CHAPTER 4

Virology and Virologists—1926

Nicely to observe the History of Diseases, in all their Changes and Circumstances, is a Work of Time, Accurateness, Attention and Judgment; and wherein, if Men through Prepossession or Oscitancy, mistake, they may be convinced of their Error by unerring Nature and Matter of Fact. . .

John Locke to Thomas Molyneux, January 20, 1692/3

Q: Dr. Rivers, I wonder if you could give me some notion of how your work day began.

Rivers: When I first came to the Institute, I used to get up very early in the morning and walk a mile from my house to catch a street car, which at that time ran from Forest Hills along Queens Boulevard to the foot of the 59th Street bridge in mid-Manhattan. It was my custom to walk from the bridge to the Institute, which then as now was at 66th Street and York Avenue. I did this every day, seven days a week. I was usually the first one into my laboratory and the last to leave, and my day rarely ended before 10 o'clock in the evening. When I first came to the Institute, my wife saw very little of me, and she used to complain that some of our neighbors in Forest Hills doubted that she was married, because they never saw her husband. Eventually they did get to see me and realized that my wife was an honest woman.

For some reason or other, I have never been able to produce or do anything without working hard at it. I suppose there are some people who have had the good fortune to be able to turn out good research results without working too hard, but they are rare, and I am certainly

not in that category. I will admit that some great discoveries have been stumbled on by accident; but remember, you don't stumble unless you are walking. The fellow who stumbles on a discovery in science certainly has to be working. There is no substitute for work in science, and I have always regarded results without work as a fairy tale.

Q: Could you tell me the circumstance that led to your first compendious review of viruses?

Rivers: In 1926, I was asked by the Society of American Bacteriologists to help organize a symposium on viruses for their annual meeting, which by custom took place during Christmas week. This particular year it was held in Philadelphia. The paper I prepared was a review of what was known of viruses to that time—it was very general and dealt with such subjects as the various diseases caused by viruses, their size, filterability, and problems of immunity and cultivation. The problem of cultivation of viruses was a particularly ticklish one for me to handle, because the views I held on this subject were diametrically opposed to those held by Dr. Flexner. The issue, moreover, was crucial because it involved a basic postulate or definition of what a virus actually was.

Both Dr. Flexner and Dr. Noguchi had long claimed that they had isolated the causative agent of poliomyelitis from the poliovirus, and that it was in fact a globoid body that was capable of being grown on lifeless media. My own view of the cultivation of viruses was quite different, and I didn't mince any words. Quoting from the paper which I gave at this meeting, I said:

> In general it can be said that . . . no worker has proved that any one of the etiological agents of the diseases [shown] in Table I down to mumps are susceptible of cultivation in the absence of living cells. A satisfactory explanation of the difficulty experienced in cultivating the viruses on artificial media is not easily found. Their small size alone should not necessarily make them insusceptible to cultivation. Nor does it seem to be a question of delicacy or sensitiveness, because many of them are extremely resistant to chemical and physical agents. Furthermore, no viruses have been found multiplying free in nature. *Therefore, the viruses appear to be obligate parasites in the sense that their reproduction is dependent upon living*

cells. Whether this reproduction occurs intra- or extra-cellularly is a debated question.[1]

Before I went down to Philadelphia, I made an appointment to see Dr. Flexner to show him my paper. I did this because I didn't think that it was proper for me to speak against the views of my boss, without letting him know ahead of time that I was going to do so. After he finished reading it, I asked him if he thought it was right or wrong, or if he had any objections to my making the speech. Dr. Flexner looked me square in the eye—and I think that the old boy was sincere. "Rivers," he said, "every man has a right to his own opinion." He didn't say that he agreed or disagreed with me; all he said was, "Every man has a right to his own opinion," meaning that I could go ahead, and I did. I could never tell whether the old guy—and he was a smart old devil—had his tongue in cheek or not. He certainly gave me every opportunity to do what I wanted to do. Whether he believed what I believed, I don't know. But I will say this: he did a lot more for me than my immediate boss, Dr. Cole, would have done. Cole was a wonderful person, but he was not as bold or courageous as Dr. Flexner. Dr. Flexner would stick his neck out. Dr. Cole was very careful not to. And Dr. Flexner stuck his neck out for me quite a bit. For instance, when the psittacosis virus came along, I told Dr. Flexner I needed more money. I was careful not to say how much, and without batting an eye the old fellow handed me $10,000. I don't have to tell you that in the early thirties that was a lot of money. Flexner would do such things, although he wouldn't admit a mistake if he could get out of it.

Q: Dr. Flexner wasn't the only one at the Institute who held the view that viruses could be grown on lifeless media. Didn't Dr. Peter Olitsky at this time publish a paper on the growth of tobacco mosaic virus on lifeless media? [2]

Rivers: Through the years, Peter and I have fought about a lot of things, and sometimes I was right and sometimes he was right, and I

[1] T. M. Rivers, "Filterable viruses: A critical review," *J. Bacteriol.*, vol. 14:228 (1927).

[2] P. K. Olitsky, "Experiments on the cultivation of the active agent of mosaic disease in tobacco and tomato plants," *J. Exptl. Med.*, vol. 41:129 (1925).

will admit that on some occasions he has made me sit up and take notice. I will tell you of some of those times later; for now, let me tell you one little story. For a long time, I and a lot of other virologists had an article of faith, namely, if you spotted intranuclear inclusion bodies in a cell, it meant that that cell was infected by a virus. Well, one day the little devil invited me to his laboratory to look at some cells. He got me to swear that the intranuclear inclusion bodies that I saw were virus produced, and then with great glee proved that he could produce like bodies through use of aluminum hydroxide. I am awful fond of Peter, awful fond of him, and I think I should tell you a little more about him.

Peter is a graduate of the Cornell Medical School and got his early training in medical research at the laboratories of the Department of Health in the City of New York and the Mt. Sinai Hospital. He is a small and gentle person, and I have always found it remarkable that such a mild little fellow had all the adventures that he has had. In 1916, Peter went to the Sierra Madre Mountains in Mexico as part of a commission to investigate a typhus epidemic. Several years before, on just such a mission, Howard Taylor Ricketts had contracted typhus fever and died. Peter also had the misfortune to contract typhus—he was terribly ill—and I understand that they shipped him out of Mexico in a box car to die, but he survived to join the Rockefeller Institute in 1917.

During World War I, the Rockefeller Institute worked very closely with the army, acting as a laboratory and training school for doctors to learn various bacteriological techniques. Peter was one of the teachers in this school, and later, when a series of meningitis epidemics broke out in various army camps, he and a number of other people were sent into the field to help bring them under control. Actually, because of Simon Flexner's early work in the preparation of an effective serum against meningitis, the Institute was often called upon for advice in how to deal with this disease. When a cerebrospinal meningitis epidemic hit Hong Kong in the spring of 1918, the British government asked the Institute to send an expert to help bring the epidemic under control. Dr. Flexner sent Peter out to the Far East to instruct the British in the preparation of an antimeningococcus serum.

After the war, Peter returned to the Institute, and, together with Dr. Fred Gates, settled down to a study of influenza. In 1922, they isolated some pleuropneumonia-like organisms from influenza cases, which they called *Bacterium pneumosintes*. In the manner of scientists everywhere, they ruminated about the organisms they had isolated and very tentatively suggested that they might be the inciting cause for influenza. Hells bells, when the newspapers got hold of the story, they blew it up into something like "Rockefeller Institute savants find cause of influenza." There was a great deal of excitement, because influenza was a topic of wide public interest—people still remembered the epidemic of 1918 with some terror—but the only trouble was that *Bacterium pneumosintes* was no more the cause of influenza than Pfeiffer's bacillus—and you remember the claims that Blake and I made for that bacillus. I guess Peter has since learned not to speculate out loud, because through the years he has been forced to deny claims that he never made in the first place.

In 1925, the U.S. Department of Agriculture borrowed Peter to help European scientists study foot-and-mouth disease, which, as you know, is virus induced. It's a terrible disease, and we in this country have only had it on two occasions, once in Texas and once in California. I want to tell you that, when it showed up, farmers or ranchers didn't wait to examine which cattle had it and which cattle didn't; they just dug trenches, marched all their cattle to it, killed them, and buried them. Only by such drastic treatment were they able to halt the disease and keep it from getting established. It is such a terrible disease that no one in the country outside of the scientific laboratories on Plum Island is allowed to work with the virus. However, you can work with the virus of vesicular stomatitis, a disease of horses which in some ways is like the virus of foot-and-mouth disease. Peter made some interesting epidemiological findings about the virus, but little of it had immediate import for control of the disease.[3]

[3] Olitsky was part of a special commission which was formed by the Bureau of Animal Industry of the U.S. Department of Agriculture to study foot-and-mouth disease in 1925. In addition to Olitsky, the commission contained Harry W. Schoening, of the Bureau of Animal Industry, and Jacob Traum, of the University of California. In Europe it worked in close cooperation with Louis Boëz, of the Institute of Hygiene in Strasbourg. For details on the work of this commission, see *Report of the Commission to Study Foot and Mouth Disease*. U.S. Department of Agriculture, Bureau of Animal Industry, Technical Bulletin 76, 1928. Rivers is not entirely fair in his evaluation of Olitsky's

A lot of Peter's early work was good, but certainly not as arresting as his later work on the encephalitides and poliovirus. (I'll talk about that work later.) I don't think he will be sore at me if I say that he wasn't in Landsteiner's class as an investigator—few people were. But Peter had one quality that Landsteiner and others at the Institute never had, and that was his quality as a teacher and a person who creates interest. Peter was and still is, although he is retired, a crackajack teacher, and I am not kidding when I say that some of the best virologists in the country have come out of his laboratory. Herald Cox, Jerry Syverton, Albert Sabin, Isabel Morgan, Jordi Casals, and Walter Schlesinger among others, all worked with him. I suppose the fellows I have left out will be sore at me. I say this because the virologists that Peter trained are intensely loyal to him. Do you know that when he retired, they wrote a letter of commendation of him to the Board of Scientific Directors of the Institute. That in itself, I expect, is not remarkable; what makes this particular letter exceptional is that, when you read it, you think it's children speaking about their fathers, instead of workers talking about their boss.

It's a long introduction, and now I just want to say that Peter's claim for growing tobacco mosaic virus in lifeless media was all wrong. Actually, at that time I think that Peter knew very little about plant pathology and virology. Louis Kunkel had not yet come to the Institute, and I don't think there was anyone around who could have given Peter cogent advice about tobacco mosaic virus. I expect that Peter undertook this work because Dr. Flexner told him to. Flexner had a habit in those days of asking Peter to do things, and often he was hard on him when he didn't deserve it. Peter, being a mild gentleman, took all of this; if it had been me, I would have talked back and been fired.

Q: To get back, Dr. Rivers, how did the symposium turn out?

work. At least one immediate import for the control of the disease was Olitsky's finding that sodium hydroxide in 1% solution killed the virus within a minute, a discovery that saved many barns from being burnt to the ground. Another important result of Olitsky's research was the discovery of methods of diagnosis of vesicular stomatitis of horses and its separation and differentiation from foot-and-mouth infection. See P. K. Olitsky, "Virus diseases of mammals as exemplified by foot-and-mouth disease and vesicular stomatitis," in T. M. Rivers (ed.), *Filterable Viruses*. Williams & Wilkins, Baltimore, 1928, pp. 205–232.

Rivers: The symposium was very successful. As a matter of fact, after it was over, I was asked by the people at Williams and Wilkins to edit a book for them on viruses. I agreed and asked several of the people who had participated in the symposium to submit extended versions of their papers for publication. However, I didn't limit my choice to those who were at the conference, and I also invited several people who were expert in virology, whose fields I felt should be represented in a general volume on viruses. I will admit I wasn't high-minded in all my choices. For instance, in one case I chose a fellow for his name value and not because he had anything in particular to contribute. That was Alexis Carrel. I am not particularly proud of that choice, but the others I think met the test. They included Lloyd Aycock, Harold Amoss, Jacques Bronfenbrenner, Edmund Cowdry, Rudolph Glaser, Ernest Goodpasture, Louis Kunkel, Peter Olitsky, and Stuart Mudd. One choice at least marked the beginning of a long and friendly relationship.

When I was asked to put the volume together, I thought it would be nice to have a section on plant viruses, a subject about which I unhappily knew nothing. One day at lunch I mentioned my dilemma to Edric Smith, the business manager of the Institute, and he told me that, if I went up to the Boyce Thompson Institute in Yonkers and talked to L. O. Kunkel, I would find the kind of a man I wanted to take part in my enterprise. I took his advice and discovered what others before me had also found, namely, a superb plant pathologist and virologist, one of the greatest this country has ever had. Kunkel at that time had already done superb work on the viruses that attacked sugar cane and pineapples, and within a year after our meeting he was to come to the Institute to start up its Division of Plant Pathology.

Kunkel was an amiable but tight-mouthed individual, but in all the years that I knew him we had only one battle. It was a continuing one although quietly fought. He never pushed me, and I never pushed him, but we both certainly had firm convictions on the subject. Kunkel always believed that the honor of being the father of virology belonged to the Russian Dimitri Iwanowsky, because he showed that the agent that caused tobacco mosaic disease passed through a filter. He did this work in 1892. My own choice for that honor was the Dutch plant pathologist, Martinus Beijerinck, who in 1898 repeated

Iwanowsky's experiments with tobacco mosaic disease but went one step further and passed the disease by filtrates to healthy plants. There is no doubt that Iwanowsky made the first observations; the difference for me lay in the fact that, while Iwanowsky always believed that the agent that went through the filter was a little bacterium, Beijerinck realized that it was a new agent and put his neck out by calling it a living contagious fluid. You know, I was never able to persuade Kunkel to my belief.

Q: Dr. Rivers, your volume is titled *Filterable Viruses;* today most books dealing with the subject are simply titled *Viruses.* Could you tell me why you used the word filterable and what importance it had, if any?

Rivers: First off, let me say that there was a row about how to spell the word "filterable." Up until the time I published my book, just about everybody spelled it "filterable." Then someone with nothing better to do investigated the root of the word, found that it went back to the latin *filtr* and claimed therefore that the adjective ought to be spelled filtrable. Some scientists always want to be right and began to spell it that way. I think that sometimes usage makes the spelling of a word right, even though we later find out that it is wrong. This proved to be the case with regard to spelling "filterable"; I and the British people working on viruses decided that we would keep on spelling according to usage. Today only the purists spell it filtrable. You know, usage is a great thing. I come from a part of the world where everybody uses the word ain't. The old saw says ain't ain't in the dictionary, but like filterable it persists, and like filterable I think it's here to stay.

In the early days of virology, filterability was rather important because it was the only way that workers had of differentiating the so-called viruses from bacteria. Even at the time that I began my work, there were people who thought that viruses were no different from bacteria. Hideyo Noguchi, for example, thought that they were small bacteria that were merely a little bit difficult to grow on regular media. He felt that all you had to do was find the right medium and you could grow any virus. He wasn't the only one who believed that.

Dr. Earl Baldwin McKinley, who was professor of bacteriology at the George Washington University Medical School in Washington, D.C., had the same belief and spent a great deal of time trying to prove it. Later, while collecting air samples to find what bacteria if any were to be found in the upper atmosphere, McKinley died. The plane he was on disappeared and everybody aboard was lost. Although McKinley believed that you could grow viruses on artificial lifeless media, his death was a great loss to virology. It is my opinion that if he had lived he would have contributed a great deal to virology, because he was active in the laboratory and possessed a keen imagination.

In the early days, filterability was important from still another point of view, in that it could give us a rough approximation of the size of the virus. Generally speaking, three types of porcelain filters were used in laboratories. One type was labeled V. This was a coarse filter with relatively large pores and would let organisms of the size of from 8 to 10 microns through. The second was called N or normal. Here the pores were slightly finer and would allow organisms of 5 to 7 microns through. The third was called W or *wenig* (the German for little), and organisms of the order of 3 to 4 microns would go through. Practically all the viruses that we know will pass through filters of these three types. I should add here very quickly that this is not a foolproof standard, because there are some organisms like the pleuropneumonia-like group that will pass filters and are not viruses at all. Some virologists in fact have been wanting to eliminate trachoma and psittacosis from the virus list (they go through large filters with a little difficulty), because they respond to chemotherapy and most viruses do not. I personally consider them viruses and have kept identifying them as such in the volume I later edited on *Viral and Rickettsial Infections of Man.*

Q: Dr. Rivers was there any particular reason for dedicating your volume on *Filterable Viruses* to Dr. Charles E. Simon.

Rivers: Yes. Dr. Simon was a professor at the School of Public Health of the Johns Hopkins Medical School whom I had known for some years before I came to the Rockefeller Institute. I was always

friendly with him; however, I didn't dedicate the volume to him merely out of friendship. I dedicated it to him because he got away with murder.

Although Dr. Simon was an elderly man, he was one of those who in the United States very early appreciated the future of virus research. It was through his efforts, for example, that the first laboratory devoted exclusively to the study of the viruses in the United States was established at the School of Public Health at Johns Hopkins. Sometime during the early twenties, Dr. Simon went to Europe and brought back a load of viruses—many of which should never have been brought back into the country. (He must have looked pretty innocent, because he got them through customs without being held up.) One of those viruses was fowl plague. Fowl plague is a devastating disease of poultry which is not present in this country, and the Department of Agriculture, I might add, has very stringent regulations about bringing it in—I know because on several occasions I tried to get a strain for Karl Landsteiner with no success. As I say, Simon smuggled a strain in, and his lab began to work with it. A technician whose name I have forgotten was assigned the chore of keeping it going in chickens and he did his job well—that is, until he was faced with the dilemma of doing his job and going on vacation. He solved it by taking his infected chickens along with him on vacation, to a farm in southern Maryland. Damned if the plague didn't get loose among the chickens of that farm. All hell broke loose, and there was one heck of a time keeping fowl plague from spreading throughout Maryland. If that disease had become established, it would have been an economic calamity. I am not exaggerating when I say it would have cost the poultry industry millions. They probably would have hung poor Charles Simon. Luckily for him and the chickens of the United States, fowl plague didn't get established, and I had the privilege of dedicating my book to him—it's not often that a man with foresight gets away with murder.

Q: Dr. Rivers, I would like to quote to you some remarks that you made on the nature of immunity in your volume on *Filterable Viruses:*

Another interesting feature concerning the immunity to virus diseases is the fact that only active virus protects against a second inoculation of the

same virus. In other words, it is doubtful with a few exceptions whether an injection of a virus completely inactivated leads to a protection against the same virus in an active state.[4]

Rivers: First, I would ask you to keep in mind that the statement was made in 1928 and made on the basis of information existing at that time. I did not discard that notion for some years, and I will tell you later under what circumstances I came to change my mind.

The problem of immunity in virus diseases was, and for that matter still remains, a knotty one. For instance, in 1928 we knew that, with few exceptions, persons who had recovered from diseases caused by so-called filterable viruses had lasting immunity. What we didn't know, and still don't know, is why that immunity persisted. Some investigators were of the opinion that lasting immunity was due to repeated infections that were so mild that only the first infection attracted attention. Others claimed that lasting immunity was the result of the persistence of the virus in the once-infected individual. I must say, in all candor, that I inclined to the latter view, because there were plenty of examples in the literature relating to viral infections of animals that supported it. For example, Sir Arnold Theiler's laboratory in Praetoria, South Africa, followed a horse with a virus-induced South African horse sickness for 14 years, and, although the horse was immune to the disease, virus was recovered from the blood regularly throughout the entire period.[5]

Gillies de Kock, another South African investigator, made observations of another disease in horses known as swamp fever, or infectious anemia, and obtained virus regularly from seemingly recovered animals. His work gave considerable support to the theory that a prolonged infection can persist for a long time in a host which is refractory to reinfection. It is for this reason that any horse that has ever had a history of swamp fever is not used for the making of serum for human beings.[6]

Closer to home, in 1927 Dr. Rufus Cole and Dr. Ann Kuttner of

[4] T. M. Rivers (ed.), *op. cit.*, p. 9.

[5] A. Theiler, *African Horse Sickness.* Union of South Africa, Department of Agriculture, Scientific Bulletin No. 19. Praetoria, 1921.

[6] G. v. d. W. DeKock, *A Contribution to the Study of the Virus, Haematology, and Pathology of Infectious Anemia of Equines under South African Conditions.* Union of South Africa, Department of Agriculture Scientific Bulletin, 9th and 10th Report. Praetoria, 1924.

the Rockefeller Hospital discovered that, once guinea pigs were infected with salivary gland disease, they also carried the virus with them throughout life and remained immune to reinfection.[7] Indeed, once an adult guinea pig was infected with the virus, you couldn't reinfect it, even if you injected the virus into the brain. However, if you caught a young guinea pig and separated it from its mother very early, you could cause or produce a beautiful encephalitis by injecting the virus into the brain. The reason for this was that guinea pigs were born free of the disease and only contracted it when exposed to the contaminated feces of their parents. Later, Dr. Kuttner demonstrated that the salivary glands were not necessary for the persistence of the virus. Although the virus is usually found in the salivary glands, when Dr. Kuttner removed these glands experimentally, she found that the virus moved to the parotid. It was as if the virus had a mind of its own and could think. Of course, it didn't—the point is that it persisted, and if its usual home was missing or unavailable it quickly found another.

Some years later, some virus diseases that occur in humans gave evidence which, for me, buttressed the notion of the persistence of virus in immune people. In 1931, for example, Dr. Wilbur Sawyer discovered circulating antibodies against yellow fever virus in a human case who had been exposed 75 years before and who, since that time, had lived outside the yellow fever zone.[8] Eighteen years later, Dr. John Paul of Yale made similar observations of the persistence of circulating antibodies against type 1 and 2 poliovirus. In 1949, while examining the Eskimos of semi-isolated Barrow Village in Northern Alaska, Dr. Paul discovered that none of the inhabitants in the village under the age of 19 had neutralizing antibodies against type 2 polio, while over 80 per cent of the population above this age possessed such antibodies. Further study revealed that most of the population above the age of 40 had neutralizing antibodies against type 1. The data gathered correlated very well with information of polio epidemics in the region in 1905 and 1930. Now, I don't know how to explain the presence of Sawyer's and Paul's circulating antibodies unless there is

[7] R. Cole and A. G. Kuttner, "A filterable virus present in the submaxillary glands of guinea pigs," *J. Exptl. Med.*, vol. 44:855 (1926).

[8] W. A. Sawyer, "Persistence of yellow fever immunity," *J. Prevent. Med.*, vol. 5:413 (1931).

some persistence of the virus. I should hasten to add that not all virologists would agree with my conclusions; in fact, I know some that would heartily disagree.[9]

Q: Dr. Rivers, while you seem willing to debate with one and all on the problem of the cultivation of viruses, immunity, and so forth, there is one problem that you go out of your way to avoid, and that is the interesting problem of whether viruses are living or nonliving organisms.

Rivers: I won't deny that this particular problem was interesting. I will, however, say that I thought discussion of this problem with the amount of knowledge we had at hand in 1927–28 sterile, and I was not and am not particularly given to sterile metaphysical exercises. First, let me point out that no two scientists in 1928 could agree on tests to act as criteria for the presence of life. Then again, we knew little about the cell and its relation to viruses. Today, we confidently speak of the role of nucleic acid in the process of replication and infectivity of viruses; what we tend to forget is that the work that this knowledge is based on is comparatively recent. Please keep in mind that the work of the Schramms, Fraenkel-Conrats, and Commoners was about a quarter of a century away in 1928. What, for example, did we know of cell types in relation to virus reproduction in 1928? Let me just quote what I said on this subject at that time:

> In view of the fact that viruses apparently multiply only in the presence of living cells, it is advisable to ascertain what kinds of living cells promote their reproduction best, and what effect upon the cells is induced by this reproduction.
>
> Species Specificity—A remarkable species specificity is exhibited by many viruses. Rous' sarcoma grows only in chickens. Sanarelli's virus of infectious myxomatosis and Virus III are active only in rabbits. The salivary-gland virus described by Cole and Kuttner apparently affects only guinea pigs. A wilt virus that attacks one kind of caterpillar is innocuous for other caterpillars. The virus of poliomyelitis is active only in man and the monkey.[10]

[9] J. R. Paul and J. R. Riordan, "Observations on serological epidemiology," *Amer. J. Hyg.*, vol. 52:201 (1950).

[10] T. M. Rivers (ed.), *op. cit.*, pp. 13–14.

As you can see, we didn't know a hell of a lot; actually it would be more honest to say that we knew damned little. Take the specificity of poliovirus; we literally didn't get to home on this problem until 1959, when Jerry Syverton and his boys at the University of Minnesota published a wonderful series of papers in the *Journal of Experimental Medicine*. This work is very important and bears some further comment. In 1958, Dr. Syverton and two of his associates, Dr. John Holland and Dr. Leroy MacLaurin, discovered that the limitation of poliovirus infectivity to primate cells was governed by the specific interaction between the protein coat of the virus and the cell surface receptors. A short time later, they showed that if they took only the viral ribonucleic acid (without its protein coat) and exposed it to usually insusceptible nonprimate cells (in vivo and in vitro) those cells would produce infectious poliovirus, protein coat and all.[11] Now we couldn't have done a piece of work like that in 1928 if our lives depended on it, and all the metaphysical debate on whether viruses were living or nonliving wouldn't have helped us one whit. I still don't think much of the interesting problems you speak of, but today I think I could give you a definition of life that would make viruses "living organisms," whereas in 1928 I couldn't. "Life," we might say, "is the process that goes on due to the activity of enzymes and coworking substances under the direction of nucleic acid." Or you can shorten it into "Life is a continuum directed by nucleic acid."

Q: Dr. Rivers, while we have spoken of several of your colleagues at the Rockefeller Institute in some detail, we have only spoken of Dr. Flexner peripherally, and, since he was the director of the Institute for the first twelve years of your tenure, I wonder if you would tell me of your relations with him when you first came to New York.

Rivers: I worked in the Department of the Hospital, and Dr. Cole, as director of the hospital, was my immediate boss. Dr. Flexner and Dr.

[11] J. J. Holland, L. C. McLaren, and J. T. Syverton, "The mammalian cell-virus relationship. I. Attachment of poliovirus to cultivated cells of primate and nonprimate origin; II. Adsorption, reception and eclipse of poliovirus by HeLa cells." *J. Exptl. Med.*, vol. 109:475, 487 (1959); "III. Poliovirus production by nonprimate cells exposed to poliovirus ribonucleic acid," *Proc. Soc. Exptl. Biol.*, vol. 100:843 (1959); "IV. Infection of naturally insusceptible cells with enterovirus ribonucleic acid," *J. Exptl. Med.*, vol. 110:65 (1959).

Cole did not bother each other about what went on in the hospital; yet I probably saw as much of Dr. Flexner as I did of Dr. Cole, because Flexner was interested in viruses. He was at that time one of the leaders in the United States in polio research and deeply interested in other virus diseases, notably encephalitis. I was rather surprised to find that Dr. Flexner was interested to the extent that he would send me notice of articles on viruses. For example, he would look through the *Journal of the AMA*, the back of which was devoted to abstracts of current literature, and frequently he'd cut out these abstracts and place them on a card—I suppose his secretary did it—and send them over to me, if he thought they were things that I should read. On occasion, when he had read an article on viruses that he liked, or questioned, he would call me over to his office and would want to know if I had seen it. If I had, we would then sit down to discuss it.

My relations with Dr. Flexner were very happy, and we got along exceedingly well together. At times he was very complimentary, and I should add that, generally speaking, he was not a man given to profuse compliments. I remember that, shortly after my book on *Filterable Viruses* came out in 1928, he gave a luncheon for some distinguished scientists and invited me. I was probably the youngest man at this particular luncheon, and Dr. Flexner, in introducing me to these people, some of whom I'd never met before, made the remark that I was the author of a recent best seller, a book on filterable viruses. Well, I'd never considered that my book could be called a "best seller," but these are exactly the words that Flexner used. He did this on several other occasions, and I thought he went out of his way to do it. Most people were intimidated by him. You take as relatively easy-going a fellow as Dochez—when Dochez first came to the Institute, he had the opportunity of working with Dr. Flexner, and Dochez just wouldn't work with him. As he once put it to me, "I was afraid of the Old Man." I don't know that I would have worked with him either. Not because I didn't respect him, but because he and I didn't see eye to eye on the nature of viruses, and I'm sure that we would have busted each other's brains out, because we were pretty much the same kind of specimen. It's not wise for fellows too much alike to be too close together. But Dr. Flexner and I got along, even though he knew

I didn't always agree with him. I wasn't scared of him, not the least bit scared of him.

When I first came to the Institute, I came as an associate, and at the end of two years I was increased in rank and became an associate member, and they increased my salary a little bit—the salaries were not large. I spent the next three years as an associate member. In the spring of 1927, five years after I had come to the Institute, the board met and reappointed me for another three years as an associate member and, if I remember correctly, gave me a slight raise in salary upon reappointment.

A short time afterward, Francis Blake and Milton Winternitz from Yale came down to see me, and offered me the professorship of pediatrics at Yale at $4000 a year more than I was getting at the Institute. Dr. Howland had died, and Ned Park, who was a professor of pediatrics at Yale, went down to Hopkins to take Howland's place. That left the chair of pediatrics open at Yale. It was early in the week, and Blake and Winternitz—I knew both of them very well—asked me if I could give them an answer by Friday, because it was getting to be late in the year, and they wanted to get a professor to fill the opening. I told them I'd try to reach a decision by the end of the week.

I went to see Dr. Flexner and told him about the offer I had received from Yale. Well, Flexner talked to me for about a half an hour about how well I had done at the Rockefeller Institute in the previous five years, and what a bright future I had ahead of me at the Institute if I kept on doing as well in the future as I had done in the past. He was extremely nice.

After he'd talked to me about a half hour, he stood up. We all knew that, when Dr. Flexner stood up, it meant that the interview was over. I got up and said good-bye to him. I got over to the door, turned the door knob, and was just getting ready to pull the door open, when Dr. Flexner said, "Come back here, Rivers. Come back here, Rivers. You haven't told me what you are going to do."

I said, "Well, Dr. Flexner, you didn't ask me what I was going to do."

He said, "I'm asking you now."

I said, "All right, I'll tell you. If I'm not made a member of the Rockefeller Institute, I'm going to Yale. You say I'm good, that I

know how to do research, and that I've got a good future at the Institute, but you've only offered me security for three years. The boys at Yale don't know whether I can teach pediatrics or not, because I have never had a teaching job. They're gambling on me. I may be a bum teacher, I may run a rotten department of pediatrics, but they're giving me $4000 a year more than you are, and security for life, and you ain't giving me anything except a promise!"

I said, "If I am not made a member, I am going to Yale."

He said, "Well, look, Rivers, I can't do anything about it now, the board has already met."

I said, "Dr. Flexner, did you ever hear of the telegraph office? All the people on the board know me. You can get an answer as to whether or not they want me as a member of the Rockefeller Institute very quickly. If you don't make me a member of the Rockefeller Institute before Friday morning, I'm going to Yale." And I walked out of the office.

I didn't hear anything more, but Friday morning, when I got to my office, Edric Smith, the business manager of the Rockefeller Institute, was sitting in my office waiting to tell me that I'd been made a member of the Rockefeller Institute.

I'll tell you one thing: the Institute was still a little bit stingy. Although they'd given me a slight raise when they reappointed me as an associate member, when I was made a member it was without any further increase in my salary. In those days they were like that. Dr. Flexner used to say, "If we gave enough money to attract a man here because of the salary, then we'd get the wrong kind of people. We keep our salaries down, so if a person comes here and lives on it we know he wants to do research." That attitude obtained even when Dr. Gasser and I took over, after Dr. Flexner and Dr. Cole had left. We didn't blow the salaries up very high. We raised them a little bit, because they were pretty tight. But it's true that, if you give a large salary, you have all kinds of people coming in and wanting to do research. Research is something that ought to be done by people who want to do it so bad they'll sacrifice a little bit.

Q: Dr. Rivers, did Dr. Flexner ever restrict your activities outside the Institute?

Rivers: I think that it would be fair to say that on many occasions Dr. Flexner urged me not to get mixed up in things that would keep me from the laboratory. For instance, in the spring of 1928, Dr. Rudolf Kraus of Berlin invited me to be editor of an international journal of virology which he was trying to establish, and Dr. Flexner very quickly put a damper on the project. I still have the letter he wrote to me on that occasion and will quote a portion of it.

> . . . I have yet another reason for your keeping yourself free. I should hate you to put your valuable time into editorial work and especially editorial work of an international nature.
>
> Still another point is that Europeans are used to publishing long papers. They can do this because the publisher charges so much for so many pages constituting a volume and issues volumes irregularly. To carry on this kind of business a business organization is required; it does not exist in the United States. I believe, too, European contributors expect pay for papers based on their length. All this you see would make the publishing of an international journal in the United States expensive and extremely bothersome and time consuming. I do not see how you could undertake the responsibility.[12]

Flexner, of course, was quite right. I should also add that, even if he had given his blessings, I would have turned Dr. Kraus down, because I was of the firm belief at that time that virology was too young to be considered a separate discipline. Today there is a very fine journal in the United States, which is specifically dedicated to problems in virology, and is edited by Dr. George Hirst of the Public Health Research Institute of New York. In 1928, such a journal would have been premature.

Now what I said just now doesn't mean that Dr. Flexner turned down everything; as a matter of fact, there were times when he urged me to take on certain chores. In 1937 Mayor Fiorello La Guardia invited me to join the Board of Health, and Dr. Flexner kept after me until I did. He always said that there were certain things that people at the Rockefeller Institute should do as a civic duty, and he made it plain to me that, with my knowledge of infectious diseases, I should feel proud to serve on the Board of Health. I gave my time and energy to the board for 18 years, and to this day, I am a member emeritus.

[12] Simon Flexner to Thomas Rivers, July 15, 1928 (Flexner papers).

Sometimes it was time consuming to go to meetings, but, hell, I enjoyed it; don't you for one minute think that I didn't. I must have, because it cost me money to be on the board. Members received no pay; however, when a new member was sworn in, it was necessary for him to sign a special registry. The fee for signing that registry was four cents—money that La Guardia never returned to me—so you see I can rightfully claim that joining the Board of Health cost me.

Q: Dr. Rivers, did Dr. Flexner ever ask you to assume clinical duties outside the Rockefeller Hospital?

Rivers: On occasion he did, but since I was a clinician—and for that matter still am—I never objected to such requests. As a matter of fact, as head of the infectious disease ward at the Rockefeller Hospital, I was frequently asked by doctors who had no connection with the Institute to see people on consultation. I did this without charge because I was on full time at the Institute and considered it as one of the obligations of my post.

I think that Dr. Flexner's requests to me to see people shed light on one part of his personality that he was very careful to keep hidden. Frequently, he is presented as being cold and austere. I am not saying that he wasn't tough or that he couldn't be mean—he could, believe me—but he also was tender with people, and often with people who had no claim on him. Once, when he was in Washington, someone took him to see a boy who had muscular dystrophy. The boy's parents were plain people and were visibly disappointed when Flexner explained that he was a pathologist and could really not give them the expert clinical advice they sought. He, of course, knew that the boy had muscular dystrophy and that nothing could be done, but, to make them easier in their mind, he promised to send someone from the hospital to examine the boy and eventually asked me to go. It was no great imposition, because I was about to attend a scientific convention in Washington anyway, and when I arrived in the capital I went to see this family. The poor lad had an unmistakable case of muscular dystrophy, and I had the unpleasant job of telling his mother and father that the disease had no known cure, and that the inevitable outcome was death at some future time. I explained that

doctors couldn't give the exact time the boy had, because it varied from case to case.

They seemed to accept this knowledge quietly. I suppose they had been told this previously, so it didn't come to them as a shock or a surprise. However, it was plain that they were looking for some happier news. They thought that, since I came from the Rockefeller Institute, I would tell them that it wasn't muscular dystrophy, or that, even if it were, the Institute had worked out a cure. I don't know why people had that view of the Institute, but some people did. They looked on the Institute as the home of miracle workers. It is too bad they didn't know us as we actually were; then they would have known that we were just common ordinary everyday folk.

Occasionally my hospital duties took me into private homes. The purpose of these visits was twofold: first, to see whether the hospital should admit the patient, and, second, to get permission to do autopsies. It must be remembered that the Rockefeller Hospital was a research hospital, and the only patients who were admitted were those whose condition had particular interest for the staff. I remember that I once went down to Elizabeth, New Jersey, to look at a patient who, I had been told, had eastern equine encephalitis. A careful examination, however, revealed that the poor fellow had lethargic encephalitis. He was over the hump of the original infection but, like so many of the victims of that disease, he had been left with permanent injury, and I had to tell the family, as gently as I could, that the patient would be better off in a hospital for chronic diseases.

Getting an autopsy is, of course, very important for every doctor and hospital, because it is the place that you go to for final judgments on the medical knowledge you possess, and the care you are furnishing your patients. There is no appeal from the autopsy table. Actually, every patient that came into the Rockefeller Hospital—either personally or some responsible member of the family—signed a slip giving permission for an autopsy in case of death. The truth is that those signed slips had no legal validity; however, only in a few cases was the hospital ever denied autopsy. It was a precious and valued privilege and extraordinarily helpful to us in performance of our clinical duties and research.

Q: Correspondence in Dr. Flexner's letter files reveals that, during the period 1927–1931, you and Dr. Cole frequently fought over the question of extra laboratory help.[13]

Rivers: During my early tenure at the Rockefeller Institute, I learned very quickly that, if I was to run my laboratory efficiently and well, my animal keepers would have to be extraordinarily careful in handling the infected monkeys, rabbits, and mice that I worked with, and that my technicians would have to use faultless aseptic technique. To accomplish these things, it was plain that I would need more help. Well, it took me a long time to persuade Dr. Flexner and Dr. Cole to this point of view. The first impression that was made on them came when Wilbur Sawyer, Paul Hudson, and Stuart Kitchin returned from Africa and began to work with yellow fever virus and monkeys in the Rockefeller Foundation laboratories, which were then located at the Institute. The animal house where those infected monkeys were kept can only be described as a disgrace. Moreover, the laboratory space allotted to Sawyer and his group was entirely inadequate. Anyone with half a grain of sense could have predicted what was going to happen, and it did. Within a very brief time Dr. Sawyer, Dr. Hudson, Dr. Kitchin, and two of the technicians contracted yellow fever and became my patients on Ward One. They were damned sick, and I was sore because it could have easily been prevented. At that time, Dr. Cole was one of the scientific advisors to the International Health Board of the Rockefeller Foundation, and when I complained about conditions he decided to make an inspection. He took one look at the animal house and laboratories and got madder than hell, and I want to tell you that in short order the Institute got new facilities for the boys working with yellow fever.

However, it was still not easy to persuade Dr. Cole or Dr. Flexner that my labs also needed the same treatment because I was working with highly infectious psittacosis virus. My labs were then in Founders Hall, and they couldn't have been more centrally located. If you

[13] Rufus Cole to Simon Flexner, December 10, 1928, February 4, 1930, June 20, 1930 (Flexner papers). In fairness to Cole, it should be pointed out that he was primarily concerned that Rivers was attempting too much and that this tendency was dangerous for the development of his career.

went to the lunch room you had to pass them, if you went to the business office you had to pass them, if you went to the ladies' room you had to pass them, or if you went to the library you had to pass them. To complicate matters, a short narrow alleyway was all that separated the windows of my labs and the windows of the library. Well, neither Dr. Cole nor Dr. Flexner ever wanted to understand why I wanted dustproof doors and windows installed in my labs.[14]

I don't think that it was penury on their parts; rather I think that it was a habit of mind of investigators who had been brought up in an age of bacteriology. For example, after the yellow fever laboratories had been cleaned up, Dr. Frederick Russell, who was director of the International Health Board, came over to make an inspection. He looked around and said, "I don't like a clean laboratory. Whenever I see a laboratory like this, I feel like taking a bottle of ink, putting it on a string, and swinging it around my head until it is empty."

Older bacteriological workers felt that a working laboratory should be dirty; a clean one was a personal affront to them. It took them a long time to realize how clean and careful you had to be when you worked with viruses. For instance, I found that it was almost impossible to work with more than one virus when I worked with vaccinia. It made no difference how careful I was, or what techniques I used; in the end, all of the animals in our laboratory became infected. I don't

[14] Rivers here is unfair to Dr. Cole. Cole well understood the dangers involved and wrote strongly in Rivers' behalf to Simon Flexner.

Rivers and Berry are working with psittacosis. Rivers came to me yesterday a little disturbed about the working facilities so I went over the whole matter with him and Mr. Smith. The experiences in Baltimore, Washington, and now in Park's laboratory, make the situation a bit disturbing. Three of the women who have been working with Park and Krumwiede have come down with what they think is psittacosis, and Park telephoned me yesterday that they were going to stop their work and would send all their material up to Rivers. You know of course about the death of Anderson in Washington and Stokes in Baltimore.

Rivers is very anxious to continue with his work and I feel that this is a great opportunity for him. I wish, however, that he might have better facilities than are afforded by the dark room in which they are working. Should not men working on easily transmissible diseases, such as yellow fever and psittacosis, have large light rooms in which every precaution to avoid infection can be taken? I think Mr. Smith is writing you today about what may possibly be done. The only space we have in the hospital is that which Binger used. That could be cleaned out and would be suitable, but I don't think it would be advisable to bring that work into the hospital. I doubt if there would be any danger of the virus getting out of the laboratory, but if any cases should arise I fear we would be open to criticism.—Rufus Cole to Simon Flexner, March 6, 1930 (Flexner papers).

want to blame only bacteriologists; sometimes even experienced virologists don't understand how careful you have to be. As late as five years ago, some of the world's best virologists had to relearn this lesson. If it weren't for Jerry Syverton, they still wouldn't know how easy it is for HeLa cells to contaminate tissue cultures.[15]

Q: Dr. Rivers, what about Dr. Cole's complaint to Dr. Flexner that you stole Dr. Muckenfuss from Bronfenbrenner's laboratory? [16]

Rivers: I think that Dr. Cole misunderstood this particular situation. In my early days at the Institute, a lot of the things that I did were misunderstood because I respected no boundaries. It is true that I proselytized for virology among young investigators, and that I did try to get people in the Institute laboratories, as opposed to the hospital laboratories, to work on things I was interested in. I did this on the general theory that, if they did it, I wouldn't have to. But I never stole anyone, and I surely didn't steal Ralph Muckenfuss.

Muckenfuss, who was an M.D., was at that time working with Jacques Bronfenbrenner in the Institute laboratories on bacteriophage. You know, in the early days of virus research, very few investigators regarded phage as a virus. Felix d'Herrelle, one of the discoverers of phage, certainly believed that it was a virus, and demonstrated his belief by calling it Protista. Bronfenbrenner and I shared this belief, and if you look at my book on *Filterable Viruses* you will find that Chapter 9—which was written by Bronfenbrenner—is devoted to this subject.

Muckenfuss stayed for a short while with Bronfenbrenner—I believe no more than two years—but in that period they did several very nice papers together. I still remember that in one paper they showed that phage in the absence of bacteria did not respire. Some investigators at the time claimed that, because phage did not respire, it was not alive. However, respiration is not the sole indication of life or death, and an investigator named Ohga at the Boyce Thompson Institute very dramatically demonstrated that lotus seeds that had been buried for hundreds of years in India—and which certainly

[15] Rivers' reference here is to discussion at a conference on nonprimate cells susceptible to polioviruses which was held in New York, November 27, 1957.

[16] Rufus Cole to Simon Flexner, January 12, 1928 (Flexner papers).

didn't respire very much during this period—began to sprout when put under proper environmental conditions.[17]

I think that it was Muckenfuss's general interest in viruses, rather than my proselytizing, that brought him to my laboratory. I know that Bronfenbrenner was glad to have him come and certainly never raised any objections. If it had been a steal, he would have raised the roof. Looking back, I would say that Muckenfuss benefited from his stay with me. In 1929 he was appointed assistant professor of bacteriology at the Washington University Medical School in St. Louis, and in 1937, after the retirement of Dr. William H. Park, he was hired to take charge of the laboratories of the New York City Board of Health. I might add that he got both jobs because, in addition to being a first-rate bacteriologist, he knew something about viruses.

In fairness to Dr. Cole, I must admit that I was a handful, because I did do my damnedest to expand my laboratory and get new workers. But that was no secret; everybody knew it, including Dr. Flexner, and on one occasion he even helped me get an assistant. In 1929 a young German investigator from the Koch Institute named Eugen Haagen came to the Rockefeller Hospital. Originally, he was supposed to work with Alexis Carrel; however, he was so nationalistic that Carrel refused to take him. Dr. Flexner didn't order me to take him, but he made it obvious that he would be pleased if I did. I grabbed Haagen, not because he knew anything about virology, but because he was expert in working with tissue culture, and I wanted very much to undertake some experiments with vaccinia using tissue-culture techniques. Haagen later proved to be very helpful in that work.

Actually, all the youngsters who came to work with me in those early years worked out well—with one notable exception—a young Chinese named Dr. Chen P. Li.

In 1928, Dr. Carl tenBroeck of the Division of Animal Pathology of the Institute went to China as visiting professor of bacteriology at the Peking Union Medical College. While in China, Dr. tenBroeck worked with Dr. Li and, although they only worked with bacteria, he was sufficiently impressed with Li's abilities to recommend him to

[17] I. Ohga, "The germination of century-old and recently harvested Indian lotus fruits, with reference to the effect of oxygen supply," *Contribs. Boyce Thompson Inst. Plant Res.* vol. 1:289 (1926).

me. I accepted him, and the Rockefeller Foundation gave him a fellowship to come to America to work with me. Li had wonderful technical ability, and the first year he was with me he worked out the cultivation of vaccinia in minced chick-embryo tissue and Tyrode's solution. It was done very well, and at the end of the year I approved renewal of his fellowship without hesitation.

I wanted him to continue his work on the cultivation of viruses in tissue culture, but for some reason or other Li decided that that wasn't what he wanted to do. I do not now remember the proposal he made, but I do remember telling him that it wouldn't be rewarding. I'll be damned if he didn't put on a sit-down strike. Half the times I wanted him, I couldn't find him, the other half he spent in the library reading. I just couldn't get him to do any work. It wasn't ugly, no harsh words were spoken; it was just a sit-down strike.

I took it for about two months, and finally I called the Rockefeller Foundation and asked them to send him back home. I guess he never expected that I would take such drastic action, and I know it came as a shock to him. It was a terrible loss of face, and face, as you know, means a great deal to people in that part of the world. He returned to China and on several subsequent occasions tried to patch up relations with me. During World War II, Li became a general in the Chinese Nationalist army and was in charge of preparing all the vaccine virus for the army. He did a bang-up job; however, when it became apparent to him after the war that Chiang would not hold against the Communists, he emigrated to the United States. (I forgot to say that one of his children was born in the United States.) In time he got a job with the U.S. Public Health Service and was assigned to the laboratories they maintain in Montgomery, Alabama. The head of the laboratory at that time was Dr. Morris Schaeffer. Schaeffer is a good virologist and knows how to run things, and fortunately he and Li hit it off. Together, they established type 1 polio in the brains of mice by intraspinal inoculation and got an excellent attenuated strain, which is now known as the Li-Schaeffer strain. So, in spite of everything, Li has turned out all right. I don't hold his sit-down strike against him, and I guess that by now he understands that if you are running a laboratory you can't have too many viruses going at the same time or you get tied up.

Q: I would like to discuss now some of the studies that you undertook between 1926 and 1930. I find it particularly interesting that in the midst of your work on viruses you returned to study the growth requirements of bacilli, a problem you hadn't been concerned with in years.[18]

Rivers: Before I came to the Rockefeller Institute, it is true that I had done much work on the growth requirements of influenza bacilli of the hemolytic and nonhemolytic varieties. However, when I arrived at the Institute, Dr. Cole told me that I had best drop that work because Dr. Ernest Stillman at the hospital was already working on a like problem and that he didn't want the two of us to get tangled up. Now, that attitude was general throughout the Institute. For instance, it was understood that no one in the Institute laboratories would work on the pneumococcus, because the pneumococcus was reserved for Dr. Avery and his boys at the hospital. I never saw much in that rule, but I went along with Dr. Cole and stopped work on the influenza bacilli. However, I kept my organisms and passed them. There was good reason for this. At that time, we had no typed culture collection, and after one had worked up organisms like the ones I had and knew their growth requirements, why, it was the better part of wisdom to keep them going, and I did. Today, of course, things are a lot easier. If a laboratory needs a particular culture, let us say, for teaching purposes, there is no necessity of passing the organisms every few weeks throughout the year; all you have to do is send some money to the typed culture collection and buy what you want or need.

If it had been up to me, the chances are that I wouldn't have done another thing with these bacilli, but in 1926 a very bright young Englishman named F. C. O. Valentine came to work with me at the hospital. He didn't look particularly English; he was dark, with very black hair and dark eyes, and I always like to speculate that some Spaniard of the Spanish Armada did make it to shore and made a private conquest. Valentine wasn't particularly interested in viruses, but he had a first-rate mind, and one day he came to see me. "Dr. Rivers," he said, "I have been thinking about the growth requirements of in-

[18] F. C. O. Valentine and T. M. Rivers, "Further observations concerning growth requirements of hemophilic bacilli," *J. Exptl. Med.*, vol. 45:993 (1927).

fluenza bacilli. According to Avery, the true influenza bacillus requires both 'X' and 'V,' parainfluenza bacillus Rivers requires only 'V,' and hemoglobinophilus canis only 'X.' If you take a medium which has neither 'X' nor 'V,' and put all three strains in, they ought to multiply. It seems very likely that the bacilli that need 'V' must make 'X,' and vice versa."

It was a very nice supposition for a youngster to make, and when we put Valentine's idea to the test—and it was his idea and not mine—we found that it worked out in precisely the way he imagined it would.

Q: Dr. Rivers, together with Dr. Valentine and Dr. Eldridge, you also did some work on experimental measles during this period, and I wonder if you would give me some of the background of those experiments.[19]

Rivers: Before I came to the Institute, Francis Blake and James Trask had reported that measles was caused by a filterable virus, and that by obtaining the virus from the blood and nasal pharyngeal washings of human patients they could, through intratracheal and intraperitoneal inoculation, produce experimental measles in monkeys. However, they were unable to propagate the virus indefinitely in monkeys. During the twenties, two very good and respected workers, Ruth Tunnicliffe and Newell S. Ferry, attacked Blake and Trask's work, and claimed that measles was the result of a streptococcus infection. It was this state of affairs that led me to start my own experiments on measles.[20]

[19] Report of Thomas Rivers to the Board of Scientific Directors of the Rockefeller Institute for Medical Research, 1927.

[20] See further F. G. Blake and J. D. Trask, "Studies on measles. Susceptibility of monkeys to the virus of measles," *J. Exptl. Med.*, vol. 33:385 (1921); R. Tunnicliffe, "The cultivation of a micrococcus from blood in pre-eruptive and eruptive stages of measles," *J. Amer. Med. Assoc.*, vol. 68:1028 (1917); "Further studies on a diplococcus in measles. A measles skin reaction," *J. Infect. Diseases*, vol. 37:193 (1925); R. Tunnicliffe and A. L. Hoyne, "Further studies on a diplococcus from measles. Prevention of measels by immune goat serum," *J. Infect. Diseases*, vol. 38:48 (1926), and N.S. Ferry and L. W. Fisher, "Measles toxin. Its preparation and application as a skin test, as an immunizing agent, and for the production of an anti-toxin," *J. Amer. Med. Assoc.*, vol. 86:932 (1926).

Q: How did you set up your experiments? What questions did you attempt to answer?

Rivers: I had no reason to doubt Blake and Trask's claims, and I began with the proposition that measles was a virus infection. My initial experiments were designed to answer such questions as:

When can one be reasonably certain that the virus of measles is in the blood stream in amounts sufficient for experimental work? Is the virus in the rash present in amounts suitable for experimental work? If so, how long does it remain active in the rash? Can one obtain the virus from the lesions in the skin after it has disappeared from the blood? Is there some way of preserving the virus in the blood or in some organ so that it retains sufficient activity over a long enough period of time to permit of its filtration and use for prophylaxis? [21]

Let me say here that I very quickly confirmed the work that Trask and Blake had done. For example, I was able to demonstrate that the virus of measles was in the blood for about 48 hours prior to the appearance of the rash. I got a particular kick out of being able to show that the active agent was present in skin lesions, and that if you took affected bits of skin very early, macerated them, and injected the material intracerebrally or intratesticularly in monkeys, you could produce experimental measles. However, before you begin patting me on the back, let me say that there was one thing that I couldn't do, and that was to pass measles from one monkey to another. Today, I understand what happened, but in those days it was a great frustrating mystery. The fact is that monkeys pick up measles virus very easily and carry it, and many of my monkeys developed an immunity before they even reached my laboratory. If they didn't get infected on the way to the lab, they had plenty of opportunity to pick up the virus in the animal house. I kept all of my experimental monkeys in the same room—those that I had already artificially inoculated and those that I hoped to infect in the future—and while it is true that I kept them in separate cages it made no difference, because my animal keeper, in the performance of his daily tasks, unwittingly carried the virus from cage to cage. I am not surprised now that we couldn't pass the virus from monkey to monkey, and that we didn't always get a take.

[21] These questions quoted by Rivers from miscellaneous notes in folder marked Measles (Rivers papers).

I never wrote a paper on experimental measles because I didn't think that I had anything really to add to the literature. Why should I waste people's time by making them read such a paper? But this is not to say that the research was a waste. It wasn't—I had a lot of fun, and I did learn a hell of a lot.

Q: Dr. Rivers, how do you explain Dr. Tunnicliffe's findings?

Rivers: I don't know. I can't account for the results claimed to have been attained in many scientific experiments. Some scientists see what they want to see. I remember that around 1926 Dr. Yves Kermorgant of the Pasteur Institute claimed to have isolated a spirochete from a mumps patient,[22] and I'll be damned if some of my medical brethren didn't begin treating patients with neoarsphenamine. Some even claimed to have gotten excellent therapeutic results. Some docs are just plain unadulterated uneducated experimenters, and they don't know what they have to do experimentally to prove whether a thing is true or not. I feel sorry for them, but I can't accuse them of being dishonest—there's a difference. Occasionally you will find a smart scientist that fudges and he knows he's fudging —but thank God, there are not many of those.

I knew Dr. Tunnicliffe and knew her very well. She was a good and respected worker, but on several occasions she was able to get strep viridans out of the throats and conjunctival fluid of measles patients and became convinced that they were the inciting cause of measles. The thing she apparently forgot was that you could get strep viridans out of practically anybody's throat. I think that Dr. Tunnicliffe was just about the only person in my time who believed that strep viridans was the cause of measles; nearly everybody believed that it was caused by a virus.

Q: Dr. Rivers, there were any number of virus diseases which were thought to be caused by strep. Didn't Dr. Edward Rosenow of the Mayo Clinic contend that poliomyelitis was caused by a strep? [23]

[22] Y. Kermorgant, "Contribution à l'étude de l'étiologie des oreillons," *Ann. Inst. Pasteur*, 39:565 (1925); "Sur l'étiologie des oreillons," *Ann. Med. Paris*, vol. 19:301 (1926).

[23] E. C. Rosenow, "Streptococci in spinal fluid in acute poliomyelitis," *J. Amer. Med. Assoc.*, vol. 91:1594 (1928).

Rivers: He did indeed, and he kept to that belief from before World War I to the day he died. I knew Dr. Rosenow, and in many respects I considered him a first-rate bacteriologist. He was a sincere man and sincere about his work, but he didn't know anything about viruses. It was his contention that he got strep viridans out of the spinal fluid of patients with polio, and that he could produce polio in rabbits by injecting them with strep. To save my soul, I don't know how he did all of this. Of course, he was one-hundred-per-cent wrong. Actually, as far as the virus of polio is concerned, it is practically never found in the spinal fluid. If Rosenow was looking for the virus of polio, the spinal fluid was just about the sorriest place to look—I think that it probably turns up there maybe once in a thousand times.

Dr. Flexner had a running battle with Rosenow on this problem for over a quarter of a century, and I had one run-in with him at a meeting held before the Association for Research in Nervous and Mental Disease during Christmas week in 1931. I was pretty savage with him. Do you think that helped? Hell no, if you ask me for my candid opinion, I think that most of the audience present believed Rosenow. It took a long time to educate doctors to understand the nature of viruses.[24]

Q: Dr. Rivers, one of the viruses you studied at this time was fowlpox virus. Could you tell me what led you to study this virus? [25]

Rivers: Looking back, I would say there were two major reasons. The first related to the virus itself. Fowl pox, as you know, is a common disease of the barnyard, and it recurs in epidemic form in many

[24] Olitsky adds this note.

While Dr. Flexner and Dr. Rivers had verbal "running" battles at meetings with Dr. Rosenow, I was delegated by Dr. Flexner to experiment with the problem of streptococcus as the possible causal agent of experimental poliomyelitis in monkeys, and of herpes febrilis. In these tests I was associated with Drs. P. H. Long and C. P. Rhoads. We could find no evidence to warrant a conclusion that streptococcus was the cause of either infection, as stated by Rosenow. But the latter resented our statements in publications, and at many meetings (which I did not attend) Rosenow in histrionic addresses leveled devastating criticisms against me, personally, for daring to report such findings. (private communication).

Cf. P. K. Olitsky, C. P. Rhoads, and P. H. Long, "Relation of streptococci to spinal fluid in experimental poliomyelitis," *J. Amer. Med. Assoc.*, vol. 92:1725 (1929).

[25] Report of Thomas Rivers to the Board of Scientific Directors of the Rockefeller Institute for Medical Research, 1928.

countries. As a rule, it is not fatal; however, it is a disease which leads to great economic loss because it affects the egg-laying activity of all infected fowl. In 1928 it presented an interesting problem because, although virologists had long been able to transmit fowl pox by direct inoculation, its rapid spread under natural conditions in the barnyard remained a mystery. Ernest Goodpasture—who was a great investigator, by the way—pointed out about that time that, even if you put infected fowl together in the same cage with healthy fowl and let them pick at one another, the pox did not spread very readily. He had expected the reverse to happen. Well, Goodpasture's finding intrigued me, and, as I read through the literature, it became apparent that farmers as well as some scientists were of the opinion that insects, flies or mosquitoes were instrumental in the spread of the disease. However, no one put the idea to the test. I therefore decided to undertake experiments to ascertain whether mosquitoes were of any significance in the spread of fowl pox.

The probability is that I would not have undertaken this series of experiments if it hadn't been for the particular people I then had working with me in the laboratory. In addition to Dr. Muckenfuss and Dr. Haagen, whom I have spoken of before, I had a visitor in my lab for several months, named Israel Kligler. Dr. Kligler was a bacteriologist who had previously worked for the Rockefeller Foundation and had done some very handsome work on malaria and mosquitoes. It was an ideal situation; I had two fellows who knew something about viruses and another who knew something about mosquitoes but nothing about viruses. I just put one and two together and got a very neat experiment. Too often people think that beginning an experiment depends on only one lab. It doesn't. You not only have to depend on the work that others do before you; you also are dependent on material in their possession. I was able to get my experiments under way when Dr. Howard Andervont, who had previously worked on fowl pox, very kindly sent me some pox to work with. Actually, the experiment was not difficult to do. We took a mosquito, placed it in a test tube, and then placed the tube over an infected wattle or comb. When we were sure that the mosquito had fed on the lesion, we took him and let him feed on a perfectly healthy hen. There was no doubting the evidence that the mosquito was the culprit in transmitting

fowl pox in nature. In the beginning, I thought that nobody paid much attention to this work. A number of years afterward, I was at a convention in San Francisco listening to Sir Frank MacFarlane Burnet—he wasn't a sir then, just plain Frank Burnet—talking about the spread of infectious myxomatosis from rabbit to rabbit by mosquito. I sat listening with my mouth wide open, because it was my fowl pox experiment done over in rabbits. Well, you know me, after the meeting was over I asked Burnet if he had ever seen my paper on fowl pox. He smiled and nonchalantly said, "Why sure, Dr. Rivers, that's where we got the idea."

Q: Dr. Rivers, for me, one of the most interesting pieces of research engaged in during your early tenure at the Institute was growing vaccine virus in tissue culture. Were you the first to grow vaccine virus in tissue culture?

Rivers: I don't want to disappoint you again; you historian fellows are always looking for a first, and I can unequivocally say that I was not the first even to attempt the growth of vaccine virus in tissue culture. I believe the credit for that belongs to Constantin Levaditi [26] of the Pasteur Institute. If I remember correctly, Dr. Levaditi infected an animal with vaccine virus and then took a nerve cell from that animal and put it in a hanging-drop tissue-culture setup and after a certain number of days demonstrated that the virus was still present. So far as I can remember, there was no proof that the virus had multiplied in that setup; at most, I think all one could say was that it survived.

[26] Tissue-culture work in the United States began under the auspices of Leo Loeb and Ross Harrison. It should be borne in mind that the question put to Rivers was not about tissue-culture work in general but the cultivation of vaccine virus in tissue culture. His remembrance of Levaditi's investigation is undoubtedly an outgrowth of his collaboration with Alexis Carrel, for Levaditi's work is the first one cited in the paper they later prepared. Although Levaditi tried to cultivate viruses in tissue culture, he did not work with vaccine virus, but initially used poliovirus. C. Levaditi, "Symbiose entre le virus de la poliomyélite et les cellules ganglions spinaux, a l'état de vie prolongée in vitro," *Compt. rend. soc. biol.*, vol. 74:1179 (1913). I later discovered that the first report of the cultivation of vaccine virus in tissue culture was made by E. Steinhardt, C. Israeli, and R. A. Lambert, "Studies on the cultivation of the virus of vaccinia," *J. Infect. Diseases*, vol. 13:294 (1913).

The next investigators to try this were headed by Robert Nye and Frederick Parker, Jr., at Harvard, and, if memory doesn't fail me, they passed vaccinia through several cultures of rabbit testicular tissue and got a multiplication of virus.[27] Still later, Alexis Carrel and I did a little piece of work at my request to see whether we could get a multiplication of virus in plasma clot medium. I don't think very much of that work, but it did look as if we too had some multiplication of the virus.

In 1928 Dr. Hugh B. Maitland and his wife, of the Department of Bacteriology of the University of Manchester in England, concocted a medium that consisted of minced chicken kidney suspended in a mixture of chicken serum—I believe, one part—and Tyrode's solution—two parts. They claimed that after three days there was no detectable growth of cells in that culture and that, when vaccine virus was added to it, it multiplied.[28] Now the Maitlands were both experienced investigators—you might even say superb investigators—and there was no doubt in my mind that the virus multiplied. What bothered me was the claim that the virus grew in the absence of living cells. I just couldn't swallow that. Hell, it hit at my fondest beliefs. I decided therefore to test the Maitlands' findings.

I repeated their experiments as carefully as I could, and, like them, discovered that vaccine virus indeed did multiply in a medium of normal fresh kidney cells plus Tyrode's solution and chicken serum. However, whereas the Maitlands believed that their medium was not a tissue culture and actually thought autolysis of cells to be complete in three days, I demonstrated that many cells remained viable for as long as five days, and that in such instances their medium was capable at times of supporting multiplication of virus. It was definite that the vaccine virus did not multiply in the absence of living cells. But let me just point out that, in spite of my findings, the work of the Maitlands was most important for the study of viruses, because they found a medium for the easy cultivation in vitro of vaccine virus and other infectious agents of a viral nature.

[27] R. F. Parker, Jr., and R. N. Nye, "Studies on filterable viruses. I. Cultivation of vaccine virus," *Amer, J. Pathol.*, vol. 1:325 (1925).

[28] H. B. Maitland and M. C. Maitland, "Cultivation of vaccinia virus without tissue culture," *Lancet*, vol. 2:596 (1928).

Q: Weren't there other attempts at that time to see if you could get viruses to grow or multiply outside of the living cell?

Rivers: Just what are you referring to?

Q: I have particular reference to the work of Dr. Olitsky and Dr. MacCartney testing the survival of rickettsia separated from living host cells by collodion membranes.[29]

Rivers: I remember that. When the question came up of whether viruses could exist or multiply in the absence of living host cells, some investigators, among them Dr. Olitsky and Dr. MacCartney, decided to test that idea by implanting collodion membranes containing rickettsia in the peritoneal cavities of experimental animals. As I remember it, Olitsky and MacCartney later reported that the rickettsia survived approximately thirty-one days. I objected to these experiments, because I felt that the collodion sacs with their contents acted as foreign bodies, and, instead of the rickettsia being brought into close relation with normal host cells, they were brought into indirect contact with the fibrous capsule, by which the bags had become surrounded.

With the help of Ralph Muckenfuss—and I should add here that he did all the work—I put vaccine virus in a cell-free mixture of serum and Tyrode's solution, placed it in a collodion sac, in dialyzing apparatus, outside of which there was a preparation of living kidney cells in serum and Tyrode's solution. We soon discovered that under such conditions the virus retained its activity. It appeared to me then that the living cells had something which was capable of reaching the virus through diffusion of the semipermeable membrane. I didn't know what it was; nobody knew.

[29] The implication of the question asked here by the interviewer is deceptive. Olitsky and McCartney did not use collodion capsules as a way of maintaining rickettsia free from living cells. The object of the experiment was to supply oxygen to the organisms under such conditions as to extend their survival time. P. K. Olitsky and J. E. McCartney, "Experimental studies on the etiology of typhus fever: V. Survival of the virus in collodion sacs implanted intra-abdominally in guinea pigs," *J. Exptl. Med.*, vol. 38:691 (1928).

Q: Dr. Rivers, I don't want to press you, but how do you explain the persistence of the belief that it was possible to grow viruses on nonliving media? During the early thirties, for example, several notable claims were made that it was possible to cultivate vaccine virus on lifeless media. The work I have in mind is that by Dr. Arthur Kendall in America and Dr. George H. Eagles in England.

Rivers: Let's talk about Kendall first. Dr. Kendall was a bacteriologist and a good one. During World War I, he had done some very good work on intestinal bacteria, and during the twenties made significant contribution to our understanding of bacterial metabolism. He knew little or nothing about viruses; however, in 1931 he published an article in *Science*, in which he claimed to have grown vaccine virus on a lifeless medium of his own concoction known as K medium. Previously, he had had some success growing typhoid bacilli on this medium, and his claims began to attract attention. I didn't take Kendall's claims very seriously, and they didn't concern me until Dr. Thomas Futcher, who was one of my teachers at the Hopkins, invited Kendall to give the annual guest lecture before the Association of American Physicians. Futcher, who was a wonderful clinician, knew very little about bacteriology and virology, and, after it became generally known that he had invited Kendall, a number of his friends who were conversant with Kendall's work urged him to withdraw this invitation. Futcher was a gentleman and refused to do so, but as a concession asked Hans Zinsser and myself to attend the meeting and discuss Kendall's paper.

I hadn't intended to test Kendall's work but, when Dr. Futcher asked me to discuss the paper, I repeated the experiments. I gave it an honest whirl but, as you might suspect, I got no proofs of Kendall's claim. But I did come armed for the discussion. After Kendall gave his paper, Futcher called on me. I was a much younger man than Kendall, and I was also a younger man than most of the people in the Association of American Physicians, because I hadn't been a member very long. So I got up and, in a very temperate manner, called the fellow a liar. Not in so many words. Actually, all I said was that I couldn't repeat the experiment and I therefore didn't believe his findings were true (see Appendix A).

I was very temperate about it, but Zinsser wasn't. When I got through, Dr. Futcher called on Hans. He was standing in the back of the hall, and he did his trick. The moment he was called on, he began to talk, and he talked all the way down the aisle to the platform. Every eye was on him, and nobody missed a word that he said. You know, this was characteristic of Hans. I saw him do it at Harvard. He would stand in the back of the classroom—they are steeply banked—and talk all the way down to the desk and never lose a student.

Well, Hans did this down there, and he just gave Kendall bloody hell. I'd never seen Hans so hot in all my life. I had to agree with everything he said—but I really felt sorry for poor old Kendall—he just sat there and took it. I will never forget that, when Hans sat down, Popsy Welch felt so bad for Kendall that he got up and said, "You know, you folks shouldn't be so tough on Dr. Kendall. After all, he might be right. I don't know whether he is or not—but you oughtn't to be so hard." Hans was tough, but this time he had every right to be.

Q: Dr. Rivers, while one can accept the fact that Dr. Kendall as a bacteriologist knew little about viruses, that stricture surely cannot be used against Dr. Eagles.

Rivers: Eagles' papers on the growth of vaccine virus in lifeless media cost me two years' work—yet I don't blame him entirely. The person I hold most responsible is Hideyo Noguchi. Noguchi had a tremendous influence on scientists throughout the world, and at one time most of them believed that you could cultivate just about anything in the Noguchi medium. All you needed was his long narrow test tube, a bit of rabbit testicle or kidney, a deep layer of broth, and the virus or bacteria you were working with, and you were in business.[30] Now, this belief was not restricted to beginners; respected and

[30] Olitsky writes:

The medium described here by Dr. Rivers was first devised by Theobald Smith in 1899 and could be considered as an historical forerunner of the Maitland type. Its chief ingredients were a fragment of kidney (rabbit, later monkey or rabbit) plus fresh, unheated ascitic fluid collected under sterile conditions from human beings, generally cases of hepatic cirrhosis. The fluid contained cells, and the presumption was that they and the cells from the tissue could have been viable for several days at least. The medium became

experienced investigators believed it too. Bill MacCallum, professor of bacteriology at the Hopkins believed it and John Ledingham, later Sir John Ledingham, director of the Lister Institute, believed it. As a matter of fact, Ledingham came all the way from England to learn from Noguchi personally about his special medium, and I am sure that it was Ledingham who spread the gospel to other investigators at the Lister Institute, like Eagles and McClean.

About 1932 Eagles and one of his associates, Dr. McClean, reported that they had successfully cultivated vaccine virus in a "cell free" medium.[31] What they did was to take an extract of rabbit kidney, suspend it in a mixture of serum and Tyrode's solution, and ground and centrifuged it at high speed to get rid of as many cells as possible. The material was then frozen (in a mixture of alcohol and ice) and thawed repeatedly, and, when virus was added to such extracts, it was claimed that it multiplied. Well, Sylvia Ward, who was then my technician, and I very methodically and carefully repeated the work of Dr. Eagles, and I want to tell you that in no instance were we able to show that vaccine virus multiplied in a "cell-free" medium. We did discover that grinding and repeated freezing and thawing of Eagles' medium did not in every case get rid of all the cells, and in some instances cells not only remained alive but proliferated. In such cases, the virus multiplied. Some years later, Dr. Albert Sabin, who worked at the Lister Institute during this period, told me that the technique used in Eagles' laboratory was not exactly faultless, and that in several instances virus multiplication occurred because the pipettes used in culture transfers were not sterilized properly.

I think that Eagles' experiments were the last gasp of folks who said you could grow viruses on nonliving media. So far as I know, no one has done it yet. However, this doesn't mean that they won't. Up to now, it seems that the living cell is the only thing that can provide the factor that's necessary for the growth and multiplication of a virus. But I can easily imagine the day when somebody will come

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known as the Noguchi medium from his use of it in 1911 and later. Dr. Fred Gates and I renamed it Smith-Noguchi, for Noguchi only added some modification (private communication).

[31] G. H. Eagles and D. McClean, "The cultivation of vaccine virus in a cell free medium," *Brit. J. Exptl. Pathol.*, vol. 12:97 (1931).

along and put the necessary chemical components together to have a virus made in a test tube—shake it—and create a virus in the absence of the living cell. Until now, nobody has been able to perform this trick, and it's still safe to hold that viruses multiply or are multiplied by the living cell.

In the early days of virology, I had to defend that theory pretty vigorously, although the evidence supporting my position was present in the literature. For the life of me, I don't see why it was so hard for me to convince people. The only reasonable explanation I can find at this late date is that sometimes science is held up because people of great renown hold on to their ideas and refuse to give them up. Some years ago, I expressed that notion at some length in a paper I gave before the American Philosophical Society on polio research in the United States.

> Progress in poliomyelitis research [I said] has not been continuous. In fact, at times we have gone backward instead of forward, and, when we have gone forward, it has been by fits and starts instead of in a smooth, steady manner. At the roots of progress in poliomyelitis research, as in all research, lie proper concepts and adequate techniques. These have been acquired more slowly in relation to poliomyelitis than is the case regarding other viruses. Because of this, many errors have been made and workers have taken part in many wild goose chases. Those who have made the errors, unless they refuse to admit them and to give up false concepts, should not be held in low repute, for not infrequently their mistakes, if recognized, make easier the paths of other investigators. There are times, however, when workers of great scientific repute continue to misconstrue the meaning of their data or will not admit inadequacies in the techniques employed by them. When this happens, progress may be materially impeded and much effort must be expended in tearing down the false edifice before a true one can be built. Thus, "no one has the right to encumber science with premature assertions," for "an erroneous affirmation which has taken a day to construct requires sometimes twenty years to overthrow." [32]

Several weeks after that article appeared in the *Proceedings of the American Philosophical Society*, I received a note from Justice Felix Frankfurter of the United States Supreme Court. He apparently had read the article—although for the life of me I don't know why—and

[32] T. M. Rivers, "The story of research on poliomyelitis," *Proc. Amer. Phil. Soc.*, vol. 98:254 (1954).

wanted to know where I got the quotation I used in the paragraph I just quoted. I told him that I got it from a book by Charles Richet called *The Natural History of a Savant* and advised him that if he wanted to have many laughs to read it. I advise you to do the same—it's a wonderful wise and witty book. In 1931 when I gave a talk to the Pacific Northwest Medical Association in Butte, Montana, I quoted extensively from that book. I remember that old Ajax Carlson of the University of Chicago was in the audience. He was the only one in the entire hall who wasn't wearing a tuxedo. He had his chair tilted back against a post and an old cap pulled down over his eyes. I thought the old son-of-a-gun was asleep, but he wasn't. He listened to every word I said, and when I got through he got up and spanked hell out of me. He made it plain that he didn't think much of me for quoting from a book written by a man who in later life became a spiritualist and translated by another who did the same. It made no difference to him that Richet won the Nobel prize for his work on anaphylaxis and that Sir Oliver Lodge had been an eminent scientist. The fact that they had both embraced spiritualism in later life was enough for old Ajax to condemn them to hell and me along with them for quoting the book. I didn't care what they believed in their old age. Hell, if Carlson had argued that the Nobel prize committee made a mistake in giving the prize to Richet for work on anaphylaxis, why then I might have gone along with him. I have always believed that the prize for that work should have gone to Theobald Smith.

Q: Dr. Rivers, I'd like now to turn to a consideration of your work on growing vaccine virus in tissue culture. For example, the strain of virus that you work with is of historical interest, and although you mentioned something of this before in passing I wonder if you would begin by telling me how you came to work with it.

Rivers: As I mentioned before, Hideyo Noguchi had passed a strain of vaccine virus that he had received from the New York City Board of Health through a number of generations of rabbits by intratesticular inoculation, with the idea of making a bacteria-free vaccine virus for human use. He was successful; however, in the process his virus mutated and no longer produced an encephalitis in rabbits. Well,

that aroused my interest and I sent to the Board of Health for another batch of the original strain sent to Noguchi. I was particularly interested in the original source of the virus. At that time Charles Tyler of the Board of Health wrote me the following note:

> Regarding the history of our strain of vaccine virus: the following statement appears in the Yearly Report of the New York City Board of Health for 1874–75:
>
> "We began vaccinating with virus of the same stock as that which had been supplied by the late Dr. Loines of the Eastern Dispensary and myself for about 5 years and which had been used and sold by him for about twenty years previously. This virus was originally obtained from England by Dr. Loines and in all probability was descended from the stock furnished by Jenner. As it always developed characteristic Jennerian vesicles and as it always thoroughly protected from small pox those upon whom it was used, Dr. Loines never thought favorably of employing any other."
>
> The same strain of virus has been in use since the time of this report. The virus has been "humanized" at various times, usually from one to three times yearly.[33]

I think the evidence is pretty straightforward, enough for me to claim that I was working with an historic strain.

Q: Were there any other reasons for cultivating vaccine virus in tissue culture?

Rivers: Yes. About that time, there were many reports claiming that encephalitis followed vaccination against smallpox. Actually, there were such cases and, while they were more numerous in Europe than in the United States, the antivivisectionists and antivaccinationists in this country used the occasion as pretext for vigorous attacks on the medical profession in general and those engaged in experimental medicine in particular. I didn't think that polemical debate with such people would be fruitful. As a matter of fact, I thought it more likely that such debate would merely add fuel to a fire already kindled. Instead, I thought that the best method of combatting such attacks against vaccination would be the preparation of a better and cleaner

[33] Quoted from T. M. Rivers, "Cultivation of vaccine virus for Jennerian prophylaxis in man," *J. Exptl. Med.* vol. 54:453 (1931).

vaccine virus. It seemed logical to me that, if I cultivated the virus in tissue culture that I would get what I was looking for. Together with Dr. Li, I worked out a nice technique for growing the virus on minced chick embryo suspended in Tyrode's solution. I mention this because I found that other media permitted the entry of unknown virus into the cultures as contaminants. There is nothing more to be said about this except that the actual work for cultivating a virus in tissue culture suitable for purposes of vaccination in man was done with Sylvia Ward.

I was gratified to learn that, although the virus was propagated in cultures for a considerable time, it seemed to have lost none of its characteristics—enough to encourage me to ask Dr. Alfred Hess, who was a very well-known pediatrician, if I could inoculate some of the kids whom he had medical charge of in an orphan asylum with my vaccine. He agreed, because those kids had to be vaccinated anyway. I did, and I want to tell you I was not pleased with the results I got, because they were just as ugly as one would get with the straight virus furnished by the Board of Health, if not more so. At that time, I gave up any idea of using the virus in human beings. However, as I cultivated it in generation after generation in tissue culture, I noticed that it became less and less virulent for rabbits generally. On several occasions, I pepped it up by putting it back into the testicles of rabbits; eventually, however, I got a strain that I couldn't rejuvenate. Yet that strain, given intradermally into children, produced very little if any reaction—usually a red spot, slight induration—but the tissue would not break down and the children were not sick. When I subsequently tested those children, they were pretty much immune to the city vaccine virus.

I was pleased as punch. I thought it would be a nice way to vaccinate people, since they would not have ugly scars and were not likely to get an encephalitis after vaccination, as they sometimes would after the use of more virulent strains. Six months later, when I re-inoculated the children, I thought they had much more reaction to the Board of Health vaccine than they should have had. Well, Sylvia Ward and I studied this problem very carefully and finally came to the conclusion that the kids were not as thoroughly protected as they should have been, and I gave up trying to get the Board of Health to

use my attenuated vaccine virus. You know, even with the vaccine that the city uses now, you don't get lifelong immunity, and if you go abroad you can't get back into the country unless you've been vaccinated within the last three years. In sum, you might say that I discovered some interesting things about getting an attenuated strain of virus by using tissue culture, but nothing that was of real practical value.

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