was greater than it was in man. Hammon, therefore, argued that at best an arbitrary dosage would have to be selected. The question was, how much?

Some investigators following Dr. Joseph Stokes's reports that a small amount of gamma globulin would protect against hepatitis, urged that the dose be small. Dr. Hammon himself was inclined to give a relatively large dose instead of a small one. But I think it should be kept in mind that most investigators were agreed that the dose could not be above 10 cc. In the end, Hammon divided his children into three weight groups. To the first, which ranged up to 35 pounds, he gave 4 cc; to the second, which ran from 36 to 60 pounds he gave 7 cc; and to all those above 60 pounds he gave 10 cc. Heck, he couldn't have given much more without having a first-class revolt on his hands. I don't think there is a kid in America who would have stood, let us say, for an inoculation of 10 cc in each buttock without complaint—it just would have been too damn painful, and in the end it would have made the trial impractical. After the first day of such an inoculation, the kids would have gone into hiding.[22]

Q: Dr. Rivers, how far did the Foundation go in designing the gamma globulin field trials?

Rivers: Let's get one thing straight. The gamma globulin field trials were designed by Bill Hammon. It is true that the National Foundation held a number of conferences to discuss the field trials and that

[22] For discussions of the problems attendant on the formulations of a field trial for gamma globulin, see Proceedings of the Round-Table Conference, *op. cit.* Minutes of a meeting of the Committee on Immunization, May 17, 1951; *ibid.*, July 6, 1951.

everybody and their aunt at these conferences made suggestions about placebos, dosage, and a hundred other problems that haven't been mentioned, but they were nothing more than suggestions. In the final analysis, the field trial was carried out according to the specifications drawn up by Dr. Hammon. It has never been the policy of the Foundation to tell an investigator how to do an experiment. The Foundation could turn down a man's proposals, or they could accept a man's proposals but, once they accepted, they let him alone, which is as it should be.

Q: Dr. Rivers, how did you feel about the gamma globulin field trials?

Rivers: That's easy, I supported them. During the last conference called by the Foundation to discuss the feasibility of putting on a gamma globulin field trial, there was a hell of a debate. If you will examine the minutes of that conference, you will find that at one point I got up and made a statement that on its face sounds idiotic. "Gentlemen," I said, "let's throw scientific discussion out of the window, and let's do the experiment." After several meetings of discussing Dr. Hammon's proposals backward and forward, I had become convinced that we could talk about them for another ten years and still not reach a conclusion. Under the circumstances I felt that the only way to reach a conclusion was to put the experiment on—I was probably influenced in making my statement by Sir Francis Bacon who is once reputed to have said (at least everybody quotes him as saying), "Don't think—experiment!" I like the sentiments of that statement, except I have always felt that he should have said, "Experiment, but for God's sake don't stop thinking."[23] I am appalled by the idea of doing an experiment without thinking.

Now why did I support the trials? I want to make it perfectly clear that I did not support them because I was interested in using gamma globulin as a public health measure. I never thought that. I did sup-

[23] Dr. Rivers is mistaken here. The sentiments on experimentation which he ascribes to Bacon were made by John Hunter in a letter to Edward Jenner, August 2, 1775. "I thank you for your experiment on the hedgehog; but why do you ask me a question by way of solving it? I think your solution is just; but why think—why not try the experiment?" The letter is cited in John Baron, *The Life of Edward Jenner M.D.* Vol. 1. Henry Colburn, London, 1838, p. 33.

port them because I felt the trials might furnish virologists with information that would be helpful in making a vaccine. By 1951 virologists had discovered a number of things that made a vaccine a distinct possibility. First, Isabel Morgan had already shown that formalinized inactivated poliovirus could be used for immunization purposes; second, John Enders had demonstrated that poliovirus could multiply in nonnervous tissue; and, third, the immunologic typing program carried on by the National Foundation was rapidly coming to the conclusion that there were three major immunologic types of poliovirus. At that time, however, we still did not know whether poliovirus reached the central nervous system from the portal of entry by way of the nerves or the blood stream. If it traveled by way of the nerves, most virologists were resigned to the fact that protection could only be achieved by a high antibody titer, similar to the one indicated by Isabel Morgan. If, on the other hand, it traveled by way of the blood stream, then the titer of antibody could be much smaller. One of the crucial things we had to know was whether a low antibody titer would protect; if it did, then by gosh we had a possibility of making a vaccine.

Now, whether other people on the Foundation's Immunization Committee wanted to know that, I just couldn't say. I talked about it, but whether they ever heard me I don't know. You can talk to a guy until you are blue in the face, but it doesn't necessarily follow that he hears a word you say. I can't say that everybody on the Immunization Committee appreciated my reasons, but the fact is the entire committee joined with me in approving the field trials.

Q: Dr. Rivers, would you go so far as to say that your statement, "Let's throw scientific discussion out of the window and do the experiment" carried the day for the field trial?

Rivers: It's hard to say. I think that by the last meeting everybody realized what I had and had about reached the same conclusion. It wasn't difficult; heck, we had been discussing the question for almost two years. I don't think that I was all by myself in calling for a field trial. I just happened to shoot my mouth off a little bit sooner than the others. Let's say that something that was bound to occur was

brought to pass a few minutes sooner by my statement. That's the only credit I will take.

The first gamma globulin field trial was put on in Provo, Utah, early in September 1951, during an incipient epidemic of polio.[24] Properly speaking, the Provo trial cannot be considered a field trial, because it was not made on a scale large enough to give statistically valid results. Actually, it was a pilot study to work out the kinks and problems that Dr. Hammon was likely to run into putting on a large-scale test. If memory serves, a little more than 5000 children received gamma globulin and the placebo. Yet, in spite of its size, the results that emerged from this test were suggestive and seemed to indicate that a small amount of antibodies would protect against paralytic polio. I would say that the significance of this finding was immediately and independently appreciated by Dr. David Bodian at Johns Hopkins and Dr. Dorothy Horstmann at Yale. They assumed that, if Dr. Hammon's findings were valid, it meant that the poliovirus traveled from the portal of entry to the central nervous system by means of the blood stream, and they began to search for a viremia. If I remember correctly, they fed cynomolgous monkeys and chimpanzees poliovirus and after several days collected blood specimens from these animals and tested them for the presence of poliovirus. After some search, they discovered virus in the blood between the time of feeding and paralysis. Suffice it to say, if they had waited for the paralysis to occur they never would have found evidence of viremia.[25]

Most of the investigators who had previously looked for virus in the blood were unsuccessful because they examined the blood of animals and people who had already become paralyzed. Once Dr. Bodian and Dr. Horstmann learned that viremia in animals occurred very early in the disease, they began to look early in human beings as well and soon discovered viremias in abortive cases of polio. The interesting thing in all of this is that, several years before Dr. Bodian and Dr. Horstmann

[24] The Provo Field Trial was held on September 4–7, 1951. For a detailed discussion see W. McD. Hammon, L. L. Coriell, and J. Stokes, Jr., "Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. 1. Plan of controlled field tests and results of 1951 pilot study in Utah," *J. Amer. Med. Assoc.*, vol. 150:739 (1952).

[25] D. Bodian, "A reconsideration of the pathogenesis of poliomyelitis," *Amer. J. Hyg.*, vol. 55:414 (1952); D. Horstmann, "Poliomyelitis virus in blood of orally infected monkeys and chimpanzees," *Proc. Soc. Exptl. Biol. Med.*, vol. 79:417 (1952).

confirmed the phenomenon of viremias, a number of other workers had discovered poliovirus in the blood of experimental animals and human patients but either did not follow up their findings or else drew the wrong conclusions from their observations. For instance, as early as 1941, Albert Sabin, after feeding some cynomolgous monkeys poliovirus, observed a viremia but assumed, as sometimes occurs in other virus diseases, that during active multiplication in certain tissues the virus may be eliminated in the blood stream. It puzzled him and he ruminated about it, but he didn't follow it up. In his defense, I should say that a war was going on and he had a hell of a lot of other things to think about. An even more notable case was that of Dr. Joseph Melnick. In 1946 Dr. Melnick, with the assistance of Dr. Robert Ward and Dr. Dorothy Horstmann, examined the blood of 111 polio patients and detected poliovirus in the blood of one patient. If you examine the clinical history of this patient, you will find that the blood was taken very early in the infection—I think several hours after the onset of symptoms, and certainly before paralysis set in. Dr. Melnick took the lone case to be unimportant and certainly did not look on it as showing any necessary factor in the pathogenesis of the disease in man. You must keep in mind that Dr. Melnick's work was not done in a manner to pick up viremia—most of his patients, as I remember, were examined and bled after paralysis set in, and by that time it was, of course, too late to discover a viremia. In the circumstances, I can't blame him for looking on his one case as an aberration. I don't know why the discovery of a viremia didn't hit all investigators in the face; the fact remains that it didn't, and I suspect that there are many discoveries in science that are overlooked simply because scientists don't always appreciate what they see. Hell, look how long it took us to integrate ether into surgical procedures, or for obstetricians to learn how to wash their hands before delivering a baby. The evidence was there for everybody to see but you know, it's not the seeing, it's the appreciation of what you see, that is important.[26]

[26] See also A. B. Sabin, "Studies on the natural history of poliomyelitis (Bela Schick Lecture)," *J. Mt. Sinai Hosp.*, vol. 11:185 (1944), especially remarks on pp. 191–192; R. Ward, D. M. Horstmann, and J. L. Melnick, "The isolation of poliomyelitis virus from human extra-neural sources. IV. Search for virus in the blood of patients," *J. Clin. Invest.*, vol. 25:284 (1946). Dr. Koprowski in 1947 also demonstrated viremia in a

Q: Dr. Rivers, you mentioned earlier that the Provo trial was a pilot study. When was the first large-scale gamma globulin field trial put on?

Rivers: Actually, there were two large field trials after Provo; one was held in Houston, Texas, and the other in Sioux City, Iowa.[27] Although close to six times as many children were inoculated with gamma globulin and placebos in Houston as in Provo, the tests did not have the validity they should have had, simply because the doctors and the public in Houston did not play the game according to the rules. What happened was that during the trial many doctors gave their patients inoculations of gamma globulin on the q.t. and, while it didn't do the patients a hell of a lot good, it bollixed up the results of the trial good and proper. I hate to say this about the doctors in Houston, but they shouldn't have done this. They thought they were doing good, but they weren't.

Q: Dr. Rivers, what do you do when you are running a field trial and you find that doctors are not following instructions?

Rivers: I'll tell you what you do—you just go ahead and finish the trial and charge it up to profit and loss. You keep your mouth shut because it never pays to make the medical profession mad at you. When all is said and done, a family will trust and believe the family physician more than it trusts or believes a scientist who is connected with an institute or a foundation, no matter how eminent he may be. The scientist, after all, is a person they have never seen or met. There might be a story about him in the local newspaper, but, hell, that is no competition for the family physician who tends the family in sick-

---

polio patient through inoculating mice. H. Koprowski, T. W. Norton, and W. McDermott, "Isolation of a poliomyelitis virus from human serum by direct inoculation into a laboratory mouse," *Public Health Rept.*, vol. 62:1467 (1947).

[27] The gamma globulin field trials in Houston, Texas, ran from July 2 to 12, 1952. The trial in Sioux City, Iowa, ran from July 17 to 22, 1952. W. McD. Hammon, L. L. Coriell, and J. Stokes, Jr., "Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. II. Conduct and early follow up of 1952 Texas and Iowa-Nebraska studies," *J. Amer. Med. Assoc.*, vol. 150:750 (1952); W. McD. Hammon, et al., "III. Preliminary report of results based on clinical diagnosis," *J. Amer. Med. Assoc.*, vol. 150:757 (1952).

ness and times of crisis, and who is frequently looked up to as being infallible. You don't raise hell with the family doctor, no matter how justified you think you may be, because if you do, you quickly find yourself in trouble with the public. The National Foundation, so far as I know, never said anything about the Houston experience. Actually, it wasn't until Dr. Hammon put on his field trial in Sioux City, Iowa, that we definitely learned that a small dose of gamma globulin (calculated at 0.14 cc per pound of body weight), given intramuscularly into the buttock, would give children temporary protection against paralytic polio.

If the gamma globulin field trials had stopped after Sioux City, everything would have been all right, because to that point they had proven to be extraordinarily valuable and had taught virologists a great deal. But damn it, in 1953 the National Foundation, in collaboration with the National Research Council, decided to put on another trial to test gamma globulin as a public health measure by giving it to family contacts. Now I want to get something off my chest. When Bill Hammon originally put on the gamma globulin field trials in Provo, Houston, and Sioux City in 1951 and 1952, it was done for the specific purpose of discovering whether a given dose of gamma globulin could prevent paralytic polio—and nothing more.

In 1953, however, Bill turned around and agreed to test gamma globulin as a public health measure by giving it to family contacts, and I tell you frankly I hold this decision against him. In 1952 Bill Hammon, I, and a hell of a lot of other virologists believed that once you had an index case of polio in a family, the chances were that the whole family was infected, and giving gamma globulin to that family would not prevent polio. For a reason I still can't appreciate, Bill allowed Alex Langmuir to talk him out of this position. I don't even know why Dr. Langmuir did this, because ordinarily he is a pretty smart apple and has on many occasions, too numerous to mention, demonstrated that fact. It mystifies me that he was so far off base on this, but he succeeded in persuading Bill Hammon, and I then made it my business to try to talk Mr. O'Connor out of giving the support of the National Foundation to this new test. I told him as bluntly as I could that I thought this new test would in all probability be a waste of time, money, and effort. He heard me out and then went along with

Dr. Langmuir and Dr. Hammon. I'll say this, I don't think that Mr. O'Connor was dumb in the sense that he didn't know what he was doing. I think he believed me when I told him that giving gamma globulin to family contacts would do little if any good. Actually, I don't believe that he looked upon this test as a scientific question. By 1953 he realized that a vaccine was in the offing and that it was only a matter of time before we had one in hand. I think he was trying to buy time. I can't say for sure, because he never confided his reasons for supporting this particular test. I am not saying by this whether Mr. O'Connor did right or wrong. I am in no position to judge, because I know nothing about how to handle the public. Mr. O'Connor does. I can only tell you that I advised him against supporting this particular test.[28]

Q: Dr. Rivers, how often did Mr. O'Connor override the judgment of his scientific advisors?

Rivers: Mr. O'Connor did not override the judgment of his scientific advisory committees—he believed and trusted them. I should point out that in this particular instance Mr. O'Connor did not bring the Virus Research Committee together to advise him; instead he counseled with various scientists both inside and outside the Foundation. I suppose that because he acquired his advice in this way, he never actually felt that he was overriding the judgment of his Virus Research Committee. You must remember that a committee of the National Research Council told him the test was perfectly feasible.

[28] There can be no doubt that Rivers opposed the program carried out in 1953 to use gamma globulin as a prophylactic measure against paralytic poliomyelitis. However, he basically refuses to acknowledge that the actual purpose of the program was to use gamma globulin as a public health measure against the disease rather than as a test to discover its efficacy. Moreover, Dr. Rivers overlooks the fact that there were sharp differences between the U.S. Public Health Service and The National Foundation for Infantile Paralysis as to how the gamma globulin was to be used. Initially the Public Health Service wanted to restrict the administration of gamma globulin to family contacts. The Foundation, on the other hand, urged that the gamma globulin be administered on a community wide basis to abort impending epidemics. After some debate, the Foundation's suggestions were incorporated into the test program, and it was decided to allocate the major portion of the available supply of gamma globulin to community-wide prophylaxis. For detail on the evolution of the gamma globulin test program of 1953, see folders on Gamma Globulin, U.S. Public Health Service, 1953–1954 (National Foundation Archives).

Hell, if I bothered him too much, he could always turn around and say, "Tom, the National Research Council says to do it. You don't think you are better than they are." He could give me an argument, and I frankly wasn't going to look for a hassle with him. I'll tell you one thing, I didn't have to wait for the results of that test to know that they wouldn't come up with anything. I'll admit that to this day I have never bothered to read the final report of that test. It's written up somewhere. You read it and if it proved anything I'll eat it for lunch tomorrow.[29]

[29] *An Evaluation of the Efficacy of Gamma Globulin in the Prophylaxis of Paralytic Poliomyelitis as Used in the United States, 1953.* Report of the National Advisory Committee for the Evaluation of Gamma Globulin in the Prophylaxis of Poliomyelitis, Public Health Monograph No. 20, 1954.

CHAPTER 13

Prelude to the Salk Vaccine

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

Thomas Phaire, *The Boke of Chyldren*, 1545

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

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

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

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