CHAPTER 7

The National Foundation for Infantile Paralysis: Early Research Programs— Part 1

Rivers believes it is now time for the Research Committee to survey the field, not of knowledge, but of what we do not know of poliomyelitis. Rivers believes that when this is done, the Committee should then attempt to block out the problems....... When this is accomplished, men and institutions should be sought to carry out the broad aims which have been defined by the Research Committee.

Minutes, Scientific Research Committee of
The National Foundation for Infantile Paralysis, November 9, 1938

Q: Dr. Rivers, when The National Foundation for Infantile Paralysis was founded in 1938, did you expect, because of your previous connection with the President's Birthday Ball Commission, to serve with the Foundation? [1]

Rivers: I had no idea that I would be called on again. At that time I did not know Mr. O'Connor, the president of the Foundation, and I am sure that he didn't know me. One night soon after the National Foundation was formed in 1938, Paul de Kruif came to visit me at the

[1] The Certificate of Incorporation of The National Foundation for Infantile Paralysis was filed on January 3, 1938. See "Certificate of Incorporation of The National Foundation for Infantile Paralysis Inc. Pursuant to Membership Corporation Law." Undated, 6 pp. (Organizational files, National Foundation Archives.)

Rockefeller Hospital. He always took a great deal of pleasure in visiting me whenever he was in New York and cramming what he was doing down my throat. I don't think that he had anything against me personally; I suspect that he did this because he didn't like the Institute. Paul either likes you or he doesn't. If you differ with him a little bit, you just belong to the other clan—that's all there is to it. And I don't deny that I belonged to the Institute clan.

On this particular occasion Paul was a little tight, and he told me that I was going to be invited to join the Scientific Research Committee of the National Foundation. I hadn't at that time been formally notified of my appointment, and I have always suspected that Paul had a lot to do with making me a member of that committee. Later I learned that, after the Foundation was created, Mr. O'Connor had suggested to Paul that he arrange the formation of a number of committees to advise the Foundation on medical problems. Several such committees were formed: there was a General Advisory Committee, a Scientific Research Committee, a Committee on Public Health and Epidemics, and a Committee on Care and After Treatment. Later other committees were added. Each committee had its own members, and if I remember correctly not all of the committees began their life at the same time. I am almost certain, however, that the Scientific Research Committee was the first one to go into business.[2]

Q: Dr. Rivers, do you remember who served on this committee?

Rivers: Indeed I do. Initially the committee was composed of Paul de Kruif, Dr. Donald Armstrong, Dr. Charles Armstrong, Dr. George McCoy, Dr. Karl Meyer, and myself. I remember, because they did me the honor of electing me chairman, a position I then held for the next seventeen years. Actually, this committee had several members who had previously served on the Scientific Advisory Committee of

[2] The Committee on Scientific Research was initially organized on July 6, 1938. It was subsequently reorganized several times with accompanying name changes reflecting new functions and responsibilities. On May 13, 1940, it became the Committee on Virus Research; on September 30, 1947, the Committee on Virus Research and Epidemiology; on April 8, 1959, the Committee on Research; and on October 5, 1959, the Committee on Research in the Basic Sciences. In speaking of the work of this committee, Rivers often uses the titles of the various committees interchangeably.

the President's Birthday Ball Commission. Unlike that committee, this one had three working virologists, Charles Armstrong, Karl Meyer, and myself. I have mentioned some of Charley Armstrong's work before, but I have said little about Karl Meyer.

I have known Karl Meyer for many years and I can say unequivocally that he is a superb virologist. He is a Schweizer by birth and was originally trained as a Doctor of Veterinary Medicine. About 1910 he migrated to the United States and took a job as professor of bacteriology and pathology at the University of Pennsylvania. His work very quickly began to attract attention, and just before World War I he was invited to become professor of bacteriology at the University of California. A short time later he joined the Hooper Foundation for Medical Research and from that time has been associated with them. The Hooper Foundation in many respects is the analogue of the Rockefeller Institute, with one important difference: throughout its existence the Rockefeller Institute has had no connection with any medical school. However, the Hooper Foundation has always been closely connected with the Medical School of the University of California. I can't now begin to detail Dr. Meyer's scientific contributions; just let me say that he has made lasting contribution to our understanding of sylvatic plague, western equine encephalitis, and psittacosis.

Physically, Karl is a big man with a big voice and on the west coast he has long been known to his colleagues as King Karl. It's not too much to say that, as far as bacteriology and virology went, he ruled things on the west coast. Dr. Meyer was a valuable acquisition to the Scientific Research Committee. Before the National Foundation began its operations it was difficult to find people who were interested in or even knew very much about problems of polio. One of the reasons for this state of affairs was that the field had been more or less usurped by Dr. Flexner and the Rockefeller Institute. You could count the laboratories who could do research in this field on the fingers of your hands. The Hooper Foundation was one of those places. If I am not mistaken, it had worked on polio problems for over a quarter of a century before the National Foundation opened shop, and Dr. Meyer as its director was fully conversant with the problems presented by polio research.

Q: Did the Scientific Research Committee develop a program for the Foundation, or did you depend on receiving applications from individual investigators?

Rivers: Almost the first problem the Scientific Research Committee faced was regularizing the manner in which applications for grants were made and passed upon. During the life of the President's Birthday Ball Commission, such applications went directly to Paul de Kruif, many of which the Scientific Advisory Committee never saw. It would have been nice to see them all, but the committee never got to see them. As secretary to the Scientific Research Committee of The National Foundation for Infantile Paralysis, Paul was in the same position when the new foundation got under way in 1938. Now, nothing much passes Mr. O'Connor. Being an orderly man, an orderly thinker, running an orderly law office, devoted to everything being run in an orderly manner, you can guess that he wasn't going to put up with the hit-or-miss of what had gone before—and he didn't. At the first formal meeting of the Scientific Research Committee, which was held in joint session with the Public Health and Epidemic Committee, it was urged that a formal application blank be adopted. At Morris Fishbein's suggestion, the committee adopted the application blank for grants in aid of research used by the American Medical Association. Now, on the surface, that doesn't seem like much, but please remember that, before such a procedure was adopted, all a fellow had to do was to write a letter or note to de Kruif for consideration for a grant. It was, to say the least, a slipshod way of doing business, and it was done away with.

That first meeting was very important and, as I remember, most of it was given over to a discussion of the nature of the principal unsolved problems of poliomyelitis. Rather than trust my memory on what was said, I would like to insert here a portion of the minutes of that first meeting.

Some of these problems agreed by all present to be important and fundamental, were: (1) What is poliomyelitis? Is the disease a clearly defined entity? Is there more than one form of the virus? If so, are these forms clearly separable and identifiable? (2) Is the pathology of the disease in humans adequately worked out? No. (Much more knowledge is needed of monkey disease pathology.) (3) Is the portal of entry known certainly for humans? Not certainly. But for major epidemics, it is still presumptive that the portal of entry is by way of the olfactory area. But work should continue. (4) Axonal transmission? This appears highly probable. But is it propagated in the body by this route? Should be settled if possible. Work should continue. (5) Chemical blockade? This is certainly the most promising of known methods of prophylaxis, which may be tried in the field. Work in this field should certainly continue, in an effort to find chemicals as effective as zinc sulphate, but less irritating. (6) Basic research should continue on attempts to alter the virus with the hope of making a vaccine. There are precedents for this. Yellow fever, horse encephalomyelitis, etc. (7) The relation of polio to constitution. Rivers occupied somewhat lone wolf position here, believing that this inquiry should be prosecuted. (8) nature of the virus. Bearing in mind the crystallization of mosaic viruses, and the new physical methods of concentrating and separating viruses, effort should be concentrated on developing this inquiry on multiple fronts. . . . (9) The possibility of setting up a travelling fellowship was discussed. (10) Chemotherapy of the acute disease. This should be pushed. (11) Collection of strains of viruses during epidemic emergency. Grantees should be contacted to find out if they would serve in the field in this capacity.[3]

It was, I think, a fruitful discussion and after the meeting Paul de Kruif asked Dr. David Kramer to compile a dossier on what was not known about polio. As I mentioned before, Kramer was one of the early investigators in the field of polio and had done much clinical and experimental work with Lloyd Aycock on the Harvard Infantile Paralysis Committee. By 1938 Kramer had taken a post at Long Island University Medical School, and through de Kruif was given a minor administrative position in the Foundation. He was a good choice for the job that de Kruif had in mind, but at that particular time he was busy with his own research and paid little attention to the request made of him.

If he forgot, Mr. O'Connor didn't. In the early days, the Scientific Research Committee met in his law office at 120 Broadway, and he attended each meeting faithfully. I might add here that he still does. Mr. O'Connor thought de Kruif's idea for a survey a good one and kept pressing the matter. When he realized that Dr. Kramer wasn't going to do anything, he called me at the hospital and asked me to

[3] Minutes of the Committee on Scientific Research, National Foundation for Infantile Paralysis, July 6, 1938.

take responsibility for compiling the dossier. I wasn't enthusiastic about taking on the job, but I realized that it was something that had to be done. I'll tell you why. During the first year of the National Foundation's existence, the Scientific Research Committee received any number of applications for grants from individual investigators, and, while many were worthwhile in themselves, together they didn't seem to be going anywhere. They were too haphazard for my taste, and I thought that the Foundation would be better served if the committee surveyed the field of polio research and blocked out problems that needed solution. With such a guide in hand, I felt that the committee should seek out the men and institutions capable of handling such problems and support them with grants. I don't know whether Mr. O'Connor had such a program in mind when he asked me to take over Dr. Kramer's chore; however, I do know that when I submitted such a program to the Scientific Research Committee in the fall of 1938, I was asked by Mr. O'Connor to draw up a memorandum embodying the details of such a program.[4]

I worked on that memorandum throughout the winter of 1938, and when I thought I had a representative list of the major research problems in polio, I circularized the members of the committee and asked them to rank the problems in terms of their relative importance, and to state who in their opinion was best qualified to investigate these problems. Now I want to make one thing clear. Although I initially drew up the list of research problems, I had nothing to do with putting them in the order in which they finally appeared: that ranking was the result of a consensus of the entire committee. In this final form it became the eleven-point program which guided the National Foundation in its grant policy until the appearance of the Salk-Sabin vaccines.

Q: Was there any opposition to your proposals?

Rivers: Indeed there was. Several members of the committee didn't like my idea, among them George McCoy and Charles Armstrong. They felt that the Foundation would be better advised if it simply continued to give grants to competent investigators of accredited in-

[4] *Ibid.*, November 9, 1938.

stitutions who voluntarily expressed their wish to do research into the causes and prevention of polio. However, I will say this: when the eleven-point program came up for a vote they did not oppose it.

Q: Dr. Rivers, could you give me the substance of the eleven-point program?

Rivers: I'll do better than that. I will read the eleven-point program as it appears in the minutes of the Scientific Research Committee.

The averaging of the ratings of each problem brought it about that the eleven problems listed by Dr. Rivers were rated in the following order of importance:

1. Pathology of poliomyelitis in human beings
2. Portal of entry and exit of virus
3. Purification and concentration of the virus
4. What is to be called poliomyelitis?
5. Mode of transmission of virus from man to man?
6. Transmission of virus along the nerves [Questions 4, 5, 6 received identical average ratings]
7. Further attempts to establish poliomyelitis in small laboratory animals
8. Settlement of the question of chemical blockade
9. Chemotherapy of poliomyelitis
10. Relation of constitution to susceptibility
11. Production of a good vaccine [5]

I suppose that some people will want to know why the committee designated the pathology of poliomyelitis in human beings as the first large research problem to be tackled by the Foundation. First let me say that by 1938, while there was a good deal in the literature on the pathology of polio in monkeys, we actually knew very little about the pathology of polio in human beings.

Q: Dr. Rivers, were there any pathologists on the Scientific Research Committee?

Rivers: No. But as I mentioned before, if you were a virologist in those days (not necessarily today) you had to know pathology, be-

[5] *Ibid.*, April 18, 1939.

cause the only way you could study viruses at that time was to discover its effects on human beings or animals. By gosh, whether you wanted to or not, if you worked in virology you sooner or later developed into a pretty good pathologist. So it's fair to say that, although the committee had no pathologists, the virologists on the committee did have an appreciation of the significance of pathology for an understanding of polio.

If you look at the early literature of polio you frequently find it referred to as Heine-Medin disease. Heine and Medin are the names of two doctors. Jacob von Heine was a German physician who as early as 1840 made shrewd observations on the nature of polio, while Oscar Medin, a Swedish physician later in the 19th century, helped clarify the picture with good clinical descriptions of the disease during an epidemic. The interesting thing about Heine's observations was that he assumed, on the basis of his clinical observations, that the primary lesion of polio would be found in the anterior horn cells of the cord. It was he who called polio spinal infantile paralysis—and it always gives me a kick that he did this, because he never had a chance to study any post-mortem cases of polio.[6]

In time doctors began to disregard Heine's observations, and when I was a young doctor it became fashionable to speak about a perivascular infiltration as being characteristic of polio. As I began to learn about viruses, I thought less and less of that particular idea. It just couldn't be—not if my idea that viruses were obligate parasites that could only grow and multiply in the presence of living susceptible cells was correct. Actually there was enough in the literature for us to question the notion of a perivascular infiltration. For instance, sometime around 1929 or 1930, E. Weston Hurst demonstrated that the primary attack of polio in the nervous system was on susceptible neurons, and that the inflammatory reaction that pathologists found was the result of this neuronal damage. He maintained that it was the death of these cells which led to an infiltration of the tissues with polymorphonuclear leucocytes. Dr. Albert Sabin at the Rockefeller Institute was another investigator who very early helped clarify the pathological picture of polio.

[6] The early history of poliomyelitis is described in P. H. Römer, *Epidemic Infantile Paralysis,* William Wood, New York, 1913; International Committee for the Study of Infantile Paralysis, *Poliomyelitis,* Williams & Wilkins, Baltimore, 1932.

Q: Dr. Rivers, you have mentioned Dr. Sabin earlier. Before you describe his pathological work can you tell me how you first came to meet him?

Rivers: I first came to know Albert Sabin when he worked with William H. Park at the New York City Health Laboratories down at the foot of Fifteenth Street on the east side of Manhattan. Dr. Park at that time, among other things, was working on problems of polio and had as one of his assistants an attractive and bright young Canadian investigator named William Brebner. One day Dr. Brebner was bitten on the hand by one of the monkeys being used in an experiment. People had been bitten by monkeys before, and Dr. Brebner paid the bite little mind. About a week or ten days later he noticed that his hand was becoming weak, and soon after it became paralyzed. Within a few days the paralysis spread to his respiratory center and brain and he died.

Dr. Sabin had worked with Dr. Brebner and at the autopsy got some material for examination. I believe he got a portion of the brain, although I am not sure, and after very careful work isolate a virus.

At the same time, Frederick Gay, a professor of bacteriology at the College of Physicians and Surgeons of Columbia, also got some material from the autopsy and, with the help of one of his assistants, a young lady named Holden, also isolated a virus. Dr. Gay and Miss Holden contended that the virus they had isolated was herpes simplex virus; Dr. Sabin on the other hand argued that it was a new virus, and in honor of Bill Brebner called it B virus. A first-class hassle developed. Well, Sabin was never bashful, and he came up to the Institute to tell me about his fight with Gay and to show me his work. I went over his work more than once and finally became convinced that he was right, and so I supported him in his fight with Gay. Dr. Gay himself never talked to me personally about this question. No matter. In the end Sabin won out and most investigators accepted B virus as a new virus. Subsequently several other workers were bitten by monkeys and died, and this same virus was recovered. An examination of the blood of the implicated monkeys revealed that they had antibodies against the virus—in other words, they had previously had a viral infection but had recovered. Today it is established that B virus is a virus disease of monkeys, and while it is not necessarily fatal to monkeys it is practically 100-per-cent fatal to rabbits.

In 1933 Sabin received a fellowship and went to England to work at the Lister Institute. Here he had the benefit of working with such virologists and bacteriologists as Sir John Ledingham, E. Weston Hurst, and G. H. Eagles and, as I mentioned before, he later put me on the track of why Eagles was getting positive results growing vaccinia virus in the presence of nonliving cells. We corresponded some during this period, and when Sabin got ready to return to the United States he wrote me and told me he was looking for a job. I went to see Dr. Flexner. "Look, Dr. Flexner," I said, "Here is a nice young Jewish boy who is as smart as all outdoors. He has worked with Dr. Park, and at the Lister Institute and knows a great deal about viruses. I think we ought to give him a job." Well, Dr. Flexner listened and later asked Peter Olitsky if he would take him on. Olitsky agreed and when Sabin returned from England he came to work at the Institute. God, he was a sight when he arrived. He wore tweed jackets and fancy vests and smoked a pipe. He was the most elegant dresser in the entire Institute, but, more important, he quickly showed that he was also capable of doing elegant work in the laboratory.[7]

[7] Dr. Peter Olitsky, who was Albert Sabin's chief at the Rockefeller Institute, gives this account of the hiring of Dr. Sabin:

Albert Sabin when he came to the Rockefeller Institute was less than 30 years of age; this may explain some youthful display of dress which amused Dr. Rivers. He was appointed during the autumn of 1934 as assistant but began his work in January 1935. He was advanced to associate in 1937 and left the institute in the autumn of 1939 to take on duties as associate professor of pediatrics at the University of Cincinnati. Thus he spent something less than 5 years in my laboratory.

A month or two before his arrival I was warned by several well-meaning persons, I presume, including certain ones in favor with the Lord and with men, that it was a mistake for me to accept him. The reasons given were nonsensical: one said he would appropriate for his use all the monkeys in the place! (What superiority over those who spend so much laboratory time on cross-word puzzles!) Others, including Dr. Rivers, pointed to personality problems, but none denigrated his work (except one who knew nothing about it). I had, however, my own opinion on his amazing genius, and having worked successfully with geniuses before, I was anxious to have him as an associate. The next few years showed the justification of my action, for what he produced was not just superior but brilliant ("elegant," Dr. Rivers says): working with infinite patience and most careful technique, precise planning, detailed and elaborate recording of observations, accurate measurements and, especially, an incisive analysis of a problem (and its corollaries) and skillful tests with rigid controls.

Perhaps there was one answer for the belief of his critics: he could see much further than they and could see whatever he looked at more thoroughly and clearly, and thus could promptly relate the significance of a problem to the world at large. In his forth-

Dr. Olitsky's laboratory at that time was working on problems related to local and general immunity in virus infections and paid particular attention to poliovirus and the viruses of equine encephalomyelitis. Sabin had had previous experience with viruses, and quickly became a productive member of Olitsky's team. Together with Olitsky, he worked on such problems as preventing polio infection in monkeys by chemical treatment of their nasal mucous membranes, and examining whether structural host factors in the peripheral and central nervous system of mice and guinea pigs influenced the invasiveness of certain neurotropic viruses. For instance, Olitsky and Sabin had found that, when they took a neurotropic virus and instilled it in the noses of young mice, that it progressed along the olfactory nerve to the olfactory region of the brain, giving rise in the end to a fatal encephalomyelitis. When they conducted like experiments with older mice, they found that the virus never went beyond the olfactory region of the brain, and was in fact blocked from proceeding further. These older animals, as far as I remember, never showed any clinical signs of disease. Sabin and Olitsky reasoned that the virus was arrested because of certain physiological and structural host factors, and that these factors varied with age and the species of animal infected. It was a nice piece of work and typical, I think, of the wide variety of work that went on in Dr. Olitsky's laboratory at this time.

The work I remember best of this early period was Dr. Sabin's and Dr. Olitsky's in vitro cultivation of poliovirus. I remember it because it was beautifully done and because it demonstrates again the role that chance plays in science.[8]

Sometime in 1935 or thereabouts, Dr. Olitsky's laboratory obtained from one of the New York hospitals a three- or four-month-old human embryo taken from a Caesarian section. Using tissue from the brain, cord, kidney, lungs, and liver of the embryo, Sabin and Olitsky prepared several different tissue cultures and inoculated them with a filtrate of the Institute's MV virus. They soon discovered that, while

right, confident manner, he would explain to them and, man being what he is, they would resent being given the answer by a tyro much younger than they (private communication).

[8] A. B. Sabin and P. K. Olitsky, "Cultivation of poliomyelitis virus in vitro in human embryonic nervous tissue," *Proc. Soc. Exptl. Biol. Med.*, vol. 34:357 (1936).

the virus multiplied readily enough in nervous tissue, it would not grow in the presence of nonnervous tissue. That work was so meticulously done that I believed it was absolutely correct. Hell, it was correct, and every working virologist that I know believed it, with the possible exception of John Enders at Harvard.

To this day, I don't know why John didn't believe that work. I suppose it's his nature. He is a great old skeptic who never believes anyone right off, and I expect he just didn't take this work as proved. In 1949 John made everybody sit up when he reported that he was able to grow poliovirus in nonnervous tissue. (I believe that he used the foreskins obtained from circumcision in his initial experiments.) I'll discuss John Enders' work at length later; for now, let me say that I read his paper over and over looking for a flaw. In the end I had to believe he was right. It wasn't easy, because I damn well knew that Olitsky and Sabin were also right. Hell, I saw their work with my own eyes—I watched them—and yet both couldn't be right.

By this time Sabin had moved to the Children's Hospital in Cincinnati, and so I went to Olitsky. "Look, Peter," I said, "I believe you and Sabin, but I can't disbelieve John Enders' results. There must be a reason for his findings. The only way I can figure it out is that the MV virus that you used in your experiments has mutated and become neurotropic. Why don't you find out if this is so?"

It wasn't a profound thought; it had occurred to other workers at the Institute and was discussed quite freely at lunch and elsewhere. In the end, Sabin, I believe, did investigate this problem and discovered that the MV virus, because of the very large number of intercerebral passages in monkeys, had become a variant that lacked the property of multiplication in nonnervous tissue.

Now this is an example of the role that chance plays in science. If Olitsky and Sabin had worked with another strain of poliovirus, the chances are that they would have been able to grow the virus in nonnervous tissue, and we would have had a breakthrough of major proportions in making a vaccine. As it turned out, we had to wait fourteen years for this particular breakthrough.

Q: Dr. Rivers, can you now tell me about Dr. Sabin's work on the pathology of polio?

Rivers: Yes. Actually Sabin did several very nice pieces of work on the pathology of polio, and all of them have one thing in common: they grew out of work that went on in Peter Olitsky's laboratory at the Rockefeller Institute. Let me begin by repeating that Dr. Simon Flexner had very early demonstrated that, when poliovirus was instilled nasally in rhesus monkeys, it entered the central nervous system by way of the olfactory nerves and bulbs. That experiment was accepted as conclusive, and it quickly became an article of faith among polio investigators, many of whom then assumed that the nose and respiratory tract were the portal of entry for the virus in man. Not everybody accepted this notion. Dr. Olitsky and a number of other investigators remained skeptical, skeptical enough to devise experiments to test the hypothesis.

In 1937 Dr. Olitsky and Dr. Sabin discovered, after a series of experiments performed in monkeys, that when polio invaded the central nervous system by pathways other than by the nose there were no pathological changes or lesions in the olfactory bulbs; they suggested that an examination of olfactory bulbs in human cases might resolve the problem of whether the virus had its portal of entry via the olfactory nerve.[9] In 1939 Sabin did an experiment which fortified him in the belief that the olfactory bulb was not necessarily the portal of entry for poliovirus in animals. A number of investigators, among them Lloyd Aycock of Harvard, had reported that, following tonsillectomies, several cases of bulbar polio had developed. Since little experimental work had previously been done on the tonsils and pharynx as a route of polio infection, Sabin decided to investigate this possibility experimentally. He soon found that, if he injected poliovirus into monkeys via the tonsillopharyngeal route, they came down with bulbar polio; however, in no such case was he ever able to detect poliovirus in the olfactory bulbs.[10]

Now, before I go on, I want to make a number of things clear. First, I want to underline the fact that it was unusual in most post mortems of human polio to examine the olfactory bulbs. They are not easily accessible in the skull and most pathologists overlooked them.

[9] A. B. Sabin and P. K. Olitsky, "The olfactory bulbs in experimental poliomyelitis," *J. Amer. Med. Assoc.*, vol. 108:21 (1937).

[10] A. B. Sabin, "Experimental poliomyelitis by the tonsillopharyngeal route," *J. Amer. Med. Assoc.*, vol 111:605 (1938)

Second, several years before Dr. Sabin examined the olfactory bulbs in human polio, one or two other investigators in the United States attempted such examination, but their findings were not conclusive. Indeed, if I am not mistaken, a year or so before Sabin published the results of his findings on olfactory bulbs in human polio, two Australian investigators, Dr. Charles Swan and Dr. Graeme-Robertson did a very careful study of the olfactory bulbs taken from polio victims of the 1937 epidemics in Australia.[11] They found that the olfactory bulbs were free from pathological changes and reached the conclusion that infection by the olfactory route in man was less common than had been previously thought. So far as I know, Sabin worked independently of the Australians and the fact that he did what others were doing should not take away from his accomplishment. The fact remains that he did his work beautifully and, after he published it, it became perfectly clear that the theory that the olfactory pathway was the usual portal of entry of the virus in man would have to be discarded.[12]

Sabin did one other piece of pathological work on polio which I think deserves to be mentioned because it too served as corroboration in ruling out the olfactory bulbs and respiratory tract as a portal of entry for the virus. When Sabin was at the Rockefeller Institute, he and Dr. Olitsky undertook to determine the pathways taken by neurotropic viruses within the central nervous system. It required meticulous pathological work and afforded good training for Sabin. In 1941, a little more than a year after Sabin moved to the Children's Hospital in Cincinnati, he determined to undertake a similar piece of work in relation to poliovirus. With the help of Dr. Robert Ward he began to trace the distribution of poliovirus in nervous and nonnervous tissue, chiefly I suspect as a way of determining the site from which the virus invaded the central nervous system and its mode of spread within that system. Using various tissues taken from the autopsies of polio victims, Sabin and Ward discovered that, next to the

[11] C. Swan, "The anatomical distribution and character of the lesions of poliomyelitis," *Australian J. Exptl. Biol. Med. Sci.*, vol. 17:345 (1930); E. G. Robertson, "An examination of the olfactory bulbs in fatal cases of poliomyelitis during the Victoria epidemic of 1937–38," *Med. J. Australia,* vol. 1:156 (1940).

[12] A. B. Sabin, "The olfactory bulbs in human poliomyelitis," *Amer J. Diseases Children*, vol. 60:1313 (1940).

central nervous system, poliovirus was to be found predominantly in the alimentary tract.[13]

I don't want to give the idea that Dr. Sabin was the only person at this time who did good work on the pathology of polio. As a matter of fact, we didn't get a complete picture of the pathology of polio in human beings until Howard Howe and David Bodian at Johns Hopkins completed their now classic work on the neuropathology of polio in the early 1940's.

Q: Dr. Rivers, didn't the National Foundation also support the work of Dr. Howe and Dr. Bodian?

Rivers: Yes they did, but you know it took several years before the Foundation was able to get them in the fold, and I am afraid that I was partly to blame for that state of affairs. Perhaps I ought to explain that last statement a little more fully. I believe that the first agency to support the work of Dr. Howe was the President's Birthday Ball Commission. In 1937, before the Commission shut up shop, Dr. Lester Evans, of the Commonwealth Fund, came to see me at the Rockefeller Hospital. "Tom," he said, "the President's Birthday Ball Commission is going out of business, and I think that we would like to take over one or two of their grantees—whom would you support?" I told him that if I were in his shoes I would go after Dr. Howe and Dr. Aycock—I may have mentioned somebody else but I don't remember now. Lester took my advice and for the next five years the Commonwealth Fund supported the researches of these people. When the Scientific Research Committee began to search for people to do research on the pathology of polio, my recommendation came home to roost, because we soon discovered that two of the best people in the country qualified to pursue such research were being supported by the Commonwealth Fund and had no need of a grant from us. Do you know what is most important in making a grant? I can tell you now that it is not only money; what's more important is having people who are capable of having ideas and doing the job. Hell, if it wasn't for the grant which the Foundation made to Johns Hopkins

[13] A. B. Sabin and R. Ward, "Natural history of human poliomyelitis; distribution of virus in nervous and non-nervous tissues," *J. Exptl. Med.*, vol. 73:771 (1941).

University in 1942, Dr. Bodian and Dr. Howe would probably still be supported by the Commonwealth Fund.

Q: Dr. Rivers, could you tell me about the genesis of the grant to Johns Hopkins University?

Rivers: I can, but before I do I think that I ought to clarify one thing—the grant went to the School of Public Health and Hygiene at Johns Hopkins and not to the Johns Hopkins Medical School. To my mind the person primarily responsible for the grant was Kenneth Maxcy.

Q: Dr. Rivers, before you tell me about the purpose of the grant I wish you would take a moment or two to tell me about Dr. Maxcy.

Rivers: Maxcy was in my class at the Johns Hopkins Medical School in 1915 and, as I mentioned earlier, he and I were assistant residents together on Dr. Howland's service way back in 1917. We were old friends and for that matter still are. After World War I, Dr. Maxcy joined the U.S. Public Health Service and soon made an international reputation by his work on murine typhus. In 1929 while studying an outbreak of typhus in South Carolina and Georgia, Maxcy came to the conclusion that the reservoir of the disease would probably be found in rats and mice and was probably spread to the human population by means of fleas or mites. The thing that stands out in my mind about this work is that Maxcy reached his conclusions on the basis of reasoning from the epidemiological data.[14] He himself did not mention the reservoir or vector. Later Hans Zinsser, while investigating an outbreak of typhus in Mexico, showed that the red flea was responsible for the spread of this separate variety of typhus. Maxcy's work paved the way and it was a classic. As a matter of fact, it is one instance where a single piece of work resulted in a man's being elected to the National Academy of Sciences.

In 1929 Maxcy left the Public Health Service and became a professor of preventive medicine at the University of Virginia. I don't

[14] K. F. Maxcy, "Typhus fever in the United States," *Public Health Rep.*, vol. 41:1735 (1929).

know how long he remained there—I believe that he moved out to Minnesota for a while—but in 1938 he joined the School of Public Health and Hygiene at Johns Hopkins as professor of epidemiology. It was in this capacity that he approached the National Foundation for a grant sometime during the fall of 1941.

Q: Dr. Rivers, can you give me the substance of Dr. Maxcy's proposals to the Foundation?

Rivers: Maxcy felt very strongly that, if a dent was ever to be made on the polio problem, it would be necessary to plan a comprehensive program which would not only study the spread of the virus in the human body but would study its distribution in the community as well. To achieve this end, he wanted to establish a permanent research center at the School of Public Health and Hygiene at Johns Hopkins that would devote itself to the study of polio and other virus diseases. The key to his plan was to gather a nucleus of research workers in pathology, anatomy, virology, and epidemiology and later, as the situation demanded, to add people from such collateral fields as biochemistry and physics. Maxcy was astute enough to recognize that, to get and keep such people, he would have to get enough funds to establish his center for a period of not less than five years. Today, in the era of large grants, it is hardly any news if a researcher asks for a half a million dollars for five years, but back in 1941 research grants were made on a year-to-year basis and were far more modest. It took courage for Ken to ask for a whopping grant on a five-year basis. I might add that it took just as much courage on the part of the National Foundation to give it to him. It certainly wasn't the style of giving grants for medical research at that time.

Q: Dr. Rivers, I have a host of questions to ask you. First, did Dr. Maxcy discuss these plans with you personally?

Rivers: You are damn right he did. Ken is no fool. He knew that eventually the proposal would come before the Virus Research Committee, and it was no secret that I was the chairman of that committee. There was and is nothing wrong with discussing ideas—it is one way that people have of clarifying thought—but I can tell you now that I could give him no indication of what would happen to his grant once it reached the committee. I could only speak for myself, and the important thing to remember is that the final decision for making or not making a grant did not rest with me. I talked with Ken about his grant proposal, and I didn't keep these talks secret from the Foundation. You can bet your sweet life that I kept them informed. I am sure that Ken did the same.

Q: How did the Johns Hopkins Medical School react to Dr. Maxcy's proposals?

Rivers: As I remember it, Louis Weed, who was then the director of the Medical School, and Lowell Reed who was dean of the School of Public Health and Hygiene, both thought highly of Maxcy's plan. The only snag in the beginning came from some of the Medical School faculty who were sore at the Foundation for discontinuing a grant which had previously been made to one of the orthopedists at the Medical School. I don't know why that grant was discontinued, because it was made by a different committee at the Foundation. I will say that it was one of those matters that was raised and then forgotten—it never really interfered in the negotiations between the Foundation and the University.

Q: Dr. Rivers, what was the reaction of the Foundation to the proposals?

Rivers: I think that it would be fair to say that from the beginning, Maxcy received a sympathetic hearing from various officials of the Foundation, particularly Mr. O'Connor. The biggest problem that Maxcy faced was in recruiting personnel or, to put it a different way, persuading the Foundation to give him a long term grant so that he could get the personnel he wanted. I would say that, from the outset, that Dr. Maxcy regarded Thomas Turner, Howard Howe, and David Bodian as the nucleus of his staff. There is no doubt in my mind that Ken felt that initially he and Tommy Turner would pursue the epidemiological problems relating to polio, while Bodian and Howe would concentrate on problems relating to the pathology of polio in the laboratory. It was a nice division of labor and a nice team.

Q: Dr. Rivers, can you give me some biographical data about the team?

Rivers: Well, let me tell you about Tommy Turner first. Tommy took his medical training at the Medical School of the University of Maryland, and very early in his career joined Johns Hopkins as an instructor in the Department of Medicine. I don't know how it happened, but he developed an interest in syphilology and early in the 1930's took a job with the International Health Division of the Rockefeller Foundation to study syphilis and yaws in the West Indies. I believe that he did a great deal of work among the Carib Indians. You know, some authorities maintain that the Carib Indians infected Columbus's crew with syphilis, and that was the way the disease was introduced into Europe. I don't know how accurate that theory is—I have my doubts—but let me say that when European settlers later reached North America, they sure as hell reintroduced the disease.

After completing his work with the Rockefeller Foundation, Tommy joined the School of Public Health and Hygiene at Johns Hopkins as a professor of bacteriology. I would say that Turner offered no problem to Dr. Maxcy since he was already a member of the School of Public Health and Hygiene. Actually at that time Dr. Turner was already under grant by the National Foundation to do a study of the distribution of polioviruses and their neutralizing antibodies in the population of the Eastern Health District of Baltimore. That area in Baltimore was an excellent place to do such research; for years it had served as a proving ground for public health problems for the School of Public Health and Hygiene, and its residents were accustomed to having medical investigators show up to take bloods and detailed medical histories. The war interrupted Dr. Turner's work, but you know eventually he showed that a very high percentage of the population in the Eastern Health District had neutralizing antibodies against the Lansing strain of poliovirus (type 2). I don't think we realized the meaning of that finding at that time, because we still didn't know how many types of poliovirus there were—although some investigators were beginning to suspect that there was more than one immunological type.

The real personnel problem Dr. Maxcy faced was in obtaining the services of Dr. Howe and Dr. Bodian. Dr. Howe at the time was an associate in anatomy at the Johns Hopkins Medical School, and had for a period of years prior to Maxcy's request done very creditable work in pursuing a neuroanatomical approach to problems of polio. In 1939 that approach bore splendid fruit when he joined forces with David Bodian. Howe is about nine or ten years older than Bodian, and I would like to say a few words here about the younger man, who is a most unusual scientist. Although I am going to say complimentary things about Bodian, I don't want anyone to get the idea that that means that Dr. Bodian and I haven't had our battles. Hell, we have had some dingdong fights, although I must say that, by nature, Bodian is a gentleman and not given to fighting the way I am.

Bodian was originally trained as an anatomist and took a doctorate in that field. After receiving his Ph.D. he went on to take an M.D. as well. His ability was very early recognized and the dean of neurologists in the United States, Dr. L. Judson Herrick, on more than one occasion in the thirties told me that, as far as he was concerned, Dave Bodian was the best neurologist of his age in the country. I am skipping ahead, but I don't think you would get any argument if you added that today there is no one in this country—or for that matter anywhere else—who knows more about the pathology of polio than Dave Bodian.

In 1939 Bodian came to Johns Hopkins as a research fellow and teamed up with Dr. Howe. Within two years they did a number of neuroanatomical and pathological studies of polio that established them as one of the important polio research teams in the country. For example, they helped work out the rate of progression of poliovirus in the sciatic nerve, and later discovered that axonal section was sufficient to make two different groups of highly susceptible nerve cells refractory to destruction by poliovirus. Some of their pathological studies were just as arresting. It was they who found that nonparalytic cases of polio could have as severe pathological involvement as paralytic cases, the difference being that in nonparalytic cases the destroyed motor neurones in the spinal cord were too scattered to involve a single functional muscle group sufficient to produce a noticeable functional loss. Perhaps one of the prettiest pieces of pathological work that they did was on the portal-of-entry problem in human polio. Here they confirmed Sabin's observations on olfactory bulbs and helped establish the alimentary tract as the region of virus proliferation, adding at the same time to our knowledge of the distribution of pathologic lesions in the motor cortex.

I don't know why I am telling you all this—all you have to do is to pick up their volume on *Neural Mechanisms in Poliomyelitis* and read for yourself.[15] It is a classic piece of work. My only regret is that much of this early wonderful work of Dr. Howe and Dr. Bodian was done under the auspices of the Commonwealth Fund—but please believe me when I say that they had enough glory left for the National Foundation. I am not exaggerating when I say that their later work was one of the important keys for our understanding of existing immunological types of polio, and that their laboratory played a singular role in the ultimate development of an inactivated polio vaccine. I will discuss this story in some detail later.

Q: Dr. Rivers, given Dr. Maxcy's idea for a research center and the investigative team he chose to carry on these researches, was there much difficulty in getting the grant through the Foundation?

Rivers: Lord, yes. I don't know how many conferences were held between Dr. Maxcy, Dr. Gudakunst of the Foundation staff, and myself. I will say this: it didn't take long for us to agree that it was necessary for people of the stature of Dr. Howe and Dr. Bodian to have job security and assurance that their research work would be supported and have continuity. To help things along, the Johns Hopkins Medical School assigned Dr. Maxcy lab space in the new Hunterian Laboratory building, facilitated the transfer of Dr. Howe from the Medical School to the School of Public Health and Hygiene, and appointed Dr. Bodian as an associate in neurology. Yet in spite of every-

[15] As an example of the fruitfulness of research of this team, see *Johns Hopkins Hosp. Bull.*, vol. 69, No. 2 (1941), which is given over completely to the work of Bodian and Howe. The papers in this issue were forerunners of the volume, *Neural Mechanisms in Poliomyelitis*, Commonwealth Fund, New York, 1942.

one's agreeing and wanting the grant, it took several months before the final agreement between the Foundation and Johns Hopkins was actually worked out. The basic problem that the Foundation faced was devising a formula for making a long term research grant that would be satisfactory to all parties. At that time there were few guides that could be used for making such a grant, and Mr. O'Connor was very conscious of the fact that such an agreement would probably serve as a model for other long term grants which the Foundation might make in the future. He took his time, conferred with people, and often argued with them. He is a damn good lawyer, and it is something that one might have expected him to do. I think that it is fair to say that the agreement which finally emerged was the product of many minds, both inside and outside the Foundation. I will say this: although it was carefully drawn and meticulous in defining the rights and obligations of the Foundation, the University and the researchers, it was nevertheless a surprisingly flexible agreement.

Q: Dr. Rivers, do you remember the substance of the agreement?

Rivers: Yes. In return for a grant from the Foundation of $300,000 for a period of five years, Johns Hopkins University agreed to establish a research center in the School of Public Health and Hygiene which would devote itself to the study of polio and other virus diseases. Administrative control of the new center was placed very firmly in the hands of the director of the center, and although it was a very legal document I want to tell you that there were no ifs, ands, or buts, that all the research undertaken by the center was to be determined solely by the director of the center and his associates. In other words, neither the Medical School nor the Foundation could tell them what to do. It was and is an excellent principle. To maintain liaison between the new research center and the Foundation, a special committee composed of Mr. O'Connor, Dr. Morris Fishbein, Dr. George Ramsey, and myself was created. As I remember, our only real function was to look over the yearly budgetary requirements made by the new research center and to give advice if called upon. Actually the controls set up to police the long-term grant were no different from those established for the smaller yearly grants. In other words, the grantee had to set out clearly what the purpose of his research was, make progress reports of his work, and render a semiannual accounting of expenditures. The one big difference was that the new research center could not submit a budget of more than $75,000 for any one year.

Looking back at this first long-term grant, I would say that it had one basic flaw—namely, giving a set sum of money to be spent in a five-year period. It didn't take the Foundation too long to recognize that it was difficult for a researcher to project his needs very accurately over a period of five years. Hell, in any given year things might open up and he might need three or four times the amount of money actually allotted to him; and while the original sum granted might seem quite large by absolute standards, it could easily be a straightjacket for an investigator with a hot lead. Mr. O'Connor is a hard-headed lawyer, and he generally doesn't let contracts get broken very easily, but he does know which way is up, and when this flaw became apparent the Foundation developed a new way of making long-term grants.

Dr. Harry Weaver, who became director of research at the Foundation after World War II, was chiefly responsible for working out this new technique—it is one, I might add, that the Foundation still uses. Under the new system the long-term grant is essentially a guarantee of the salaries of key personnel in a given laboratory for a period of from three to five years. Each year, quite apart from this grant, such a laboratory can make application to the Foundation for an expediting grant. The expediting grant is made on a yearly basis and takes care of such items as lab supplies and equipment, laboratory technicians, animals, and so on. Its size actually depends on what is going on in the lab at the time. If a lab needs $100,000 it can ask for $100,000, if it needs but $30,000 it can ask for $30,000. The virtue of the expediting grant from the Foundation's point of view is that it gives the committee making the grant a chance to take a look at what is actually going on in the lab, and to make their evaluation on hard current needs, rather than on nebulous projected ones.

Now, if an expediting grant is cut off—as sometimes happens—each of the men on long-term grant has a chance to call on a fund of $2,000 which is kept aside for him, so he can finish a given piece of work. Today the government makes it easier for everybody by giving laboratories $100,000 a year for ten years and the lab can do what it wants. Hell, that's nice but I don't think that it's the right way to give away money.

Q: Several months before the School of Public Health and Hygiene at Johns Hopkins requested a grant from the Foundation to set up a research center to study polio and other virus diseases, a similar request had been made by the School of Public Health at the University of Michigan. Can you tell me how that grant request came to be made?

Rivers: I don't know the genesis of this grant although I suspect it originated in talks between Paul de Kruif and Henry Vaughan who at that time was the commissioner of health of the City of Detroit. Sometime in 1940 the University of Michigan received a considerable grant of money from the Kellogg Foundation and the Rockefeller Foundation to establish a school of public health at the University of Michigan Medical School. The Medical School had long had an excellent reputation and there had been people at Michigan who had made considerable contribution to the field of public health. For instance, Dr. Victor Vaughan the father of Henry Vaughan who served as dean of the University of Michigan Medical School until 1921, was a distinguished figure in the American public health movevment almost from its inception to his death; Dr. Frederick Novy of the Department of Bacteriology had trained I don't know how many generations of bacteriologists, and Dr. Nathan Sinai had even at that time made a considerable mark on problems of medical care. There were others, but these are three who immediately come to mind.

Paul de Kruif, being a loyal graduate of the University of Michigan and knowing Dr. Henry Vaughan very well, fell in with an idea to establish a virus laboratory at the new school of public health. As I say, I don't know who exactly originated the idea; all I know is that in the spring of 1940 the Scientific Research Committee received an application from Dean Furstenburg of the University of Michigan Medical School for a grant, in his words ". . . to establish and maintain a permanent central laboratory of virology where specimens from all parts of the United States may be sent for study and comparison;

to conduct fundamental investigations primarily in the field of infantile paralysis; to develop methods and provide facilities for the epidemiologic studies of infantile paralysis in the field; to train virologists." [16]

Q: Dr. Rivers, before you go on, since this application was made prior to the one made by Dr. Maxcy, might I ask whether this was the first time the notion of such an independent laboratory had come up? [17]

Rivers: No, it had been discussed before. Actually, it was something that was in the air. At this very time, in New York, I was helping to establish the Public Health Research Institute, an organization that I am happy to say has since taken an important position in virus research in the country. (I'll have more to say about this laboratory later.) There were members on the committee—and I'll admit that initially I was one of them—who thought that it might be a good idea for the National Foundation to establish its own independent research laboratories, rather than to have one associated with a school of public health at Michigan. I thought it would be handier to have it in New York and, if I remember correctly, even made the suggestion that such a laboratory seek a connection with the New York University. Now that idea persisted and came up a number of times during the early years of the Foundation. Just after World War II the notion of an independent virus institute was argued very cogently by Dr. Reuben Gustavson who was then chancellor of the University of Nebraska. Dr. Gustavson felt that investigations of infantile paralysis were handicapped by the fact that men who were interested in certain aspects of the disease were not trained to undertake more fundamental studies involving basic physics, biochemistry, electron microscopy, and so forth. It was his impression that more could be gained by creating a "virus institute" where all phases of the problem could be attacked simultaneously—especially if the institute were associated

[16] A. C. Furstenberg to Basil O'Connor, May 1, 1940 (CRBS #22, University of Michigan, 1940, National Foundation Archives).

[17] See here, especially, Minutes of the Virus Research Committee of The National Foundation for Infantile Paralysis, May 13, 1940, where the question of creating an independent virus laboratory is discussed.

with a university that was strong in the basic sciences. As I remember, he suggested the University of Chicago as a likely place.

Well, we argued the question backward and forward, and Dr. Henry Viets, who at that time acted as personal advisor to Mr. O'Connor, finally put the idea to rest. He very forcefully pointed out that the National Foundation was at that time supporting most of the virus research in the United States, and that if a virus institute were founded the Foundation would have to use grantees that it was already supporting to staff it. He felt that it was a better idea to support such workers in their own labs, in the hope that, by spreading its money among various top-notch institutions, the Foundation would avoid the stultification that sometimes comes in research because of ingrowth in a particular institution. I have had more than one fight with Henry Viets in my time, but on this issue I feel that he was right and that we made the right decision not to establish an independent virus institute.

Q: Dr. Rivers, to get back to the University of Michigan, were there any problems associated with giving the grant?

Rivers: I think that the first problems that we faced were the problems of who was going to run the laboratory and what rank he was going to hold in the school. Well, the latter question wasn't too difficult, because we initially agreed that the director of the lab should hold the rank of either associate professor or professor. The question of getting a fellow to direct the laboratory was much more difficult, and the University of Michigan agreed to let the Foundation beat the bushes for a qualified virologist, subject in the final analysis to approval by university authorities. The Foundation appointed Paul de Kruif, Charley Armstrong, and myself to look for the guy. I want to tell you, it wasn't an easy job.

The first fellow we went after was Herald Cox. Dr. Cox had earned a Doctor of Science degree at the School of Public Health at Johns Hopkins—I want to stress that it was an earned degree; not an honorary one; there is a helluva difference—and came to work early in his career at the Rockefeller Institute. He worked in Dr. Olitsky's lab and got a wonderful training in doing experimental work with various viruses including polio. If I am not mistaken, Dr. Olitsky and Dr. Cox were among the first to try out chemical blockade as a prophylactic measure for polio in this country.

About 1936 Dr. Cox left the Institute and took a post as bacteriologist with the U.S. Public Health Service. While serving at the laboratories in Hamilton, Montana, he recovered a rickettsia from a tick that caused Q fever. Prior to the time that Cox isolated his agent, it was thought that Q fever was restricted to Australia; however, Cox demonstrated that it had a wider geographic distribution than had hitherto been thought. For his part in the discovery, that rickettsia today is called *Coxiella burnetti*. Originally it was simply called *Rickettsia burnetti* after Frank Burnet who helped classify it as a rickettsia.

Cox, as I say, was a very attractive candidate and I wasn't the only one who thought so; Charley Armstrong thought so and so did the Public Health Service. I don't know for sure, but I think they pressured him to stay. In the end, Cox turned us down because he wanted to complete the studies on rickettsia which he had begun the year before. We just happened to have come at the wrong time.

Q: Whom else did you go after?

Rivers: The fellow I wanted very badly was one of my old boys, Dr. Jerome Syverton. In 1935 Jerry left the Rockefeller Institute to join George Berry at the University of Rochester Medical School, as an associate professor of bacteriology. I knew what Jerry could do from his work with me [18] and with Peter Olitsky, and I was satisfied with his development. Although he was then only 33, I supported him very strongly. In the end the boys at Michigan turned him down, largely, I suspect, because Jerry held out for a full professorship and they felt a young fellow that age shouldn't be a full professor. Jerry's subsequent development as a virologist, I think, shows that he warranted the confidence I had in him.

[18] Dr. Syverton never worked in Dr. Rivers' laboratory. The slip is, however, indicative of the high regard Rivers had for Syverton. During his tenure at the Rockefeller Institute, Syverton worked under Peter Olitsky.

Q: Dr. Rivers, the first candidates that you mentioned have one thing in common: both are alumni of the Rockefeller Institute. In your search for a director, did you incline toward people who had been trained at the Institute?

Rivers: Not at all, not at all. Oh, I know what you are thinking, but bear in mind that in 1940 there weren't many trained virologists in the United States who were capable of taking over the directorship of a new virus laboratory. Senior investigators already had jobs, and it just so happens that many of the younger people with a lot on the ball were trained at the Rockefeller Institute. This doesn't mean that we didn't consider people from other institutions—we did. As a matter of fact, very early in our search for a man, Henry Vaughan on his own wrote to John Gordon at the Harvard Medical School and asked him for likely candidates. That was a good move. Harvard had a first-rate bacteriology department and had long been interested in virus disease. In the spring of 1939 the Harvard Medical School had a bang-up meeting on virus and rickettsial diseases—it was so good that later the proceedings were published as a book and for a long time afterward served as a text.[19] Well, Dr. Gordon got in touch with Hans Zinsser and Hans recommended two fellows who were then working in his setup—LeRoy Fothergill and John Enders. As I remember, Hans wrote that if we wanted someone who had clinical experience we should go after Fothergill, but that John Enders was more ingenious in the lab.

Dr. Vaughan wanted a lab man and so he invited Enders out to Ann Arbor. Enders was then 43 years old, and I want to tell you that he made quite an impression. Vaughan wanted him, but in the end John wouldn't come. I believe that the main reason he turned the post down was that he felt that the major policy of the laboratory would be decided by the School of Public Health, and that the laboratory would essentially be a practical lab and serve under epidemiology, and that he wouldn't have a chance to develop his theoretical work. I also believe that there was an unspoken reason.

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

John is a hidebound, rockbound, every-other-kind-of-bound New Englander, and I think nothing less than a charge of dynamite is ever going to loosen him from that part of the country. He just likes where he was born and brought up.

Q: Dr. Rivers, some correspondence I have seen suggests that you weren't too enthusiastic about Dr. Enders at that time.[20]

Rivers: Yes, I would have to say that that is true. To be sure, it would be very nice to say that I recognized from the beginning that John Enders was a genius in the laboratory and would in time win a Nobel prize. Hans Zinsser had such high regard for John, almost from the time he came to work in his lab, but I didn't, and I will tell you why. John had his own means and could literally do just what he wanted to do—and if he wanted to be casual he could be. I just didn't know how much self-discipline he had. In his early days as an investigator, I don't think that John was as industrious as he is today. If he was, God knows I didn't know it, and I know he is industrious now.

Q: Dr. Rivers, was the committee disappointed when Enders turned the job down?

Rivers: Yes, we were. At that point Karl Meyer wrote to us and suggested that we consider John Kessel for the post. Dr. Kessel was in many ways a good suggestion; he was a professor of bacteriology at the School of Medicine of the University of Southern California, and had done considerable research on problems of polio. As a matter of fact, the National Foundation had early supported his research, and as chairman of the Scientific Research Committee I personally approved many of the grants made to him. I must say, however, that I opposed his selection as director, because I had the feeling that Dr. Kessel never quite finished a piece of work. Perhaps I am being unfair because you know, on more than one occasion Dr. Kessel came near to making a number of basic observations about the nature of poliovirus.

[20] See, especially, T. M. Rivers to Basil O'Connor, June 13, 1940; Donald Gudakunst to Henry F. Vaughan, July 22, 1940 (CRBS #22, University of Michigan, 1940, National Foundation Archives).

For instance, he was one of the first—along with investigators in Australia, Howard Howe and David Bodian in Baltimore, and Trask and Paul at Yale—to suspect that there was more than one immunological type of poliovirus. Although he pursued the question diligently he always seemed to come up against a blank wall.

You know, too often we tend to forget the obstacles that many of the early investigators of poliomyelitis faced. First, practically everybody believed that there was only one immunological type of polio. Challenging an accepted idea is hard enough, but this particular idea also contributed to careless lab practice. Up until about 1940, the only animal you could use in polio experimentation was the monkey. It was an expensive animal, and many investigators, in order to cut costs, would sell their monkeys to dealers if they survived given experiments and appeared hale and hearty. The dealers, in turn, would resell the monkeys to other laboratories. Under such conditions, an investigator could buy a monkey from a dealer and have no reason to suspect that the animal had ever even seen a poliovirus when, in fact, it may have had all three types of poliovirus. And how was one to know at that time which type or combination of types it had had? No one knew about types. You can imagine how cockeyed some of the experimental results were, and they were cockeyed! I think that some of Dr. Kessel's early experimental misfortunes came from using monkeys that had previously been used in polio experiments. Today it's easy enough to understand what happened; at that time I didn't know, and I'll admit I had a down on Dr. Kessel.

Q: Dr. Rivers, I wonder if part of that down was also due to the rivalry of the Hooper Foundation and the Rockefeller Institute.

Rivers: Oh, I'll admit that there was rivalry between boys on the west coast and boys on the east coast. Sure, but I really don't think that it played as significant a role as your question seems to imply. I think we gave a fair shake to both coasts in our search for candidates. There just weren't that many qualified virologists around. Hell, at one point we even made a concerted effort to get Ernest Goodpasture from Vanderbilt, but he turned us down flat. I guess we would still be looking if I hadn't thought of Tommy Francis.

Q: Dr. Rivers, what brought Dr. Francis to your attention? What were his qualifications for this particular job?

Rivers: I knew Francis very well and I liked him and the work that he did. Tommy is an M.D., and received his medical training at the Yale Medical School. In 1928, after an interneship and residency at the New Haven Hospital, he came to the Rockefeller Hospital. He was then interested in respiratory disease, and that interest brought him to Dr. Avery's laboratory, which was almost exclusively concerned with problems relating to the pneumococcus. Dr. Francis, like any young doc in the Hospital, had many clinical duties but in a very brief period he demonstrated to anyone who was looking that he was no slouch in the lab. Together with Bill Tillett, who had earlier worked with me, Dr. Francis helped delineate the role played by type-specific polysaccharides in pneumonia immunity. In 1933 when Patrick Laidlaw, Wilson Smith, and Christopher Andrewes found the virus that produces human influenza, I said to Tommy. "Look, Francis, there are a hell of a lot of guys in this country who are working on pneumococcus, but nobody, as far as I know, knows anything about human influenza. Why don't you jump on the virus bandwagon fast and get to work on human influenza?" Well, I worked on him for a while and, when I thought I had convinced him, I went to see Dr. Cole and urged that Francis ought to be allowed to try his hand at investigating human influenza. Dr. Cole thought the idea a good one and provided Francis with a lab in Founders Hall. In a very short time—a year at most—Francis confirmed the results of Laidlaw, Smith, and Andrewes, by successfully infecting ferrets with a strain of virus recovered from influenza patients during an epidemic in Puerto Rico. (This is the famous PR-8 strain.) I need hardly add that that confirmation was of great help in establishing the viral nature of human influenza.[21]

[21] Dr. Francis makes the following observation on Rivers' comments:

I asked Dr. Rivers to come see Dr. Cole with me because I wanted to look for a virus which I suspected was a precursor of pneumococcal lobar pneumonia, and that was the work I began in 1933. I used ferrets, and the influenza material which led to isolation of PR-8 virus came about through Dr. Wilbur Sawyer of the Rockefeller Foundation, to whom it had been reported that there was an epidemic in Puerto Rico (private communication).

Soon after he completed this work, Francis did an even neater trick—he successfully passed human influenza to mice and, by so doing, made available an animal obtainable in large numbers for experimental purposes. Well, that about opened the door. Through the use of the mouse, it became possible to type strains of influenza virus recovered from very widely separated parts of the world. For instance, Francis was the first to show that Puerto Rico, Philadelphia, and English strains of human influenza virus were serologically alike. Together with Dick Shope, he was then able to demonstrate that, although swine influenza virus was serologically distinct from human influenza virus, if you repeatedly inoculated a mouse with human influenza virus, the serum of that mouse might develop the capacity to neutralize swine influenza virus as well. I cite all this early serological work on human influenza virus because, in 1940, it culminated in Francis's isolating a human influenza virus which was totally unrelated immunologically to the earlier type A viruses. Dr. Francis designated this new type as type B, and he soon proved that it too was capable of causing widespread outbreaks of influenza in man. This particular work was exceptionally important, because it made investigators aware of the presence of two immunologically unrelated types of human influenza virus—a factor that was a key in the consideration of any immunization program to control epidemic influenza. I think you can see from this why I was excited about Tommy Francis.[22]

Q: Dr. Rivers, at the time you suggested Dr. Francis for the Michigan post, was he still at the Rockefeller Hospital?

Rivers: Lord, no! In 1936 the International Health Division of the Rockefeller Foundation indicated that they wanted to take over on a

[22] For details of some of the early important work engaged in by Dr. Francis and his associates on problems of influenza, see T. Francis, Jr., "Transmission of influenza by a filterable virus," *Science*, vol. 80:457 (1934); T. Francis, Jr., and T. P. Magill, "Antigenic differences in strains of human influenza virus," *Proc. Soc. Exptl. Biol. Med.*, vol. 35:463 (1936); "Antigenic differences in strains of epidemic influenza virus. 1. Cross neutralization tests in mice," *Brit. J. Exptl. Pathol.*, vol. 19:273 (1938); T. Francis., Jr., and R. E. Shope, "Neutralization tests with sera of convalescent or immunized animals and the viruses of swine and human influenza," *J. Exptl. Med.*, vol. 63:645 (1936); T. Francis, Jr., "A new type of virus from epidemic influenza," *Science*, vol. 92:405 (1940).

large scale the influenza studies begun by Dr. Francis at the Institute and asked Dr. Cole if he would release Dr. Francis to their setup at the Institute. Dr. Cole agreed, and Tommy moved over to the laboratories of the Rockefeller Foundation. Two or three years later, the New York University Medical School invited Dr. Francis to join their staff as professor of bacteriology. When I asked Tommy if he would take the job at Michigan, he was a professor at New York University Medical School.

Q: How did Dr. Francis react to the offer?

Rivers: Almost the first thing that happened was that Tommy came to see me at the hospital. I can still see him pacing back and forth in my office. He had qualms—partly it was his nature, because as far as personal things go Tommy is a fella who just hates to make up his mind; the other was the qualm of leaving a job that was running smoothly and taking on a new kind of a job, as professor of epidemiology. Like John Enders, Francis was worried about having the lab as an arm of the School of Public Health and wondered how much time he would have for independent research. He indicated to me in no uncertain terms that he didn't want to be tied down to polio. Well, I was in no position to tell him how much Dr. Vaughan would try to boss him because I didn't know. But I could tell him that the Foundation never tied anyone down exclusively to polio research.

Q: Dr. Rivers, I wish you would explain that last point in greater detail.

Rivers: When the National Foundation first started its work, it was difficult to find people who knew how to do polio research or were even interested in doing such research. I think that it is fair to say that, in large part, such research had been usurped by Dr. Flexner and the Rockefeller Institute. To be sure, there were others but they were just a handful and often their work was hampered by the fact that they couldn't afford the monkeys so necessary to experimental work. Monkeys were damned expensive and the cost discouraged more than one investigator. Even in the late thirties we actually knew very little about the nature of poliovirus. To be sure, a number of interesting leads were opening up, but they were tentative; often we didn't know what question to ask. Many virologists when faced with an insoluble question with one virus frequently would turn to another virus about which they might know a little bit more, to see if they could get any insights into the problem they faced. Dr. Olitsky's lab at the Rockefeller Institute, for example, not only worked with poliovirus but extended their investigations to other neurotropic viruses for precisely this reason, and I might add that they were not the only ones.

As chairman of the Scientific Research Committee I had a certain amount of influence with Mr. O'Connor—I think that other people did too, Karl Meyer, for example—and from the beginning I tried to tell him that sometimes it was necessary to go clear around the barn in order to get an answer in virus diseases. I made it plain that, if we wanted answers to problems in polio and they were not forthcoming, it might be to our advantage to study related viruses where we had better information and techniques. You know, on more than one occasion, Theobald Smith said that the good research man was the man who knew how to ask the right questions of nature. Albert Einstein expressed the same thought by saying that a great hypothesis was frequently of more importance than its proof. He himself proposed the theory of relativity but never proved it. Actually, some ten years after he proposed his hypothesis, a group of British scientists proved it. Now, I don't know the name of those scientists, and I am willing to bet that you don't either. The point is that it is no mistake, because we rightly honor the fellow who proposed the theory rather than the fellows who did the proving. It is not that the latter work is not scientifically important; it is, it is just less important than the hypothesis. Asking the right question is the key to understanding in science.

During the late thirties, we had to learn how to ask the right questions of poliovirus. In part, we learned from an examination or investigation of other neurotropic viruses, and I believe that it is to Mr. O'Connor's credit that he understood the necessity for the Foundation to support such related research. If you look at some of the early grants made by the Foundation, you will find that they were not made for polio alone but for polio and related viruses. The prime example that comes to mind is the grants made to Dr. Karl Meyer's lab at the Hooper Foundation. Originally those grants were made to study the epidemiology of poliomyelitis in the western states. However, when it became apparent that the diagnosis of polio cases was made difficult by the coexistence of epidemic encephalitis, the grant was broadened to include epidemiological studies of other neurotropic viruses rather than polio alone.

In research you have to be prepared to go anywhere, and I want to tell you that Dr. Meyer and his boys and girls—the team included Bill Hammon, Beatrice Howitt, and Bill Reeves—did a bang-up job in working out the epidemiology of western equine and St. Louis encephalitis. It wound up with all of us learning through their work that western equine encephalitis was transmitted from bird to bird by mites, and from birds to horses and men by mosquitoes. (That's true of eastern equine encephalitis, as well as of St. Louis encephalitis.) It was beautiful, beautiful work; yet the chances are that, if we had had a lot of people asking us for money for polio research, we would probably have given it to them in preference to giving it to Dr. Meyer. In the end, the work of Dr. Meyer's team not only made it easier to make a differential diagnosis between epidemic poliomyelitis and epidemic encephalitis, it also trained a good many people in the fundamentals of virology. I am proud that the Foundation supported this early work in encephalitis—it was some of the prettiest work done under Foundation support.[23]

[23] See also W. McD. Hammon, B. N. Carle, and E. M. Izium, "Infection of horses with St. Louis encephalitis virus, experimental and natural," *Proc. Soc. Exptl. Biol. Med.*, vol. 49:335 (1942); W. McD. Hammon, and B. F. Howitt, "Epidemiological aspects of encephalitis in the Yakima Valley, Washington; Mixed St. Louis and western types," *Amer. J. Hyg.*, vol. 35:163 (1942); W. McD. Hammon, W. C. Reeves, B. Brookman, and E. M. Izium, "Mosquitoes and encephalitis in the Yakima Valley, Washington. I. Arthropods tested and recovery of western equine and St. Louis viruses from *Culex tarsalis coquillet*." *J. Infect. Diseases*, vol. 70:263 (1942); W. McD. Hammon, W. C. Reeves, and E. M. Izium, "Mosquitoes and encephalitis in the Yakima Valley, Washington. II. Methods for collecting arthropods and for isolating western equine and St. Louis viruses; IV. Summary of case against *Culex tarsalis coquillet* as a vector of the St. Louis and western equine viruses," *J. Infect. Diseases*, vol. 70:267, 278 (1942); B. F. Howitt, and W. Van Heinck, "Relationship of the St. Louis and the western equine encephalitic viruses to fowl and mammals in California," *J. Infect. Diseases*, vol. 71:1179 (1942). These papers are but a sample of the work done by Meyer's laboratory on the problem of encephalitic viruses, under grant of The National Foundation for Infantile Paralysis.

Now, that kind of far-ranging support for Dr. Meyer's lab was not an isolated case. For instance, when Dr. Margaret Smith began her work under Foundation grant, she studied the development of neutralizing antibodies in mice to Lansing strain poliovirus and ended by studying the transmission of St. Louis encephalitis virus by chicken mites.[24] It didn't matter one bit to the Scientific Research Committee; the important thing was that it furthered our understanding of neurotropic viruses. Actually, Dr. Francis didn't really have to worry that the Foundation would restrict him to epidemiological studies and poliovirus. To be sure he has done such studies, but the Foundation has also supported him in investigations designed to explore the relationship between chemotherapy and virus disease. So I wasn't wrong in the advice I gave Tommy. Everybody benefited when he moved to Michigan—the University, the Foundation, and Tommy.

Q: Did Dr. Francis's laboratory have any particular problems in getting under way?

Rivers: None that I remember. Although Tommy Francis started his laboratory from scratch in 1940, within a year it was doing excellent work in the epidemiology of polio—tracing the dissemination of the virus in particular communities and examining the incidence of family outbreaks in the midwest. In addition to this work, he set up a first rate program for training young virologists. The work went so well that in the spring of 1943 the Foundation awarded Francis a grant of $120,000 for a period of three years. I would like to add that the model for that grant was the one that had been worked out earlier for Dr. Maxcy's group at the School of Public Health and Hygiene at Johns Hopkins. A short time later, it was used again for a grant made to the Yale polio laboratory. As for problems, the only problems Dr. Francis had during these early years was with his monkeys, many of whom died of TB. The lack of healthy monkeys to work with interfered with his laboratory programs—not enough to stop him, but enough to gray him a little or develop an ulcer.

[24] M. G. Smith, R. J. Blattner, and F. M. Heys, "Further isolation of St. Louis encephalitis virus: Congenital transfer in chicken mites," *Proc. Soc. Exptl. Biol. Med.*, vol. 59:136 (1945).

Q: Dr. Rivers, I am glad you mentioned the Yale polio laboratory because many of the important epidemiological observations of polio in our own time have come from this unit. I wonder if you would mind speaking with me about them.

Rivers: I don't mind. I am very fond of Dr. John Paul and the boys and girls in his laboratory.

Q: Dr. Rivers, I think that you will agree with me that one of the early key figures in the Yale polio laboratory was the late Dr. James Trask. Could you give me your impressions of Dr. Trask?

Rivers: Dr. Trask was slim, walked straight, and was addicted to wearing derby hats which made him stand out. He would have stood out in other ways. He was an odd looking man, and when you looked at him you couldn't help feeling that he didn't have any sense at all, that he was a dumbbell. Now the truth is that Dr. Trask was anything but a dumbbell. He was as sharp minded an investigator as you would ever want to find, and he was possessed of a good deal of courage. Early in his career he had worked at the Rockefeller Institute with Francis Blake, and together they had done the classic piece of work on measles that I mentioned earlier. When Dr. Blake left the Institute to go to Yale as a professor of medicine, Dr. Trask went with him as an assistant professor of medicine. He remained in Dr. Blake's department for several years, and later, sometime around 1926 or 1927 shifted to the Department of Pediatrics under Dr. Grover Powers, where he took charge of the infectious disease service. I don't know the reason for the shift, but Dr. Trask remained in the Pediatric Department until his early tragic death in 1942 in an army camp somewhere in the midwest. Just let me add here that, for his contributions to our understanding of polio, a victory vessel was named in Dr. Trask's honor during World War II.

You know, you really can't speak about Dr. Trask without speaking of Dr. John Paul, because many of the early polio investigations at Yale were done under the joint auspices of Trask and Paul. Paul was entirely different from Trask. He was and is conventional—he dresses like everybody else and, as far as I know, has never worn a derby hat in his life. Dr. Paul is a graduate of the Hopkins and very early had a deep and abiding interest in pathology. I would say that much of his early career in medicine was devoted to pathology. After graduation from the Hopkins Paul went to the University of Pennsylvania Medical School where in time he became director of the Ayer pathological laboratories. In those early years he was more concerned with rheumatic fever than he was with poliovirus. I don't think that I am far from the mark when I say that he didn't become interested in viruses until he came to Yale and teamed up with Trask in forming the Yale polio lab sometime around 1931. Dr. Paul worked in the Department of Preventive Medicine.

Q: Dr. Rivers, can you give me some account of the kind of work that Dr. Trask and Dr. Paul were engaged in?

Rivers: I don't think that I can do it justice by a summary from memory, but since you ask I will make the attempt. Please keep in mind that what I am about to say is a summary and that I have forgotten many things, although at one time I followed the work of Dr. Paul and Dr. Trask very closely. Let me begin by saying that during the first two decades of this century much of the polio research that went on in the United States was of a laboratory variety, devoted to producing experimental polio in monkeys. I think that it is fair to say that by 1930, although we knew a hell of a lot about polio in monkeys, we didn't know very much about the disease in human beings. This, however, is not to say that there wasn't any good epidemiological work that had been done on human aspects of the disease—there was. As a matter of fact, Dr. Charles Caverly in Vermont and Dr. Wade Frost of the U.S. Public Health Service had both done classical epidemiological work on polio.[25] What I am trying to say is that the

[25] Rivers' reference here is to Charles S. Caverly, President of the Vermont State Board of Health who in 1894 wrote the first report on epidemic poliomyelitis in the United States. All of Caverly's papers on poliomyelitis have been reprinted in *Infantile Paralysis in Vermont 1894–1922: A Memorial to Dr. Charles S. Caverly*, Burlington, Vermont, 1924. Wade Frost was one of the pioneers in the U.S. Public Health Service who early devoted himself to the study of the epidemiology. See W. H. Frost, "Epidemiologic studies of acute anterior poliomoyelitis, I. Poliomyelitis in Iowa, 1910; II. Poliomyelitis in Cincinnati, Ohio, 1911; III. Poliomyelitis in Buffalo and Batavia, N.Y., 1912," *Hyg. Lab. Bull.* No. 90, 1913.

majority of people who did research in poliomyelitis during this early period had gotten away from human beings. It is to Dr. Trask's and Dr. Paul's credit that they went back to the human patient, and, beginning with the Connecticut epidemics of the early 1930's, began investigations designed to learn about the nature of polio virus and the various clinical circumstances under which it could be found.

I would like to say here, and I don't think that Dr. Paul would dispute this point with me—you might check with him later—that both he and Dr. Trask were much influenced in their point of view by the work of the great Swedish epidemiologist Dr. Ivar Wickman. Dr. Wickman's work was well known in the United States; and although it was originally done about 1905 or 1906 a translation in English had appeared in the United States before World War I. Dr. Wickman, for example, early held that polio was conveyed from person to person by those afflicted by an abortive type of polio or by healthy persons who carried the virus without ill effect. He supported these contentions by working out the foci of the spread of the disease in the school epidemic of 1905 in Sweden.[26] Dr. Paul and Dr. Trask did not forget this work, and during the Connecticut epidemics they paid very close attention not only to the paralytic cases that occurred in given families, but also to the minor illnesses in those families that had been passed off by doctors as colds, tonsillitis, grippe, or what have you. In a very brief period, by means of isolation of virus and antibody tests, Dr. Paul and Dr. Trask identified these so-called minor illnesses as examples of subclinical polio infections. Quite apart from the importance of these studies in charting the incidence and distribution of polio in various Connecticut communities, I believe that it was these immunological studies which led Dr. Trask and Dr. Paul to suspect that there was more than one immunological strain of poliovirus. It's easy enough to say now, but it was not easy to say this in 1933 or 1934 because orthodox opinion, led by Dr. Simon Flexner at the Rockefeller Institute held precisely the opposite point of view. I might add that it wasn't easy to fight with Dr. Flexner, because few could challenge his authority in the field of polio. Hell, he was *the authority*.

Oddly enough, I believe that both Trask and Paul were fortified in

[26] I. Wickman, *Acute Poliomyelitis*. Nervous and Mental Disease Monograph Series, No. 16. New York, 1913.

their belief of the multiplicity of polio strains because of a piece of research that they did with Leslie T. Webster under the auspices of the Rockefeller Institute on the "so-called" polio epidemic of 1934 in Los Angeles, California. I say "so-called" because, while it is true that a strain of polio was eventually isolated from the cases studied in that epidemic, the likelihood today is that that particular epidemic was caused by either a Coxsackie or an ECHO virus. (At that time of course we had not yet developed the technique of identifying Coxsackies through passages in infant mice, and we were at least 15 years away from using tissue cultures in identifying ECHOs, so there is no way of really knowing today what kind of an epidemic it was.) There was relatively little paralysis during this particular epidemic, and I remember that some docs even thought it was a diphtheria epidemic. While Dr. Trask and Dr. Paul were out in California, they paid a great deal of attention once more to abortive cases of polio in family groups and sharpened their immunologic techniques of isolating virus and doing antibody tests.[27]

Q: Dr. Rivers, besides this work on the epidemiology of abortive polio in human beings, and the work that led to an understanding that there was probably more than one immunologic type of polio virus, didn't Dr. Paul and Dr. Trask do one other piece of work that was important for the understanding of how polio passed from one individual to another?

Rivers: If you would let me catch my breath, I would tell you without prompting. In 1938, while examining the feces of a baby who they suspected was an abortive case of polio, Dr. Paul and Dr. Trask isolated a strain of poliovirus which they named the SK strain, in honor of the baby from whom they recovered the virus. It was a most

[27] J. R. Paul and J. D. Trask, "Detection of poliomyelitis virus in so-called abortive types of the disease," *J. Exptl. Med.*, vol. 56:319 (1933); J. R. Paul, R. Salinger, and J. D. Trask, "Studies on the epidemiology of poliomyelitis, methods and criteria for the detection of abortive poliomyelitis," *Amer. J. Hyg.*, vol. 17:587 (1933); J. R. Paul, and J. D. Trask, "Comparative study of recently isolated human strains and passage strain of poliomyelitis virus," *J. Exptl. Med.*, vol. 58:513 (1933); "Neutralization test in poliomyelitis; comparative results with four strains of virus," *J. Exptl. Med.*, vol. 61:447 (1935); J. R. Paul, J. D. Trask, and L. T. Webster, "Isolation of poliomyelitis virus from nasopharynx," *J. Exptl. Med.*, vol. 62:245 (1935).

interesting finding, because it gave support to another idea that orthodox polio investigators had also opposed for many years, namely, that polio was more likely an intestinal rather than a respiratory disease. The corollary to that notion was that virus that was passed in stools was instrumental in the spread of polio epidemics. I would say that this work, in conjunction with the later work of Dr. Albert Sabin on olfactory lobes in human polio, and the work of Dr. David Bodian and Dr. Howard Howe on the neuropathology of polio, did much to finally settle the debate among virologists on the problem of portal of entry of poliovirus in human infection.[28]

Q: Dr. Rivers, would you say that it was the recovery of poliovirus from feces of abortive cases of polio that turned the attention of investigators to the fly as a possible transmitting agent in the spread of polio?

Rivers: Before I discuss your question, let me say that the initial impact of the discovery of poliovirus in the feces of abortive and paralytic cases of polio by Dr. Trask and Dr. Paul made them focus their attention on sewage as the likely agency in the spread of polio. I would like to add that they got quite an argument when they published such views. I personally didn't think much of that particular idea, because polio epidemics hit good sanitary environments and clean healthy kids with more force than it did slums, where the kids might have been scrawny and dirty, and certainly not as well fed. One of the important corollaries of the sewage idea was that polio epidemics might be water-borne, and Dr. Paul and Dr. Trask pursued that notion very carefully. In this way they went back to an idea of old papa Kling, the Swedish epidemiologist, who pointed out that some of the early polio epidemics in Sweden followed streams.[29] Well, again they could find no hard proof that water was actually related to the spread of polio epidemics. I opposed them on these ideas, but I don't know that I wouldn't have done the same had I been in their shoes. You question things in science and you take nothing for

[28] 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).

[29] C. Kling, "Recherches sur l'épidémiologie de la polimyélite," *Svenska läkartidn. sällsk. handl.,* vol. 55:23 (1929).

granted until it's either proved or disproved—I should add in all honesty that this is easier to say than to do.

In answer to your question, I would say that, long before Dr. Trask and Dr. Paul did their work, many investigators thought of the fly as a likely agent in the spread of polio. In 1913, for example, Dr. Wilbur Sawyer tried to transmit polio by means of the stable fly. I don't think that he was the only one, because Dr. Milton Rosenau of Harvard School of Public Health and Dr. John Anderson of the U.S. Public Health Service tried the same trick.[30] I might add that several years later Dr. Simon Flexner at the Rockefeller Institute did his damnedest to destroy that notion and had some success. Nevertheless, some people through the years held on to that idea. When Dr. Trask and Dr. Paul published their findings on poliovirus in feces, a number of investigators began to reexamine the role of the fly in epidemic polio. If I am not mistaken, one of the first to do so was Dr. Albert Sabin. By this time, Dr. Sabin had already left the Rockefeller Institute and taken up a new position at the Children's Hospital in Cincinnati. Together with Dr. Robert Ward, who worked with him at the time, Dr. Sabin collected flies from the vicinity of various polio epidemic areas and isolated poliovirus from such flies. At about the same time, members of Dr. Paul's team, particularly Dr. Joseph Melnick, also trapped flies in epidemic areas and were also successful in demonstrating that such flies either harbored or carried poliovirus.[31]

While there was evidence that pointed to the fly as a possible carrier, proving it as an actual transmitter was much more difficult. After World War II, the Yale team headed by Dr. Melnick sprayed an area somewhere in the midwest with DDT during a polio epidemic, and, while there was decrease in the amount of flies, such decrease had no apparent effect on the course of the epidemic itself. If my memory

[30] W. A. Sawyer and W. B. Herms, "Attempts to transmit poliomyelitis by means of the stable fly," *J. Amer. Med. Assoc.*, vol. 61:461 (1913); J. F. Anderson and W. H. Frost, "Transmission of poliomyelitis by means of the stable fly," *Public Health Rept.*, vol. 27:1733 (1912); M. J. Rosenau, "Poliomyelitis transmitted by the biting fly, *Stomoxys calcitrans*," *Public Health Rept.*, vol. 27:1592 (1912).

[31] A. B. Sabin and R. Ward, "Flies as carriers of poliomyelitis virus in urban epidemics," *Science*, vol. 94:590 (1941); "Insects and epidemiology of poliomyelitis," *Science*, vol. 95:400 (1942); M. Power and J. L. Melnick, "A three year survey of the fly population in New Haven during epidemic and non-epidemic years for poliomyelitis," *Yale J. Biol. Med.*, vol. 18:56 (1945).

doesn't fail me, at about the same time the government carried out a like experiment in the southwestern part of the country, during a double epidemic of typhoid and polio. In this particular case, although the typhoid epidemic diminished considerably, the polio epidemic continued unabated. After these experiments, the notion that flies played an important part in the transmission of polio just petered out.[32]

Q: Dr. Rivers, can you give me any indication of the attitude of the Virus Research Committee toward the work of Dr. Trask and Dr. Paul?

Rivers: That's an easy question to answer. Both Dr. Trask and Dr. Paul were supported in their work by the President's Birthday Ball Commission, and when the National Foundation was created in 1938 that support continued. Actually, the first research grant ever made by the Foundation was to Trask and Paul. The Virus Research Committee thought very highly of their work (which I have just outlined) and felt it worth pursuing. I don't remember any time when Dr. Trask and Dr. Paul made application for support that the grant didn't go through. They were not ivory tower laboratory workers, and when the occasion demanded it they didn't mind doing shoe leather work in the field. As a matter of fact, when polio epidemics broke out during the late thirties and early forties, it was very unlikely that you could find them in their laboratory. Invariably they would hop trains to the scene of the trouble. It didn't matter where it was—Canada, Indiana, West Virginia, Alabama, or New York—an epidemic was the signal to collect stools and examine sewage in the epidemic area. Later they would return to the laboratory and try to devise more refined methods for detecting poliovirus taken from such sources.

Q: Dr. Rivers, was their work exclusively epidemiological in character?

[32] J. L. Melnick, R. Ward, D. R. Lindsay, F. E. Lyman, "Fly abatement studies in urban poliomyelitis epidemics during 1945," *Public Health Rept.*, vol. 62:910 (1947); for further detail of government activity on the problem of the fly and its relation to dysentery and neurotropic virus disease, see J. Watt, "Insect control methods," and G. E. Quinby, "Insect control methods," in Proceedings of a Round Table Conference on the Importance of Insects in the Transmission of Poliomyelitis. Washington, D.C., January 9–10, 1948, pp. 67–117 (National Foundation Archives).

Rivers: No. No. They did other things as well. For instance, before World War II, most of the monkeys used in polio research came from the Far East and the Philippine Islands. When our supply of monkeys began to dwindle around 1940, Dr. Trask and Dr. Paul decided to investigate whether monkey species from other parts of the world were susceptible to polio. For a year or two they experimented with the green African monkey, and it was they who made the discovery that it was highly susceptible to polio. One of the things I remember best about these particular experiments was that Dr. Trask and Dr. Paul were able to bring this species down with an intercutaneous inoculation of poliovirus, and later recovered the virus from the stool. It was a nice technique and I believe they later demonstrated that they could bring other species down by the same method.

The search for another monkey species that would be susceptible to polio was quite an important task, and perhaps I ought to say a word or two here about the general problem of the laboratory animal in polio research. In 1939, when Charley Armstrong demonstrated that Lansing (type 2) poliovirus would go in cotton rats, the Foundation began to encourage a number of its grantees to search for other animals that might supplant the monkey in polio research. Such a search went on for a very long time and animals all over the world were tested. I could swear that at one time or another almost every animal that we could get our hands on had polio stuck into it—even gerbils. In case you don't know what a gerbil is, it's a rodent that looks like a rat and inhabits the Sahara Desert. That search was unsuccessful and the monkey remained a problem for the Foundation. During the war years it was a particular problem. Let me explain.

Prior to World War II, the Foundation purchased its monkeys from a New York animal dealer named Henry Trefflich. In 1940 you could still get a good healthy monkey in New York for between $10 and $15; however, as the usual sources of supply in the Far East were cut off by the war, the prices for monkeys began to rise. Early in 1942, the National Foundation decided to buy and ship monkeys from India under its own auspices. I can tell you that that decision made Mr. Trefflich very unhappy, but I can't say that it ended the problem. Although between 1942 and 1943 the Foundation was able to buy and ship approximately 11,000 monkeys from India, no more than

3000 survived passage and disease to reach research laboratories. After the war, the monkey still continued to be a problem, and in 1952 the Foundation was finally compelled to establish a monkey farm in Okatie, South Carolina, to help supply the needs of its grantees.

Q: Dr. Rivers, in one of the early grant applications made by Dr. Trask and Dr. Paul, I noticed a request for special equipment, in this particular case, an ultracentrifuge. Other applicants, of course, made like requests. What was the attitude of the Foundation toward requests for equipment?

Rivers: When I began virus research, virologists used very little special equipment in the laboratory. However, by 1940 the ultracentrifuge, the electron microscope, Tiselius apparatus had become a part of the armamentarium of the virologist. Such equipment was used and needed. As I remember, Dr. Trask and Dr. Paul wanted an ultracentrifuge to help them isolate poliovirus from the bacteria and other toxins found in the highly contaminated fecal material that they were using as a source for their virus. It was a perfectly legitimate request and the Foundation granted it.

In general, however, the Foundation didn't like to make grants for equipment, any more than they liked to build laboratories or buildings. From time to time, during the early years, the Foundation deviated from that rule, but only under pressing or unusual circumstances. As far as policy goes, the Foundation has always felt that a university or medical school should assume the burden for furnishing equipment or constructing a building or laboratory; on the other hand, it has always been willing to furnish money for animals, expendable supplies, and technical help. I would like to point out that in virus research the latter is not an inconsiderable item.

In the beginning, when the Foundation allocated funds for the purchase of special equipment, such equipment remained the property of the Foundation and in theory could later be shifted to other grantee laboratories who had need of it. During the late 1940's, a modification of that rule was instituted, and, if the Foundation did not reclaim equipment that had been purchased with its funds within a year after the completion of a given grant, the equipment became the property of the grantee institution.

Q: Dr. Rivers, in the fall of 1942, Dr. Paul put in a request for a grant of $150,000 for a period of five years. What was the reaction of the Virus Research Committee to this request for a long-term grant? [33]

Rivers: I don't remember that it caused any commotion. You must remember that by 1942 a precedent for making long-term grants had already been established by the Foundation. Furthermore the Yale polio unit was not an unknown quantity to the committee. Actually the Foundation had supported Dr. Trask and Dr. Paul on a yearly basis since 1938, and as I have already indicated they did excellent work on the epidemiology of polio. To be sure, Dr. Trask had died early in 1942, but in John Paul the committee knew it had a tried and tested investigator who had imagination and drive, and that the laboratory had some damn good youngsters in Dr. Joseph Melnick, and Dr. Herbert Wenner. At the time, Dr. Paul actually had great need for such a long-term grant. In the beginning of its existence, the Yale polio unit had obtained a good deal of support from the Department of Pediatrics of the Yale Medical School. This department furnished laboratory space and funds from its departmental budget; however, when Dr. Trask died there was no one in the department to pick up the burden of polio research and the connection between the polio unit and the department was cut. Dr. Paul who was in the Department of Preventive Medicine was then faced with the burden of reorganizing and shifting the polio unit to his own department. It was not an easy job and was complicated by the war. In 1942 the headquarters of the Army Neurotropic Virus Disease Commission was established at Yale, and Dr. Paul, as leader of the investigative unit of that commission, had new burdens put on his laboratory facilities. He not only had to have continuity to keep and attract first-rate personnel, he also had to expand his lab facilities. The Virus Committee didn't have to have a picture drawn for it—it knew the necessity and importance of supporting the continuation of Dr. Paul's epidemiological work, and it granted his request.

[33] See J. R. Paul, Application for grant to the National Foundation for Infantile Paralysis, October 22, 1942 (CRBS #1, Yale University, 1941, National Foundation Archives).

Q: Dr. Rivers, if you examine the long-term grants made by the Foundation you find that all the grants have one thing in common, namely, they are all in one way or another concerned with problems relating to the epidemiology of polio. Was the Virus Research Committee ever concerned with making grants that overlapped?

Rivers: I can't honestly say that that problem ever bothered the committee. To be sure Maxcy, Francis, and Paul all indicated that they would be working on problems of epidemiology of polio, but the Lord knows there were enough problems in the epidemiology of polio at that time to keep twenty laboratories at work without jamming each other up. I don't think that it ever occurred to the Virus Committee that Dr. Francis and Dr. Paul, for example, would ever tread on each others toes because they were working on like problems. So far as I know, they never have. When we made a decision to give a grant to a laboratory, we not only looked at the work that they said they were going to do; we also paid a great deal of attention to the fellows who were going to do the work. Hell, it made no difference to us that Francis and Paul both said that they were going to work on the epidemiology of polio; we knew enough about them to know that they defined problems and worked in the laboratory in ways that were uniquely their own. Even if they didn't, I don't think that we would have hesitated to give them grants. We have never given a damn if three, six, or nine laboratories worked on the same problem.

In science, if a discovery is made it has to be corroborated; nothing is accepted on faith, and the fact that laboratories work on the same problem makes the task of checking results easier. Also, if one laboratory gets a good lead, you have a better chance of exploring possibilities if you have a number of other laboratories working on the same or like problems. Overlapping is not a problem in science; I think it is a necessity.

Q: I think that, to this point, we have touched on most of the problems relating to pathology and epidemiology cited in the eleven points of the Virus Research Committee. There are, however, two problems of the eleven that I wish you would make comment on. The first relates to chemical blockade. By the summer of 1938, wasn't it fairly conclusive that chemical blockade was not a practical method of dealing with the polio problem?

Rivers: I wouldn't say that it was conclusive. I believe that the committee was only agreed or convinced that the techniques that had been used to administer the prophylactic—whether zinc sulfate or picric acid—were defective. I believe we were all anxious to discover if a more effective method could be devised to administer the prophylactic. It was one of those experiments that had not been properly wound up and completed. Actually, the committee lost interest in this subject very rapidly and, as I remember, never voted any money to prosecute further work in this field.

Q: The second problem relates to the ninth point in the eleven-point program, that of chemotherapy. Isn't it almost an article of faith among virologists that few if any viral infections, with the possible exception of psittacosis, respond to chemotherapy?

Rivers: There were good reasons for the Virus Research Committee to turn to chemotherapy. In 1938 viologists were still impressed by the mess caused by the Brodie-Park and Kolmer polio vaccines and were determined to prevent such a debacle from occurring again. You will notice that the last research category the Virus Research Committee thought should be supported was the development of a vaccine. We just weren't ready for vaccines at that time, and I think that we were wise in staying away from them.

Chemotherapy, on the other hand, offered a possible approach to the solution of the polio problem. By 1938 chemotherapy had marked success with certain bacterial diseases, and it was perfectly natural to wonder whether chemotherapeutic agents would work on viruses in general and polio in particular. Paul de Kruif was very active in pushing this point of view in the committee and at one time suggested that the Foundation establish relationship with American Cyanamid Corporation to test the effect of certain drugs on polio. Nothing much came out of this particular suggestion, but it was a notion that very definitely was in the air at that time. Certain workers who were struck by the success of the use of sulfapyridine in treating pneumonia wanted to rush off and try it on polio. That happens very often in research. If something successful is accomplished in one field, a hundred hands want to apply it in another field and they go looking for money.

The Foundation at that time did give money to one or two laboratories to work on chemotherapy of polio, but nothing much came of that research. Now that doesn't mean that the idea of chemotherapy was a bad one. It just means that at that particular time we didn't have the biochemical techniques to develop it in a satisfactory way. If you want my opinion, I believe that the ultimate answer to virus disease lies in chemotherapy. But it is also plain that it will be necessary for us to know how the host cell manufactures virus before we can develop a chemotherapeutic agent which will halt that process without harming the host cell. Quite a trick, believe me, but, as sure as I am sitting here, someone will crack it. As a matter of fact, the Foundation is supporting such studies now in Igor Tamm's laboratories at the Rockefeller Institute and Tommy Francis's laboratories at the University of Michigan. They don't talk much about chemotherapy —but that's in back of their heads, believe me.

CHAPTER 8

The National Foundation for Infantile Paralysis: Early Research Programs—Part 2

The Foundation is a holding company for the People. It has several justifications—as critic, as originator, as catalyzer.

Dr. Alfred E. Cohn, *Minerva's Progress*

Q: Dr. Rivers, late in 1939 the post of medical director was created in the National Foundation. Could you tell me what events led to the creation of this post?

Rivers: Up to the time a medical director was appointed in the Foundation, most of the applications for grants were received by a secretary in Mr. O'Connor's law office. This girl, although very competent, had no medical experience, and consequently had no idea whether these applications were worth looking at, much less supporting, and as a result dumped all the applications, the good as well as the bad, into the laps of the various committees. For instance, during the very early days of the Foundation, the Virus Research Committee had to spend a hell of a lot of time just sorting grant applications before they could settle down to discuss those worth discussing. It was a time-consuming job and I can tell you that I and other committee members didn't like it too well. There were other problems. When the various chapters of the Foundation began to give direct medical