CHAPTER 5

The Process of Virus Research—1930

But what created mind can comprehend
Their number, or the wisdom infinite
That brought them forth, but hid their causes deep.
John Milton, *Paradise Lost*

Q: Dr. Rivers, as a physician and investigator, were you bound to the hospital and laboratory? Did you ever get a chance to see what was happening in the world outside the Institute?

Rivers: I most certainly did. In 1930 I attended the First Microbiological Congress in Paris as one of the representatives of the Rockefeller Institute. Before I went, Dr. Flexner urged me to speak on the problem of poliomyelitis but I refused. Although I was quite familiar with what was going on in polio research, the truth is that I had never worked with the virus, and I felt I shouldn't meet my peers talking about a subject in which I had no personal experience. Instead I decided to report on psittacosis. I was then working with psittacosis virus and knew much about it, but even more important almost every virus laboratory throughout the world at that time was interested in the disease. The paper I prepared was very brief, and I don't think it ran more than 800 words. If you look through the proceedings, you will find that, with small exception, speakers had no more than 800 words at their disposal.

Given this state of affairs, it should come as no surprise when I tell you that I didn't hear anything particularly new about viruses at the

congress, and that I got very little out of the papers as they were given in the meeting hall. However, this was the first time I ever saw a certain thing happen. A fellow got up to give a talk and he, like other speakers was limited to 800 words. Well, what can you say in 800 words? You can hardly get started. The chairman was understanding and let the speaker go over his time, and on he went. A short time later when the chairman tried to call a halt, he found that the speaker would not stop. The words kept pouring out until, at the chairman's suggestion, three people in the front row of the audience got up and bodily removed the speaker from the room.

I had never seen this done before and several years later, at the Second International Poliomyelitis Conference held in Copenhagen, I was faced with a like problem. I was chairman at an introductory session which was devoted to virus research in general. Prior to the conference the National Foundation had invited the Russians to participate in the sessions but had never received any reply to their invitation. Assuming that the Russians were not coming, the sessions were planned accordingly. Well, a day or two before the conference opened, a small group of Russians appeared and declared that they were ready to participate in the sessions. We were sore but we maneuvered the program so as to allow the Russian delegation a speaker at this preliminary session. I will never forget him—he was a queer little fellow with a beard down to his upper chest. His talk was just as queer, because he kept insisting that all the pioneer work in polio had first been done in Russia. That didn't bother anybody, but what was annoying was that he gave no indication that he was ever going to stop talking. Had I let him, I think he would have spoken into the night. Finally, some people in the audience got up and toted him away. Nine years later at the Fifth International Poliomyelitis Conference, held in Copenhagen, Russian behavior changed markedly. This time they replied to their invitations and sent an excellent delegation composed of Dr. Anatoli Smorodintsev, Dr. Mikail Chumakov, Dr. Valentin Soloviev and Dr. Marina Voroshilova who contributed knowledgeably and helpfully to the discussions.

To get back to the First Microbiological Congress in Paris, I do want to say that the congress gave me the opportunity to meet and see people I had heard and read about. For example, I heard Serge

Winogradsky, one of the pioneer soil microbiologists in the world, give a paper, I saw the distinguished clinician, Dr. Arnold Netter, and I spoke to old Dr. Émile Roux who you may remember followed Louis Pasteur as director of the Pasteur Institute.[1] During the conference I made a special effort to see the room at the Pasteur Institute that is dedicated as a memorial to Pasteur. It was something to see. You know, the French have a way of doing such things for their distinguished citizens, whether they are generals or scientists. I think that they pay more tribute to their scientists than we do. Our scientists never get much from the public except an occasional bawling out.

On the last day of the congress Dr. Harry Plotz of the Pasteur Institute put Dr. Thorvald Madsden of Denmark, Dr. Jules Bordet, and me in a taxicab and took us to a top notch club for dinner. I should add that it wasn't the kind of a club that scientists usually go to, but by the same token I want to say that we didn't need any instructions on how to enjoy ourselves. We had a hell of a good time.

My trip to Paris in 1930 was not the only jaunt that I made out of the country during my early years at the Institute. In the fall of 1934 I was invited to attend a medical congress in Argentina, and I took advantage of the opportunity to visit Brazil as well. It was the first trip that I made to Latin America since my stay of 18 months as a second year medical student in Panama back in 1912. In those days few people traveled by air, and traveling to Europe or South America was usually by ship. It was a nice way of going because it gave you a chance to rest and meet people. I remember that on this particular trip I ran into Yandell Henderson, the physiologist from Yale, and he proved to be a most interesting shipboard companion.

We landed in Rio de Janeiro and before I had a chance to find out if I was lost, Fred Soper of the Rockefeller Foundation met me and took me in hand. It was through Dr. Soper that I met Dr. Carlos Chagas, who at that time was director of the Oswaldo Cruz Institute, who showed me the first cases I had ever seen of Chagas disease. Dr.

[1] The succession to Pasteur's post as director of the Pasteur Institute was slightly different. Upon Pasteur's death, Émile Duclaux was appointed director of the Pasteur Institute, while Dr. Émile Roux took the post of associate director. When Duclaux died in 1904. Roux succeeded to the directorship. W. R. Bulloch, *A History of Bacteriology*. Oxford University Press, London, 1938, pp. 362, 393.

Soper and one of his associates, John Kerr, then took a lot of time to brief me on the research work that the Rockefeller Foundation was doing on yellow fever in Brazil. The thing that still sits in my mind after all these years is not the people I met, but an experiment I saw going on in one of the laboratories. A young doctor who was the brother of Dr. Miguel Ozorio, the minister of Health and Hygiene, was trying to treat cancer by means of increased oxygen tension. He found, for example, that if he subjected his animals to increased oxygen tension they usually died. However, if he took the precaution of starving them for several days before the experiment, they lived and, in some, cases of sarcoma were cured.

I believe that, at most, I spent three days in Brazil and then left for Argentina. The congress was held in a place called Rosario. Looking back I would say that it was much like the AMA conventions held in this country. In one week's time, approximately 1500 papers and communications were read. I myself gave two papers—one was a general review of virology, the other a review of research on psittacosis. Some of the conferees gave as many as ten papers. I don't think that many were particularly distinguished, but people sat and listened and later commented on them.

In my free time, I visited the medical school attached to the University at Rosario. The buildings and laboratories seemed to be well equipped, but I couldn't for the life of me tell whether it was adequate for the student body. I say this because the equipment and rooms I saw would be adequate for 50 students in a class, but many of my informants told me that some classes had between 250 and 300 students. I could never judge for myself, because at the time of my visit the medical students were out on strike, and all I could count were the soldiers who surrounded the University.

Thirty years ago, medicine in Argentina followed the model provided by French medicine, the texts used were largely French, and when students finished school they sometimes went to France for postgraduate work. I would say that the Argentina of that day had many good physicians and surgeons, but it also had a good many serious deficiencies. For instance, nursing was extraordinarily bad and, outside of Dr. Angel Roffo's Institute for the Study and Treatment of Cancer, there were few facilities for training nurses. In part, that situ-

ation stemmed from the public attitude toward women, which incidentally frowned upon proper wellborn women doing nursing. Medical research was pretty much in the same category, and outside of the work done by Bernardo Houssay at the Physiological Institute in Buenos Aires, there was little in Argentine medicine that could be dignified by calling it research. I remember that in the lecture room of the large Maternity and Gynecological Hospital run by Dr. A. Peralto Ramos the motto, "Medicine is Art not Science," was displayed very prominently. Still, if you searched you could find a tradition of experimentation. While in Rosario, I found a rare volume on *viruela*—smallpox—by José Penna, who has been called the Jenner of South America. I tried to purchase it, only to be told by the owner, Dr. Recaldo Cuestas, that it was not for sale. Before I left he very graciously gave it to me as a gift.

Q: Dr. Rivers, I would like to turn your attention to the research you did in those years. Could you tell me how you came to do work with the psittacosis virus?

Rivers: In 1929 and again in 1930, there were serious outbreaks of psittacosis or parrot fever in California and New York. The death rate was fairly high, and a number of laboratories, particularly the Public Health Service Laboratory in Washington, D.C., and the laboratories of the New York City Board of Health began to work on the disease. Within a very short period of time, investigators as well as technicians in these laboratories started to come down with the pneumonias that were typical of psittacosis. The laboratories that were doing the research were no amateurs. In Washington, for example, Charles Armstrong, one of my classmates at the Hopkins, ran the show. Well, it made no difference because 16 people came down with psittacosis. What made it embarrassing was that some of the people weren't even in Armstrong's laboratory and worked on a different floor. In New York, two technicians in Dr. Charles Krumwiede's laboratory came down and it was the latter event which helped bring the virus to my laboratory. Let me say that Dr. Krumwiede was an extraordinarily gifted worker and the fact that two of his technicians came down with a disease under investigation would, under ordinary circum-

stances, not have deterred him from pursuing his research. The fact is that, just about the time Krumwiede started his work on psittacosis, the poor devil discovered that he had a carcinoma of the bladder, and it was this which decided him to give up working with the virus and led him to offer it to the Rockefeller Institute. Dr. Flexner accepted the virus and then called me over and told me to work on it.

Actually I began my research on psittacosis about a year after it became a public health problem in the United States. Soon after I started my research, all of the laboratories in the United States, save my own at the Rockefeller Hospital, stopped working on the disease, and for a period of approximately two years, material from every patient in the United States who came down with psittacosis was sent to my laboratory for diagnosis.

Q: Was there much difficulty in differentiating a pneumococcal pneumonia from the respiratory infection caused by psittacosis?

Rivers: In the beginning I believe that many general practitioners had such difficulty. However, there was no difficulty in the laboratory in differentiating between the lesions caused by a virus and a bacterium. At one point in my investigations, I described quite clearly the microscopic changes that one would find in lungs which were invaded by psittacosis virus. There was, however, a debate among virologists as to what constituted portal of entry for the virus.

Both Dr. Karl Meyer in this country and Dr. Samuel P. Bedson in England claimed that the virus was transmitted by the bite of an infected bird. It is true that many people who fed their parakeets by mouth were bitten, and there were cases where parrots became annoyed with people and bit them on the hand. It was thought that the virus entered the bloodstream in this fashion. I didn't think much of this theory for several reasons. First and foremost was the fact that the pathology of psittacosis in man and the monkey was in the lungs, and, when I injected my experimental monkeys intraperitoneally or intracerebrally with the virus, I could make them sick or kill them, but I could never produce a pathological lesion in the lung. The only time I could get a pathological sign in the lung was when I inoculated them intratracheally. Secondly, I always found it odd that most of the

16 cases that came down with psittacosis in the laboratories of the Public Health Service in Washington never even saw a parrot or parakeet. When Charley Armstrong demonstrated the virus in fecal droppings of parrots, what happened in Washington became clear. Armstrong's experimental parrots were kept in the basement of the old Hygienic Laboratories in Washington. It was an old red brick building, and the only thing hygienic about it was its name. I want to tell you that the basement where those birds were kept wouldn't win any medal for cleanliness. When parrots relieve themselves, they have a way of standing on the side of the cage, and instead of putting their feces and urine in the cage, they usually put it on the floor of the room in which they are kept. Armstrong's birds carpeted the floor of that basement with feces and urine, and the cockroaches that infested the building completed the job by transporting the virus to the desks of workers throughout the building.

You know I argued the problem of transmission of psittacosis virus for over 20 years with Karl Meyer, and I couldn't get the son-of-a-gun to admit he was wrong until a general conference on psittacosis which was held in honor of "Red" Beaudette in the mid-fifties.[2]

Q: Dr. Rivers, you mention a debate on portal of entry of the virus. Wasn't there also one on diagnosis?

Rivers: If there was a debate, I don't think it was much of one. Dr. Bedson—and by the way he was a very careful and good worker—claimed that he could demonstrate the virus of psittacosis by taking blood from an infected patient and injecting it into a parakeet or a lovebird. Well, to put the matter bluntly, I didn't think much of this work. In the first place, one might not always find the virus in the blood, and secondly Karl Meyer had previously demonstrated that many parakeets were already naturally infected. My own ideas for diagnosis came from some of the work that Krumwiede did. Krumwiede early demonstrated that the mouse was susceptible to psittacosis, and that encouraged me to experiment with the white mouse.

[2] Rivers here has reference to a conference called by Dr. F. R. Beaudette to discuss the problems of diagnosis, epidemiology, and control of psittacosis in 1956. A similar conference was held in 1953 but was not attended by Rivers.

I'd like to point out that for a long time the Rockefeller Hospital had used the white mouse to make diagnoses of lobar pneumonia. These particular mice were beautiful to work with, they were highly susceptible to the virulent type 1, 2, and 3 pneumonias, and they handled the nonvirulent ones with ease. We soon discovered that, if we took the sputum of an infected patient and put it intraperitoneally into our white mice, that within a few days they would come down with psittacosis.

Now, telling whether or not our mice had psittacosis was not a hit or miss affair. Although the pathological lesions of psittacosis in the human host were always in the lungs, in mice the lungs were rarely affected; instead the most constant and characteristic changes were to be found in the liver and spleen. In 1930 a German worker by the name of Walther Levinthal demonstrated that, if you took a smear of a liver infected by psittacosis, you invariably found clusters of bodies —almost like a little colony—growing in the cytoplasm of the cells of the liver. When you saw these "minute" bodies your diagnosis was just about 100 per cent.[3]

What makes all of this ironic is that, today, nobody ever makes a diagnosis of psittacosis any more than they make a diagnosis of lobar pneumonia. The moment a patient has any signs in the lungs and runs a high fever, the doctor gives him an antibiotic. It doesn't mean that we don't have the disease, because we still have it. It's present in parrots from Brazil, turkeys from Texas, and ducks from Long Island.

[3] W. Levinthal, "Die Ätiologie der Psittakosis," *Klin. Wochschr.*, vol. 9:654 (1930). Peter Olitsky adds this note on Levinthal:

Walther Levinthal came to the Rockefeller Institute in 1925 and remained about four months observing the methods that we used in my laboratory. He was a member of the staff of the Robert Koch Institute at Dahlem, then under the direction of Fred Neufeld, the discoverer of different types of pneumococci. Dr. Neufeld held the highest opinion of young Levinthal's character and capability. My impression also was that he was a remarkable worker with great potentialities and deserving of encouragement and facilities to be able to express his superior talents. He returned to the Robert Koch Institute in 1926 and continued to study the pneumococcus and later psittacosis. In 1930 he reported what is known in the literature as the "Levinthal bodies," as the causal agents of psittacosis. . . . In 1933 with the accession of Hitler to power, Levinthal was compelled to leave his country. He sought a position at the Rockefeller Institute through me; however, on referring the matter to Dr. Flexner, [I learned that] his application could not be granted, since a large number of talented Germans were ahead of him and no place could be found. He settled in England, and the last I heard from others was that he was practicing medicine in the provinces there (private communication).

Some investigators have even found the virus in chickens. But we just don't make any diagnosis. People are filled with antibiotics, and that's it.

Q: Sir MacFarlane Burnet says that anyone working with psittacosis usually has some good stories to tell. Could you favor me with some? [4]

Rivers: I don't know whether the stories I could tell would be interesting. The only thing that I can promise is that they will have some relationship to the work that I did. During the outbreak of psittacosis in New York in 1930, a girl came into the Rockefeller Hospital with what seemed to be a virulent pneumonia. We ran the usual tests on her and soon discovered that she didn't have a pneumonia at all but was infected with psittacosis. What made this particular case interesting was the fact that the patient had not been near a parrot or parakeet. Well, we talked to her and talked to her until she finally remembered that some time before, while walking through Central Park, she and her mother came upon a sick pigeon on one of the paths. They felt so sorry for the bird that they picked it up and took it home to care for it. However, in spite of their efforts it soon died. I began to wonder why the mother wasn't sick when sure enough she too showed up with a virulent pneumonia. These two ladies were the first patients the Rockefeller Hospital had from whom we were able to recover psittacosis virus. Just about that time Dr. Karl Meyer of the Hooper Foundation published a paper in which he claimed to have isolated the psittacosis virus in racing pigeons. There is no doubt that the honor of pointing this out first belongs to Karl. However, the work we did at the Rockefeller Hospital nailed it down.

These two ladies were not the only confirmation we got of the widespread distribution of psittacosis virus in birds. A short time after they left the hospital, a barber from Brooklyn showed up with a case of psittacosis. He too never saw a parrot or a parakeet, but he did have a pet troopial. In case you don't have a book on ornithology handy, troopials belong to the mockingbird family. This particular troopial was a wonderful bird—it sang well—and was the picture of health,

[4] F. M. Burnet, *Viruses and Man.* Pelican Books, London, 1953, p. 153.

and I hated like hell to destroy it but I did. I felt bad about it until I discovered that the bird was just full of psittacosis virus. You know, Meyer didn't call it psittacosis. He had to call it ornithosis. Psittacosis means a disease you get from psittacine birds while ornithosis means a disease you get from birds. Today the word ornithosis has pretty well dropped out of the picture. I think we all know that what a lot of these birds have is a form of psittacosis.

Q: Dr. Rivers, while you were working with psittacosis, wasn't a virus discovered that was similar to psittacosis yet markedly distinct from it? [5]

Rivers: Yes, that particular virus was found by Dr. Geneserio Pacheco and some of his coworkers in Brazil. Originally, he claimed that it was psittacosis. However, some of the descriptions in his papers bothered me, and I asked him to send me some of the virus so that I might investigate further. Pacheco was very kind and sent me all the virus I wanted. Soon after I began my experiments, it became obvious that Pacheco's virus was not psittacosis. For one thing, I could not carry it in mice or for that matter in any other lab animal that I tried. Actually, initially the only way I could successfully carry it was from parakeet to parakeet. Later I discovered that I could pass it from one embryonated egg to another. Occasionally a chick would be born from an embryonated egg that had been infected with this virus, and for about a day or two you could find inclusion bodies in the chick. On one or two other rare occasions, we took a day-old chick and injected large amounts of the Pacheco virus and found that we could get a very mild infection.

By and large, however, Pacheco's virus limited its activities to psittacine birds. I doubt very much whether it would bother a human being. I could almost swear that it wouldn't. It differed from psittacosis virus in one other respect—while the psittacosis virus invariably caused colonies of elementary bodies to show up in the cytoplasm of liver cells, Pacheco's virus had the beautiful characteristic of producing intranuclear inclusions in affected cells, much like the bodies produced by herpes and pseudo rabies. The differences in host range and

[5] T. M. Rivers and F. F. Schwentker, "A virus disease of parrots and parakeets differing from psittacosis," *J. Exptl. Med.*, vol. 55:911 (1932).

in intracellular pathology were sufficient to differentiate between psittacosis and Pacheco's virus. Today, I am almost embarrassed to say that I don't know what finally became of the Pacheco virus, because I didn't keep it in my laboratory.

If you look at the back of one of the first experimental papers I did on psittacosis [6] you will find a picture of George Berry dressed up like a Ku Kluxer with a parrot on his arm. He is wearing long rubber gloves, a rubber apron, and a special mask fitted into a hood going over his head. That was just Berry's way of protecting himself while working with psittacosis. Paul de Kruif made fun of that picture because he had the unique and outlandish notion that it wasn't right for a man who was working with highly infectious material to protect himself. Paul, I guess, has always believed in heroics. Well, protection or not, poor George came down with psittacosis. It's ironic. I never became infected, although I never even wore a gown in the laboratory. The reason I didn't wear protection was not that I was a hero—far from it—I didn't wear anything because I was more comfortable working with my sleeves rolled up. I always figured that if I was careful not to have anything touch my clothes I was safe. The trouble with gowns, masks, and gloves, was that they gave you a false sense of security and you were less careful while working. Hell, if you touch psittacosis virus with a damp gown, the virus will go right through that gown and get on your clothes, and before you know it you are contaminated.

Q: Dr. Rivers, looking through your papers on psittacosis, I notice that some of the animals you worked with that recovered from psittacosis didn't necessarily gain immunity. While your rabbits and parakeets did, your mice and monkeys didn't. Did this cause you any difficulty? [7]

Rivers: You know, I never really did make up my mind about the question of immunity to psittacosis. Parrots are birds of long life and live in many instances from fifty to seventy years. There is reason to

[6] T. M. Rivers, G. P. Berry, and D. Sprunt, "Psittacosis: Experimentally induced infections in parrots," *J. Exptl. Med.*, vol. 54:91 (1931).

[7] See especially T. M. Rivers, G. P. Berry, and C. P. Rhoads, "Psittacosis, observations concerning the experimental disease in parrots, mice, rabbits, guinea pigs and monkeys," *J. Amer. Med. Assoc.*, vol. 95:579 (1930).

believe that certain parrots, once infected with the virus, can remain infected from twenty to thirty years without giving any outward sign of infection. In my own experience, I have examined several birds that were at least fifty years old that seemed perfectly healthy; yet after we killed them we were able to recover virus from them without any difficulty.

Some of my patients who had psittacosis, like Dr. Berry, had very few, if any, neutralizing antibodies in the blood. To be sure they had complement-fixing antibodies, but complement-fixing antibodies have very little if anything to do with immunity to virus infection. At one time, you know, I devised a method for vaccinating man against the disease. First I experimented with monkeys and discovered that those who had recovered from psittacosis were more refractory to reinfection by the intratracheal route than my normal controls. Later I administered large amounts of active psittacosis virus intramuscularly to monkeys and learned not only that they would not come down with serious infection, but that such vaccinated monkeys had neutralizing antibodies in their sera and were again more refractory to the disease than my control animals. It was these results which encouraged me to try my hand at human vaccination. I used a live virus which previously had been passed through the brains of mice, and actually I was the first to take it. The first dose, I remember, was large enough to kill 10,000 mice. However, I had very little reaction to it. I felt a little lackadaisical for a day, and my temperature went up to a hundred, but nothing much happened. Subsequently I took several more doses, the last one large enough to kill ten million mice, but again nothing happened. Of course, it was impossible to test my refractory state by intratracheal inoculation; however Francis Schwentker worked out a tricky neutralization test which, when conducted with sera taken before, during, and after vaccination, clearly indicated that after vaccination I had an increase of neutralizing antibodies in my sera.

I will admit that there weren't a hell of a lot of neutralizing antibodies, and the amount present wasn't very striking—but you could read it. Subsequently, I immunized a number of people who were working with me in the laboratory, on the general theory that a little protection was better than none. However, nothing much came out of this particular phase of my work, and my techniques for vaccina-

tion were thrown into the ashcan when it was discovered that an antibiotic could very handily take care of a psittacosis infection. About the only thing that did happen was that I was elected to the Walter Reed Society—its membership, as you know, is made up of scientists who have experimented on themselves.

Q: Dr. Rivers, in looking over your published papers I am struck by the fact that you do not concentrate your efforts on investigating one particular virus, but rather study several seemingly dissimilar viruses. In 1932–33, for example, you worked with Rift Valley fever virus.[8] Could you tell me how you came to investigate this virus?

Rivers: It never made any difference to me what virus I worked with—the important thing was the question I wanted answered. In the early days of virology, we knew relatively little about the general nature of viruses, and any virus investigated turned up new and useful information. I would like to add that I never went out of my way to study this or that virus; sometimes it was just chance that would lead to particular experiments. Rift Valley fever, for example, is a natural disease of sheep found in Africa. I didn't go to Africa to study this virus—it came to New York. Originally the virus was investigated by English workers, and it was an Englishman named Dr. George M. Findlay who brought it to the United States. Nobody as far as I know ever asked Findlay to bring it, and I still don't know why he did, but I do know that early in the fall of 1932 he showed up with it at the Rockefeller Institute and gave a sample to the yellow fever laboratory of the Rockefeller Foundation. He also gave a sample of the virus to a young Canadian worker in Dr. Flexner's laboratory named Ronald Saddington, and it was through Saddington that I came to investigate the virus.

Several weeks after receiving his sample, Dr. Saddington came down with what seemed to be an infection. He had chills, fever, sore throat, and a general aching all over. The symptoms certainly were nothing to be alarmed about, and Saddington, being the kind of fella he was, tried to carry on in the lab. This went on for a day or two, and

[8] F. F. Schwentker and T. M. Rivers, "Rift Valley fever in man," *J. Exptl. Med.*, vol. 59:305 (1934).

finally he came into the hopital and became my patient on Ward One. Because he had been working with Rift Valley fever, I naturally suspected that he might have it, and after I eliminated the possibility of strep and other bacterial infections, I drew some of Saddington's blood and made several intraperitoneal injections in mice. Mice as you know are very susceptible to Rift Valley fever, and within 48 hours they came down with an illness which by proper pathological technique was shown to be the disease.

At the time Dr. Saddington came into the hospital as a patient, his blood had no antibodies against Rift Valley fever virus. Later, however, he did develop antibodies, so we were further assured that our diagnosis was correct. At no time was I concerned about Saddington's recovery, because Rift Valley fever in man is usually not fatal. Saddington was recovering rapidly when he began to complain of pain in the calf of one of his legs—I've forgotten now which leg. An examination revealed that he had developed a thrombophlebitis, or a clot, in the vein of his lower leg. He was immediately put to bed, his leg was elevated, and he was given instruction not to move around. It was the usual treatment for such a condition, but it didn't seem to do much good. When Saddington began to complain that the pain seemed to be traveling up the leg, I decided to have a surgeon over to discuss the feasibility of putting a ligature on the femoral vein. After much discussion and debate, I concluded not to do it and it was, I am sorry to say, probably the wrong conclusion to draw.

Saddington was kept quiet and for several days he seemed to get better. Then one day he suddenly began to develop severe pains in his chest. The thrombosis in his legs began to break up, and when the clots reached the lung they caused pulmonary infarcts. The next several days were very stormy. I don't remember how many infarcts he had but he was very sick. Then the attacks subsided. The poor devil had had a rough time—but he seemed to be over the hump. I remember that he began to plan a trip to the West Indies for his convalescence. One morning at five o'clock I received a phone call from Francis Schwentker at the hospital who told me that Saddington was dead. We later did an autopsy and found a huge clot in the heart. Saddington had obviously died immediately. Saddington's case, I suppose, is the only human case of Rift Valley fever that ever ended fatally, although, strictly speaking, he didn't die of Rift Valley fever

at all, but of a thrombophlebitis brought on by the disease.

After Saddington's death I stopped working with the virus. I froze and dried it and put it away in an icebox. I also cleaned up the places where we had kept mice that were infected. A year later, several workers in another laboratory came down with Rift Valley fever. One was Thomas Francis, Jr., who today is a professor at the University of Michigan. The other was a technician named Sal Spatola, who still works at the Institute. For the life of me, I still don't know how they contracted the disease. I am positive they weren't working with the virus, and the virus which I had frozen, dried, sealed, and put away in the icebox was still in its place untouched.[9]

[9] Dr. Olitsky makes this comment on Dr. Rivers' implied criticism of Dr. Findlay:

I must come to the defense of Brigadier General G. M. Findlay, RAMC. I am sure that he did not give the Rift Valley virus sample to Saddington, as Dr. Rivers says, since he did not know him at the time. It is more likely that Dr. Findlay, a scholar and gentleman, presented it to the director, Dr. Flexner, following custom. Dr. Saddington was then attached to Dr. Flexner's laboratory and the latter would have turned this material over to Dr. Saddington to keep or work with since Dr. Flexner was busy with executive duties. More important, at the time that Dr. Findlay presented this gift, it was not known here how invasive the virus was for laboratory personnel. After Saddington's death, that became common knowledge, and the Rift Valley virus was placed with typhus fever rickettsiae and other agents as dangerous to workers, even to those not directly handling the material (private communication).

It is interesting to compare Dr. Olitsky's comments with a letter that Dr. Rivers wrote to Rufus Cole two years after Dr. Saddington's death.

February 18, 1935

Dear Dr. Cole:

The following is a record, complete as far as my knowledge is concerned, of Rift Valley fever virus since its introduction into this country by Dr. G. M. Findlay.

Dr. G. M. Findlay without being requested to do so brought into this country Rift Valley fever virus September 2, 1932.

A sample was given to the Yellow Fever Laboratories of the Rockefeller Foundation.

While Dr. Findlay was here, Dr. R. Saddington, working in Dr. Flexner's laboratory, obtained directly from Findlay a sample of the virus.

Dr. Saddington developed Rift Valley fever December 2, 1932. I recovered Rift Valley fever virus from his blood. This was the source of the virus with which I have worked and which I now have.

No one in my laboratory has handled the virus except Dr. Schwentker and myself. All animals were thoroughly isolated in my "psittacosis room." We fed the animals and cleaned the cages ourselves.

In August 1933, two monkeys were immunized against the virus in order to have a source of diagnostic serum. These animals were isolated during the process of immunization. After it was completed they were returned to the main animal house and are now in Room A 11. We have seen no indications that they are carriers.

Late in the spring of 1934 Dr. Schwentker and I carried out a few experiments with

Q: Dr. Rivers, didn't you also work with another virus disease of sheep at this time called louping-ill? [10]

Rivers: Yes. However, please keep in mind that the virus that causes louping-ill is quite different from the one that causes Rift Valley fever. Louping-ill is a disease of sheep found in northern England and Scotland and, although it has been known for a long time, its viral nature was only established about 1930. I should add that it is also found in sheep in Russia and the Middle East. I was once told—I don't know how accurately—that the word louping comes from the Scotch for leaping. When sheep get the disease it affects their central nervous system, and they begin to leap in a characteristic fashion. Be

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the virus in mice. The last experiment was finished June 18, 1934. The mice were destroyed and we cleaned up the containers and the room housing the animals. On May 22, 1934, we stored some dried virus. I still have it and so far as I know none of it has disappeared.

During the latter part of August and most of September 1934, E. Hayes and F. Compolier (my laboratory boys) were cleaning and painting the "isolation room" or "psittacosis room."

E. Hayes was sick from October 5th to October 16th, 1934. Dr. Parker thought he had influenza and obtained "washings" for Dr. Francis. From these washings Dr. Francis obtained Rift Valley fever virus. Hayes did not come into the hospital.

The Bureau of Animal Industry knows that I have the virus in my laboratory and has not requested me to destroy it. I have letters on file regarding this matter.

So much for the history of the virus in my laboratory. Now I shall relate the story, as far as I know it, of the virus in the Yellow Fever Laboratory. Dr. S. F. Kitchin was its custodian in that laboratory and did some experiments with it. On February 21, 1933, T.W.N. came down with Rift Valley fever. On September 6, 1933, V.G. came down with Rift Valley fever. On October 9, 1933, G.W.M. came down with Rift Valley fever. On October 19, 1933, Dr. Sawyer had a talk with Dr. Flexner and between October 19, 1933, and November 2, 1933, all the virus in the Yellow Fever Laboratory was destroyed. According to Dr. Sawyer, their laboratory has been without virus since November 2, 1933.

Unless Hayes contracted the disease from dust (the virus must have been at least several months old in the dust of the room at the time he painted the isolation room) or unless there are carriers of the virus, I cannot explain how Hayes contracted the infection. Dr. Francis and Sal most likely caught the disease from the animals infected with Hayes' virus.

Sincerely yours,

THOMAS M. RIVERS

Dr. Rufus Cole
The Rockefeller Hospital

[10] F. F. Schwentker, T. M. Rivers, and M. H. Finkelstein, "Observations on the immunological relation of poliomyelitis to louping-ill," *J. Exptl. Med.*, vol. 57:955 (1933).

that as it may, let me say that I received my strain of louping-ill virus in the fall of 1932 from Dr. G. Mackie of the University of Edinburgh. Actually it was given to me personally by a young South African scientist named M. H. Finklestein, who came to this country in 1932 as a fellow of the British Medical Research Council, and who for a brief period was a volunteer worker in my laboratory.

A short time before I received the virus, Dr. E. Weston Hurst in England pointed out that louping-ill was capable of producing in monkeys a disease which pathologically seemed to be quite similar to poliomyelitis. These findings interested me, and I thought that I should try to find out whether there was in fact an immunological relationship between the two viruses. In the back of my mind was the possibility that, if the two viruses were immunologically related, I might try to use louping-ill virus for immunization against polio much like we used vaccinia against smallpox. There was no problem about experimental animals since it had already been shown that louping-ill could be transmitted experimentally to mice, monkeys, and swine. We were much aided in our work by Dr. Flexner who supplied us with monkeys who were immune to polio. I should add here that I use the word we because Dr. Finklestein did most of the work although it was done under my direction. He was a smart hombre and I will admit that he annoyed me because he knew that he was smart, but he worked well. After we devised a method of immunizing monkeys to louping-ill, we inoculated one set of louping-ill immunized monkeys with polio, and another set of monkeys immunized to polio with louping-ill, and found nothing to indicate that the two viruses were even remotely related immunologically. I suppose you might say that you could guess the outcome of these experiments, but in science you don't guess; someone has to do the job. Later, when we discovered that white mice contract louping-ill when the virus is dropped into the nose, Dr. Leslie Webster and I decided to investigate the pathogenesis of the disease in mice, and in particular to learn whether serum therapy had any value.

Q: Dr. Rivers, before you rush on, I wish you would stop to tell me something about Dr. Webster and the nature of his work. Save for an obituary notice in *Science,* and a warm dedication in John Paul's re-

cent volume on *Clinical Epidemiology*, there is little personal data about Webster in historical literature.[11]

Rivers: I knew Leslie Webster very well, and as a matter of fact Jordi Casals and I wrote the obituary notice in *Science* that you mentioned. Webster was a graduate of the Johns Hopkins Medical School and after graduation spent a year in the Department of Pathology. In 1920 Harold Amoss persuaded Dr. Flexner to invite Webster to the Rockefeller Institute. Dr. Flexner did, and Webster remained at the Institute until his death in 1943. Webster was a man of great intelligence and vision, but he had a great deal of difficulty in expressing himself verbally, because he stuttered very badly. The interesting thing about his stuttering was that it didn't hamper him when he sang. Webster played the piano and when he would sit down to the piano he could sing a song without stuttering one bit. It was, however, painful to try to carry on a conversation with him, but that didn't interfere with his intelligence.

Up to the time that Webster first came to the Institute, the epidemiology of disease had been studied largely in human populations. The obvious difficulty here was that it was impossible to control conditions so that one could examine epidemiological problems experimentally. Webster, on the other hand, decided to study the spread of typhoid in mouse populations. Before anybody begins shooting, just let me say very quickly that Webster was not the only one who had that idea; and that several English workers, among them William W. Topley, Graham S. Wilson, and Major Greenwood had the same notion. I don't know who was first. Actually, I think that they developed their ideas simultaneously and independently.[12] I do know that they later disagreed on the meaning of their findings. Both

[11] T. M. Rivers and J. Casals, "Leslie T. Webster," *Science*, vol. 98:167 (1943); J. Paul, *Clinical Epidemiology*. University of Chicago Press, Chicago, 1956; P. K. Olitsky, "Leslie T. Webster," *Arch. Pathol.*, vol. 36:536 (1943).

[12] There can be little doubt that in this instance the English investigators had priority. In 1919 Flexner had observed the early work of William Topley and his associates in experimental epidemiology and was so impressed with its possibilities that, upon his return to the Rockefeller Institute, he began similar experiments in collaboration with Harold Amoss. When Amoss left the Institute in 1922 for another post, Leslie Webster took over the work in experimental epidemiology and developed it independently. Cf. G. W. Corner, *op. cit.*, pp. 197–200.

Webster and his English counterparts quickly learned that, when *B. enteritidis* (mouse typhoid) was introduced into a population of susceptible mice, an epidemic ensued which, while fatal to many, always left some survivors. They also found that when they added immigrants to such populations they could maintain the infection indefinitely. However, in spite of this, a certain number of mice always resisted the infection. I believe that Topley, Wilson, and Greenwood felt that the survivors had become immunized, and they contended that the constituents of the uninfected population were alike with regard to their initial resistance to an infection. Webster, on the other hand was convinced that individual mice in the population were innately resistant to typhoid infection at the outset, and that indeed various individuals in the population might differ widely in their initial resistance to infection. Very early, I would say about 1922, Dr. Webster began selective breeding experiments with mice to determine not only whether unexposed mice were all alike in their resistance to infectious agents, but more important whether mouse strains of uniform susceptibility or resistance could be developed. At one point in his work he did develop a strain of mice, 95 per cent of whom were highly susceptible to mouse typhoid, and another line, 95 per cent of whom were resistant to mouse typhoid infection.

I watched Webster's work with great interest, and pretty soon I got the idea that it might be nice if Webster would attack the problem of the epidemiology of virus disease in mice. Well, that was easier said than done, but I persisted, and when the louping-ill virus came along I finally convinced Webster that he ought to study the pathogenesis of the disease in mice, and in particular to investigate the value of serum therapy. I must say that Webster's work was beautiful—it was well thought out and well executed. He quickly demonstrated that, if you put louping-ill virus into the nose of a mouse, it traveled up the olfactory lobes into the brain and eventually down the cord.

Now, what I am about to say is strictly from memory and might not be 100 per cent accurate, but I seem to remember that he was able to show that lesions were present in the cord at least 24 hours before the animal showed any visible sign of illness. Now, this finding was in accordance with the belief that I had, namely, that, once a person was infected with a virus, it was very difficult to influence that in-

fection by the use of serum. Now, there are exceptions. For example, in measles it is about ten or eleven days from the time of exposure to the appearance of Koplik spots in the mouth and, from then, another two or three days before a rash appears on the body. Well it has been known for some time now that, if you give convalescent serum during the first six days after a known exposure, you can prevent the disease. From six days until Koplik spots begin to appear in the mouth, most physicians think that you can influence the severity of the disease if you give serum. However it's pretty definite that once Koplik spots appear in the mouth, it makes no difference how much serum you give; you just cannot influence the severity of the disease, either feverwise or as to the amount of rash you have. Now, measles happens to be a disease with a long incubation period. In a disease like yellow fever, where the incubation period is much shorter, it would be very difficult to demonstrate any effect of convalescent immune serum.[13]

Today of course very little serum is used for the treatment of virus diseases, but that has not always been so, and up until the early nineteen thirties the tendency was in the other direction. Actually, serum from animals or from convalescent human beings was used to treat a wide variety of viral infections. For example, for a very long time, convalescent human serum was used prophylactically and therapeutically in polio cases. It used to be that doctors would draw off a lot of spinal fluid and inject quite a bit of convalescent serum intrathecally for the treatment of polio. This went on for years, until the New York Academy of Medicine around 1931–32 put on an experiment to test the efficacy of serum therapy for polio and discovered that it was no use at all. Since that experiment, so far as I know, few if any doctors have ever worried about the serum therapy for polio. Let me tell you, however, that it was just harder than all outdoors to make doctors believe this initially. Hell, they had been using diphtheria antitoxin against diphtheria and it worked, they had been using antipneumococcal serum against type 1 pneumonia and it worked, so why should they believe that it wouldn't work against viruses? Everybody just believed that it had to work. Trying to sell a new idea in medicine is like

[13] The principles stated by Rivers, based chiefly on clinical observation, are also applicable to experimental viral infections. See P. K. Olitsky and A. C. Saenz, "Serum treatment of western equine encephalitis in mice determined by the course of viral infection," *Proc. Soc. Exptl. Biol. Med.*, vol 68:200 (1948).

trying to elect a completely unknown man to be president of the United States. It takes a lot of doing.

I would like to add here that before I finished my work with louping-ill, I found myself in a hassle with the government. Shortly after Dr. Webster began working with louping-ill, he and two of his technicians came down with the virus and became my patients in the hospital. After they were discharged, Dr. Schwentker and I wrote a brief paper on louping-ill in man, and all hell broke loose. Someone in Washington, by one of those strange coincidences, read that paper and the one I had previously written on Rift Valley fever in man and wanted to know how in the name of goodness I came to be working with two viruses that were prohibited from coming into the country. They made it plain that in their view I had broken the law, and they were going to throw the book at me. I just wrote back and told them that they had the wrong fellow, that I didn't bring the viruses into the country, and had in fact gotten them from my patients at the Rockefeller Hospital. I said that I saw no reason why I shouldn't get such viruses out of a patient I was caring for. But if the truth is known, I was whistling, and I thank goodness they didn't press me. I suppose they could have given me the works. Perhaps they decided that what I had learned was worth the risk. I don't know but I'd like to think that. In the end they left me alone, but I want to tell you they put a tight clamp on those two viruses' moving around the country. At the present time, so far as I know, nobody is working with those viruses.

Q: Dr. Rivers, was it very difficult in those early years to differentiate between the various virus diseases? For example, between St. Louis encephalitis and louping-ill?

Rivers: The answer to that question rested in large part on how well a virologist knew his pathology. For instance, St. Louis encephalitis and louping-ill both go in monkeys, and if you knew anything about the brain and cord you could differentiate between these two viruses pathologically. Louping-ill in the monkey does peculiar things, the animal can become paralyzed, but invariably the most marked clinical symptom is ataxia. The reason for this is that the louping-ill virus pri-

marily hits the Purkinje cells in the cerebellum. Don't misunderstand me, other parts of the cerebellum are involved, but the salient cells that are affected are the Purkinje cells. Subsequently I used sections from the cerebellum of monkeys infected with louping-ill to illustrate that infection and destruction of cells are primary phenomena in virus disease, and that inflammatory reactions are secondary. You know, I could kill a monkey infected with louping-ill, and if I caught him at the right time, every Purkinje cell would be gone. It was as if somebody had taken a forceps and picked out the cells leaving, little holes in their place. There would never be any evidence of inflammation. The only thing you could notice was that the tissues seemed to be a bit more watery. Inflammation came later, and it could easily be shown that it was due to the products of the dead cells, which are very irritating and cause inflammation.

In 1939, when I gave the Lane Lectures at Stanford University, I used pictures of the cerebellum of monkeys infected with louping-ill to underline this point. I assure you it was very dramatic to see every Purkinje cell missing from what seemed to be a normal cerebellum. Actually at that time you couldn't attract the average doctor unless you produced something dramatic. Like everything else, I suppose, when you have got to learn something that you didn't know before, or you have to alter your ideas, you don't do it easily. You have to be hit over the head. I used these pictures as my club.

Q: Dr. Rivers, I wonder if we could shift the focus of our examination from viruses per se, and take up a peripheral but important piece of research you did on allergic encephalitis in 1933.[14]

Rivers: In 1922 and for several years thereafter, in England, Holland, and other European countries it had been noticed that, following vaccination against smallpox, quite a number of people developed encephalitis. This postvaccinal encephalitis, as it came to be called, was far more prevalent abroad than it was in this country, although we did have our share of cases. Why there was such an outbreak at that time, I don't think anyone will ever know. Some of those

[14] T. M. Rivers, D. H. Sprunt, and G. P. Berry, "Observations on attempts to produce acute disseminated encephalomyelitis in monkeys," *J. Exptl. Med.*, vol. 58:39 (1933).

affected died, most recovered; however, in some cases there were unfortunate aftereffects. Now it had been noticed that, following certain diseases like measles, chickenpox, and influenza, and certainly following vaccination against rabies, that similar kinds of illnesses occurred. Some investigators in England and Europe were of the opinion that the condition arose because of the direct action of the virus on the brain, and that postvaccinal encephalitis was really a viral encephalitis.

I couldn't agree with this point of view, because I thought that the pathological signs that were found in postvaccinal encephalitis were definitely different from that found in an encephalitis produced, let us say by St. Louis encephalitis virus. In the latter case, where there is a direct action of the virus on the brain, the neurones in the gray matter are attacked, they die, and you have an inflammation around the dead cells. In postvaccinal encephalitis, the pathological picture is strikingly different. Here the white matter is attacked, and there is a distinct and startling demyelination around the blood vessels, particularly the small veins. There was one man in England at that time who agreed with me. His name was E. Weston Hurst. Dr. Hurst pointed out that in distemper in dogs (a virus disease) you actually could get two kinds of encephalitis, one that came early in the disease and another that came several weeks later, sometimes after the dog had about gotten over his original infection. He too was able to show that the pathological picture in such cases was markedly different. The problem still remained, as to how the postvaccinal encephalitis occurred. Well, like many another before me, I began to study the literature and I soon discovered that the question was not as new as I thought, and that it had come up earlier with rabies therapy. I learned that, in the early days of the use of the Pasteur rabies vaccine, some patients did come down with a peculiar demyelinating encephalitis, and that even in those days there was a big row as to whether this was due to the direct action of a virus that might have stayed alive in the vaccine or whether it had come about through the injection of foreign brain tissue into human beings. The more I read the literature the more fascinated I became, and I finally decided to see what would happen if I injected brain tissue into monkeys.

I killed perfectly normal rabbits, ground up their brains and began

to inject monkeys. I honestly didn't know how long I was going to do this, but for the next several months I injected about 1 cc of an emulsion of such brain tissue into monkeys twice a week. I figured I would just keep on doing this until something happened, or until I got disgusted and quit. This went on for approximately six months until one day Francis Schwentker, who was working with me, came in and said, "Tom, there is something the matter with those monkeys."

I said, "For Pete's sake, let's go over and have a look." Sure enough, one or two of the monkeys were slightly ataxic and looked kind of seedy. A day or two later they began to tremble and became weak in the legs, and very shortly thereafter they became so ataxic that they couldn't get around the cage. At this point I killed them. When I examined them, I found to my astonishment a remarkable change in the cord and brain. It was a demyelinating encephalitis. I must say that it didn't exactly look like the postvaccinal encephalitis that we saw in human beings, nor the kind described following rabies. But there was destruction of brain tissue, there was demyelination, and a lot of the lesions were around blood vessels, particularly veins.

It was extraordinary to learn that it was possible to kill an animal by repeatedly injecting it with some other animal's tissue. While Dr. Schwentker and I had not used the monkey's own brain we had no reason to believe that it couldn't be done. Later we showed that rabbit brain would do it in rabbits, and still later Dr. Elvin A. Kabat and Dr. Abner Wolf at Columbia University proved that it could be done in monkeys. They operated on a monkey, took out its frontal lobe, and froze and stored it on ice while the monkey recovered. They then took the lobe that they had stored, ground it up, added Freund's adjuvant, and injected the emulsion into the same monkey. That monkey got sick from its own frontal lobe, and I want to tell you that Kabat and Wolf didn't have to wait for their results six months like Schwentker and I had to.

To me, it's a profound biological phenomenon to learn that the tissues of a person or animal can create antibodies that will result in disease or the death of that person or animal. In the recent past, Dr. Ernest Witebsky in Buffalo, New York, and some English workers simultaneously demonstrated that Hashimoto's disease (acute thyroiditis) was caused by antibodies against the thyroid. Many workers

are now entertaining the idea that rheumatoid arthritis is due to auto-antibodies and are even suggesting that many of the chronic diseases that we call degenerative are caused in a like manner. Herein I think lies a lot for the future.

The work I did on demyelinating encephalitis is probably the nicest piece of work I ever did, and it wasn't in virology. To be sure, I was trying to get an answer to what might follow an infection of viruses, but it turned out to be a whole new field. Today a lot of people talk a great deal about allergic encephalitis, and the ironic part is that they don't connect me with it at all.

Q: Dr. Rivers, in previous conversation you have mentioned that pathologists know very well when a virus is infecting the brain. However, unless they should find particular inclusion bodies, it is difficult to differentiate one encephalitis from another. What do you do when you are presented with a new virus, let us say, the one that causes lymphocytic choriomeningitis?

Rivers: I remember that, sometime during the winter of 1934, Dick Shope of the Division of Animal Pathology of the Rockefeller Institute and Bill Edwards, a house painter at the Institute both showed up on my ward with complaints that suggested involvement of the meninges and possible involvement of the brain. Dr. Thomas McNair Scott, who is now professor of experimental pediatrics at the University of Pennsylvania Medical School, was working with me at that time, and I put him in charge of both cases. Tom took spinal fluid from the patients, put it intracerebrally and intraperitoneally in mice and began to watch the mice. After two or three days the mice that had received the inoculations began to show certain peculiarities, and Tom called me in to look at them. We did nothing at that time, but a day or two later, when the mice were obviously sick, we killed them and isolated a medium sized virus. After making a series of transfers in mice, we became confident that the virus we had found truly came from the patient's spinal fluid and not from the animals we were working with; it was unlike any virus I had worked with before, and I thought we had discovered a new virus.

However, after talking around and searching the literature I discov-

ered that this was not so. It turned out that Charley Armstrong of the National Institutes of Health had isolated a similar virus several months before. As I remember it, Charley isolated his virus from a patient who was originally diagnosed as having St. Louis encephalitis. Well, this poor fellow died, and Charley began to pass material taken from him to monkeys. In the first passage, the clinical picture fitted with that generally found in St. Louis encephalitis; however, after several passages, the clinical picture began to change, and when Charley made a pathological examination of the monkey he not only found lesions that were usually observed in viral encephalitides, but he also found a marked involvement of the meninges, ependyma, and the choroid plexus. Given these findings, Charley named it lymphocytic choriomeningitis. I'd like to add that at that time there had never been any autopsy on human beings for this condition—it's a relatively mild disease in humans—and that the disease was named for a condition found in monkeys and mice.

About the same time this was going on, Eric Traub of the Division of Animal Pathology of the Rockefeller Institute at Princeton was trying to produce hog cholera in mice. He was injecting hog cholera material into the brains of white Swiss mice when, lo and behold, a good many of them came down with an encephalitis. At first he thought that he had adapted hog cholera to mice, but then he noticed that his control mice, which had received sterile normal broth, also came down with the same kind of disease. A careful examination revealed that practically all of the mice in the Princeton laboratories were carrying this virus in a latent form, and that it was passed from mother to offspring.

When Tom Scott and I found our virus, it didn't immediately occur to us that our virus was the same as that found by Armstrong and Traub. I do not remember now who suggested that we compare our viruses, but someone did and, on comparison, it turned out that they were identical.

I can understand how Dick Shope got his infection. He was working with Princeton mice and they were loaded with the virus. But for the life of me, I don't know where Bill Edwards got his. I know that none of the white mice that we were using at the Institute were infected, because if they had been they never would have shown any-

thing when we inoculated them with Shope's and Edwards' spinal fluid—so they were clean. The origin of Bill Edwards' infection remains a mystery to me.

It can be said that the virus was discovered independently in three separate laboratories almost simultaneously. The honor for naming the disease goes to Armstrong. In the middle thirties we saw quite a bit of lymphocytic choriomeningitis in human beings and it seemed that people all over the country were showing up with this queer disease. And you know, by gosh, even before I stopped working on viruses the disease seemed to disappear. Today you practically never hear of anyone being infected with lymphocytic choriomeningitis.

Q: Dr. Rivers, with the continuing identification of new viruses, was there a tendency on the part of general practitioners to ascribe unknown infections to viruses? How many laboratories were set up to do routine diagnostic work of viral infections?

Rivers: To be sure, there was a tendency on the part of some practitioners to ascribe all unknown disease to virus infection, and I might add that there is such tendency now. If a doc can't readily find the cause of a disease, he sometimes says to the patient, "You are infected with virus X." Whatever X may mean, it means he doesn't know. On the whole, I would say that doctors during the thirties could quite readily differentiate a viral from a bacterial infection. In cases of meningitis, an examination of the spinal fluid could readily show if the patient had a viral or a bacterial meningitis. If it was bacterial, the spinal fluid was usually cloudy (although it is true that in tuberculous meningitis the fluid can be fairly clear) and microscopic smears would turn up meningococci, strep, or other bacteria, while if it was viral the spinal fluid was clear.

In my day, when a physician got a case that presented meningeal signs like lymphocytic choriomeningitis he looked to see if it satisfied the criteria [15] laid down by the Swedish pediatrician Arvid Wallgren,

[15] Sudden onset of meningeal symptoms associated with a slight or moderate increase in the number of cells, especially lymphocytes, in a bacteria-free spinal fluid; a benign course with no complications; the absence of a focus of acute or chronic infection in the vicinity of the brain, for example sinusitis; and the absence from the community

and if it did he called it acute aseptic meningitis. Wallgren considered this condition as a clinical entity and that bothered me. It was plain that there were many different kinds of infections of the central nervous system that would fall under Wallgren's description of aseptic meningitis, and it was almost impossible to differentiate, by clinical means alone, a case of acute aseptic meningitis caused by the virus of lymphocytic choriomeningitis from those produced by another agent. I later wrote a paper attacking Wallgren, but let me make plain that that didn't make him any less a great man. He was a great pediatrician, and in my view, although I later attacked him he made an important contribution through his use of the term, acute aseptic meningitis. Keep in mind that he was out in front of the boys.

During the thirties there were few laboratories that were set up to do routine virus diagnostic work. In New York, for example, if a general practitioner turned up what he thought was a case of psittacosis or lymphocytic choriomeningitis, he would send me the patient's blood or spinal fluid for examination. He did this, because he knew I was working on these diseases. In other parts of the country doctors might call on Ernest Goodpasture or Karl Meyer or Lloyd Aycock. Today a certain number of cities and states have set up virus diagnostic laboratories that can with a reasonable amount of speed and not too much expense give the general practitioner an accurate diagnosis. For instance, Werner Henle's laboratory at the University of Pennsylvania is supported by the state to do routine diagnostic work for viral diseases in Pennsylvania. It's an example that can be multiplied several times over. In my day, such laboratories were lacking.

Q: Dr. Rivers, I would like to shift the focus of our attention from viruses that you worked with in the laboratory to a virus that you didn't work with, but one whose effects absorbed your attention, namely, the virus of poliomyelitis. In 1936, for example, you became associated with the President's Birthday Ball Commission, which was then one of the major agencies in the United States directing the battle against poliomyelitis. I would like to begin with a discussion of the

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of diseases known to be capable of producing irritation of the meninges. Cf. R. D. Baird and T. M. Rivers, "Relation of lymphocytic choriomeningitis to acute aseptic meningitis (Wallgren)," *Amer. J. Public Health,* vol. 28:47 (1938).

members of the commission and the circumstances that led to your joining.

Rivers: Let me say that in the beginning I did not know any of the members of the Birthday Ball Commission, like Basil O'Connor, Keith Morgan, Jeremiah Milbank, Edsel Ford, or the others who were concerned with raising funds. I did know the members of the advisory committee who were charged with the responsibility of distributing the funds collected by the Birthday Balls for research. At that time 70 per cent of all the money collected remained in the local areas and was largely used in makeshift local care programs, while 30 per cent went to the national office and was used for administrative cost and an over-all research program. The committee in charge of planning the research program was composed of Dr. Max Peet, Dr. Donald Armstrong, Dr. George McCoy and Dr. Paul de Kruif. I would say that, while the committee had distinguished people on it, it wasn't particularly prepared to deal with the problems presented by the virus of poliomyelitis.[16]

Max Peet was a neurosurgeon and a good one. He was an honest, straightforward, and upright person. I liked him, but he didn't know anything about viruses.[17] I could never see why he was on the committee, except that he was a friend of Paul de Kruif's, and anything that Paul wanted to do, Max said yes to. Dr. Donald Armstrong was a third vice president of the Metropolitan Life Insurance Company, in charge of medical affairs. He was clear minded and knew much about problems of public health, but knew little about virus research. About the only fellow on the committee who knew anything about viruses was Dr. George McCoy. Dr. McCoy was in charge of the Hygienic Laboratory of the U.S. Public Health Service in Washington. Early in his career he had done very nice bacteriological research and later was

[16] The first Birthday Ball to raise funds for Georgia Warm Springs Foundation was held January 30, 1934. Subsequently, from 1935 to 1938, this nationwide celebration of the President's birthday became the principal method of raising money to fight infantile paralysis. On December 15, 1934, a special Birthday Ball Commission of fifteen prominent people was organized to administer the funds raised by the birthday balls. To aid the commission in its work, a special scientific advisory committee was formed early in 1935 and began making grants to medical investigators on May 28, 1935. The first sixteen grants made totaled $241,000.

[17] In 1937, Max Peet helped isolate Lansing type 2 poliovirus.

the boss of such excellent experimentalists as Dr. Joseph Goldberger and Dr. Charles Armstrong. I would say that Dr. McCoy had more scientific knowledge about viruses than anyone else on the committee. However, he had very little to say about what was to be done. Without a doubt, the most important member of the advisory committee was Paul de Kruif.

Paul de Kruif was and is an interesting man. Originally he took his Ph.D. in bacteriology at the University of Michigan under the tutelage of Frederick G. Novy, one of the great bacteriologists in the United States at the beginning of this century. After he got his Ph.D. he came to the Rockefeller Institute and worked in the laboratories. I want to tell you that de Kruif did excellent work. Together with John Northrup, he described the rough and smooth colonies of salmonella. I don't think I am exaggerating when I say that de Kruif and Northrup had within their grasp one of the most important phenomena in bacteriology, but unfortunately they were never able to exploit it. Later when the English bacteriologist Dr. Joseph A. Arkwright pointed out that the rough colonies were nonpathogenic and the smooth colonies were pathogenic, he was knighted.[18] In the thirties the same phenomena was shown to be true with pneumococci as well. de Kruif had the makings of a great scientist. I know him well and, even though I know that he doesn't like me, I can't refuse to say that at one time he had these great possibilities. He never got a chance to develop them at the Institute because Dr. Flexner fired him. Around 1922 de Kruif wrote an anonymous attack on the Institute in a popular magazine which he signed M.D. When Flexner discovered that it was de Kruif who wrote the piece he fired him. Now I want to make it clear that de Kruif was not fired for writing the article. He was fired—in Flexner's words to me as well as to de Kruif—for not signing the article. I don't think that de Kruif would have been fired if he had signed the article.

Dr. Flexner put great store on having the courage of one's convictions and standing up and taking responsibility for one's thought and actions. For instance, I informed Dr. Flexner that I was going to at-

[18] The implication of Rivers' statement is misleading. Arkwright's research on bacterial variation started several years before de Kruif began his own experiments and was carried on independently of de Kruif. Arkwright's knighthood was conferred for a broad range of bacteriological research. See C. J. Martin, "Joseph Arthur Arkwright, 1864–1944," *Obit. Notices Fellows Roy. Soc.*, vol. 5:127 (1945).

tack him publicly at a meeting of the Society of American Bacteriologists on one of his fondest scientific beliefs, the globoid bodies of poliomyelitis, and nothing ever happened. He didn't try to stop me and he didn't fire me. When Dr. Olitsky and Dr. Long presented scientific proof controverting Flexner and Noguchi's theory, the article was printed with Flexner's blessing in the *Journal of Experimental Medicine*. Flexner was like that.

Paul de Kruif's rupture with the Institute was complete, and soon after he took a great public revenge. Sinclair Lewis was at that time preparing to write his novel *Arrowsmith*, and de Kruif became his advisor on scientific problems. The McGurk Institute so beautifully satirized in the novel is the Rockefeller Institute. Most of the members of the Institute found their way into the novel, Jacques Loeb, John Northrup, Peyton Rous, Simon Flexner, and others. They were recognizable although never identified by name. Some of those portraits were etched in acid, and the book [19] remained a topic of conversation at the Institute for a long time.

[19] Paul de Kruif's autobiography also contains an account of his stay and separation from the Rockefeller Institute. While his version contains substantially the same facts as are related by Rivers, the nuances de Kruif gives these facts make for another interpretation. See P. de Kruif, *The Sweeping Wind*. Harcourt, Brace & World, New York, 1962, pp. 16–51. Peter Olitsky, another contemporary of de Kruif's at the Rockefeller Institute, offers these observations on de Kruif's relations with the Institute and with Flexner:

I had been Paul's next-door neighbor at the Rockefeller Institute during a considerable period of his stay at the Institute (1919–1922). We learnt a great deal about each other and were quite friendly; there was always something of interest to hear in his laboratory—talk of shop and gossip—and he had a captivating way in which he entertained his visitor. Many persons thought as I did; consequently his laboratory was usually the scene of much sociability. On the day he was dismissed from the Institute by Dr. Flexner, I met Paul on his way out; he was deeply aroused and excited and said that he had a "waspish pen" and would settle accounts with Flexner in a way to get his revenge for this dismissal. I tried to dissuade him from such action but was turned down.

Dr. Flexner felt that the lay articles, papers, and books published by de Kruif, whether anonymously or not, had the appearance of having the approval of the Rockefeller Institute (as advertised by Hearst's International Magazine, for example), and that the responsibility for his publications was therefore forced on the Institute without any editorial consent for de Kruif's literary work, in advance of publicaion. Flexner thus justified his stand on [de Kruif's] dismissal.

On the other hand, de Kruif's colleagues at the Institute regarded his microbiologic work as superior and excellent, strikingly original and obviously important, and himself as a young genius of great possibilities. They expressed amazement by his divagation into the field of journalistic writing and tended to blame Mencken and others of the Smart Set*—a contemporary magazine of the avant-garde of the early twentieth century,*

Later de Kruif demonstrated that he had great possibilities as a writer. I don't exaggerate when I say that his books, *Microbe Hunters* and *Hunger Fighters,* were read by hundreds of thousands. He had a style that had never been seen before in popular scientific writing and it caught on—to such an extent that other writers tried to copy him. I suppose that that is the final accolade for a writer. The tragedy is that, although Paul has been a successful writer, he has never realized his potential as a writer. I suppose that during the thirties Paul de Kruif was probably the world's leading writer in the field of medicine and science, and I suspect it was this preeminence which brought him on the advisory committee of the Birthday Ball Commission.

Q: Dr. Rivers, if you examine the grants made by the Birthday Ball Commission, it appears that very little of the funds was expended for learning about the fundamental nature of polio virus.

Rivers: If my memory doesn't play me false, Louis Weed, Joe Stokes, Howard Howe, and Lloyd Aycock all received grants which allowed them to pursue questions relating to the fundamental nature of the virus. But you are right when you imply that most of the re-

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long since defunct—for the loss of de Kruif to science: they believed that these editors of the Smart Set *had taken de Kruif from the straight and narrow and well-defined road of science and steered him onto the winding, wide, and unmarked way of journalism. In this, Norman Hapgood of* Hearst's International Magazine *also had a definite, directive hand. Mencken is described in the* Columbia Encyclopedia *as writing "pungent, iconoclastic criticism, aimed chiefly at all complacent attitudes." The editors believed that there was a field for their kind of writing in science, even though science is never complacent. I endeavored to discuss these matters with my neighbor, but he believed me timid and reactionary. After his establishment as a going concern in journalism, he lost his zest for laboratory investigation, for Professor Elser of Cornell told me he kept a place open for him for a long time without any success in trying to get him back to his original aptitude for microbiology.*

One must say, however, that he made a brilliant success, not only of his short experience in scientific research, but also of his writing for the lay reader. Indeed, even Dr. Flexner acknowledged the excellence of his Microbe Hunters.

I must add here that . . . Albert Sabin, when he was my associate, related how he had completely abandoned his course in dentistry and changed over to study medicine, for after reading [Microbe Hunters] *he became imbued with, and carried away by, the idea of wearing the shining armor of a microbe hunter* (private communication).

For those interested in examining further the role of de Kruif in the writing of Sinclair Lewis's *Arrowsmith,* see M. Schorer, *Sinclair Lewis, An American Life.* McGraw-Hill Book Co., New York, 1961; C. Rosenberg, "Martin Arrowsmith, the scientist as hero," *Amer. Quarterly,* vol. 15:448 (1963).

search funds went toward developing a vaccine. As a matter of fact, Dr. William H. Park received a great deal of money from the Birthday Ball Commission for just such a purpose.

Q: Did the Rockefeller Institute get such help? After all, the Institute pioneered in the field of polio research in the United States.

Rivers: As I mentioned earlier, de Kruif and Flexner didn't get along, and it should come as no surprise that the Institute didn't get any money from the Birthday Ball Commission. I doubt whether the Institute would have taken it even if it had been offered, first, because Mr. John D. Rockefeller, Jr., did not allow anyone from outside—either government or private agencies—at that time to contribute to the support of the Institute research projects, and, second, because Dr. Flexner did not think that it was possible to make a practical vaccine against polio at that time.

Paul de Kruif did know William H. Park and considered him a very distinguished scientist and one certainly worthy of support. Let me add that Dr. Park in his heyday was a great. He was an original and had made important contribution to our understanding of diphtheria, influenza, and measles. In the late twenties Park became interested in polio and tried to develop a horse serum against the disease. As might be suspected, the serum he developed didn't work. Park, and for that matter other workers at that time, didn't know that there were three types of polio, and even if the antiserum Dr. Park made in a horse had worked it would only have been good against one type of polio. Dr. Flexner was pretty acid about this work and I suppose part of it went back to the fact that there was no love lost between the two men. Now what I am going to tell you is rumor, gossip, hearsay—call it what you will—but it was common talk among the bacteriologists of my day.

You may remember that I told you earlier that Flexner, Park, and Lewellys Barker in 1899 were part of a commission to investigate dysentery in the Philippine Islands. During the course of that expedition, a new dysentery organism was discovered. The honor of that discovery went to Dr. Flexner and the organism was named after him. The story goes that Dr. Park always felt that he was the true dis-

coverer of the bacillus and that it should have been named after him. Now, I don't know who discovered the bacillus. I don't care to know if Flexner did or Park did. This was gossip that went the rounds and was used in explanation of why Flexner and Park were not friends.[20]

Be that as it may, I want to tell you that, if Dr. Park ever needed polio material for experimentation, he always sent to Dr. Flexner for virus, and his request was always filled and promptly. That was one of Dr. Flexner's attributes, and it still is one of the attributes of the Institute. If we have something at the Institute that other people want, other people usually get it.

In the early thirties Park teamed with a young Canadian bacteriologist named Maurice Brodie to produce a formalinized inactivated vaccine against polio. Dr. Brodie had trained at McGill. Early in 1930 he showed up at the Institute with a letter from one of his professors saying that he wished to learn about poliovirus. Dr. Flexner was very nice, took him to his laboratory, and turned him over to Peter Haselbauer. Peter is what I would call a very high-class technician. He came to the Institute when he was a young boy—just out of high school, I believe—and Dr. Flexner trained him as a technician. He spent his entire life at the Institute and became in fact Dr. Flexner's technician. He was associated with Dr. Flexner in polio research almost from the beginning of Dr. Flexner's own researches in 1909, and so he knew a great deal about the MV virus used at the Institute. Peter was a pretty smart hombre and, although he didn't have formal collegiate training, he was good. Flexner would write out the protocol for the experiment, and Peter would do it. Peter, of course, was in no position to form an opinion as to whether the old man was right or wrong about a given experiment, because he didn't

[20] There is no doubt that there was a great antipathy between Dr. Park and Dr. Flexner. In this respect, what Dr. Rivers says above is true. The reasons that Rivers ascribes for that antipathy are, however, a complete myth. Dr. Park was not a member of the Philippine expedition, and there was never any debate between Dr. Flexner and Dr. Park over the discovery of *Shigella flexneri*. The bad feeling between the two scientists stemmed from Dr. Park's public attack on the efficacy of Dr. Flexner's serum treatment of meningitis before the Harlem Medical Society and in the public press (see *New York Evening Post*, January 16, 1912). Later when Dr. Flexner's treatment was proved effective, Dr. Park took the position that Dr. Flexner had merely copied the ideas of the German physician, Dr. Georg Jochmann (see correspondence in folder marked Meningitis Serum, Flexner papers). The myth here created is, however, revealing of Rivers.

have the background, but, as I say, he was a superb technician and Flexner could rely on him. Peter taught Brodie about the MV virus for about a month or six weeks, and then Brodie returned to McGill. After that I didn't hear about Brodie for several years. Actually, I didn't hear of him again until he came to New York University as assistant professor of bacteriology in the Medical School and had joined forces with Dr. Park to try to produce an inactivated formalinized vaccine against polio.

At the time Dr. Brodie came to work with Dr. Park, Park was failing, and as a matter of fact he later became very senile. On several occasions Brodie came to see me at the Institute to discuss problems related to making an inactivated vaccine and while I listened to what he had to say I said very little in reply, because I didn't want to hurt Dr. Park's feelings. By 1935 Dr. Brodie claimed that he had an inactivated formalinized vaccine that was capable of inducing immunity in monkeys and humans. Among other things, he maintained that he had developed a minimal completely paralyzing dose of virus. He carried out his titrations to five and six decimal places. Don't ask me how he got such titrations because I don't know. I do know that I didn't believe them. Later Brodie took a lot of people, bled them, and did antibody titers. Many adults, as you know, have antibodies against type 2 polio. Brodie claimed that, when he gave them formalinized suspensions of virus, he could demonstrate a rise in antibodies. Well, while the amount of stuff he injected might have acted to cause an increase of antibodies, I seriously doubt whether it could have induced the antibodies to come to the point where he could demonstrate them.[21]

Everything, as I say, came out just right, and Brodie and Park persuaded public health officials in California to allow them to immunize about 7000 children with their vaccine. Dr. Ralph Muckenfuss who had earlier worked with me at the Rockefeller Institute, was at this time associated with Dr. Park, and he told me—and you might confirm my remarks with him to see if I have unintentionally distorted what I am about to say—that the vaccine was made in the most incredible sloppy manner.

[21] On this particular point, see also M. Schaeffer and R. S. Muckenfuss, *Experimental Poliomyelitis,* The National Foundation, New York, 1940, pp. 80–82.

The question we now come to is whether any of the children who received the Park-Brodie vaccine came down with polio as a result of using the vaccine. Dr. Norman Topping, who was with the U.S. Public Health Service in California at that time, has maintained that some of the children who received the Park-Brodie vaccine could have come down with polio as a result of the vaccine, because they came down within the proper incubation period after having received the vaccine. However this, as far as I know, has never been proved. It is unquestionable, however, that some of the children who received the Kolmer live-virus vaccine at that time did come down with polio.

Q: Dr. Rivers, in retrospect, there are a number of disquieting aspects to the Park-Brodie vaccine incident. Isn't it true that, long before immunization with the Park-Brodie vaccine took place in California, workers at the Rockefeller Institute were skeptical of Dr. Brodie's and Dr. Park's findings?

Rivers: That is true. Dr. Flexner was very skeptical of this work, and I believe he asked Peter Olitsky to see if he could repeat Dr. Brodie's experiments. Dr. Olitsky, with the assistance of Dr. Albert Sabin and Dr. Perrin H. Long, then tried to see if they could immunize monkeys following Brodie's procedures and had no success at all. I watched them. They did a nice job, but they found it impossible to repeat Brodie's work.[22]

[22] Dr. Olitsky disputes Rivers here.

Dr. Rivers' memory is somewhat dim here. What happened was that I had started in 1935 on this work of reexamination of Kolmer and Brodie's experiments, employing ricinoleate (Kolmer) and formalin (Brodie) as virucidal agents, adding tannin for control and untreated virus (infected monkey brain) as another control, to note whether an effective vaccine could thereby be produced for use in monkeys. I later requested my associate, Herald Cox (Drs. Sabin and Long were not available then) to join me in this work. I had great respect for his ability and skill and desired to continue work on the polio problem.

The virucidal agents were used in the dosages prescribed by Kolmer and Brodie. We found that, in general, if these chemicals did not act a sufficient time, the vaccine by itself could produce polio in monkeys; if they were applied over longer periods of time and killed the virus, no immunity, except rarely, was induced to a test dose of virus given into the brain of vaccinees, but antibody could be found in the blood. Also, it was difficult to find an end point for formalin; ricinoleate was generally ineffective. Dr. Cox did well in this work and this was the beginning of his researches on polio, which he

Q: If that is true, why didn't the Institute make an attempt to halt the immunization program projected by Dr. Park and Dr. Brodie?

Rivers: Well, California is a long way from New York, and I expect that the people in California were much more cognizant of Dr. Park than they were of Dr. Flexner. Park's name was awfully well known the world over.

Q: Come now, Dr. Rivers, Dr. Flexner was surely as well known as Dr. Park. Even if what you say is true for California, how do you explain the fact that the U.S. Public Health Service allowed vaccination with the Park-Brodie vaccine in North Carolina and Virginia? They surely had as much respect for Dr. Flexner's name as for Dr. Park's name.

Rivers: Well, all I can say is, it's against the law to do many things, but the law winks when a reputable man wants to do a scientific experiment. For example, the criminal code of the City of New York holds that it is a felony to inject a person with infectious material. Well, I tested out live yellow fever vaccine right on my ward in the Rockefeller Hospital. It was no secret, and I assure you that the people in the New York City Department of Health knew that it was being done. Then again, the statutes of the City of New York plainly say, if there are cases of yellow fever in the city a yellow flag should be flown in the harbor for all to see. I don't know whether anyone saw such a flag flying when I had several yellow fever cases on my ward in 1931.

Unless the law winks occasionally, you have no progress in medicine. For instance, it was plainly against the law for people at the Sloan-Kettering Institute and the Memorial Hospital several years ago to inject people with what they thought were oncolytic viruses. The Department of Health and the lawyers running the city knew about it but again they did nothing. They cooperated. Actually, you

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continued after his departure from my laboratory with brilliant success (private communication).

For further detail of this work, see P. K. Olitsky and H. R. Cox, "Experiments on active immunization against experimental poliomyelitis," *J. Exptl. Med.*, vol. 63:109 (1936).

have such laws to keep unprincipled people from taking advantage of an unsuspecting public. Remember that Dr. Park, Dr. Brodie, and Dr. Kolmer were well-known scientists. For instance, John Kolmer's name was known all over the United States, because of the excellent book he had written on serological techniques. I don't think that there was a laboratory in the country that didn't make use of that book. They were not penny ante fellows.

Q: Dr. Rivers, apparently there were a number of people who did have second thoughts about both the Park-Brodie and Kolmer vaccines. Wasn't a meeting arranged by the American Public Health Association in October 1935 to discuss the safety of the Park-Brodie and Kolmer vaccines? [23]

Rivers: Indeed, there was such a meeting, and I was asked to go out to Milwaukee and be the hatchetman. I kind of dreaded the job because I liked Dr. Park, but believe me I didn't mind jumping on Dr. Brodie and Dr. Kolmer. The meeting was much like any other meeting run by the Public Health Association. Brodie and Kolmer had been asked to prepare papers and I was asked to discuss them. While I remember the substance of my remarks, I don't remember the detail and I would like to submit here a typewritten copy of the remarks I prepared for that meeting. You can insert it later. [See Appendix B.]

I remember that there was subsequent discussion of my paper by Brodie, Park, and Kolmer, but I don't think that anything conclusive happened. After the meeting Dr. Foard McGinnes asked me if I would join another symposium on poliomyelitis to be held at the meeting of the southern branch of the American Public Health Association in St. Louis the following month.[24] This time I was asked to prepare a formal paper on immunity in virus diseases with particular reference to poliomyelitis. Dr. Brodie, Dr. Park, and Dr. Kolmer were again asked to prepare papers describing their work on polio immunization, and in addition Dr. Robert Onstott and Dr. Alexander Gilliam of the U.S. Public Health Service, who were associated with field

[23] Meeting of the American Public Health Association, Milwaukee, Wisconsin, October 8, 1935.

[24] Dr. Rivers' reference here is to the Fourth Annual Meeting of the Southern Branch of the American Public Health Association, held on November 19, 1935, in St. Louis.

studies of polio vaccination in North Carolina, were also asked to prepare papers.

The paper I presented was later published in the *American Journal of Public Health,*[25] and if you examine it I think you will find that while I made more extensive remarks about the nature of immunization to virus diseases in general, the substance of my remarks about the Park-Brodie and Komer vaccines was the same as those I had made a month before. But I want to tell you that the meeting in St. Louis was very different from the one held in Milwaukee—the difference was James P. Leake of the U.S. Public Health Service. Dr. Leake was a very distinguished field officer who had had a long experience with polio, dating back to the epidemic of 1916. He was in charge of the immunization program in North Carolina and had followed very closely the polio cases that appeared after use of the Kolmer live-virus vaccine. Because Dr. Onstott and Dr. Gilliam were officially giving papers on behalf of the U.S. Public Health Service, Leake was not at the meeting in an official capacity. However, just as soon as I finished giving my paper (mine was the last in this particular session) and the floor was open to discussion, Leake was on his feet. I want to tell you, he was hot under the collar. He presented the clinical evidence to the effect that the Kolmer live-virus vaccine caused several deaths in children and then point-blank accused Kolmer of being a murderer.

All hell broke loose, and it seemed as if everybody was trying to talk at the same time. A little later Dr. Brodie got up and said, "It looks as though, according to Dr. Rivers, my vaccine is no good, and, according to Dr. Leake, Dr. Kolmer's is dangerous." He sat down and Dr. Kolmer got up. He didn't refer to me at all. He just said, "Gentlemen, this is one time I wish the floor would open up and swallow me." He then sat down.

Jimmy Leake used the strongest language that I have ever heard used at a scientific meeting and when he got through speaking both vaccines were dead. It took something like Jimmy Leake's statement to put an end to the vaccines. When you say somebody is committing murder, people usually stop and think. I believe that the vaccines would have died a natural death within a year, but Leake killed them

[25] T. M. Rivers, "Immunity in virus diseases with particular reference to poliomyelitis." *Amer. J. Public Health,* vol. 26:136 (1936).

then and there—you didn't have to wait twenty-four hours. The vaccines were dead and so were careers. Within a very short period of time, Brodie was fired from his post at New York University, and Kolmer and Park retired.[26] It was because of the Park-Brodie vaccine that I was asked to come on the advisory board of the Birthday Ball Commission.

Q: Could you explain the last statement a little more fully?

Rivers: Yes. Paul de Kruif and the rest of the boys on the Birthday Ball advisory board were afraid to tell Dr. Park that he couldn't get any more research funds. They had to have somebody like me—a rough-neck—to get the job done. After I came on the commission, Dr. Park never got another cent. For the life of me, I couldn't see why he got all that money in the first place. I would have been in favor of giving some of those funds to Lloyd Aycock of the Harvard Medical School and David Kramer of the Long Island Medical School. Now that is not hindsight. Both Dr. Aycock and Dr. Kramer had had a long experience with polio through their association with the Harvard Infantile Paralysis Commission and knew polio from the clinical as well as experimental side. Aycock and Kramer ironically did receive some money from the Birthday Ball Commission, to test the results of the Park-Brodie vaccine immunizations in North Carolina. Later when the National Foundation came into existence, Dr. Kramer, who by that time had moved to the Department of Health of the state of Michigan, received several grants and did interesting work developing

[26] The printed record of the discussion at this meeting in the *American Journal of Public Health* does not contain the harsh language that Rivers claims was used by Leake. Here Leake is pictured as saying, "I beg you, Dr. Kolmer, to desist from the human use of this vaccine." It is very probable, however, that Leake used stronger language, and the editor of the *American Journal of Public Health* later altered it for purposes of publication. Soon after my interviews with Rivers I had occasion to speak with Leake about this point, and he told me that, while he didn't remember the exact words he used at the meeting, he did remember that he had used some very harsh language. Cf. "Discussion of poliomyelitis papers," *Amer. J. Public Health,* vol. 26:148 (1936).

Rivers' account in one respect misconveys the outcome of the failure of the vaccines. The burden for that failure was publicly borne by Dr. Brodie. Dr. Park was retired with honors, Dr. Kolmer continued a useful and productive career as a professor of medicine at Temple University School of Medicine until his retirement in 1957. Only Brodie was fired and disgraced.

a killed vaccine against polio. If I am not mistaken he got very suggestive results in mice—but again no one took them very seriously.

Q: Dr. Rivers, live-virus and inactivated-virus vaccines were not the only ways thought of by doctors to protect against polio. Didn't some investigators like Dr. E. W. Schultz attempt to prevent infection through intranasal irrigations with various chemical agents such as tannic acid, zinc sulphate, and picric acid? [27]

Rivers: Dr. Schultz was not the only one who tried this. Peter Olitsky and Albert Sabin at the Institute tried it, and so did Charley Armstrong of the U.S. Public Health Service. I believe they all used different chemicals, but the general idea was to see if, by treating the olfactory nerves with chemical solutions, they could prevent the virus from traveling along the olfactory nerves to the brain. At that time Dr. Flexner thought that the virus traveled in lymph channels around the nerve to the brain but later W. E. Le Gros Clark in England proved that it traveled along the nerves themselves.[28] The experimental work with sprays in animals was suggestive, and in 1936 Dr. Armstrong tried using picric acid and alum sprays on children in Alabama. Armstrong was never able to prove whether the children whose noses he had sprayed were protected against polio. Actually, he never got a chance to run the controlled experiment he needed, because

[27] The interviewer here was not as precise as he might have been in posing the question. There is no doubt that as early as 1934 Peter Olitsky and Herald Cox had demonstrated that a dilute tannic acid solution put into the nostrils of white mice served to protect them transiently against an intranasal installation of equine encephalitis virus. Subsequently this technique was independently and almost simultaneously adopted by Charles Armstrong, Edwin Schultz and Peter Olitsky in their experimental poliomyelitis research. See P. K. Olitsky and H. R. Cox, *Science*, vol. 80:566 (1934); C. A. Armstrong and W. T. Harrison, "Prevention of intranasally inoculated poliomyelitis of monkeys by the installation of alum into the nostrils," *Public Health Rept.*, vol. 50:725 (1935); E. W. Schultz and L. P. Gebhardt, "Prevention of intranasally inoculated poliomyelitis in monkeys by previous intranasal irrigation of chemical agents," *Proc. Soc. Exptl. Biol. Med.*, vol. 34:133 (1936); A. B. Sabin, P. K. Olitsky, and H. R. Cox, "Protective action of certain chemicals against infection of monkeys' infection of monkeys with nasally instilled poliomyelitis virus," Abstract, *J. Bacteriol.*, vol. 31:35 (1936); article later printed in full, *J. Exptl. Med.*, vol. 63:877 (1936).

[28] Rivers has reference here to W. E. Le Gros Clark, *Anatomical Investigation into the Routes by Which Infections May Pass from Nasal Cavities into the Brain.* Ministry of Health Reports on Public Health and Medical Subjects, No. 54 H. M. Stationery Office, London, 1929.

parents in Alabama started to spray children on their own and the kids he did spray resisted so much that he never knew whether he had in fact thoroughly applied the spray in the nasal vault.

Later the spray idea was given an extended test in Toronto, and the doctors there concluded that the spray would not protect because you couldn't apply it properly without putting the child on his back and lowering his head in such a manner that he would receive the full effect of the spray in the nose. It certainly wasn't a procedure that could be used for spraying large populations of children. Max Peet tried to devise a practical technique for spraying large groups of children but never came up with a practical solution. The sprays were not without danger—some of the people who received the spray lost their sense of smell. One such person was Dr. Donald Fraser of the Connaught Laboratories. He never regained it to the time he died. He told me once that the only objection he had to this loss was that he couldn't enjoy his sherry anymore. You know, you smell sherry instead of tasting it. Given these results, spraying of the nose with zinc sulphate, picric acid, or what have you fell into disuse. However, when the National Foundation came into being in 1938 people still spoke of sprays and the Foundation was quite prepared to support such a program if someone came up with a decent testing plan. No such plan was ever presented, and the sprays also died a natural death.

Q: Dr. Rivers, I still can't understand why the major research support of the Birthday Ball Commission was directed to problems of immunity, rather than dealing with basic problems relating to the poliovirus per se—for instance, trying to type the virus.

Rivers: I am not sure I understand all of this myself. You know, when the St. Louis encephalitis virus was discovered, in very short order it was differentiated from other encephalitic viruses like Japanese B, western equine, eastern equine, Venezuela, and so on. That never happened with poliovirus, largely, I believe, because Dr. Flexner and Dr. Noguchi kind of overpowered people, even people of great repute. While they never outright said so, they acted as if there were only one poliovirus, and if Noguchi and Flexner felt that there was only one poliovirus, why in hell should a young investigator just

out of Podunk question them and try to type viruses? I think this also held true for the question of portal of entry for the virus, although here I believe chance played a role as well.

Dr. Constantin Levaditi of the Pasteur Institute early claimed that he could bring down monkeys by feeding them poliovirus by mouth. Dr. Flexner, on the other hand, always disputed those findings because he couldn't infect his monkeys using this technique, although he could infect them readily enough by dropping the virus into the nose. Dr. Flexner worked with the *Macacus rhesus*, and he was absolutely right—you can't bring the rhesus down by feeding it virus. Levaditi on the other hand was working with the cynomolgous monkey, which can be brought down by feeding. If Flexner had used the cynomolgous in his experiments,[29] he would have found out that monkeys can be brought down by feeding. It so happens that the mouth is the portal of entry for the poliovirus in humans. I don't know how many years were used up in debating whether the portal of entry was the nose or mouth. Progress was held up purely by chance because a big man like Flexner was using the rhesus monkey. If Flexner had used the cynomolgous monkey, the chances are that we might have had a vaccine that much sooner.

Q: Dr. Rivers, how would you characterize the research accomplishments of the President's Birthday Ball Commission?

Rivers: Minus. If you take the good things that they did, and subtract the bad things that they did, you get a minus. It doesn't mean that everything they did was rotten or useless. It means that when you add and subtract you get a minus. That's all.

[29] Rivers overlooks here that, soon after Dr. Flexner learned that Dr. Levaditi in cooperation with Carl Kling had reported experimental infection of cynomolgous monkeys by the feeding of poliovirus, he undertook to restudy the whole question of the mode of infection. The particular feeding experiments he undertook were not successful, and he concluded that the gastrointestinal tract played no considerable part as a portal of entry of the virus in man or monkey. See the report of Simon Flexner to the Board of Scientific Directors of the Rockefeller Institute, 1932, and S. Flexner, "Respiratory vs. gastrointestinal infection in poliomyelitis," *J. Exptl. Med.*, vol. 63:209 (1936).

CHAPTER 6

The Rockefeller Institute Hospital—1937

. . . In my laboratory . . . we work with and think of tobacco mosaic virus much as we would with simple organic molecules.
Dr. Wendell Stanley, *Some Chemical, Medical, and Philosophical Aspects of Viruses: An Address,* 1941

Q: Dr. Rivers, on July 1, 1937 you took over the duties of director of the Rockefeller Institute Hospital—did appointment to this post come as a surprise to you?

Rivers: The answer to that question is yes and no, and I am sorry to give you such a tentative reply. Dr. Flexner had retired as director of the Institute in 1935 and was succeeded by Dr. Herbert Gasser. Everybody knew that Dr. Cole was reaching the age of 65 and would retire as director of the hospital in 1937, so there was reason to believe that a new director of the hospital would be appointed. There were many people in the country who could have been chosen to fill the post, and I have since heard that certain good people were considered. I won't mention their names, but I will say that they were equally as good as I was and in one or two cases even better. I think the reason I got the job was that by 1937 the Board of Scientific Directors of the Institute knew me very well, and even more important the new director of the Institute, Dr. Gasser knew me. Gasser had been a classmate of mine at the Hopkins, and in the two years he had been director of the Institute he had a chance to renew his acquaintance with me and to relearn things about me.