CHAPTER 11

Some Aspects of Poliomyelitis Research—1946-1948

The solution of the major problems related to infantile paralysis will not materialize out of the cerebrations of one individual or of a small advisory group. On the contrary, the solutions to these problems will come forth only if properly qualified investigators are stimulated to approach these problems in a critical and thorough fashion.

Dr. Harry Weaver to Dr. Hart Van Riper, *Interoffice Communication, The National Foundation for Infantile Paralysis,* August 9, 1946

Q: Dr. Rivers, I would like to examine with you the developments in polio research in the immediate postwar period as you saw them from your vantage point as chairman of the Virus Research Committee of the National Foundation.

Rivers: The first order of business that I became involved in when I returned to the Foundation after the war had nothing to do with research per se or with polio. It involved editing a textbook called *Viral and Rickettsial Infections of Man.* Although I had previously edited a volume on *Filterable Viruses* in 1928, in no sense did the idea for this particular book originate with me. That honor belongs to Paul Clark of the University of Wisconsin. Dr. Clark was a grantee of the Foundation and in 1946, while making a request for some extra monkeys for experimental purposes, he urged the Foundation to undertake the publication of a new textbook on virus diseases. I have that letter in

front of me and I would like to quote a portion of it because it very clearly expresses what motivated Dr. Clark to make that suggestion.[1]

> . . . Quite a different matter has been forcing itself upon our minds during the past month. I am giving the course in filterable viruses now for the first time since the war began, and find the lack of a suitable text a serious handicap. Van Rooyen and Rhodes [2] is, of course, excellent, but is too long, not sufficiently discriminating as to material included, repetitious, too expensive for class recommendation, and not available at the moment. The Harvard Symposium [3] is the one I must of necessity recommend as the only one available, but it covers only a small fraction of the field. I have been wondering whether the Foundation would feel it appropriate to subsidize the publication of a text on filterable viruses to be written by a number of men actually working in the different fields. A very considerable editorial problem would be involved, but if each chapter were the task of a person specifically interested, the labor might not be too great.

There was one other reason, not mentioned by Dr. Clark, which made a new textbook on viruses desirable. By 1946 we were beginning to crystallize some of our ideas about viruses and, while it is true that we didn't have all the answers, there was nevertheless a great need for putting what we did know between the covers of a book so that we would have material available to train a new generation of virologists. I believe that this latter factor weighed very heavily with the Foundation and when the General Advisory Committee of the Foundation finally agreed to subsidize the publication of such a book, they made it plain that they wanted it to be oriented to medical students and general practitioners rather than to experts in virology. It was only after the project was finally approved that I was asked whether I would accept the responsibility for editing the volume. I accepted, but on condition that a companion volume on bacterial and mycotic infections be done as well.

I had two reasons for making that suggestion and both were practical. First, most medical students in 1946 were taught their virology in general courses of bacteriology, where they were held responsible for

[1] Paul Clark to Donald Gudakunst, February 18, 1946 (CPERT Appr. #45, Text, *Viral and Rickettsial Infections of Man*, National Foundation Archives).

[2] C. E. Van Rooyen and A. J. Rhodes, *Virus Diseases of Man.* Oxford University Press, London, 1940.

[3] Harvard School of Public Health Symposium, *Virus and Rickettsial Diseases.* Harvard University Press, Cambridge, Mass., 1940.

learning not only about viral infections but about bacterial infections as well. The textbooks that they used were heavily weighted with bacteriological material with but a thin layer of material on virus diseases. I didn't want to repeat that mistake in another direction. Second and equally important was the fact that René Dubos had then just recently returned to the Rockefeller Institute from Harvard University and this made available an ideal editor for the companion volume I had in mind.

Dr. Dubos was and is an extraordinarily gifted bacteriologist and in my opinion one of the greatest this country has ever had. I have known him almost from the moment he came to work in Dr. Avery's department at the Rockefeller Hospital in 1929.

Dubos is a man of industry, a man of imagination, and a man of culture. He is extraordinarily well read not only in microbiology but in the fields of art and literature as well; and although he hasn't to this day lost all of his French accent, he uses English words beautifully, whether he speaks or writes. If you want to test the truth of what I say, you have only to read his biography of Louis Pasteur [4] or his book on *The Bacterial Cell.*[5] Although the latter is a highly technical volume, it has since its publication in 1945 become a best seller.

In 1942, after thirteen years at the Institute, Dr. Dubos received an offer of a research professorship at the Harvard Medical School and accepted. It was shortly after his first wife died, but whether that event had anything to do with his going I don't know. I do know that I was sorry to see him go and I made every effort to talk him out of it. "Look, René," I said, "you are not going to like being a professor at Harvard or for that matter anywhere else. You are going to find that from now on much of your time is going to be taken up with teaching, administration, and committee meetings. This is what happens when a man becomes a professor at a university; and the bigger and better the name of the university, the more committee meetings they have. I am sure you are going to be fed up with this. However, when you are ready to come back to the Institute, just call me and I'll talk to Dr. Gasser. I am sure that he will be glad to have you back."

Within two years Dubos called me. I never asked him why he wanted to come back, it was enough for me that he wanted to, and

[4] R. J. Dubos. *Louis Pasteur, Free Lance of Science.* Little, Brown, Boston, 1950.
[5] R. J. Dubos. *The Bacterial Cell.* Harvard University Press, Cambridge, Mass., 1945.

Dr. Gasser, I might add, felt the same way. Upon his return to New York, Dubos decided that he would concentrate his research on the tubercle bacillus, a subject in which he had had no previous experimental experience. I am happy to say that since 1946 Dr. Dubos and his coworkers have made any number of fundamental discoveries about the nature of the tubercle bacillus. I should add that these findings were often made in the face of great opposition of older workers in bacteriology because Dubos introduced new techniques in experimenting with tubercle bacilli and expressed unorthodox ideas about the nature of TB and other bacterial infections.

Q: How did Dr. Dubos feel about editing a new volume on bacterial and mycotic infections?

Rivers: I think that the idea of doing such a volume intrigued him. On any number of occasions he had voiced his dissatisfaction with many of the then current textbooks on bacteriology. Editing a new volume in effect gave him a chance to spread his wings and put across his own ideas. I don't think that he looked upon it as a chore. He is a good writer himself, and apparently has the knack of editing whatever comes to him quickly and easily. I can honestly say that money was not a consideration in accepting the editorship, neither for Dubos nor for me. Although the Foundation made generous provision for the prospective contributors to both volumes, nothing was said in the beginning about an extra stipend for the editors. René and I just assumed that we would be paid for whatever chapters we wrote. However, when the final manuscripts were deposited with the publishers, we both received a handsome check from the Foundation in the mail. It was unexpected and a very pleasant surprise.

Q: Dr. Rivers, when you earlier described planning the additions to the Rockefeller Hospital, you said you didn't like to work with a committee, yet correspondence in the National Foundation files indicates that in planning your book you went out of your way to have a committee. As a matter of fact you held a special meeting to discuss the book.[6]

[6] This meeting was held on June 14, 1946 (CPERT Appr. #45, *op. cit.*).

Rivers: It is true that a meeting was held to discuss the preparation of the book but I would hardly call the people attending that meeting a committee. They were people I had already chosen to do certain chapters. They will probably get angry with me when they read this, but the fact is I didn't call them together to ask them for any advice; I called them together to tell them which chapters they would write and how many pages each chapter would have. As a matter of fact, prior to the meeting I had prepared a model chapter on epidemic keratoconjunctivitis, which set forth the format that I wanted followed. I did this so the book would not look like a Jacob's coat or a patchwork quilt. I think that everybody at the meeting understood this and agreed with me. However, I don't want to leave anybody with the impression that, after I told them, they just went away and did what I asked. The virologists that I know are just not built that way, and I remember that we had a vigorous discussion of the various subdivisions of my format, and I am not so sure now that I didn't make changes in the format as a result of these discussions.[7]

Most of my trouble in planning the book did not come from my fellow virologists; it came from one of the senior members of the General Advisory Committee of the Foundation. This particular person—and I am not going to tell you his name—had seen a table in a magazine called *Scope* which was put out by the Upjohn Company of Kalamazoo, Michigan, which purported to give a complete tabulation of diseases caused by viruses. He was so impressed by what he saw that he urged the Foundation to sponsor the publication of that table for physicians and medical students. When he suggested that it might help me with the organization of my book I went up like a roman candle. I don't want to be misunderstood. Medicine in the United States would not be where it is today unless we had good commercial houses to make our modern medicines. I believe in them.

[7] Dr. Peter Olitsky, who was present at the organizational meeting, writes:

Dr. Rivers generously grants here to the coauthors of his book an independence which they found themselves unable to assert, because the executive, legislative, and judicial powers were contained in one person, the editor, Dr. Rivers. The assembled authors were told precisely how many words to write, how many references to give, and how to set them up; how to arrange subjects and many other "laws." If there was any desire to change the rules, there was then no Supreme Court to which an author could go for a judgment. At the meeting, however, the valuable suggestions by the group related to the addition of certain viruses not mentioned in the "format" and the inclusion of other technical material (private communication).

But there are times when these houses stray from their task of making medicine and try to usurp the function of education. I am not saying that this particular table was wrong; it wasn't. I just thought that it would be bad policy for the Foundation to look to a commercial house for education, especially on the eve of publishing a book designed to educate medical students and general practitioners on virus and rickettsial diseases.

In retrospect, I would say that both my book and Dr. Dubos's book were completed with a minimum of trouble. I can't speak for René, but for myself I would say that the major problems that I had with my authors were some originally submitted chapters that were too sophisticated for medical students, while others wanted to do too much. Beyond that, they all did their assignments and, I must say, did them superlatively well. The proof is in the pudding. Both volumes, since their original publication in 1948, have been widely adopted in medical schools throughout the country. There is a continuing demand for them, and in the past 13 years both volumes have gone through three editions to keep up with the rapid changes that have occurred in virology and bacteriology.[8] It may be immodest to say this, but I believe that these books have more than fulfilled the original purpose for which they were made.

[8] New editions of the volumes edited by Dr. Rivers and Dr. Dubos appeared in 1952 and 1959. In 1959 Dr. Frank Horsfall joined Dr. Rivers as coeditor of the volume, *Viral and Rickettsial Infections of Man*. One measure of the change in each of the new editions is to be found in the number of contributors. In 1948, for example, Rivers called on 26 virologists to contribute to his volume. By 1952 that number rose to 30, and by 1959 to 44. An indication of the change in content is contained in the following excerpt from the preface to the third edition.

The present volume contains 46 chapters, some 7 more than the second edition. Three of the new chapters deal with common features of viruses and the infections they induce. These are "Biochemistry of the Virus Infected Cell," "Virus-Host Cell Relation," and "Chemotherapy and Virus Infection." Two other new chapters are devoted to groups of viruses that have been discovered since the second edition appeared: ECHO viruses and Adeno viruses. The earlier chapter on "Viral Encephalitis" has been supplanted by 4 chapters concerning "Arthropod-Borne Animal Viruses" and the infections they induce. The previous chapter on poliomyelitis has been expanded to 3 chapters, "Poliomyelitis," "Poliomyelitis: Pathogenesis and Histopathology," and "Poliomyelitis: Control." One chapter on a recently identified disease, "Hemorrhagic Fever," has been added.

In 1965 Dr. Frank Horsfall and Dr. Igor Tamm coedited a fourth edition of *Viral and Rickettsial Infections of Man*, and Dr. René Dubos in collaboration with Dr. Jules Hirsch edited a fourth edition of *Bacterial and Mycotic Infections of Man*. All editions were brought out by Lippincott and Company, Philadelphia.

Q: Dr. Rivers, while publication of textbooks was one way of transmitting knowledge to a new group of budding virologists, what did the Foundation do to keep senior workers abreast of new developments in virus research?

Rivers: One of the techniques that the Foundation had for keeping workers informed of what was going on in virus research was to hold conferences. This practice began very early in Foundation history. If I remember correctly, the first idea for holding such conferences came from Albert Sabin who early in 1940 suggested that the Foundation hold a meeting in conjunction with the Society of American Bacteriologists to discuss some of the then current problems in polio research. Nothing much came of that particular suggestion; however, when Ernest Goodpasture made a similar suggestion later that year, the Foundation changed its attitude.[9] In 1941 a series of lectures on Infantile Paralysis were arranged, to be given at Vanderbilt University. Paul Clark, Charles Armstrong, Ernest Goodpasture, John Paul, Frank Ober, and I all participated in this series. The lectures were well received and unhappily later published in book form.[10] Today, of course, they only have historical value and demonstrate what we didn't know. For instance, if you examine my lecture on immunity to polio, you will find it cockeyed as hell. I am ashamed to say that I even suggested at that time that the principles of immunity might be different for poliovirus. The Vanderbilt lectures marked the beginning of the conference idea, which, after World War II, was developed with a vengeance by the Foundation. I do not think that I am far from the mark when I say that the National Foundation has

[9] Albert Sabin to Basil O'Connor, February 26, 1940 (Albert Sabin, Public Relations files, National Foundation Archives). Although Dr. Sabin's idea was initially rejected, it was well thought of and became the subject of a discussion at a meeting of the Virus Research Committee on May 13, 1940. Subsequently, Mr. O'Connor called Ernest Goodpasture and asked if Vanderbilt University would sponsor a special symposium on poliomyelitis. At no time, however, did Dr. Goodpasture initiate such a discussion. See Ernest Goodpasture to Basil O'Connor, September 23, 1940 (CPERT Appr. #8, National Foundation Archives). Some years later, the National Foundation, in reply to another request by Sabin, agreed to sponsor a joint round-table conference with the Society of American Bacteriologists. See Albert Sabin to Donald Gudakunst, October 26, 1942; Donald Gudakunst to Albert Sabin, November 2, 1942 (Society of American Bacteriologists, Public Relations files, National Foundation Archives).

[10] *Infantile Paralysis: A Symposium Delivered at Vanderbilt University, April 1941.* National Foundation for Infantile Paralysis, New York, 1941.

used the technique of conferences more than most voluntary health agencies. To my mind, they have been extraordinarily important as catalysts to the research programs supported by the Foundation. I think that if one wanted to trace the history of the development of polio research in the United States after World War II, there would be no better way of doing it than by examining the give and take at these conferences.

From time to time in the past people have come to me and said, "Tom, why does the Foundation need all these conferences? We can hardly keep up with the stuff that is printed in journals. It's just a waste." I am amused by this argument, because implicit in it is the notion that the printed page is the ultimate in knowledge. Now, everybody damn well knows that no scientist ever delivers himself completely in any article he writes. He prints what he feels he can show and prove publicly. A scientist has a hell of a lot of stuff in his head that he can't prove, and a conference offers him a chance to speak about what is on his mind. When scientists speak and argue with one another you have the beginnings of cross-fertilization of ideas. I have never been convinced of the notion that cross-fertilization of ideas only begins with the printed word.

Q: Dr. Rivers, who arranged these conferences for the Foundation? Who, for example, was responsible for choosing the topics for discussion at these conferences?

Rivers: I don't know that I can answer that question in a straightforward manner. Sometimes ideas for conferences came from grantees of the Foundation, and other times they came from within the Foundation itself. But I do know that between 1946 and 1953 not one conference was ever held that did not in some way revolve around Harry Weaver. I would like to take a moment now to speak about Dr. Weaver, because to my mind he was one of those who later made extraordinary contribution to the successful development of polio vaccines. Harry Weaver is a Ph.D. and a trained anatomist. Early in his career, he had worked closely with John Toomey on polio problems; later, however, he left Cleveland and became a professor of anatomy at Wayne University Medical School in Detroit. I first came to know

about him when he made application to the Foundation in 1940 for a grant to study the relationship between nutrition and polio. However, I didn't know him personally during this period and, I am sorry to say, had nothing to do with bringing him to the Foundation. I believe that the person who hired him for the Foundation was Don Gudakunst. When Dr. Gudakunst died early in 1946, Dr. Weaver was made director of research. Although he was trained as an anatomist, he understood the problems of doing research and very quickly became cognizant of what was going on in polio research. I should explain that Dr. Weaver is very agile mentally, and learning never presented much of a problem to him. I don't want to be misunderstood. I don't mean by that that Harry Weaver knew everything; he didn't and he knew that he didn't, but he had a wonderful quality of being bold. In research you often need a person like Harry Weaver around, you know, someone to kick over the traces, or someone to encourage people to see what the grass is like on the other side. In other words, a catalyst. Harry Weaver performed that function beautifully.

In large measure Dr. Weaver was responsible for developing the first important conference held by the Foundation after the war, on the mechanisms of immunity in polio. Originally there was some opposition within the Foundation to holding such a conference. Dr. Henry Viets, who was one of Mr. O'Connor's most important advisors during this period, thought that such a conference would be premature. I think that in part you can put Dr. Viets's opposition down to the fact that he was a neurologist and had not kept up with developments in immunology during the war. However, in fairness to Dr. Viets, I should point out that not everybody was equally enthusiastic when this particular conference proposal was made.

When it was suggested that the conference be held in Baltimore, Kenneth Maxcy of Johns Hopkins also opposed it. Ken knew what was what, but he didn't want to be burdened with acting as host just as a new semester was getting under way. His attitude always amused me because the work of the Hopkins polio research team was of the highest order, and, as a matter of fact, it later turned out that one of the best and most important papers given at this conference was that presented by one of his own people, Dr. Isabel Morgan. I give you

these details so you can get some idea of the kind of problems that Harry Weaver had to deal with in getting a conference under way. Most virologists at the time thought that a conference on immunity was a very worthwhile idea, and just about everybody who was anybody came.[11]

It was a most exciting conference, and a great many new ideas and findings were presented, and, as you might suspect more than one argument developed. I remember that one of the first papers presented at that conference was by Dr. Sidney Levinson and his colleague Dr. Albert Milzer of Chicago, who were both very active investigators in polio at this time. They presented a paper in which they claimed that they had induced an intracerebral immunity to poliomyelitis in mice by vaccination with ultraviolet-treated virus.

Dr. Levinson no sooner finished reading that paper when I was on his back. First, I have never thought much of irradiating viruses to make them inactive, and, so far as I know, to this day no vaccine has ever been sold on the market that has been inactivated by irradiation. To be perfectly fair, I think that I ought to add that my objections to Dr. Levinson's technique of inactivation may have been based on prejudice and personal bias more than on fact, because more than one investigator has since used these techniques successfully in the laboratory. Secondly, and more important, I didn't think much of immunizing mice. I mentioned before that Dr. David Kramer, one of the early polio investigators in this country, succeeded in immunizing mice to polio as early as 1942, but nobody ever got het up about it. Now if Dr. Levinson had immunized a monkey with his inactivated vaccine, why then I might have sat up and taken notice, but the fact is that he didn't. I wasn't the only one who felt this way about Levinson's work. Karl Meyer was another. I remember that during the discussion of Levinson's paper, Karl got up and said, "You have got to explore the mechanism in different species of animals. What you do on mice is not necessarily applicable to man, monkeys, guinea pigs or other species. I can look at a mouse and immunize him." Karl was dead right. Come to think of it, I'll bet that Karl could immunize a mouse by looking at him.

[11] Round-Table Conference on the Mechanisms of Immunity in Poliomyelitis. Baltimore, September 17–18, 1946.

Q: Dr. Rivers, there can be little doubt that one of the most arresting papers given at the Baltimore conference was the one presented by Dr. Isabel Morgan on "The Role of Antibody in Immunity to Poliomyelitis." [12] Since Dr. Morgan early in her career worked at the Rockefeller Institute, I wonder if you could tell me something about her before we discuss the implications of her work.

Rivers: Let me begin by saying that Isabel Morgan is the daughter of the late Nobel laureate Thomas Hunt Morgan. Originally Thomas Hunt Morgan was a member of the Biology Department at Columbia University. However, around 1926 he was called to the California Institute of Technology to help develop work in genetics, and as a result Isabel got much of her education on the west coast. Later she returned to the east and took a Ph.D. in bacteriology under Stuart Mudd at the University of Pennsylvania. I could never understand why Dr. Mudd didn't hang on to her. You know, often we don't see the gold right under our nose. I know that Dr. Mudd didn't, and immediately after graduation Isabel joined Peter Olitsky's laboratory at the Rockefeller Institute. I want to tell you that it didn't take her long to demonstrate that she was a crackajack experimenter.

You may remember that I mentioned earlier that Dr. Olitsky, in collaboration with Dr. Herald Cox, had made me sit up in 1936 [13] when they demonstrated that they could immunize guinea pigs against equine encephalomyelitis with a formalinized inactivated virus. When Isabel first joined the Institute, she carried on this work and confirmed the quantitative relationships between the vaccine and degree of immunity. She demonstrated beyond cavil that, depending upon the amount of antigen given, that one could obtain a degree of immunity with formalinized inactivated virus equal to that yielded by active virus. I stress this work because it took a great deal of courage on the part of Dr. Olitsky, Dr. Cox, and Dr. Morgan to work and speak along these lines, because the prevailing opinion, my own included, was that only active virus could give rise to a satisfactory

[12] I. M. Morgan, "The role of antibody in immunity to poliomyelitis," Proceedings of Round-Table Conference on the Mechanisms of Immunity in Poliomyelitis. Baltimore, 1946, pp. 16–20.

[13] H. R. Cox and P. K. Olitsky, "Active immunization of guinea pigs with the virus of equine encephalomyelitis," *J. Exptl. Med.*, vol. 63:745 (1936).

immunity. Well, I and others were wrong, and they were right.

Later she helped develop work which Albert Sabin and Olitsky originally began on the differences between young and old animals in their resistance to viral infection and their capacity to produce an immune response. For instance, she and Olitsky showed that the capacity for immunization against eastern equine virus—both by resisting a test dose of virus and by the amount of antibody produced—increases with the age of mice, and that, while very young mice had no capability of producing immunity against an intracerebral test dose, they did show a measurable peritoneal immunity which increased with small increments of age. There was an important supplementary find to these studies, namely, that there was a correlation between the titer, that is, the amount of antibody, and the degree of cerebral resistance to the equine virus.[14]

I would like to point out here that it was during Dr. Morgan's stay in Dr. Olitsky's laboratory that she first began to work with polio virus. In 1941, Dr. C. E. Van Rooyen, of the Royal Army Medical Corps sent me specimens of nervous tissue and blood sera of victims of a polio epidemic that occurred among soldiers of the British Army in North Africa. I later turned these specimens over to Peter Olitsky for investigation and, with the assistance of Walter Schlesinger and Isabel Morgan, he isolated three separate strains of poliovirus. Interestingly enough, one of these strains was later successfully transmitted to mice and designated as MEF[1] or Case 1 of the Middle East Forces. It was the second polio strain that went in mice, the first being the Lansing strain which was isolated by Charley Armstrong of the U.S. Public Health Service.[15] You know, in the beginning Char-

[14] See I. M. Morgan, "Influence of age on susceptibility and on immune response of mice to eastern equine encephalomyelitis virus," *J. Exptl. Med.*, vol. 74:115 (1941); I. M. Morgan and G. I. Lavin, "Immunizing capacity of virus of eastern equine encephalomyelitis inactivated by ultraviolet light," *Proc. Soc. Exptl. Biol. Med.*, vol. 47:497 (1941); I. M. Morgan and P. K. Olitsky, "Immune response of mice to active virus and to formalin-inactivated virus of eastern equine encephalomyelitis," *J. Immunol.*, vol. 42:445 (1941); I. M. Morgan, R. W. Schlesinger, and P. K. Olitsky, "Neutralizing antibodies in the cerebrospinal fluid in relation to cerebral resistance to equine encephalomyelitis virus," *J. Bacteriol.*, vol. 43:83 (1942).

[15] This is a slip of the tongue on Dr. Rivers' part. The Lansing strain of poliomyelitis was first isolated by Dr. Max Peet in 1937. Dr. Rivers undoubtedly has reference here to the fact that Dr. Armstrong was the first to pass Lansing virus successfully to cotton rats and guinea pigs in 1939.

ley just didn't want to accept MEF[1] as a new isolate and maintained that it was identical with his Lansing strain. I guess he thought that Peter had picked his strain up accidentally in the lab. Time, however, proved that he was wrong, and today MEF[1] is accepted as a type 2 poliovirus reference strain.

I watched Isabel Morgan very carefully during her years at the Rockefeller Institute. Hell, I watched anyone at the Institute who worked with viruses carefully, and it was apparent from the very beginning that, girl or not—and by the way she was a very handsome looking girl—Isabel knew which way was up. In 1944 she left the Institute and joined Dr. Howe and Dr. Bodian at the Hopkins. I was sorry that the Institute lost such a promising worker, but I think that she did the right thing. It is not that Dr. Olitsky contained her—I think that Peter has always given his workers a good deal of freedom —it's just that I don't think that she could have advanced very far at the Institute. As I said earlier, few Ph.D. ladies ever had much of a chance for advancement at the Institute during the early days.

Q: Dr. Rivers, I have heard you say that the paper that Dr. Morgan gave at the Baltimore conference made everybody sit up. Could you tell me why the paper had that effect?

Rivers: In this paper, Isabel Morgan went back to a problem she had earlier worked with in Dr. Olitsky's laboratory. In essence she wanted to learn whether she could vaccinate a monkey with inactivated virus to the point where she could induce resistance to an intracerebral inoculation. In addition, she also wanted to see whether a correlation between antibody and resistance could be established. As I remember, she inactivated a Riley strain of poliovirus with formalin and, by giving monkeys multiple intramuscular inoculations of such inactivated virus, finally induced resistance to intracerebral inoculations in her animals. She also discovered that her immune monkeys had a titer of 1/3000 of antibody in the serum.

I didn't doubt that Isabel was able to get her monkeys to the point where they could resist an intracerebral inoculation of live poliovirus. The thing that bothered me was the number of injections and the amount of cord and brain material she had to put in monkeys to

achieve her titer of antibody. I, and many others at the meeting, just didn't think that using cord and brain material was a practical approach for protecting human beings.

I would like to make an aside here. Earlier I told you that Jules Freund of the Public Health Research Institute, during the war, had devised an adjuvant or a substance which when added to an antigen enhanced antibody response. In an effort to produce a rapid antibody response, Isabel tried using Freund's adjuvant with her inactivated virus. Initially she thought that it would largely act on the virus; what she forgot to remember was that her inactivated virus was but a minimal fraction of the material she was injecting into her monkeys, and that by far the larger part of that material was nervous tissue. In a very short time, her monkeys came down with an allergic encephalomyelitis. It was an important finding and she recognized it as such, but essentially it was a result that had come about as an accident.

You may remember that in 1935 Francis Schwentker and I had produced an acute disseminated encephalomyelitis in monkeys by giving them injections of normal rabbit brain emulsions. The only trouble with those experiments was that it sometimes took us more than a year to bring our monkeys down. At approximately the same time that Isabel Morgan was working on her immunization experiments using Freund's adjuvant, Elvin Kabat, an immunochemist at Columbia University, who was interested in demyelinating diseases, decided to use Freund's adjuvant in emulsions of normal rabbit and monkey brain tissue, to see if he could cut the time period in inducing an acute disseminated encephalomyelitis. He quickly found that, by using Freund's adjuvant, he could bring his monkeys down in a period of from two to five weeks. The results in Dr. Kabat's laboratory were identical with those produced in Dr. Morgan's laboratory. I think that Dr. Morgan did her trick a little earlier than Dr. Kabat, but, as I said, her results came about accidentally while Dr. Kabat's experiments were specifically designed to produce an allergic encephalitis experimentally.[16] The important thing in all of this is that we got an independent corroboration of a most important biological phenomenon.

[16] E. A. Kabat, A. Wolf, and A. E. Bezer, "The rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants," *J. Exptl. Med.*, vol. 85:117 (1947).

Q: Dr. Rivers, isn't it true that in this particular paper Dr. Morgan never addressed herself to the problem of human vaccination? Nowhere is there any indication that she looked beyond her immediate animal tests.

Rivers: You are right, and I must say that Dr. Morgan was very wise in that attitude. There can be no doubt that what she had done was very valuable indeed, because she had demonstrated once and for all that it was possible to immunize a monkey against poliomyelitis by use of a formalinized inactivated virus. Prior to her work, Dr. Flexner had convinced us that you couldn't immunize a monkey in this manner. It took us a long time to discover that his experiments were inadequate.

Q: Dr. Rivers, was there much concern at this time with the problem of where antibody was formed?

Rivers: I don't know that there has ever been a time when virologists and immunochemists weren't concerned with this question. We are concerned with this question today, and although we have from time to time come up with a number of plausible theories, I don't think we have yet come up with a really satisfactory answer. Take Isabel Morgan. When she was doing her immunization experiments in monkeys, she sacrificed a number of her paralyzed animals and discovered antibody in high titer in parts of the gray matter of the spinal cord. While she was willing to go on record that such antibody represented local antibody production, she very wisely refused to say which cells she thought were responsible for such production. I was not surprised when Dr. Morgan spoke about the localization of antibodies in the central nervous system. For me, such localization meant there were areas in the central nervous system where damage had been done to the blood vessel wall. Generally speaking, the titer of antibody in serum is much higher than the titer of antibody in cerebrospinal fluid. I have always taken this to mean that there is a definite selectivity of what gets through the blood vessel wall into the brain tissue and eventually into the spinal fluid.

Antibodies do not go through the blood vessel wall easily. How-

ever, when you get an injured place in the central nervous system, blood vessels are either ruptured or the permeability of their walls are so altered that certain things will get through that might not have gotten through previously. Ernest Goodpasture once showed this in relation to the action of certain dyes. For example, it is well known that, if you give a normal rabbit trypan blue intravenously, the dye will not stain the central nervous system at all. However, Dr. Goodpasture showed that, if you first placed herpes simplex virus on the cornea of a rabbit and waited for the rabbit to come down with an encephalitis and then gave it trypan blue intravenously, that the dye would later collect around that part of the brain injured by the virus.

Let me just say that in 1946 investigators generally advanced two theories relating to the site of antibody formation. One group placed such a site in the reticuloendothelial system, while the other group thought it to be in the lymph nodes. Each group had evidence that made holding their particular theory attractive. In the former, for example, some investigators had discovered that one could actually depress the output of antibodies by blocking the reticuloendothelial system with phagocytic material. On the other hand, the lymphatic theory of antibody formation received good experimental support when Philip McMaster and his coworkers at the Rockefeller Institute injected typhoid bacilli into the ears of rabbits and then identified corresponding antibodies in extracts of the regional lymph nodes. Building on this work, investigators at the University of Pennsylvania under the direction of Tzvee Harris and William Ehrich later accumulated evidence that pointed to the lymphocyte as the primary source of antibodies. I think that in 1946 most people went along with Dr. McMaster and Dr. Harris.

Today we have still other alternative theories of antibody formation. Perhaps the most controversial is the one which has been recently proposed by Sir Frank MacFarlane Burnet. Briefly, Dr. Burnet argues that we are supplied with a pool of antibody making cells which collectively are capable of reacting with all potential antigens with which we might come in contact after birth, and that in entering the body an antigen selects the particular antibody making cell waiting for it and stimulates its proliferation. Burnet has suggested that a clone of the selected cell manufactures the antibody against the antigen. I don't know that I go along with Dr. Burnet, but you know

you can't help admiring him for attempting to formulate a new theory, because there are just too many facts that can't be explained by the older, more classical theories.

Q: Dr. Rivers, did the question of immunization with inactivated viruses dominate the Baltimore meeting?

Rivers: It is true that a great deal of the discussion at the Baltimore conference revolved around the use of inactivated viruses for immunization purposes in monkeys, yet I would be hard put to claim that it dominated the meeting. I say this because one paper was given at that meeting on the use of an attenuated strain of Lansing virus for immunization which later gave rise to a discussion equally as important and significant as that elicited by Dr. Morgan's paper. This paper was given by Max Theiler of the Rockefeller Foundation Virus Laboratories, who in 1951 won a Nobel prize in medicine and physiology for his work on yellow fever virus.[17]

Q: Dr. Rivers, since the Rockefeller Foundation Virus Laboratories have always been housed at the Rockefeller Institute, it is likely that you ran into Dr. Theiler long before he gave this paper, and I wonder if you would take a moment to give me a portrait of Dr. Theiler as you knew him before this meeting.

Rivers: Max Theiler is a very retiring, modest, you might even say, insignificant looking fellow—but brilliant as a researcher. He is a person who doesn't want to be told how to do anything. He will work his fingers off to prove or disprove some idea that he has had, but he just doesn't tolerate anybody messing around telling him what to do. This you know is characteristic of all good researchers. Dr. Theiler was born in South Africa a little more than sixty years ago. His father, Sir Arnold Theiler was probably one of the most distinguished bacteriologists of his day in South Africa and had acquired an international reputation for his work with trypanosomes. Max, you might say, grew up in an environment of science.

Almost as soon as he finished his studies in England he came to the

[17] M. Theiler, "A mutant strain of Lansing virus," Proceedings of the Round-Table Conference on the Mechanisms of Immunity in Poliomyelitis, 1946, pp. 29–36.

United States as an instructor at the Institute of Tropical Medicine at Harvard University. He was, I think, no more than twenty-three years old when he took up his post at Harvard. I first came to know him in 1930 when he joined the Rockefeller Foundation Virus Laboratories. It was just about that time that he succeeded in getting yellow fever virus into mice and, I want to tell you that that was quite an important achievement. Prior to that time, the rhesus monkey was the experimental animal of choice for workers in yellow fever. The virus went very well in such monkeys, but it meant that if you wanted to work with yellow fever virus, you had to have a large laboratory, with a large animal house and plenty of money, because monkeys at that time cost between $15 and $20 apiece. When Dr. Theiler succeeded in establishing yellow fever virus in mice, it meant that for the first time an investigator working with yellow fever could plan and do a great many experiments without worrying about the cost. I would like to add here that Dr. Theiler's later application of mice to animal-protection tests equally revolutionized epidemiological studies of yellow fever.

As I mentioned earlier, in 1929 and 1930 I did a great deal of work with Eugen Haagen and Ralph Muckenfuss, cultivating vaccinia virus in tissue culture in order to obtain an attenuated strain that might be used for prophylactic purposes. In these experiments I depended a great deal on the tissue culture know-how of Dr. Haagen. These experiments caught the attention of Dr. Wilbur A. Sawyer, who was then the director of the Rockefeller Foundation Virus Laboratories, and one day he came to me and asked what I thought of the idea of attempting to get an attenuated strain of yellow fever virus by cultivating it in tissue culture. I told him that I hadn't the faintest notion whether it would work, but that, if it did, it would be a wonderful thing and was certainly worth a flyer. As a result of this conversation, Dr. Sawyer brought Dr. Haagen—who by that time had returned to Germany—back to New York, and in 1932 he and Max Theiler began trying to cultivate yellow fever virus in tissue culture in the laboratories of the Rockefeller Foundation.

They had some difficulty in this early work, and I always thought that part of it could be ascribed to the fact that Dr. Haagen was not paying full attention to his work. This was the time of the rise of Hit-

ler in Germany and Haagen, who was an ardent Nazi, got mixed up in the affairs of the German-American Bund in New York. He certainly lost interest in what he was doing in the laboratory, and eventually he came to Dr. Sawyer and told him it was impossible to achieve what he, Sawyer, had in mind. With that Haagen was allowed to return to Germany.

Max Theiler, however, was not discouraged and, with the aid of Dr. Wray Lloyd and a technician named Miss Ricci, continued to work with tissue cultures. They carried on this work for at least three years, and in 1936 they achieved their first success when they established the highly virulent Asibi yellow fever virus strain in a culture whose tissue components contained minced mouse embryo. In an effort to see if they could modify the virulence of the virus, they began to cultivate it in media which contained minced mouse embryo as well as minced chicken embryo, with varying amounts of nervous tissue. I don't remember how many passages they eventually made, but, between the 89th and 114th passage, they discovered that there was a sudden modification of the virus, and that it had in fact lost its pathogenicity and become avirulent. In other words, it had mutated. To this day, Max Theiler does not know the reason for that mutation. Be that as it may, the important thing to remember is that this mutation has since become the basis for all the vaccine subsequently made against yellow fever.[18]

There is an interesting story that goes with this discovery. Prior to World War II, Japanese intelligence agents got in touch with one of the technicians at the Rockefeller Foundation laboratories and promised him a great deal of money if he would get them a strain of Dr. Theiler's attenuated yellow fever virus. The technician lost no time in telling Dr. Sawyer, who promptly notified the proper authorities in

[18] For the details of these experiments, see W. Lloyd, M. Theiler, and N. I. Ricci, "Modification of the virulence of the yellow fever virus by cultivation in vitro," *Trans. Roy. Soc. Trop. Med. Hyg.*, vol. 29:481–529 (1936). In 1937 Theiler and Hugh Smith reported the use of the modified 17D virus in man for immunization against yellow fever. "The use of yellow fever virus modified by an in vitro cultivation for human immunization," *J. Exptl. Med.*, vol. 65:787–800 (1937). In September 1938 some 59,000 human vaccinations using the modified (17D) yellow fever virus without immune serum were made in Brazil. The results established that a safe, practical live-virus vaccine against yellow fever was available for mass immunization. See H. H. Smith, H. A. Penna, and A. Paoliello, "Yellow fever vaccination with cultured virus (17D) without immune serum," *Amer. J. Trop. Med.*, vol. 18:437–468 (1938).

Washington. Subsequently the agents were arrested and the affair was hushed up. You know, there has never been any yellow fever in the Far East, although the *Aëdes aegypti* mosquito abounds in India, China, and other oriental countries. It is my guess that the Japanese may have had the notion in the back of their minds of turning yellow fever virus loose to aid in their conquest of the Far East, and wanted Theiler's attenuated strain so that they could make an effective vaccine to immunize their troops. Thank God for an honest technician. If this was their purpose, given the existence of the *Aëdes aegypti* mosquito in the Far East, they could have created one hell of a mess.

Although Dr. Theiler during these years concentrated his efforts on yellow fever virus, from time to time he also worked with poliovirus. Sometime during the early part of World War II—I don't know exactly when—Dr. Theiler received a sample of Lansing strain poliovirus from Dr. Charles Armstrong and almost immediately started to make serial passages in cotton rats and mice. After a while he noticed that the virus that had passed through mouse brains began losing its pathogenicity for monkeys, and in time he discovered that it had become attenuated. He then determined to see if this attenuated strain of Lansing virus would produce an immunity in monkeys that would withstand a subsequent intracerebral challenge of virulent virus. At the Baltimore meeting he reported that, while a majority of the monkeys which he had inoculated with the attenuated Lansing strain developed an immunity to an intracerebral challenge with SK virus, when they were challenged with the then-designated-virulent Philadelphia strain of poliovirus, they all became paralyzed. Dr. Theiler's findings raised once more a question that had long been nagging polio investigators.[19]

As I indicated earlier, many investigators beginning in the thirties began to suspect that there was more than one type of polio. Although they suspicioned this, nobody ever got down to brass tacks to see exactly how many types there were. For one thing, everybody knew that it would take a lot of time, money, and help to get such a job done, and secondly there were a hell of a lot more interesting

[19] It should be pointed out that, at the time of these experiments, Max Theiler was not personally concerned with the problem of the existence of different types of poliovirus.

things to do in polio research than to type the various strains of poliovirus that had been gathered by laboratories throughout the years. Many senior investigators when approached to do the job turned it down flat.[20] In the end the National Foundation had to pay to get the job done.

Beginning in 1948 it gave grants totaling well over a million and a quarter dollars to John Kessel, Louis Gebhart, Jonas Salk and Herbert Wenner to type all the extant strains of polio. Come to think of it, that's a pretty rotten way of putting the matter, because it sounds as if I'm kind of looking down my nose at the people who did the typing. Well, I'm not looking down my nose at these boys. Sure it was scut work and, for a scientist, almost doing day labor work like digging a ditch, but these boys realized that it was a ditch that had to be dug. They were good people, and I must say that I respect them more than the people who didn't want to undertake the typing. Actually, I believe that Dr. Salk and Dr. Wenner, who were youngsters at that time, gained a great deal of important experience by participating in the typing program.

Q: How necessary was the immunological typing program?

Rivers: To put it plainly, we had to know just how many immunologic types there were if we were ever going to make a vaccine. It was one of those things that we had to know without any ands, ifs, or buts. But I do want to emphasize that, although the typing program first got under way in 1948, the problem of rigorously defining the nature of poliovirus, or for that matter other viruses, was not a new one, and had in fact been agitating virologists for some time before.

I can best explain what I mean by speaking about a closely related matter, namely, the nomenclature and classification of viruses. If you look at my essay on "Some General Aspects of Filterable Viruses" in the volume on *Filterable Viruses,* which I edited in 1928, you will find that I made a rough classification of various diseases caused by filterable viruses. As we learned more about viruses in the decade that

[20] Dr. Harry Weaver, who was director of research of the National Foundation during this period, says that Dr. Rivers is mistaken here. I have not found any documentary evidence that bears on this point one way or the other, and it may well be that such offers and refusals were made verbally.

followed, that classification lost its usefulness. I might point out that the same problem of classification was faced by investigators who worked with plant viruses. For example, at the Third International Congress for Microbiology, which was held in New York in September 1939, Francis O. Holmes, who was a plant pathologist at the Rockefeller Institute, made an early attempt to classify phytopathogenic viruses. I mention this so that you can see that the problem of classification and definition of viruses was not limited to poliovirus alone. It was a problem incident to the growth of virology as a discipline, and, I might add, it is still a problem today. At present an international committee under the chairmanship of Sir Christopher Andrewes is still hard at work trying to establish a classificatory system for viruses.

At the Fourth International Congress for Microbiology, which was held in Copenhagen during the summer of 1947, the problem of classification and nomenclature of poliovirus was specifically made an issue. At that time, there was some debate among investigators as to what restrictions should be put on the use of the term, polioviruses, as opposed to the term encephalitic viruses. More important, some confusion also existed among investigators regarding the status of murine viruses which caused paralysis and their suitability as models in polio research. I would like here to say a word about this latter problem. In many stocks of mice, a mouse is occasionally found with a paralysis of its hind legs. In 1937 Max Theiler isolated a virus from such a mouse, and it became known as Theiler's virus. Dr. Theiler himself called this condition a spontaneous mouse encephalomyelitis. However, because the virus caused paralysis, some investigators began to speak of it as mouse poliomyelitis. I can tell you that this rather upset Dr. Theiler, because never in the wide wide world did he believe that this was polio. There was no more reason to call this paralysis mouse poliomyelitis than it is to call the paralysis in human beings caused by Jap B encephalitis virus, polio. In the end, the congress recommended that, when investigators used the term poliomyelitis virus, that they always modify it with the name of the host in which the strain naturally occurs. It also urged that, when investigators had to decide whether a given strain was rodent-adapted, that stress be

laid on the size and physical properties of the virus and its immunological relationship to the parent strain.[21]

Many of the virologists who attended this meeting on nomenclature felt that these recommendations did not adequately cover the problem, among them Dr. John Paul, the director of the Yale polio unit. In the months following the congress, he and his associate, Dr. Joseph Melnick, circularized virologists in the United States with alternative suggestions for defining and classifying poliovirus. Harry Weaver at the National Foundation kept a close watch on these developments, and I'll tell you why. As I mentioned before, one of the outcomes of the conference in Baltimore on mechanisms of immunity in poliomyelitis was the realization that the time had come for virologists to know just how many immunologic types of poliovirus existed.

After that meeting Dr. Weaver designed a questionnaire to elicit the characteristics of the various strains of poliovirus which were then to be found in various laboratories throughout the country. The answers which the Foundation received indicated in no uncertain terms what was not known. No one, for example, was able to say whether the hundreds of strains in laboratories represented one immunologic type, ten immunologic types, or one-hundred-and-fifty immunologic types. No one could say whether all the extant immunologic types had already been isolated. There was no information at the time whether a polio epidemic was caused by one or several immunologic types, or whether variations in the form of human disease were due to different immunologic types. Nor could anyone say whether there was any geographical limitation to the spread of the various immunogenic types. In short, we only knew that there was more than one type.

[21] In 1945 Dr. Peter Olitsky named the spontaneous encephalomyelitis of mice "Theiler's disease," and showed that Dr. Theiler's original isolate was distinct from two other strains that Dr. Theiler subsequently isolated and also called spontaneous encephalomyelitis viruses. Dr. Olitsky designated Dr. Theiler's first virus as TO (Theiler's original) and the latter two as GD-VII and FA. Although Dr. Olitsky considered Dr. Theiler's original mouse virus as a good model for poliomyelitis, he regarded the GD-VII and FA strains to be more characteristic of the encephalitic viruses. See P. K. Olitsky, "Certain properties of Theiler's virus, especially in relation to its use as a model for poliomyelitis," *Proc. Soc. Exptl. Biol. Med.*, vol. 58:77–81 (1945).

When John Paul began to send around his proposals to modify the recommendations on nomenclature and classification of polioviruses made by the Fourth International Congress for Microbiology, Harry Weaver, sensing the importance of pursuing the problem of immunologic types, arranged a meeting of interested virologists for early in January 1948 to discuss the question.[22] That meeting was most important, because it indicated to the Foundation that methods had been established which would allow for the accurate differentiation of the various immunologic types. It also led later to the formation of a small ad hoc international committee on nomenclature, which, under Foundation sponsorship, shouldered the burden of developing a provisional system of nomenclature and classification of poliovirus. During the summer of 1948, this committee presented the fruits of its labor to the First International Polio Conference in New York.[23] It was a difficult, I was almost going to say thankless, job but it was well done and after some debate a number of important recommendations were made. You can put these in later [see Appendix C].

I would like to make it clear that all of these developments were prologue to the typing program which was later undertaken by the Foundation in the fall of 1948. There is, however, no doubt in my mind that even before the Foundation put on its typing program that, David Bodian and his associates at the Hopkins and John Kessel at the University of California had already identified what later came to be known as the three basic immunologic types of polio.[24] You might

[22] Round-Table Conference on Immunogenic Types of the Virus of Poliomyelitis, Washington, D.C., January 7–8, 1948.

[23] Round-Table Conference on Methods for the Determination of the Immunologic Types of the Virus of Poliomyelitis, New York City, July 9–10, 1948.

[24] The problem of types of poliovirus is an interesting one. It can be said that by the early nineteen thirties investigators in Australia and the United States had already begun to turn up evidence of the existence of different immunological types of poliovirus. These reports while not conclusive were persuasive enough to make Dr. Simon Flexner, who has been frequently presented as being the proponent of a single type of poliovirus, to reconsider his position. It is clear that after World War II a number of investigators were aware that probably more than one type of poliovirus existed. It is difficult to establish whether Dr. Rivers' statement is completely accurate. It is certain, however, that by the end of 1949, two years before the polio typing program was completed, three immunologic types of poliovirus were spoken of. For further information, see F. M. Burnet and J. Macnamara, "Immunological differences between strains of poliomyelitic virus," *Brit. J. Exptl. Pathol.*, vol. 12:57 (1931); J. R. Paul and J. D. Trask, "Comparative study of recently isolated human strains and passage strain of polio-

well ask, why then did the National Foundation put on its typing program? The problem that the Foundation had to face actually boiled down to whether there were any more types, among the several hundred polio strains found in the United States, besides the three already isolated by both Dr. Bodian and Dr. Kessel.

It is true that the Foundation could have gambled and not spent the more than a million and a quarter dollars, and everything would have been all right, because not another type was turned up by the typing program. On the other hand, they could have been all wet. When we started typing pneumococci at the beginning of the twentieth century, we also began with three types; today we have discovered that there are well over fifty types. The same hold true for streptococci. No virologist that I know would have been willing in 1946 or 1948 to guarantee that there were only three types of polio. In science you don't guess, you do the job. The Foundation didn't lose a thing by putting on the typing program. It was, as I said, a necessary step in developing a safe and effective vaccine.

Q: Dr. Rivers, how did the virologists present at the Baltimore conference in 1946 react to the notion of making a vaccine?

Rivers: When the Virus Research Committee of the National Foundation projected its 11-point research program in 1939, developing a vaccine was made the very last order of business. I believe that everybody realized that eventually a vaccine would be made, but, after the debacle of the Park-Brodie and Kolmer vaccines of 1935, most virologists exhibited a great deal of skepticism when anybody started to discuss the possibilities of making a vaccine. I think that

---

myelitis virus," *J. Exptl. Med.*, vol. 55:513 (1933); J. D. Trask, J. R. Paul, A. R. Beebe, and W. J. German, "Viruses of poliomyelitis; immunologic comparison of six strains," *J. Exptl. Med.*, vol. 65:687 (1937); J. F. Kessel and C. F. Pait, "Resistance of convalescent *Macaca mulatta* to challenge with homologous and heterologous strains of poliomyelitis virus," *Proc. Soc. Exptl. Biol. Med.*, vol. 68:606–608 (1948). As far as can be ascertained, Dr. Bodian was the first to speak of *three* immunologic types in print. He published his findings in a series of papers throughout 1949. See especially D. Bodian, I. M. Morgan, and H. A. Howe, "Differentiation of types of poliomyelitis viruses; the grouping of fourteen strains into three basic immunologic types," *Amer. J. Hyg.*, vol. 49:234–245 (1949); D. Bodian, "Neutralization of three immunological types of poliomyelitis virus by human gamma globulin," *Proc. Soc. Exptl. Biol. Med.*, vol. 72: 259–261 (1949).

most of the virologists present at the Baltimore meeting were still skeptical, but I would be misconveying if I claimed that all were skeptical. There were some who were not. Dr. Hubert Loring of Stanford University was, for example, very vocal about the possibilities of making a vaccine. He and his coworkers had been preparing highly concentrated and purified Lansing virus and were much encouraged by the immunity that they had induced in cotton rats when they inactivated such concentrations with formaldehyde.

Come to think of it, that brought us face to face with still another important problem. It is easy enough to measure something that is active, but to measure something as small as poliovirus, in a state of inactivity useful for a vaccine, is something else again. We had to know how long a virus had to be in the presence of formalin to be *properly* inactivated. The important word is *properly*, because, if you let the inactivation go beyond a certain point, the virus can become so inactivated that it will not serve as an antigen and protect. It was not, moreover, a point that could be defined with pinpoint accuracy.

Howard Howe of Johns Hopkins was another who became enthusiastic about the possibilities of a vaccine. I remember that at the end of the Baltimore conference he got up and announced that, in the light of the papers given at the conference—and I think he had Isabel Morgan in mind more than anybody else—it was possible for the first time to reconcile discordant views about immunization of polio. Not everybody, however, was in a hurry to begin thinking about vaccines, and some even put up a red light. One of these was Bill Hammon, who at that time was professor of virology at the University of California. Some of the people at the conference became so enthusiastic about the possibilities of making a vaccine that they began to talk about standardizing laboratory procedures as a first step in clearing the decks for action. Dr. Hammon doused that idea by quietly pointing out that, until virologists knew more about existing immunologic types, it was premature to speak about standardizing laboratory procedures, and that premature standardization might inadvertently affect the development of the polio research then in progress. The go-slow remarks that I remember best were those made by Tommy Francis. Tommy has always had the ability to see things in broad perspective, and he took the occasion of the conference to point out to those

present that, if there was to be any progress in making a vaccine, not only would certain knotty scientific problems have to be solved—like the meaning of Lansing type virus for human polio—but that there would have to be better communication between workers in the field, because it was impossible to find out what had actually been done from the published papers.

The problem of communication between workers that Tommy Francis raised came up more than once during the early years of polio research. In part, it was due to the nature of the disease. Polio was a difficult disease to work with, in the field or in the laboratory, and it was never easy to get quick experimental results. Sometimes experiments took several months, sometimes a year or more, and that, coupled with the natural tendency of experimenters not to rush into print immediately, meant that there were often long delays before information reached print. Remember also that, if an investigator had an original idea, he usually tried to hold onto it until he had either proved or disproved it. Dr. Francis was not the only one who believed that communication between workers on polio was slow. Harry Weaver at the National Foundation was also troubled by this phenomenon. The postwar conferences on polio, of which the Baltimore meeting was the first, were specifically designed by him to facilitate and spur the exchange of information among polio investigators.

The success of these conferences later encouraged Harry to try to extend the interchange of ideas by asking grantees of the Foundation to agree to a circularization of their semiannual progress reports to other Foundation grantees. I can tell you that a lot of investigators didn't take kindly to that idea. Ken Maxcy wrote back that, while he and his boys at the Hopkins were in sympathy with the idea of a full and complete interchange of experience, the Foundation ought to be aware that such a plan might encourage the circularization of half-baked ideas, which in the long run might contribute to delay and misdirected efforts on the part of other investigators. Other Foundation grantees wrote in a similar vein, and some very candidly said that there would be circumstances in which they might not want to communicate a word about original findings until they had nailed things down by publication. I mention Dr. Maxcy specifically, because he later wrote to me privately and asked if I would say a good word for

his position to Mr. O'Connor. I could appreciate what was bothering Ken and the rest of the boys, and I agreed with a lot of what they said, but I believed that the advantages of Dr. Weaver's idea outweighed its disadvantages.

I was more troubled by the contemporary development of gang or group research, and no one at the time said much about that. Great discoveries are not made by committees or groups of workers; they originate in the minds of single individuals. I think that if discoveries occur in any other way it's truly an accident. I know of no important discovery in medicine or biology in the last hundred years that evolved out of gang research. You can do a hell of a lot of scut work by gang research, but the ideas for discovery are still going to come from the ideas in one man's mind. In other words, you can hire men but not ideas. I have always wanted to see an administrator try to hire a person like Dr. Avery or Dr. Landsteiner to do a specific piece of work. I can tell you now that they would be out of the laboratory before they even finished making the offer.

Perhaps I am being old fashioned, but I know that many of the older people who were at the Rockefeller Institute when I first came there felt that way. I can tell you a story that illustrates that point of view. When the Sloan Kettering Institute first opened, it wasn't considered respectable by some scientists at the Rockefeller Institute, because of the tendency to engage in gang research. Two of those scientists—and I won't tell you their names—once passed the Sloan Kettering about a year or two after it opened and stopped to inspect it. "Do you know what goes on in there?" one of them asked. "No," the other replied, "but whatever goes on in there, they do it together."

In the end most of the National Foundation's grantees, with one or two exceptions, agreed to Dr. Weaver's program of interchanging semiannual progress reports. That they did, I think, was a tribute to Harry Weaver as a coordinator of research programs in polio and a reflection of the confidence researchers had that he would protect the interests of the workers who made the reports.

Q: Dr. Rivers, would it be fair to say that in the immediate postwar period the National Foundation was in the main concerned with research on problems of immunity?

Rivers: I would not say that at all. I think that the Foundation was equally concerned with problems relating to the epidemiology of polio, and I know that it supported much fundamental research in this area during the postwar period. My own opinion is that John Paul of Yale was responsible for much of this interest and on more than one occasion prodded the Foundation to undertake specific pieces of research or to hold round-table conferences relating to epidemiology. I think that equally important was the fact that Mr. O'Connor had a deep interest in such problems, although it is true that, whenever anyone asked him if he was interested in epidemiology, he always erupted. Mr. O'Connor just doesn't like the word epidemiology. You can speak with him about how disease attacks the human population and related subjects that are the substance of epidemiology and everything will be perfectly all right, but mention the word and it's tally-ho. It is one of his idiosyncracies but I can tell you that it never interfered with getting such work supported.

As a matter of fact, early in 1947, Mr. O'Connor and John Paul got together and helped initiate one of the best conferences I ever attended on the problems of the epidemiology of polio.[25] The circumstances as I remember were these. For some years previously, John Paul and Joe Melnick had done a great deal of research relating to the fly and to sewage as mechanisms in the transmission of polio. There were, I might add, in 1947 a number of alternative theories on the mechanisms of the transmission of polio, and Dr. Paul and his associates felt that a conference might help epidemiologists and virologists clarify their ideas. Mr. O'Connor, on the other hand, was at that time faced with a rising incidence of polio and was getting restive that the Foundation had no hard information which it could give to public health officials to help control the spread of the disease. He thought that a conference devoted to epidemiology might furnish him with the information he needed. I will say this, the conference which was finally arranged was an unusual one, and quite unlike other conferences which had previously been held by the Foundation.

First, while previous conferences were almost always restricted to virologists or epidemiologists, this conference invited sanitary engineers and entomologists as well. Secondly, whereas previous confer-

[25] Round-Table Conference on the Epidemiology of Poliomyelitis, New Haven, February 14–15, 1947.

ences were exclusively concerned with a discussion of scientific papers, the participants in this conference were asked to make recommendations which would amend the regulations previously adopted by the American Public Health Association in 1945 for the control of poliomyelitis. It therefore might be said, that this meeting had an eminently practical purpose.

Q: Dr. Rivers, you mention a practical purpose. What, for example, could a virologist tell a public health officer in 1947 about the incubation period of poliovirus?

Rivers: Incubation was a difficult question to answer precisely in 1947, because not much was known at that time about the mode of spread of the disease. Nor was this the only problem. For instance, because polio assumed a wide variety of clinical forms, it was exceedingly difficult to make an estimate of the incubation period on clinical evidence. Take the problem of the first day of the disease. Everybody at the conference knew that some people could be infected with poliovirus and never show any clinical signs at all. They also knew that other people could be infected with poliovirus and only show signs of a minor illness, such as a sore throat, a slight fever, or general malaise. A doctor might tell such a patient that he had the grippe or a slight cold. Then there was the bona fide paralytic case. In the latter situation, it was fairly easy to tell when the paralysis started, but it didn't necessarily follow that it was easy to say when the disease began.

I remember that, when virologists and others at the conference tried to define the first day of the disease, a wide variety of answers were given and each one was different from the other. I have always taken the beginning of a disease to be the time when the person involved ceased to feel normal. Dictionaries usually give long, involved definitions of disease; however, I have always taken it to mean ill at ease. I'll tell you one thing, it's pretty hard even for the patient with paralytic polio to pinpoint the hour or minute when he stopped feeling all right. It would be easy enough if polio began with a sudden nose bleed, or if the patient's head fell off; but polio was never that nice and easy. It should come, therefore, as no surprise that nobody at the conference had exact answers to give on the incubation of polio-

virus. The answers varied. I think that the consensus later put incubation between 5 and 35 days, although, if memory doesn't fail me, Tommy Francis once turned up an instance of a three-day incubation period in a newborn baby.

Q: Dr. Rivers, what was known in 1947 about the mode of transmission of poliomyelitis to humans?

Rivers: In 1947 the answer on the mode of transmission of polio to human beings was still, so to speak, in the inkpot. Following the isolation of poliovirus in human stools in 1938,[26] John Paul and a number of other investigators quite naturally turned their attention to sewage. In the beginning the detection of poliovirus in such an environment was difficult, because the laboratory techniques available for this kind of investigation were crude. Nevertheless, in spite of the difficulties, within a very brief period, Dr. Paul and Dr. Trask succeeded in establishing the presence of poliovirus in sewage as well.[27] By the early forties, Sven Gard in Sweden and Joe Melnick at Yale had further refined laboratory techniques to such a point that detection of poliovirus from sewage almost became a routine matter.

To my mind, these technical innovations, combined with the singular absorption of Dr. Paul and his associates in examining the sewage in urban areas during epidemic and nonepidemic periods, gave great impetus to consideration of the problem whether the presence of poliovirus in sewage played a role in the transmission of polio. I might add that, in 1947, that line of inquiry held much promise. There was no doubt that Dr. Paul and Dr. Melnick had found poliovirus in the sewage they examined. There was likewise no doubt that in several instances they were able to bring down monkeys with virus gathered from such sources. In the end, however, they weren't able to establish that sewage was the key in the direct transmission of polio. I would like to say here that Paul and Melnick were extraordinarily careful in their published papers not even to imply such a role for

[26] J. D. Trask, A. J. Vignec, and J. R. Paul, "Isolation of poliomyelitis virus from human stools," *Proc. Soc. Exptl. Biol. Med.*, vol. 38:147 (1938); "Poliomyelitis virus in human stools," *J. Amer. Med. Assoc.*, vol. 111:6 (1938).

[27] J. R. Paul, J. D. Trask, and C. S. Culotta, "Poliomyelitic virus in sewage," *Science*, vol. 90:258 (1939).

sewage. But in spite of their meticulousness, on more than one occasion newspapers made such claims for them. I know that such stories caused Paul and Melnick a great deal of anguish, and they strongly resented the interpretations that newspapers made of their work. It made them so leery of newspapermen and publicists that at one point they even refused to cooperate with the public information division of the National Foundation. I didn't blame them then, nor do I blame them now for such an attitude.

From the point of view of the newspapers, the presence of polio virus in sewage undoubtedly made a good story. Sewage was something the public could understand. Traditionally, filth was responsible for a host of ills, and the newspapers could, following Dr. Paul's and Dr. Melnick's work in a superficial manner, get exercised that inadequate methods of sewage disposal were responsible not only for the high incidence of polio, but for a host of other public health problems as well. Let me illustrate what I mean. Although New York is one of the great cities of the world, it still dumps its sewage directly into the waters which surround it. You can look into the East River at certain times of the day and actually see feces and other sewage floating on the surface of the water. As a result of such practices, the waters in and around New York have become so polluted that New Yorkers can no longer use many of their natural beaches for swimming, nor can they eat oysters or other shellfish which are to be found in the vicinity of the harbor. As you can see, sewage was an old, natural enemy, and it seemed logical on its face to believe that, if poliovirus could be detected in sewage, that sewage somehow played a role in the direct transmission of polio to humans.

It was logical, all right; the only trouble was that it was a proposition that was not susceptible of proof. Poliovirus detected in sewage was no more responsible for the transmission of polio to humans than the poliovirus which was discovered in flies. For example, by 1947, it was likewise true that Dr. Melnick, Dr. Sabin, Dr. Robert Ward and several other investigators had already demonstrated beyond a shadow of doubt, that the flies that they had collected from the vicinity of open privies and sewage in epidemic areas were contaminated with poliovirus.[28] Dr. Ward, in an experiment in 1944, had even shown

[28] A. B. Sabin and R. Ward, "Flies as carriers of poliomyelitis virus in urban epidemics," *Science,* vol. 94:590 (1941).

that when he allowed flies which were contaminated with poliovirus to feed on peeled bananas, they contaminated the bananas to the extent that, when these bananas were later fed to several chimpanzees, one of the chimpanzees came down with polio.[29] It was, you might say, fairly good evidence that under certain conditions flies could transmit the disease. Most virologists, however, believed that this wasn't the usual method of transmission. First, no one could demonstrate that poliovirus multiplied in flies, and, secondly, several fly abatement campaigns which had been carried on in epidemic areas in 1945 and 1946 had shown no appreciable effect on the course and duration of the epidemics in question.

For me, one of the important results of the conference on epidemiology which was held in 1947 was that it confirmed me in the belief that polio was not spread by flies or sewage, but by close personal contact. I have always held Dr. Albert Casey of Birmingham, Alabama, responsible for my adherence to that point of view, and I still remember the paper he gave at that conference with a great deal of satisfaction. Through an examination of polio epidemics in Walker County, Alabama, and in Chicago during several different periods, Dr. Casey established that in over 80 per cent of the cases there had been personal contact between the polio victim and another child believed to have been in an infectious state of polio. He backed these observations with an impressive array of case histories, spinal-fluid protein determinations, and stool, throat, and mouth specimens.

However, the thing that impressed me most of all were the pictures he showed of children at play in Alabama. These children were playing some games in a field, and from time to time they would run off to an old outhouse nearby, do their job, and come back and play. What caught my attention was the fact that these children kept putting their hands in each other's mouths. I never realized before that children behaved this way. It was an eye opener. I grew up in the south, and I assure you that when children left an outhouse it was very unusual for them to wash their hands or to use nice pink toilet paper. It was more likely that they used an old newspaper or catalogue, or, if they were real hardy, bent a young tree, straddled it and walked off, to wipe themselves. The point is that children who left

[29] R. Ward, J. L. Melnick, and D. M. Horstmann, "Poliomyelitis virus in fly-contaminated food collected at an epidemic," *Science*, vol. 101:491 (1945).

the outhouse undoubtedly carried some of their feces with them on their hands.

If you think that intimate personal contact was accepted by everyone present at the conference as the mode of transmission of polio, I can tell you now that not everybody accepted that point of view. Dr. Gaylord W. Anderson, of the University of Minnesota Medical School, for example, very forcefully argued that polio was spread in a respiratory manner. Through the years, I have always had two reasons for arguing with people at meetings. Sometimes I would go after my favorites and try to push them to the limits of their findings as a way of clarifying thought. In the process, I can tell you that I bruised and hurt many an ego, because the truth is, although my purposes were good, I was never gentle. I am just not built that way. Other times I would go after people who rubbed me the wrong way.

Dr. Anderson was one of those who, for some reason or other, has always rubbed me the wrong way. This meeting was no exception and I went after him. I just didn't know what he meant when he spoke of "respiratory spread" or "contact spread." I was confident in my own mind that certain respiratory diseases could be spread by contact, just as others didn't have to be spread by contact in the sense that one had to touch something. Certain infectious agents can go through the air. Chickenpox, as far as I am concerned, is probably one of the most contagious of any of the so-called contagious diseases; yet the word contagious doesn't describe it very accurately, because contagious means touching. I have in my own clinical experience seen patients who caught chickenpox without touching anyone or anything that was contaminated. The infection in plain words was carried by air. I would like to add that such experience is by no means unique to me, and that other physicians have made like observations. My experience with hookworm in Guam fortified me in the belief that it was possible to acquire this infection merely by contact with contaminated blankets or bed clothes, even though there was no visible contamination with fecal material. And physicians had long been taught that the only way of picking up the infection was to walk in contaminated soil. I was, you might say, conditioned by my experience to be sympathetic with Dr. Casey's point of view.

I told my colleagues in 1947, and I'll tell you now, that the incidence of polio in a country runs parallel with the number of bathtubs

in the country. I think we get infected and immunized via the bathtub and the face towel. The children who leave an outhouse without washing their hands, as well as the adults and children who leave a nice pink bathroom after bathing, carry some of their feces with them. It may not be a pleasant thing to think about, but if someone has a defecation and later gets into a bathtub and washes himself, all that person does is to dilute the small amount of feces remaining after defecation. Drying oneself after the bath only succeeds in covering the body with a thin layer of feces and contaminating the towel. The bathroom is probably the most intimate part of the household: everybody visits it and, although there may be separate towels, I don't believe that children or adults in a family always use their own towels. They grab what is at hand. I believe that this is the reason that polio spreads so readily within a family. Children who play together can get their hands contaminated with virus from feces. Dr. Casey showed quite clearly that they didn't have to breathe in the virus, but that they could get it in their mouths from their hands. The point is that the virus could be spread in this way and you would still have an epidemiology similar to the so-called respiratory diseases.

Q: Dr. Rivers, your comments lead me to ask what was known of the portal of entry of the virus in 1947.

Rivers: Early in polio research, many virologists, following Dr. Simon Flexner, believed that poliovirus entered the body via the olfactory tract. By 1940 the work of Albert Sabin had effectively ruled out that idea, and by 1947 it was generally accepted, as expressed by Howard Howe, that the mucosa of the alimentary tract from the mouth to the rectum was potentially the portal of entry of the virus. However, I must emphasize that not all virologists at that time believed this doctrine as vigorously as Dr. Howe did. I think that by 1947 we were also reaching definite conclusions on the related problem of the portal of exit of the virus. By that time it had long been established that the virus did not leave the body via the urine, and most virologists, if you asked them, would have agreed that the general mode of exit of poliovirus in man was through intestinal discharge.

Some, however, adhered to the notion that the mouth might serve

as a portal of elimination. For instance, it had long been established that poliovirus could be found in the nasopharynx and the oropharynx of polio patients, but no one had ever shown that poliovirus was actually expelled from the mouth under natural conditions. It was an intriguing problem. For example, during the polio epidemic of 1912, the city of Buffalo asked the Rockefeller Institute for help in combating the epidemic. There was little that the Institute could do at that time, but Dr. Flexner sent Dr. Francis Fraser, who was then working at the Rockefeller Hospital on polio problems, to help out. One of the things that Dr. Fraser did was to take washings from the noses and throats of several of the patients he tended and sent them back to the Institute for study. Later, Paul Clark, using these washings, succeeded in bringing several monkeys down with polio.

It is interesting that Dr. Fraser did not take any saliva; if he had, Dr. Clark would never have been able to infect his monkeys, because poliovirus is never found in saliva.[30] In 1941 Albert Sabin and Robert Ward, working on problems relating to the elimination of poliovirus from the human body, demonstrated beyond a shadow of doubt that, although poliovirus could be detected in throats of polio patients, the virus was never to be found in the saliva of these same patients.[31] If that work showed anything, it showed that things in the oropharynx and the mouth don't get mixed up as badly as we sometimes imagine.

What I am about to say has nothing to do with polio, but it bears on the general proposition I have just stated. Sometime after I graduated from the Hopkins in 1915, Dr. Arthur Bloomfield, who later became professor of medicine at Stanford showed that, if you put streptococci on one side of the mouth, those streptococci stayed on that side of the mouth and went down that side of the throat and in no case did they invade the other side of the mouth and throat. To sum up, I would say that, at the time of the epidemiology conference in 1947, virologists in this country were approaching what we now believe to be the case, namely, that polio was spread through close per-

[30] S. Flexner, P. F. Clark, and F. R. Fraser, "Epidemic poliomyelitis. 14th Note: Passive human carriage of the virus of poliomyelitis," *J. Amer. Med. Assoc.*, vol. 60:1 (1913).

[31] A. B. Sabin and R. Ward, "The natural history of experimental poliomyelitis infection. II. Elimination of the virus," *J. Exptl. Med.*, vol. 74:519 (1941).

sonal contact, that the portal of entry for poliovirus was the mouth, and that the origin of the virus was largely fecal.

Q: Dr. Rivers, in the final analysis what help was the conference on epidemiology able to give public health officers on the control of poliomyelitis in 1947?

Rivers: To be perfectly candid, we could tell them precious little about the control of polio, because there were no effective means of control at that time. For example, we were always asked by public health officials whether children should be allowed to go swimming during an epidemic. If the conference in 1947 showed anything, it established the fact that we knew very little about the relation of poliovirus and water. I remember that the fellow who rammed that fact home to us was Abel Wolman of Johns Hopkins University. Dr. Wolman is a sanitary engineer by profession, but that hardly begins to tell you anything about him. Let me just say that there are few people in the world who are as knowledgeable about water as he is. He is a first-rate scientist and, as you might expect, he put some good hard questions to the virologists attending the conference. For example, I remember that he asked us whether we knew what the occurrence and viability of poliovirus was in water-carried sewage and in natural bodies of water. He also asked whether we had any chemical or physical techniques for destroying such viruses in water and sewage. They were, as you can see, reasonable questions, but ones which we could not answer at the time, and for that matter still can't answer completely. We just didn't know enough.

We could tell a public health officer or physician that it would be wise to isolate polio patients in the acute stage of their illness, or that the pharyngeal and bowel discharges of polio patients should be carefully disposed of, or that quarantine served no useful purpose, but beyond that there was little of a practical nature we could say or recommend. The fact that we knew little, however, did not discourage public health officials from asking us for answers, and during the next few years the pressure for practical measures of control continued.

During the early summer of 1949, the National Foundation held still another conference to see if our then increasing knowledge of

poliovirus warranted a revision of the previous procedures recommended by the American Public Health Association for coping with polio epidemics. Although it is true that by 1949 virologists had a keener appreciation of the nature of poliovirus and the mode of its transmission, there was still little that the conference could add to the recommendations that had been made two years earlier, save to advise that it was feasible to admit polio patients to the general wards of hospitals, provided hospital personnel carried out typhoid-like procedures of isolation. Actually, this latter recommendation constituted an important step forward in patient care, because for a long time previous many hospitals were reluctant to accept polio patients unless they could set an entire ward aside for polio use.

I can tell you that it was frustrating to many of the members of the Foundation that virologists had at that time little to offer in the way of practical methods of control, and I might add that no one was more frustrated than Mr. O'Connor. I remember that, during the course of a General Advisory Committee meeting in the fall of 1950, there was a discussion of a request to send expert help to a community which at that time was combating an epidemic. Mr. O'Connor asked those of us present what use it was to send experts to such epidemic areas. It was a reasonable question, and he was shocked when I and others told him that, from a research point of view, it was a waste of time, money, and effort. When I say this, I am not saying that epidemiology could not and did not help us understand polio. As a matter of fact, it is not too much to say that much of our early knowledge of the disease stems from epidemiological work. I am saying that by 1949 sending experts to epidemic areas was not an efficient way of acquiring new knowledge of polio.

Actually outside of John Paul and his coworkers and Tommy Francis and his boys, few virologists ever asked the Foundation to be sent into the field during epidemics and those two groups, as you know, did extraordinarily important research. On the other hand, many public health officials often asked the Foundation to send in experts during epidemics, because they felt that they might be helpful in acquainting the population with the nature of the disease. I do not believe that those officials thought the experts would actually discover anything new. In effect, they were looking for someone to hold the

public's hand. While you might say that such hand-holding epidemiology was useful from an educational or psychological point of view, it contributed very little to research.

Q: Dr. Rivers, if one looks at the developments in virus research during the late forties, one can almost sense a substantive change in the patterns and techniques of research. Would it be fair to say that, when the National Foundation invited Dr. Francis O. Schmitt of the Massachusetts Institute of Technology to address its annual meeting in 1948 on the contributions of biophysics to physiological and medical research, the invitation in a sense was symbolic of this change?

Rivers: I know very little about symbols, but I can tell you why F. O. Schmitt was invited to address the Foundation in this particular instance. Dr. Schmitt, as you undoubtedly know, is a biologist with deep interests in physiology and biophysics and one of the pioneers in this country in the application of electron microscopy to biological research. In 1948 one of Dr. Schmitt's associates, a young Argentinian physician named Eduardo De Robertis, published an extraordinary paper on electron microscopy and nerve structure.[32] Dr. De Robertis was not a virologist, but he had taken electron micrographs of living nerve fibers infected with poliovirus, which seemingly showed poliovirus particles traveling along the inside of a hollow nerve axon. That made us take notice, because several years before Howard Howe and David Bodian had conjectured that poliovirus traveled along the nerves. Still earlier, a number of investigators had claimed that tetanus toxoid and rabies virus also traveled along the nerves to the central nervous system. These electron micrographs seemed to confirm those theories, and it's small wonder that we accepted them with our mouths opened.

The Foundation invited Dr. Schmitt to address the 1948 annual meeting, because it was felt that the path he and his coworkers were charting was extraordinarily important for the future development of virus research. I must say that we weren't wrong in an over-all sense, but shortly afterward Dr. De Robertis' work washed out and we shut

[32] E. De Robertis and F. O. Schmitt, "An electron-microscope study of nerves infected with human poliomyelitis virus," *J. Exptl. Med.*, vol. 90:283 (1949).

our mouths. F. O. had a very red face for some time afterward, but, hell, I never blamed him, or for that matter De Robertis, for the failure of this work. It had only proved what I had long known to be true, namely, that scientists, even good scientists, get fooled occasionally and find what they hope to find. We all of us wanted to see virus particles traveling along nerves so bad that for a time all of us saw what Dr. De Robertis thought he saw.

Q: Dr. Rivers, I would like to pursue the question of change in virus research that I just put to you. Let me begin by quoting a statement which you made while chairing a session at a round-table conference on host-virus relationships which was held at the University of Wisconsin in October 1948.

> For a man of my age, and I am considerably older than many of you here, I have been kibitzing over the shoulders of virus workers for many years and, as a matter of fact, I probably started to kibitz when some of you were in diapers—and there is a possibility that a few of you were only statistical probabilities when I started. . . . It is too bad that some of the younger ones can't realize the mental attitude and the work that was going on in virology some thirty years ago to compare what was thought and done in those days with what is thought and done now. It is pretty obvious to some of us that miraculous advances have been made. . . . I only wish that I could live another 30 or 40 years and see what will have taken place in that length of time. Undoubtedly some of the younger ones here will have that pleasure. I'm sure that if things keep going in the next 20 or 30 or 40 years as they have gone in the past in the virus field, that many of the things that we think are now so will not be taken so then, because I can very definitely tell you that, if by some miracle some of you had been set down in meetings 30 years ago that I sat in on, they just wouldn't believe you—that is, it just couldn't happen. That is, the things that you say happen, couldn't happen, in those days. Our way of thinking and our techniques just didn't permit us to grasp that. As I grow older, it becomes a little bit harder for me to adjust myself to the rapid progress that has gone on in the virus field. Nevertheless, even though I balk a little now and then, don't forget that I'm entirely sympathetic with the guy that gets himself away out in front and takes a chance.[33]

Rivers: I think that it is fair to say that that particular conference was one of those meetings where it was apparent that a bridge would

[33] Minutes of Proceedings, Round-Table Conference on Virus-Host-Cell Relationships, Madison, Wisconsin, October 27, 1948, p. 3.

have to be constructed between the older and younger workers in virology if they were going to continue to understand and appreciate each other. Let me add that such occasions are not unique and actually constantly occur in the development of science. For instance, it happened last night when I attended a journal club meeting at the Rockefeller Hospital. A lot of youngsters were present at that meeting, some from as far away as Australia and Sweden, but, no matter what country they came from, they all had one thing in common, namely, they took ideas for granted that I and others fought over like cats and dogs thirty years ago. That habit of mind among the young is, I expect, not in itself remarkable: the young after all do stand on the foundations provided for them by the older generation.

What made it hard for me to take was the fact that no youngster present had any idea that what they were taking for granted and proved was once nebulous and debatable. Now, youngsters are not the only ones who forget; we all of us forget, and some of us forget too damn fast. Forget is a poor word; perhaps I ought to explain what I mean when I say forget.

In 1948 Lloyd Aycock of the Harvard Medical School visited the Hawaiian Islands and while there got the notion that it might be fruitful to make a study of the racial and environmental factors in the epidemiology of polio in Hawaii. Subsequently he applied to the National Foundation for a grant to conduct such a study. When his application came up for consideration, it was turned down. Now I am not fussing over the fact that it was turned down. To be completely candid, I voted against him. What bothered me then and bothers me now is that, while Dr. Aycock's application was being reviewed, some members of the General Advisory Committee of the Foundation questioned his competence. To be sure, I never considered Aycock a virologist, but as one of the pioneers of polio research in the United States I did think him knowledgeable on problems relating to the epidemiology of polio.

Why was his competence questioned? In part, I think that some members of the committee had forgotten the contributions that had been made to the understanding of poliomyelitis by epidemiologists. More important, however, was the fact that the style in polio research was changing. The committee didn't care about yesterday. If pressed,

I might even say that they didn't give a damn about today. Their attention was focused on tomorrow. Like most scientists, they only cared about the last experiment, not the next to last experiment, and certainly not the first experiment.

The conference on host-virus relationships which you mentioned was a straw in the wind. Actually it is as good a guide as I know to what some of these new styles in research were which were capturing the imagination of working virologists at that time. Work with bacterial viruses or bacteriophage was one. When I edited my volume on *Filterable Viruses* in 1928, I asked Jacques Bronfenbrenner to prepare a chapter on bacteriophage. Yet, when the volume appeared, that chapter caused some furor, because some virologists—particularly some British workers—refused to accept phage as a virus. By 1948, however, phage was not only accepted as a virus by most virologists, but, in addition, many virologists were also beginning to use it as a key in the elucidation of virus-host systems. For example, at the conference on host-virus relationships, Dr. Salvador Luria, then a professor of bacteriology at the University of Indiana, showed that through a study of phage one could begin to study the reorganization of the metabolic machinery of host cells. Today we know that viruses do not reproduce, that is, they do not multiply in the sense that bacteria multiply; they are replicated by the infected or host cell. We all agree to this now, but in 1948 we still had to be shown. The idea of replication was first coming in and involved a whole new concept of biochemistry and genetics. As a matter of fact, at that time Dr. Luria continually told us that genetics would be a necessary new tool for virologists and even began to pose virus problems in genetical terms. I am not saying by all this that we immediately embraced all that Dr. Luria told us, but there can be no doubt that he titillated us to think along these lines.

Q: Dr. Rivers, was there much concern at that time with new definitions of viruses?

Rivers: That's a game that virologists continually play at. I remember that at that meeting Dr. Philip Cohen, who was a professor of physiological chemistry at the University of Wisconsin, tried defining

a virus as an enzyme system. Well, hell, before I would accept a definition like that I wanted to know which virus he was speaking about. I don't think that anyone to this day has given a wholly satisfactory definition of a virus. I don't think that it is possible, because we still have not learned the trick of defining many different things as one. How can you define a mouse trap along with an automobile and nuclear reactor? And that's just about what one tries to do when he tries to define a virus by a single simple definition. Viruses differ tremendously in size and complexity from the pox viruses that are almost 300 millimicrons in diameter to Norton Zinder's little phage F2 that is only 10 to 15 millimicrons in diameter. There were attempts at new definitions of viruses in 1948, and in part, I think, they grew out of the fact that the field of virology after World War II was invaded by biochemists and physicists who brought their own language to deal with phenomena with which they were getting acquainted.

Q: Dr. Rivers, can you give me an example of one of these new workers?

Rivers: To my mind Seymour Cohen of the Department of Biochemistry at the University of Pennsylvania was typical of the workers who began to invade the field of virology after World War II. By training and inclination Dr. Cohen was and is a biochemist. At the time of the conference on host-virus relationships in 1948, he was still a youngster and housed in a lousy little old laboratory in the Children's Hospital in Philadelphia. But, God, he turned out beautiful work. He was, even then, as sweet a biochemist as you could find—which means, if a guy has got the goods, he doesn't have to have a large and expensive laboratory. I don't think that I am telling any tales out of school when I tell you that for years the National Foundation tried to support him in his work, but he just refused to be bothered. I don't know how many times I indicated to him that if he wanted money from the Foundation he had but to ask. I assure you that the Virus Research Committee would have given him all the money he wanted at the drop of a hat—but he never asked.

At the conference, Seymour Cohen gave a paper on the growth requirements of bacteriophage. He was not the first to work on such

problems, by any means, and it is only fair to point out that much of the important preliminary work in this area was done by Max Delbrück and Earle Evans and their associates. I cite it merely as an example of the attack that was being made by biochemists at that time on such problems as the relation of virus growth to the interior environment of the host or the infected cell. Ten years before, we couldn't even pose such problems. By 1948, however, biochemistry in relation to bacteriology and virology had developed to such a point that Rollin Hotchkiss, at the Rockefeller Institute, had even successfully devised techniques for differentiating the DNA found in phage and the DNA found in bacteria.

I don't mind admitting to you that it was pretty hard for a man like myself, who didn't have specific training in biochemistry and physics, to understand the niceties of what youngsters trained in this manner were getting at when they discussed viruses. You might say that I understood these new concepts by intuition. I wasn't completely dumb, because I knew a lot of things about viruses that the new sophisticated biochemists and physicists did not know, because they lacked my experience in pathology. I would like to take this occasion again to remind you that many of the older virologists had learned much about the nature of viruses through studying the pathology of the diseases they caused.

If you examine the minutes of the conference, you will discover that there was much discussion on what the reaction of a host cell might be to viral invasion. The comments were, of course, based on all sorts of new biochemical and biophysical data which were being elicited through the research of people like Salvador Luria, Seymour Cohen, Max Delbrück and others. However, if you go back and read the lecture I gave before the Society of American Bacteriologists in Philadelphia in 1926, you will find that I was able to differentiate what might happen to particular kinds of cells in viral infections on the basis of pathological study. For instance, I had already pointed out that, if a cell could not be stimulated to multiplication (as in a nerve cell), or if the virus acted in a rapid and explosive manner (as in foot-and-mouth disease virus, when tested on the plantar surface of a guinea pig), the reaction was destruction of the cell. In rabies and polio, one cannot see any multiplication or hypertrophy of the

cell; all one can see is injury and death. God, the lesion is there so fast, you can't see anything except destruction and death. In other viral diseases—and this is true of some of the phages—the first response of the cell is growth. The cell grows bigger and bigger and then dies. The plates accompanying Dr. Bronfenbrenner's chapter on bacteriophage in my volume on *Filterable Viruses* clearly shows this development by charting the effects of phage on *B coli.* Such experience allowed me to grasp what the younger workers were driving at. Their concepts weren't new, but their ways of doing things and expressing themselves were different from what I had been brought up on.

Q: Dr. Rivers, I think that you will agree with me when I say that the study of phage in the period following World War II had an extraordinary impact on the development of virology. Would you go so far as to say that it was a key to the study of interference phenomena?

Rivers: I won't quarrel with your first statement, and I will admit that it was a key. But I would like to point out that interference phenomena were studied long before phage became an important analytical tool in virology. If I remember correctly, plant pathologists in the early thirties were the first to demonstrate interference between various plant viruses. In 1935 Dr. Flaviano Magrassi, an Italian virologist who worked very closely with Dr. Robert Doerr, showed that, if you took a rabbit and inoculated it subcutaneously with dermotropic herpes virus, and at the same time inoculated it in the brain with a neurotropic herpes virus, the encephalitis which invariably followed inoculation with a neurotropic virus would be prevented.[34] I should point out that I and many other virologists did not accept Dr. Magrassi's work as showing true interference, because the dermotropic virus did not actually interfere with the virus which was introduced in the brain.

[34] F. Magrassi "Studi sull' infezione e sull' immunità del virus erpetico; Nota II: Sul contenuto in virus del cervello in rapporto a diversi ceppi di virus, a diverse vie d'infezione a diversi fasi del processo infettivo"; "Nota III: Rapporti tra infezione e superinfezione di fronte ai processi immunitari: sulla possibilità di profondamente modificare il decorso e gli esiti del processo infettivo già in atto," *Z. Hyg. Infektionskrankh.*, vol. 117:501; 573 (1935).

The credit for demonstrating interference between related animal viruses is usually given to Dr. Meredith Hoskins of the International Health Board, who showed that, if you inoculated monkeys with a mixture of pantropic and neurotropic strains of yellow fever virus intraperitoneally or subcutaneously, such monkeys would escape infection by the pantropic strain.[35] Following Dr. Hoskins's work, any number of virologists later demonstrated that interference could also be induced by using such unrelated animal viruses as Rift Valley fever virus and yellow fever virus and influenza A virus and western equine encephalitis virus. There were others; I just give these as examples. It is plain, therefore, that work on interference phenomena initially proceeded quite apart from the work being done on phage, although it is true that, very early, such investigators as Frank Burnet, Salvador Luria, and Max Delbrück also showed interference between some of the bacterial viruses.

I think that it is fair to say that, by 1948, while we knew about interference phenomena and had studied it, we still had little idea of the mechanism through which interference occurred. The work with phage was helpful in that it furnished virologists with important insights into the process of viral multiplication. Any number of virologists began to see that, if they could prevent phage from being absorbed on the host cell, or if they could somehow prevent phage from penetrating the host cell, or if they could interfere with the metabolism of the cell, they could prevent replication of phage. Some virologists began to look for chemical agents that might interfere with any of these processes, the notion being that if someone somehow could cause a minor change in the cells which were susceptible to the virus, one could for a time make such cells insusceptible to infection. It was such thinking, for example, which led in the late forties to several notable attempts at chemotherapy for polio. I will tell you about one of them.

About 1947 a pharmacologist named Leon Schmidt in Cincinnati discovered that two compounds, plasmacid and isoplasmacid, long known to malarialogists as antimalarials, had very peculiar neurotropic effects in monkeys. That work caught the attention of Albert

[35] M. Hoskins, "A protective action of neurotropic against viscerotropic yellow fever virus in *Macacus rhesus*," *Amer. J. Trop. Med.*, vol. 15:675 (1935).

Sabin, who quickly noted that, the drug, strangely enough, affected those areas of the central nervous system that were also hit by poliovirus. Since the distribution of polio lesions in monkeys is similar to the distribution in man, and since it was known that poliovirus would attack normal cells in preference to abnormal cells, Sabin began feeding monkeys plasmacid and isoplasmacid in the hope that such feedings would make the cells likely to be hit by poliovirus slightly abnormal and therefore insusceptible to polio. Now this was not bad reasoning for the time; however, the initial experiments carried out by Dr. Sabin were not clean-cut. In 1948 he asked the National Foundation for support to pursue this matter further. I remember that I took a trip with Harry Weaver to Cincinnati and spent a whole day listening to Sabin and examining his protocols and monkeys. The work he had done was most intriguing, and Dr. Weaver and I recommended that the Foundation let him go ahead. Unfortunately, in the end nothing came of this work. It later turned out that the interference was not as striking as we had hoped it might be; more important, the drugs were on the boundary line of toxicity, and the research was dropped. There is, however, no denying that the work was interesting. Dr. Sabin was thinking the way I and other virologists were thinking, namely, that anything that would make a cell abnormal would protect that cell against viral infection. I still think that.

Q: Dr. Rivers, if you examine the minutes of the conferences held by the National Foundation, you find that Dr. Sabin makes comments on a wide variety of subjects covering epidemiology, pathology, biochemistry, pharmacology and the like. He . . .

Rivers: He was and is irrepressible, and he just loves to talk. God, he will talk at the drop of a hat. He also just loves to take a poke at the other fellow. But make no mistake, he is qualified to work in any number of fields. He has always been my idea of a splendid man for research, although it is true that from time to time I have roughed him up.

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).