CHAPTER 3

# The Rockefeller Institute for Medical Research—1922

*. . . Never claim to have made a scientific discovery unless you have made due allowance for Nature's misplaced sense of humor.*

Christopher Andrews, "Nature, the Scientist, and the Pitfall," *St. Bartholomew's Hospital Journal,* 1924

*Q:* Dr. Rivers, when you came to the Rockefeller Hospital was any division made between clinical responsibility and research or were the two so completely integrated that it was difficult to separate them?

*Rivers:* The laboratories of the Rockefeller Institute were opened in 1901, and, while a hospital was spoken of from the beginning of the Institute, it did not come into being until 1910. Now, what I am going to say about the original plans for research in the hospital is based on some letters I have seen which were written by Dr. Christian Herter and Dr. Rufus Cole, remarks made to me by Dr. Cole throughout our long association, and hearsay. I won't say that it is the absolute truth or the only truth; let me just say that there is a great deal of truth in it. Originally, the person chosen to be the director of the hospital was Dr. Christian Herter. Herter had early made a name for himself by his observations on the nature of nervous diseases and had in 1905 helped establish the *Journal of Biological Chemistry.* He was a close friend of Dr. Welch and, like him, early saw the necessity of having laboratories in the hospital, but, as far as clinical research was concerned, he seemed agreeable to having such research in part initiated by the laboratories of the Institute. This view is best ex-

pressed in a letter that he once wrote to Dr. Simon Flexner. Let me quote part of it here.

It might at first seem superfluous to provide laboratories in the Hospital building since the large laboratories of the Institute still possess so much unassigned space. It is deemed of first importance that the physicians in charge of patients should be able to conduct certain routine examinations within the Hospital itself. To carry on such routine examinations in the main laboratories would involve considerable loss of energy and imperfect coordination of observations. On the other hand, much research work connected with patients in the Hospital could be advantageously done in the existing laboratories. . . . Under the arrangement, the various problems should be attacked under the direction of workers in the Rockefeller Institute as such problems appear to them promising. . . . Certain elasticity would exist in regard to the problems studied in the Hospital. At one time most patients in the Hospital might be chosen with a view of furthering research originating in the laboratories. At another time relatively greater attention would be concentrated on patients chosen in connection with research problems originated by the attending physicians. . . . It is conceivable that such occasions would arise where one type of disease would be studied in its different phases, on the one hand by the laboratory group of the Hospital, and on the other hand by one or more of the laboratory departments of the existing laboratory.[1]

There is little doubt in my mind that the character of clinical research at the Rockefeller Hospital would have been far different from what it eventually became had Herter taken up his post as originally planned. Unfortunately, the poor fellow came down with myasthenia gravis, and, when it became obvious that he would be unable to assume the directorship of the hospital, Rufus Cole was chosen in his place. Dr. Cole was one of the early products of the Johns Hopkins Medical School of the era of Osler and Welch, a product, you might say, of the kind that helped establish the reputation of the Hopkins as the Mecca of the medical world. When Dr. Lewellys Barker came to the Hopkins in 1905, Dr. Cole was chosen to run the Biological Laboratories. It was not an idle choice, since, for several years prior to Barker's appointment, Dr. Cole had established a reputation as a clinical investigator and instructor in medicine. After approximately two years in his post as director of the Biological Laboratories at Johns Hopkins, Dr. Cole was called to the Rockefeller Institute. I should

[1] Christian Herter to Simon Flexner, April 15, 1907 (Flexner papers).

point out, however, that he was originally called to be part of the hospital team *under* Herter. In 1908, before Cole assumed his duties as director, he made it abundantly clear to Dr. Flexner and the Board of Scientific Directors of the Institute that his ideas of clinical research in the hospital were quite different from those held by Dr. Herter. He embodied these in a long memorandum which he submitted to the Board of Scientific Directors. The nub of his argument is contained in the following excerpt:

My conception of the hospital is that it is to apply the intensive methods to clinical study as opposed to the extensive or statistical methods formerly invoked. . . . To my knowledge this is the first hospital to be endowed, in this country at least, for this exclusive purpose. Its further purpose is to extend the work of the Institute laboratories in which the method has of necessity been largely experimental. For clinical study must, from the nature of things, be largely investigative as opposed to the experimental method of a laboratory, yet I think the best results can be obtained only when the two methods can be applied simultaneously. . . . One thing that has most seriously delayed the advancement of medicine has been the physical and intellectual barrier between the laboratory and the wards of many of our hospitals. Clinical laboratories most often exist merely to aid diagnosis. I would therefore urge that the hospital laboratory be developed, so far as is possible, as a true research laboratory, and that moreover the residents of the hospital be permitted and urged to undertake experimental work on animals; and that, so far as is possible, facilities be given in the general Institute laboratories for such investigation whenever it is considered improper or impractical that such work be undertaken in the hospital laboratories. On the other hand, I think it proper and advisable that members and assistants of the Institute engaged primarily on pure experiments in the laboratory should have full opportunity in the hospital wards for the study of cases of the diseases which they are investigating. . . .

In order that neither privilege be abused, it is advisable that the rights and privileges of all be carefully defined. The relation of the present members of the Institute to the hospital must therefore be carefully defined in order that there may be the utmost harmony between them and the resident staff of the hospital. The greatest liberty of all can only be obtained by carefully defining the rights of all.[2]

Dr. Flexner's ideas about the proposed role of the hospital were in turn quite different from those held by Dr. Cole. As I understand it,

[2] Memorandum, Rufus Cole to the Board of Scientific Directors of the Rockefeller Institute for Medical Research, December 1908. Cole was appointed director of the hospital on March 1, 1909.

Dr. Flexner wanted the hospital to act as a testing ground for the ideas generated by the people who worked under him in the laboratories. They were a brilliant group and contained Ph.D.'s as well as M.D.'s, among them Phoebus Levene, Jacques Loeb, Samuel Meltzer, Wade Hampton Brown, and others. Well, right then and there, there was a showdown. Cole made it clear that the hospital was not going to be a handmaiden to the laboratories and that he and his boys were not going to test Noguchi's ideas, Meltzer's ideas, or Levene's ideas. (These are just names that I am using—I don't know whether they actually came up.) Cole was adamant that the people who took care of the patients would do the research on them. Well, Cole won the argument hands down before he came, and as a result he urged all his doctors—and they were usually young men that came into the hospital—to be as proficient in bacteriology, immunology, chemistry, and physiology as any Ph.D., and they were. Later, a large number of the doctors in the hospital, because they became proficient in these basic sciences, were made members of the National Academy of Sciences. Cole was one, Avery was one, Dochez was one, and I was one, and there were others. I would like to make it clear that we weren't elected because we were M.D.'s, because there is no section on medicine or surgery in the National Academy of Sciences; we were elected on the basis of our proficiency in one of the basic sciences.

Every now and again, the battle over the role of the hospital would flare up, but Cole stuck to his guns. Cole is a modest man, a rather timid man, until you get him mad. You had to kind of back him into a corner and get him mad before he would really shoot the works. But if you did, you would find, generally to your sorrow, that the old boy wasn't afraid to fight. The fight over the role of the hospital was one of those where Cole went all the way and in so doing helped set the standards for clinical research at the Institute and elsewhere. When Dr. Gasser and I succeeded Dr. Flexner and Dr. Cole, we never once had any fight over the role of the laboratories and hospital in research. Nor has Dr. Bronk, who is currently running the Institute, ever made any attempt to impose the authority of the laboratories over the hospital. So actually the policy which Cole established in 1910 still holds.

A lot of people in the past have made fun of the Rockefeller Hospital—and some still do—and refused to give it credit for any-

thing. But when you come right down to it and you force them to speak, they have to admit that the hospital has had a tremendous influence on clinical research throughout the country. Not nearly enough credit has been given to Rufus Cole for this influence. Cole did not begin clinical research in the United States, but he started the kind that demanded a lot more than was being demanded at the time he took charge of the Rockefeller Hospital.

*Q:* How rigid were the boundaries between the laboratories and the hospital? Did workers from these divisions ever collaborate with one another in research?

*Rivers:* There was a great deal of crossing over; however, nobody in the Institute could force anybody in the hospital to work with somebody in the Institute, and vice versa. All collaboration between workers in the hospital and workers in the laboratories of the Institute was on a voluntary basis. It was this way when I came to the hospital in 1922—I can't speak of what went on before—and it was this way when I left the hospital in 1955. It's the way things are done now: that is, if any of the boys in the hospital want to work with some of the boys in the laboratories they do it on a personal basis. They don't have to ask anyone's permission. Nobody at the Institute ever objected to a collaboration between two people by mutual agreement; by the same token nobody ever forced a collaboration. To force anything in research is not the way to get it done. The way you get research done is to find the guy who wants to do it and then give him the chance he needs.

*Q:* Dr. Rivers, when you first came to the Rockefeller Hospital, were you asked to work on viral diseases in general, or were you given a more specific assignment? The reason I ask is because there was a debate at the time between members of the Institute and other members of the medical profession on the nature of lethargic encephalitis.[3]

[3] See especially the reports of Simon Flexner to the Board of Scientific Directors of the Rockefeller Institute for Medical Research, 1920–1925; and S. Flexner and H. L. Amoss, "Contribution to the pathology of experimental virus encephalitis: I. An exotic

*Rivers:* Lethargic encephalitis or sleeping sickness, as it is popularly known, was first noted in modern times in Eastern Europe during the first world war, and became established in the United States around 1918. For several years thereafter it was a serious problem, and as late as 1926 we still had enough around the country to cause concern. To this day, no one has ever isolated the cause of this type of encephalitis although from time to time there have been claims. For example, Dr. Constantin Levaditi at the Pasteur Institute once thought he had found the cause, but Dr. Flexner and Dr. Harold Amoss took a great deal of trouble to show that he was simply working with herpes virus. Now, herpes virus injected into the brains of rabbits will cause a beautiful encephalitis. Some strains will develop an encephalitis if the virus is dropped in the cornea of an eye—in such a case it scarifies, causes a lesion, and eventually travels to the brain. Ernest Goodpasture once showed that the herpes virus could travel from the skin nerves up into the spinal cord and even down on the other side. At first, Goodpasture thought it was herpes zoster, but later it was definitely shown he was working with herpes virus, which in some cases can distribute itself in human beings and animals along nerve paths. To be sure, a debate such as you suggest was going on, but when I first came to the Rockefeller Hospital nobody told me what disease to work on, and no one even remotely suggested that I work on lethargic encephalitis.

The choice was my own to make, and I chose to work on chickenpox or to give it its medical name, varicella. I suppose I chose it in the first instance because there were a good many patients in the hospital at the time with chickenpox, and my attention was drawn to it. More important was the fact that chickenpox is a disease that you can see. Chickenpox has a vesicle. It's nice. In human beings, for example, you can differentiate chickenpox from other diseases that have vesicles, like smallpox, by the distribution of the lesions. In smallpox the distribution is mainly along the face and extremities, while in chickenpox they are mainly on the body. Furthermore, the lesions themselves show gross differences that you can see with the naked eye. Under the microscope one could also see that the inclusion bodies found in

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strain of encephalitogenic virus; II. Herpetic strains of encephalitogenic virus; III. Varieties and properties of the herpes virus," *J. Exptl. Med.*, vol. 41:215, 233, 357 (1925).

chickenpox were again quite different from those found in smallpox. In short, I chose to work with a disease that would give me something more than an indefinite fever, and that would be easy to diagnose and differentiate from other diseases that also lent themselves to experimentation. I figured that if I worked on chickenpox alone, I might not get anything and that I had better work with a similar virus to back me up. The Lord only knows why, but vaccine virus happens to be one of the nicest viruses that one could work with experimentally. Now I didn't tell Dr. Cole or Dr. Flexner that I was going to work on chickenpox and vaccine virus. I didn't have to. I started on chickenpox and, bless your soul, if I hadn't worked on vaccinia as well, I probably wouldn't have stayed at the Institute very long. The fact is, I didn't get much on chickenpox.

In the beginning, I attempted to establish chickenpox virus in rabbits and monkeys by getting material from the skin lesions of patients and injecting it into the testicles of my experimental animals, I suppose I proceeded in this fashion because Hideyo Noguchi at that time was also injecting vaccine virus into the testicles of rabbits, and I frankly copied him. I then began making serial transfers from testicle to testicle to testicle and, lo and behold, in a certain number of cases on the fourth or fifth transfer, my rabbits began to run high fevers of 105° and to have swollen testicles. When I took testicular material from such rabbits and scarified it on the skin of other rabbits, I would get a marked reddening of the skin. To top it off, I found nuclear inclusions in such testicular material that looked very much like the nuclear inclusions in varicella. I was so sure of my findings that I wrote two papers with Dr. William Tillett, who was working with me at that time, on the probable isolation of chickenpox in rabbits. To the Board of Scientific Directors of the Rockefeller Institute I confidently reported as follows:

> We believe that we are working with a virus. Furthermore, we are certain as it is possible for us to be that the virus was recovered from chickenpox patients under the conditions outlined. It is not the virus of vaccinia or smallpox. While the virus produces lesions in the rabbits very much like those of human chickenpox, we have not yet shown experimentally that the virus is the etiological agent of chickenpox. As soon as we can get some fresh cases of chickenpox we will attempt the active immunization of a

number of rabbits by injecting into them the blood of patients early in the disease. If after two or three weeks these rabbits are immune to our virus we will be warranted in assuming that we have been working with the etiological agent of varicella and furthermore we will be warranted in using the virus as a prophylactic measure against chickenpox in children.[4]

Looking back, I can thank my lucky stars for the tentativeness that I included in my papers and report, because, when I conducted confirmatory experiments, I soon found that I didn't have what I thought I had.

It was known at that time that one of the striking characteristics of most viruses was that an infection caused by them led to the appearance of a lasting immunity in a recovered animal. We soon found, on further experimentation, that rabbits which recovered from primary inoculations of our virus were refractory to subsequent inoculations of the same virus. So far so good. It was when we took the next steps that we foundered. First, we tried to protect rabbits against our virus by intravenous injections of whole blood and blood serum from patients convalescent from chickenpox, and quickly learned that it was of no help at all. Tillett and I assumed, and rightly so, that the serum of a patient who had recovered from chickenpox would neutralize chickenpox virus; however, when we took such sera and tested it against our virus in vitro, we discovered, again to our dismay, that it had no demonstrable neutralizing effect.

By this time, we were sure that we hadn't transmitted chickenpox to rabbits and almost simultaneously got confirmation from Homer Swift's laboratory in the hospital that we were in fact working with a new virus. Dr. Swift was a most interesting person. Originally he was trained at the Bellevue Hospital Medical School, but, if you ask me, one of the decisive influences in his life was his uncle, Dr. John A. Fordyce. Dr. Fordyce was a distinguished dermatologist, and then, as now, one of the dermatologist's responsibilities was the care and treatment of people who had become infected with syphilis. Through his uncle, Dr. Swift became interested in syphilis, and when he came to the Rockefeller Hospital in 1910 he made several early and important improvements in serological diagnosis and treatment of the

[4] Report of Thomas Rivers to the Board of Scientific Directors of the Rockefeller Institute for Medical Research, October 1923.

disease. Dr. Swift was one of the first in the United States to assess the value of treating syphilis with Salvarsan. In the early days, syphilis of the central nervous system (locomotor ataxia and paresis) did not respond favorably to intravenous injections of Salvarsan, and Dr. Swift, together with Dr. Arthur M. W. Ellis, a young Canadian at the Rockefeller Hospital, helped devise a treatment that effectively used Salvarsan for such cases. The Swift-Ellis method, as it came to be known, was threefold in nature. First Salvarsan was injected intravenously into the patient; after some interval of time, a quantity of blood was withdrawn, and the serum containing a certain amount of Salvarsan was separated from the blood clot; this serum was then injected intrathecally into the patient with central nervous system syphilis. It was an extremely effective treatment and remained in use until penicillin supplanted Salvarsan as the treatment of choice in cases of syphilis.

Dr. Swift did not have a continuous tenure at the Rockefeller Hospital and in 1914 left to become an associate professor of medicine at the College of Physicians and Surgeons at Columbia. Some years later he moved to the Cornell University Medical School, but he barely settled in his new post when he went on leave to join the Presbyterian Hospital Unit overseas during World War I. After the war he returned to the Rockefeller Hospital and began his intensive studies of the streptococcus in relation to acute rheumatic fever, studies which were to occupy him for the rest of his life. At the time I was working with chickenpox virus, Swift had a young English worker in his laboratory named Christopher Andrewes. Dr. Andrewes was the son of Sir Frederick Andrewes, and I should add here that several years later Christopher Andrewes was knighted on his own for his accomplishments in bacteriological and virological research. Today he is a member of the British Medical Council. As a matter of fact, I have always been convinced that he would have been knighted sooner if it wasn't for his subtle and devastating sense of humor. I loved this side of Chris Andrewes, but believe me when I tell you that it irritated some of his stuffier English brethren.

Since Dr. Swift's department was working on problems of rheumatic fever, Andrewes thought he would have a try at isolating the causative agent, which he then believed was a virus. Following my ex-

ample, he began to take blood and fluid from the joints of rheumatic fever patients and injected it into the testicles of rabbits. Lo and behold, after several testicular transfers, Andrewes' rabbits came down with swollen testicles and high fevers. At first blush, he thought he had rheumatic fever going in rabbits, and he called me to examine sections taken from the testicles of his rabbits. I took one look and said, "Hell, Chris, you've got the same thing that I got, and neither one of us has anything except something we got out of rabbits." [5]

It wasn't chickenpox virus, and it wasn't smallpox virus; it was a brand new virus and I called it Virus III. People always ask me why I called it Virus III. The answer is simple: I didn't want to give it a fancy Latin name, and since it was the third strain of the virus I experimented with, I just called it Virus III. So far as I know, it is only found in rabbits, and no other animals, including human beings, are susceptible to it.

I want to make it clear that the original purpose of my experiments was to transmit chickenpox to rabbits, and in this I was unsuccessful. However, when the results were all in, I found I had made a discovery. Now, lots of times discoveries are made through error. Have you ever heard of serendipity? Serendipity is when you start out in one place and end up in another. Research is usually serendipity. Looking back, I think that my discovery of Virus III was more important than finding that I could transmit chickenpox to rabbits. Prior to my work, nobody had ever seen Virus III in rabbits. It is a natural disease that only manifests itself when you begin to favor the virus experimentally. Then and only then, can you see the disease. Later it turned out that about 15 per cent of all the rabbits at the Rockefeller Institute were infected with Virus III. It was, you might say, also a hint that there were such things as latent viruses.

*Q:* How did you begin to handle a virus, circa 1923, when you couldn't see it? How did you even know it existed?

*Rivers:* Oh, well, there are other things you know exist without being able to see them. The only time that Ernest Goodpasture and I

[5] C. H. Andrewes has recorded a similar version of this episode in "Nature, the scientist and the pitfall," *St. Bartholomew's Hosp. J.*, vol. 32:20 (1924).

ever had any difference of opinion was when Goodpasture voiced the idea that you couldn't know a thing without seeing it. He told me that he knew about smallpox because he could see the Borrel bodies, but he maintained that you just couldn't know anything without seeing it. Well, I countered by quoting the Bible—the Devil, you know, quotes the Bible, and I think it's kind of a crime for a sinner like me to quote the Bible, but anyhow I did. "Ernest," I said, "You shall know them by their deeds." And that is the way you knew viruses circa 1923. You knew them by what they did in experimental animals, or by what they did in human beings. For example, poliovirus paralyzed the rhesus monkey, and the pathological lesions in the brain and cord were very much like the lesions to be found in the brain and cord of a human. Simon Flexner had no difficulty in working with poliomyelitis in monkeys, even though he couldn't see the virus. I worked much the same way with Virus III in rabbits. I knew what it did in my experimental animal, and I could back up these clinical and pathological observations with the immunological and serological methods I earlier described. I will say that, when you got used to the cumbersome way of doing things, it was a lot of fun. It was clinical observation that later led me to another nice piece of work with Dr. Bill Tillett.

The case was an interesting one and involved a little baby girl no more than several months of age. I suppose the baby was born out of wedlock, because it was found discarded in an ashcan. When it was found, it was taken to a city hospital where an examination revealed that it was suffering from malnutrition, exposure, and chickenpox. Because of the latter condition, it was sent to the Rockefeller Hospital for further examination. The moment I saw the patient, I realized that the distribution of the lesions was entirely different from the usual distribution of chickenpox lesions. In this case they were most pronounced on the face and extremities, with few if any lesions on the body. It didn't take me very long to realize the cause of this: the child had congenital syphilis, and the chickenpox virus had localized itself in places that were irritated by the spirochete of syphilis. It was this irritation that accounted for the abnormal distribution of chickenpox lesions, and here they followed the distribution of the lesions of congenital syphilis. At various times I saw other examples of this with

chickenpox—in one instance, where one of my patients had worn a very tight collar, I found that the chickenpox lesions made a perfect ring around the neck. I saw the same thing with measles virus. In this particular case, the child had been burned over one hip, and there were many more lesions in that area than on any other part of the body.

Now, this was a very well-known phenomenon, and neither I nor the doctors of my generation were the first to observe the effects of irritation of the skin on the distribution of lesions following certain diseases. Hundreds of years ago, the women in harems used to irritate their bodies, particularly in the extremities, to localize smallpox lesions as far away from the face as possible.

*Q:* Would you say that it was such clinical experience that later led to your experiments on the relation between trauma and infection?

*Rivers:* Oh, I got a lot of ideas from my patients. I think that it's too bad that people doing research on things related to human beings don't see more patients, because patients pose a lot of problems that you wouldn't think of by yourself. Many times it was the patient who presented the problem that I took to the laboratory. I don't think that I would have done as well in research if I hadn't seen patients. The early work that I did with streptococci came out of my clinical experience at the Rockefeller Hospital.

In 1923 or thereabouts, quite a number of people like Dr. Frederick Gay of the College of Physicians and Surgeons at Columbia, and Dr. Harold Amoss of the Rockefeller Institute, were interested in local immunity and local resistance against various infectious diseases. At that time it was not too clear what role the hemolytic streptococcus played in such diseases as scarlet fever, rheumatic fever, or erysipelas. Harold Amoss was working with streptococci and was of the belief that they did cause erysipelas. As a matter of fact, he prepared an antiserum using a streptococcus that he had helped isolate from one of his patients. Actually he didn't get much with his antiserum; at best I would say that he got a nonspecific effect, but he did contract a very severe facial erysipelas and he became my patient on Ward One at the Hospital. It was with the streptococci that I isolated from

Harold Amoss that I began my initial experiments on local passive immunity.

First, I tried to produce an immune serum by making repeated intracutaneous inoculations of streptococci into the rabbit. Such inoculations were continued for approximately a month, at intervals ranging from seven to ten days. At the end of that time, I took my inoculated rabbits and bled them and pooled the sera. When I was sure that the sera I had obtained in this fashion had immunizing properties against strep, I proceeded with my experiments. I soon discovered that an immune serum could neutralize streptococcus if I mixed the strep with the serum before injecting it into the skin of my rabbits. I also found out that, if I put the serum in ahead of time—as much as 12 hours ahead—and then later put the strep in the center of the area where the serum had previously been injected into the skin, the skin would protect against the strep, while in other areas of the animal's body not treated with the serum, the streptococcus would cause a lesion.

I spoke of this as local passive immunity. I don't know whether I was the first to use such a term. I do know, however, that other people at the same time were aware of the phenomenon, even if they didn't use the phrase "local passive immunity" in the way I did. I would like to point out that it was not always just the serum that produced this local passive immunity. I discovered that, if perfectly normal sterile broth were injected into the skin of a rabbit 12 to 24 hours prior to the injection of streptococci, this injection of normal broth would also give a certain amount of local immunity. While it was not as good as that produced by immune serum, it was very obvious that there was protection in this area. Later, when we took sections of skin from such areas, although it looked perfectly normal to the naked eye, under the microscope it was different from skin taken from an area that had no injections of normal broth. The difference was in a marked influx of polymorphs, mononuclears, and other white cells of various kinds. I think the presence of such cells was the reason those areas were protected by normal broth.

Actually, two of my friends, Francis Blake and Alphonse Dochez, were doing similar work in relation to scarlet fever. They had discovered that, if they took serum from a patient who had recovered

from scarlet fever and injected it into the skin of a patient showing a rash of scarlet fever, such an antiserum would blanch the rash of scarlet fever. It was a very nice piece of pioneer work on their part. In some of my later experiments, I decided to see if my immune serum would have an effect in stopping the rash of erysipelas in rabbits. I inoculated my rabbits with strep and waited for the nice spreading rash that was characteristic of erysipelas, and when it appeared I placed my immune serum in a semicircle at the outer edge of the rashes. Invariably, the rash would come up to where the serum was and stop, but it would spread to the area that had no serum. To me, this meant that the serum was acting locally, and I undertook to treat one or two of my patients who had erysipelas, using this technique. It would have been miraculous if such therapy had worked at the time. As you know, there are more than 40-odd types of group A strep and it would have been amazing if the antiserum against a type picked at random had matched the bug infecting my patients. If it had worked, we would have drawn the wrong conclusions. Thank God that it didn't—it was just one obstacle less in the path of Rebecca Lancefield in her typing of strep.

*Q:* Did you work only with Dr. Tillett at this time?

*Rivers:* No, I also worked with people outside of my own laboratory. Now, when I worked with people outside my own bailiwick, it was not because I liked the people especially, or because I had any particular interest in what they were doing, but rather because they were adept in certain techniques that I wanted to use in my own research. For example, while I was experimenting with streptococci and local immunity, an examination of the literature quickly showed me that I had not made any new discoveries. Other people had worked with organisms that they had gotten from erysipelas—without calling them streptococci—and had also discovered that, if they irritated the ears of rabbits with turpentine prior to injecting their material into the rabbit, it inhibited growth. A man by the name of Camus reported that, if he exposed certain areas of the skin of rabbits to x-ray and later tested such areas with organisms of erysipelas, the skin which had previously been exposed to x-ray did not respond to the

organism in the same way as untreated skin did.[6] Actually it was Camus' results that led me to collaborate with Dr. Frederick L. Gates on the effect of ultraviolet light on the growth of vaccinia. I just wanted to see if irritating the skin with ultraviolet would either increase or decrease the reaction to vaccinia.

I want to stress that other people saw the same things that I did. For example, Dr. Ernest Goodpasture was at the same time working on like problems, except that he used coal tar derivatives in his experiments. Use of chemical agents took more than one application; a physical agent like ultraviolet light, on the other hand, was easier to handle. All you had to do was pick up your rabbit and expose him to the ultraviolet light for a certain length of time, and that's all there was to it. There was no profound reason for working with ultraviolet light, except that I was lazier than Goodpasture, and Freddy Gates knew about ultraviolet light. Nothing much came from these experiments, except that we learned that the amount of energy required to kill staphylococci was approximately the same as was necessary to inactivate vaccinia.

Q: How was Dr. Gates as a collaborator?

*Rivers:* Freddy was a smart boy, and he stood first in his class at the Hopkins. He was extremely intelligent, but he was unfortunately never cut out to be a research man. He lacked the quality of imagination so necessary to research, and you just can't make a good researcher unless you have that quality. Our collaboration was smooth, and Freddy was an agreeable fellow to work with, but I seriously doubt that he understood what I was up to. Now, I am not saying that he wasn't smart, because he was—he just wasn't cut out to be a research man.[7]

[6] P. Carnot, L. Camus, H. Benard, "Action empêchante des radiations ultraviolettes sur la vaccine expérimentale du lapin," *Compt. rend. soc. biol.*, vol. 95:457 (1926).

[7] George Corner, historian of the Rockefeller Institute, holds a different opinion of Dr. Gates as an investigator. He notes that Gates's later work on the action spectra of ultraviolet light was the first definitive work on this subject, and that biophysicists today recognize him as a pioneer in this field. See G. W. Corner, *A History of the Rockefeller Institute*. Rockefeller Institute, Press, New York, 1964, p. 182. It is of interest that, in 1952, Rivers' early work with Gates caught the attention of the English plant virologist, F. C. Bawden. Bawden at that time discovered that irradiated plants recovered

*Q:* You worked with one other person outside your laboratory at this time, named Louise Pearce.

*Rivers:* Oh, well, now you are talking about someone else. Louise was a rather unusual person—or you might say an unusual woman. She stood very high in her class at the Hopkins, and it was high enough for her to get an interneship in medicine, which meant that she probably was in the first four or five in her class. She left an impression of herself at the Hopkins. As a matter of fact, I had heard of her long before I came to the Rockefeller Institute.

Even when I got to know her at the Institute, she was a rather good-looking person, and in her earlier days she must have been still better looking. I must say that by her actions at the Hopkins or at the Institute you wouldn't pick Dr. Pearce as a woman or a man. She was a research person—that is, I don't think I ever thought of her, so far as her research activities were concerned, as to whether she was a male or female. She was that good.

Louise Pearce worked in Wade Hampton Brown's department. His name should tell you that he was a southerner who came from South Carolina. I guess most kids who were born in South Carolina after the Civil War were named after this leader of the Red Shirts. At that time Dr. Brown's department was working on diseases of the central nervous system, particularly those caused by syphilis, and Louise Pearce was definitely a part of the work that went on in that department. You kind of got to the point where you didn't know that there were two people. It was Brown-Pearce this and Brown-Pearce that until you thought it was a hyphenated name.

One of the great achievements of the Institute in the early 1920's was the use of Tryparsamide for trypanosomiasis, a disease common in tropical Africa, which involved the central nervous system and ended in the patient literally sleeping to death. It is commonly known as the African sleeping sickness. The compound of Tryparsamide was

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from initial susceptibility to virus only if they were illuminated after irradiation, and he was anxious to learn whether the same thing had held true when Rivers and Gates conducted their early animal experiments with ultraviolet light. Rivers was both pleased and surprised by the query, but unfortunately he could not help Bawden. See F. C. Bawden to T. M. Rivers, April 21, 1952; T. M. Rivers to F. C. Bawden, May 1, 1952 (folder, Personal correspondence, 1952, Rivers papers).

worked out in Wade Hampton Brown's laboratory, and it was Louise Pearce who tested the effect of Tryparsamide on trypanosomiasis in the Belgian Congo in 1920 or thereabouts.[8] I have never been able to figure out why Tryparsamide was chosen to be tested, except that you might say it was Louise Pearce's intuition, because I understand that there were other compounds that showed up better in animal experiments. To this day, Tryparsamide is probably the best drug for the treatment of trypanosomiasis in human beings. As a result of her work in the Congo, Louise Pearce was decorated by the Belgian government.

Dr. Brown was a member of the Institute; however, Dr. Pearce was not, and I think that it was shortsightedness on the part of the Institute that she was not made a member. She only attained the rank of associate member. It was not too difficult for ladies to work at the Institute, but they always had trouble getting ahead—particularly the Ph.D. ladies. Whenever I found one that had promise, I always advised her to get out and get an M.D., because as long as she had just a Ph.D. no one was going to pay any attention to her. One of the people I so advised was Ann Kuttner. Well, Ann Kuttner followed my advice, went to the Hopkins for her M.D. and today is a professor of pediatrics at the New York University Medical School. During my tenure at the Rockefeller Institute, there were only two women members. One was Florence Sabin. Dr. Sabin was a member because Popsy Welch told Simon Flexner to make her one—Simon Flexner just wasn't giving memberships to ladies. The other woman member was Rebecca Lancefield. I should add that Dr. Lancefield's membership came when she was about to retire and after a lifetime of superb research on streptococci.

In 1923 Dr. Constantin Levaditi and one of his associates at the Pasteur Institute, Dr. Stefan Nicolau, reported the growth of vaccine virus in neoplasms of mice and rats. He reached several conclusions from this work, one of which was that cancer cells were unable to develop an active immunity against infection with vaccine virus and

[8] The chemical work on the compound Tryparsamide was done by Walter Jacobs and Michael Heidelberger. See G. W. Corner, *op. cit.*, p. 146. Brown and Pearce studied its toxic action and its effect on trypanosomes. L. Pearce, *The Treatment of Human Trypanosomiases with Tryparsamide*. Monographs of the Rockefeller Institute for Medical Research, No. 23, 1930, is the fullest and best account of these latter studies.

only passively partook of their host's immunity. Levaditi's observations seemed to hold great import for the biology of tumor cells and the growth of viruses.[9] I was intrigued enough with his findings to see what effect if any my Virus III had on the malignancy of a tumor, and whether it would grow in a tumor. Louise Pearce knew a great deal about tumors and had in fact been instrumental in the cultivation of an epithelial tumor called the Brown-Pearce tumor, which could be transferred from rabbit testicle to rabbit testicle. The tumor would invariably metastasize to other parts of the body and was, in fact, very very nice to work with. I knew very little about the transplantation of tumors in animals and still know little about it, but Louise Pearce knew a great deal about it, and when I told her my ideas of testing out Levaditi's findings with Virus III she agreed to work with me.

One of the first things we tried to learn was whether Virus III would grow in the Brown-Pearce tumor. Well, we inoculated some actively growing tumors and pretty soon we found out that things weren't as easy as we had suspicioned. Within two or three weeks, we learned that all of our tumors were immune to Virus III and, damn it all, we just couldn't infect them. Well, it was a finding that we were just not prepared for, but we had to accept it because it was so. We were kind of slow on the uptake here, because it took us some time to realize that what was happening was that we were transplanting the Brown-Pearce tumor to rabbits that were already infected with Virus III, and that when we made transfer from such rabbits we passed Virus III along with the tumor. Well, we learned a number of things from this impasse; the first, that the virus accidentally introduced in the tumor multiplied and survived, and the second, that the tumor at one time accidentally infected with the virus had itself acquired an immunity which it conferred upon all of its subsequent hosts.

After we discovered that the tumor carried the virus, we naturally tried to discover whether the character of the tumor was affected by its presence. We were helped here by one of those chance mistakes that frequently occur in the lab. One weekend one of our rabbits that had been inoculated with a Brown-Pearce tumor died and the animal

[9] C. Levaditi and S. Nicolau, "Vaccine et néoplasmes," *Ann. Inst. Pasteur*, vol. 37: 443 (1923).

man just forgot to put the remains on ice. When we arrived on Monday morning, Louise Pearce and I decided to test the tumor. Don't ask me why, unless it's because a lab man never assumes that anything is dead or different until he tests it. To make a long story short, we decided to transplant the tumor from the dead rabbit to some other rabbits and, lo and behold, we got some beautiful takes. When we examined the new transplants, we discovered that the tumor had lost all of its Virus III components, and we finally had a straight Brown-Pearce tumor without any Virus III. We were at last now prepared to study the effect of Virus III on the tumor. By rights, we should have gotten good results, because the Brown-Pearce tumor was epithelial in nature, and Virus III affected epithelial cells. Darn it, all we found was that while the virus would kill most of the cells it was never able to kill all of them, and they just broke out again. I don't know how many times we tried, and we transplanted in every conceivable place, but we never could get rid of all of the tumor cells.

It has been 35 years since Louise Pearce and I tried to discover the possible oncolytic effect of Virus III on the Brown-Pearce tumor in rabbits. Today the boys at the Memorial Hospital also talk about oncolytic viruses and their possible effect on human cancers. I don't know whether they know of the work that I did with Louise Pearce, but the answers they have thus far come up with are no different from what we discovered. I tell you one thing, I ain't going to take the luxury of making a prediction—I know enough not to.

*Q:* Dr. Rivers, I would like to read an excerpt of a letter to you and see if you can guess the writer.

The paper by Andrewes and Miller is unimpeachable by itself, but it brings up a point which may mean adjustment, unless this has already been had. You will note that their title is: "A Filterable Virus Infection in Rabbits, Its Occurrence in Apparently Normal Rabbits." This is of course the virus of Rivers and Tillett, with which these authors have become familiar through several years of work, and which they were realizing to be independent of the chickenpox material with which they began their rabbit inoculations. Unless Swift has an understanding with them, whereby his workers are permitted to jump into the game and announce derivation of this virus, I imagine that they will have some heartburning. A possible way would be to alter the subhead of the above title to "Occurrence of the

Rivers-Tillett Virus in Apparently Normal Rabbits." This is doubtless an unscientific name to give to a virus, but the difficulty, if there be one, is yours to adjust.[10]

*Rivers:* My guess is that it was either Rufus Cole or Simon Flexner.

*Q:* No, it was Dr. Peyton Rous. Could you tell me about Peyton Rous and his position in the Rockefeller Institute when you first came in 1922?

*Rivers:* Before I answer your question, just let me say that I don't think there would have been any heartburning about the Miller-Andrewes article. Tillett and I knew all about the work that was going on in Swift's department on rheumatic fever, and in particular about Andrewes' search for a rheumatic fever virus. As a matter of fact, as I mentioned earlier, Andrewes and Swift to a certain extent helped save Bill Tillett and me from sticking out our necks too far on Virus III. Of course, Rous didn't know all this when he read that paper, and the letter he wrote was a natural thing for him to do as editor of the *Journal of Experimental Medicine.*

If you want to know what kind of a portrait Peyton Rous presented to me in 1922, I don't mind telling you that it is the same kind of a portrait he presents to me today. Rous is one of those people who never change very much in their physical appearance, and it is only within the last year or two—and he is in his eighties—that he has begun to show some of the effects of age. He is still the same kind of a person, namely, one who has taken his pleasures in life from his work, reading, and writing. He is not much given to athletics, hunting or fishing. He and I are completely different people—it's nothing against him, and it may not mean anything against me. When I first came to the Institute in 1922, Dr. Rous had already made his mark as a scientist. In 1911 Dr. Rous demonstrated the existence of the virus of chicken sarcoma and helped prove that it was transmissible. I don't know how to stress the importance of that work other than to say that it was an important watershed in cancer as well as virus research. It was quite a discovery, and anyone who works in these two areas today owes much to Peyton Rous. Yet, I don't know whether he capitalized

[10] Peyton Rous to Simon Flexner, August 15, 1924 (Flexner papers).

on this discovery as much as he could have; otherwise I think that he would have won a Nobel prize. I know that several times his name has been put up for the prize, and rumor has it that on one particular occasion it boiled down to Rous and one other fellow, and the other fellow got it—I am not going to mention his name. I personally think that Rous should have had it. It's not too late yet. Right now the virologists, particularly those down at the National Institutes of Health, are hell bent on proving that a virus is the cause of cancer in man. I am not so sure that they are going to get away with all of this, but if they are successful I think that Rous will come into his own. Then there'll probably be a joint Nobel prize for Rous and the fellow who proves the thing in human beings.

*Q:* Was Dr. Rous engaged in virus research when you came to the Institute?

*Rivers:* By the time I had come to the Institute, Dr. Rous had moved away from the study of viruses. During World War I, he had become interested in problems relating to the preservation of blood and from that field moved over to the study of the function of the liver. He didn't move back to the study of viruses until Dick Shope came up with his very nice rabbit papilloma. It's funny to talk about tumors as being nice, especially when everybody knows they are not, but an experimenter may think they are beautiful or nice because they help him find answers to problems that bother him. In 1933 Dick Shope discovered a natural papilloma occurring in the wild North American rabbit. The interesting thing about this particular tumor was that it was virus-induced. If you ground and filtered these tumors, you could transmit like tumors to other rabbits. The tumors generally were benign. However, Rous discovered that after a long period of time they could become malignant and metastasize. The interesting thing was that these new highly malignant tumors still had the virus that was originally present in the Shope papilloma. There was a question in Rous's mind, as well as others, whether the virus and the malignant tumor had any relation to one another—when, lo and behold, the Shope papilloma virus disappeared from the tumor and Rous was just left with a highly malignant tumor. Originally, if you

got rid of the virus, you got rid of the tumor; now you could get rid of the virus and still have a highly malignant tumor, which you could transfer from animal to animal. This is where the matter now stands. Rous's shift in fields is rather interesting and shows that, although he worked on problems of the blood and liver for over 15 years, when a real opportunity presented itself for him to make new and original observations in a field he left years before, he boldly made the most of it.

I would like to say this, however. Rous has always been a lot more interested in what his virus did than in what it was. To my mind, he is not a virologist; he is still a pathologist, and the irony is that he could have been the virologist of the United States and the world, if he had so desired. It doesn't bother him; he didn't want it, he didn't desire to be that, and he is perfectly happy about the whole thing.

You know, at the time I started to study viruses, to be a good virologist, one had to be a good pathologist as well as a good clinician, because you could only study viruses by the pathological or clinical picture they presented. Today we deal with viruses on a biochemical level—we purify and crystallize them, we grow them in tissue cultures, we examine the nucleic acid, and what not. That's fine—but a lot of virologists today wouldn't recognize a patient infected with a virus any more than a newborn baby would—I think they miss a lot of the fun by not knowing what these damn things do in humans; they miss a hell of a lot of fun.

*Q:* Dr. Rivers, you mentioned Dr. Rous as editor of the *Journal of Experimental Medicine,* and I wonder if you would speak of the position of the *Journal* vis-à-vis research.

*Rivers:* I think that the *Journal of Experimental Medicine* was and is probably the best journal that is put out covering research work in the medical sciences. Every youngster and every oldster, particularly youngster, doesn't feel that he has arrived until he has had one of his papers published in the *Journal.* I know that this was true in my day, and I think that it still holds. For years, Dr. Rous and his secretary took care of getting out the *Journal* alone. Of course, when Rous got hold of a paper that he didn't understand, he would call on somebody in the institute or hospital—since they covered nearly all the essen-

tial fields in medical science—to help him out. Today the *Journal of Experimental Medicine* has a board of editors: medical research has broadened to such an extent that running the *Journal* is beyond the powers of one man. I should add that, although Rous has long been retired from the Institute, he still acts as editor-in-chief of the *Journal.*[11]

Rous was, and I suppose still is, a stickler for the right kind of English, and I know that he used to edit papers quite severely. He had certain pet peeves that you could never get by. One of them—and I think he was correct—was that he would never allow an author to speak of an animal except by means of the neuter pronoun, it. For example, a lot of doctors using chimpanzees while studying polio would refer to a he or she chimpanzee. When Rous saw this, he would always hit the ceiling and make them change it to it. He always reminded me of Dr. Howland's rule on the use of the pronoun, it, in relation to infants. Howland always spoke of an infant as it. One day, I asked him why, and he said, "When you are looking at an infant that's fully clothed, you don't know, you can't know whether it's a he or a she, and, if you say he and it's a she, the mother doesn't like it. But if you say it, the mother doesn't take offense. You are always right when you say it."

The *Journal* always had a severe restriction on the number of pages you could submit, and very rarely did an article run over twenty pages. At such times as an article did exceed the limits, the author, if he was a member of the Institute, had to pay for the excess pages out of his budget. If he wasn't a member, the extra payment came out of his pocket. There was also a limitation on the amount of illustration you could have for an article, and unless it was an exceptional article the author again had to pay for the extra illustrations. In spite of these limitations, most researchers wanted to have their articles published in the *Journal.*

When I first came to the Rockefeller Hospital, Dr. Cole used to

[11] George Corner, historian of the Rockefeller Institute, makes this observation concerning the direction of the *Journal of Experimental Medicine.* "For fifteen years Flexner was active as chief editor, assisted by Opie, 1904–1910, and Benjamin Terry, 1911–1912. In 1921 Peyton Rous was appointed coeditor. Assuming practically the whole task, he was effective editor for thirty-six years, although Flexner's name continued to be carried on the title page even after his retirement and until his death in 1946. . . . Herbert S. Gasser became joint editor in 1935, René J. Dubos in 1946, and Vincent P. Dole, Jr., in 1953."—G. W. Corner, *op. cit.*, p. 63.

rag me about my writing. He thought I couldn't write, and one day to underline the point wrote a special version of a paper I was going to submit to the *Journal*. "Take them both over to Rous," he said, "he will tell you which paper is better." Well, I went over to Rous with both papers, and although I didn't want to stay he insisted that I stay until he had completed reading both papers. When he got through, he had a great big grin on his face. "Rivers," he said, "it's very easy to know who wrote the better of the two papers. There is so much difference between them that it is almost a shame even to discuss it." He kept waving a paper in his hand. Finally, I said, "Which paper are you talking about, Dr. Rous?" "Here's the paper that Dr. Cole wrote," he said. "Anybody would know that Cole wrote this." I looked at it. "Dr. Rous," I said, "that's the paper I wrote. I didn't tell you which paper was written by whom. The paper you are holding is the paper I wrote." Rous's face turned crimson, and he got rid of me as fast as he could. Later my paper was published just as I wrote it. It was the last time that either Cole or Rous ever bothered me about my writing.

A lot of the boys at the Institute had things like this happen to them, because Dr. Flexner, Dr. Cole, and Dr. Rous were of the opinion that medical school graduates did not know how to write articles. I don't want to give the impression that only youngsters were handled roughly by Dr. Rous's editorial pencil—he made little distinction between young and old, famous and nonfamous. If a paper didn't come up to the standards in English that Dr. Rous set, it was rewritten; it didn't matter if it was a young doc in the hospital or Karl Landsteiner.

*Q:* Dr. Rivers, didn't you and Karl Landsteiner come to the Institute in the same year?

*Rivers:* Yes, we were both appointed the same year. Just let me say very quickly that I think that Karl Landsteiner was probably one of the greatest members that the Rockefeller Institute ever had. It must be remembered that he had made a name for himself long before he came to the Institute in 1922. In 1901 Dr. Landsteiner discovered that there was more than one blood group and opened the way for

successful blood transfusions, a discovery for which he won the Nobel prize in 1930. In 1909, in concert with Dr. Erwin Popper, he produced poliomyelitis in monkeys, an experiment that you might say was the beginning of the laboratory attack on that disease. I can't begin to detail the work in immunochemistry that came from Karl Landsteiner's laboratory in all the years he was at the Institute, save to say that in 1939 it culminated in the elucidation of the Rh factor in the blood, which has been so important for human childbearing and for the great impetus it has given to the study of genetics.[12] Actually, I am surprised that Dr. Landsteiner didn't get the Nobel prize a second time. He certainly deserved it.

Landsteiner was short on words either spoken or written. His reports to the Board of Scientific Directors of the Institute were rarely ever more than two or three pages; they were succinct and clear, with little attempt to pretty them up. It used to be the custom at the Institute that members on Friday afternoons would speak about the work they were doing. Landsteiner rarely ever spoke at these Friday afternoon meetings. That was true of Dr. Avery as well. However, Avery would talk to you freely in his laboratory, while Landsteiner just didn't want to talk to you about what he was doing. There was another difference between Landsteiner and Avery. While Avery turned out a great many experimenters and teachers, Landsteiner practically turned out none, with one exception, Dr. Merrill Chase, who is now at the Institute. Dr. Chase worked with Landsteiner until the day he died, and you might say that Merrill Chase arrived on his own in spite of Landsteiner. The fact is that Dr. Landsteiner wouldn't allow his boys to plan an experiment on their own. He'd call them in and give them the protocol, and they would have to carry out the experiment the way he set it out. There was reason for this. A long time before Landsteiner came to this country, he was fooled by one of his *Dieners*. The *Diener* happened to know what Landsteiner was attempting to prove by his experiments and arranged things to come out as Landsteiner hoped they would. Landsteiner went into print and a short time later discovered what his *Diener* had done and had to retract everything he said about this particular work. He never

[12] An excellent brief evaluation of Landsteiner's career is contained in P. Rous, "Karl Landsteiner 1868–1943," *Obit. Notices Fellows Roy. Soc.*, vol. 5:295 (1947).

got over it. Never. From that time forward, he suspected everybody, if you ask me, even himself, when it came to experimental results.

Dr. Landsteiner was a hard customer, and he demanded more work and longer hours of his workers than was usually demanded of workers by other people at the Institute. He had little thought for any activity except experimentation that would lead to new knowledge. I think that that attitude is best exemplified by a fight I had with Landsteiner over Clara Nigg, who was one of Dr. Landsteiner's assistants. At one time Hans Zinsser reported the growth of typhus rickettsia in tissue culture, and Landsteiner decided to do certain experiments using rickettsia grown in this fashion and put Dr. Nigg to work on it. I think that none of us at that time knew how easily typhus fever rickettsia could pass from tissue cultures to the persons working with them. I know I didn't realize it. Well, to make a long story short, Clara Nigg developed typhus fever and became my patient on Ward One at the Rockefeller Hospital.

She was pretty sick. Most anybody that has typhus fever is sick. I can't remember that any of us felt that she was going to die, but we realized that she was doggone sick. In the course of her disease she developed certain sequelae that worried us, but in time she became better. I kept her on the ward as long as I could, and if I had known what was going to happen I would have kept her longer. But I thought that she could go home and rest there without burdening a hospital bed, and so I let her go. Doggone it, no sooner did she get out of the hospital than Dr. Landsteiner put her to work as if she had never been sick. God almighty, he worked that girl eight and ten hours a day. When I found out about it, I went to see Landsteiner. I want to tell you the old boy didn't think much of my coming to him about it. He made it plain that he thought that I was monkeying with his business and that I should let him run his lab in the way he saw fit. I differed with him—I told him that Clara Nigg was still my patient and it made no difference whether she was back in his lab or not, and that until her health was back to normal she was going to do what I said, no matter what he thought.

Knowing Landsteiner, you can know that this upset the old gentleman, and he argued with me, but I stuck to my guns. Finally I told

him, "Dr. Landsteiner, if you don't play ball with me I am going to take Clara away from here, and you are not going to see hide nor hair of her for the next six months. I don't mind having Clara work for you a certain amount of time each day, but you aren't going to work her to death." He looked at me and said, "I am going to call Dr. Flexner and Dr. Cole." "Dr. Landsteiner," I said, "you won't get Dr. Cole or Dr. Flexner to change my mind because they can't. I am Clara Nigg's doctor, and you ain't going to get to first base." Well, I was firm and he finally understood. In the end, he did cut Clara Nigg's work down until I discharged her as normal.

I think this story prepares one for what happened when Landsteiner received the Nobel prize. He was working in the lab when news that he had won the prize came to him. He kept on working as if nothing had happened. When he came home that evening, he discovered that his wife had already gone to bed, but he never awakened her, and he didn't tell his wife he had received the prize until the next morning. Landsteiner was simply devoted to his work, a condition that existed to his dying day. After he retired from the Institute, he still maintained his lab and continued to work regularly. One day he simply collapsed at his desk in the lab and was brought to the hospital in bad shape. It was obvious that he had had a coronary, but the old man just wouldn't accept it and tried to return to the lab. If we hadn't restrained him, he would have. A few hours later he lapsed into a delirium, and all he spoke of was how he had to get back to his laboratory. Over and over he said, "I have got to get to my laboratory. I have experiments going that must be carried on." He spoke that way until he died.

Not everyone at the Rockefeller Institute was cast in the mold of Landsteiner, and there were a lot of people who had great world-wide reputations who I think little deserved them. One such person was Hideyo Noguchi.

Noguchi was a very colorful person, small in stature and typically Japanese in appearance. He came to the Institute because of his association with Dr. Simon Flexner, and that is a story in itself. As I told you before, in 1899 Dr. Flexner went out to the Philippines as a member of a medical commission to study dysentery in the islands.

After his work was done, he went on a sightseeing trip to Japan, and while on this trip he apparently met Noguchi.[13] I say apparently because, from the stories Dr. Flexner later told, he did not remember seeing Noguchi on this occasion. Later, not too much later, when Dr. Flexner got back to his laboratories at the University of Pennsylvania —he was at that time professor of pathology at the University of Pennsylvania Medical School—Noguchi showed up. He bowed and formally presented Dr. Flexner with a small gift and announced, "Dr. Flexner I have come to work with you." Well, this just about bowled Dr. Flexner over. He didn't know who his visitor was—he couldn't remember him—and here he was saying, "I have come to work with you."

I have heard any number of tales as to what was subsequently said and done, but the important thing is that Dr. Flexner kept him and put him to work. Noguchi did creditable work on snake venom while at Pennsylvania, and when Dr. Flexner moved to the Institute he brought Noguchi with him. Actually, I don't think that he had any choice, because, if Flexner hadn't taken him, I think that Noguchi would have taken the train from Philadelphia and come anyway. By the time I came to the Institute, Noguchi had a world-wide reputation for his work on the spirochete *Treponema pallidum*, the various media he prepared for the growth of bacteria, and the claim that he and Dr. Flexner had isolated the cause of poliomyelitis, and that it was small globoid bodies that would grow in nonliving media. I will have much to say about these claims later; for the present let me say that, when I later asked Noguchi about these claims, he wouldn't answer me and would only say that a man who had done research work for a long time had scars that he could never get rid of.[14]

[13] Rivers has mistaken the itinerary taken by Flexner and the expedition. The first stop was in Japan where Flexner and Lewellys Barker had important conversations with Dr. Shibasaburu Kitasato and Dr. Kiyoshi Shiga. Later they proceeded to Hong Kong and finally to the Philippines. See S. Flexner and L. F. Barker, "Report upon an expedition sent by Johns Hopkins University to investigate prevalent diseases in the Philippines," *Johns Hopkins Hosp. Bull.*, vol. 11:37 (1900).

[14] It is very unlikely that this conversation took place. Noguchi died in May of 1928, at least two years before the first serious scientific attack on the concept of "globoid bodies," by Peter Olitsky and his associates. Even after Olitsky's article appeared, Simon Flexner, reminiscing about Noguchi in the privacy of his diary (1931), still thought well enough of the concept to claim that the idea of the globoid bodies was really his and not Noguchi's. It seems highly improbable, therefore, that Noguchi would act as

I was always on amicable terms with Noguchi, and when I first came to the Institute it was Noguchi who supplied me with the first batch of vaccine virus that I worked with. It was an interesting batch. Originally Noguchi got his strain from the Board of Health of the City of New York, and passed it through a number of generations of rabbits by intratesticular inoculation, with the idea of making a bacteria-free vaccine virus for human use. Just let me say that this virus went beautifully in rabbits by intratesticular passage, and that it was freed of its bacterial contaminants, but I found, when I used it, that it would not produce encephalitis in rabbits. That was a rather unusual situation, and so I sent down a request to the Board of Health for some more of the original strain sent to Noguchi. I carried this new batch intratesticularly in rabbits and freed it of its bacterial contaminants. However, when I injected it into the brains of rabbits I was still able to cause an intense encephalitis. The difference in the results lay in the fact that Noguchi's batch had passed through rabbits' testicles for a longer period than mine did, and in the process had mutated. This work was the beginning of an attempt which I later made to cultivate vaccine virus in tissue culture suitable for Jennerian prophylaxis in man.

I must say that, after I got to know Noguchi better, I did not consider him a great scientist. For one thing, his general attitude disturbed me. For example, when I discovered that Virus III was not a chickenpox virus, I told Noguchi about it, and his answer ruined him as far as I was concerned. "Oh, why worry about that," he said. "Dr. Noguchi," I said, "I want to be the first one to retract and to say that I have made an error and tell why." "Oh," he said, "I'd never do that. It'll take them fifteen years to find out you are wrong." Well, a scientist just doesn't say things like that, at least a reputable one doesn't. This was Noguchi. I don't think that he was honest.[15] Now, I am

if he were in error about the globoid bodies before serious criticism had been heard. See P. H. Long, P. K. Olitsky, and C. P. Rhoads, "Survival and multiplication of the virus of poliomyelitis in vitro," *J. Exptl. Med.*, vol. 52:361 (1930). Diary of Simon Flexner: Entry, February 28, 1931, Palermo (Flexner papers).

[15] Peter Olitsky, a contemporary of Noguchi's at the Rockefeller Institute, takes sharp exception here to Rivers' evaluation of Noguchi.

*I am amazed at what Dr. Rivers states here about Noguchi's alleged duplicity. I had been very friendly with Noguchi but never heard from him such words or thoughts. He had great difficulty with English as a spoken language. His method was to translate the*

being perfectly frank. Noguchi has long had a public reputation for his work on yellow fever. The fact is, he knew nothing about the pathology of yellow fever and wouldn't know a case of yellow fever if it hit him in the face. Someone in South America once sent him material from a case of what purported to be yellow fever, and Noguchi isolated a spirochete from the material, which he called *Leptospira icteroides.*

Well, as you know, Weil's disease clinically can look very much like yellow fever and is caused by a spirochete called *Leptospira icterohæmorrhagiæ.* I don't blame Noguchi for drawing a spirochete out of the material which was sent him, but when he claimed that the organism that he got was serologically different from the spirochete that causes Weil's disease, why then I do hold him responsible. Noguchi was working in a field that he was supposed to be expert in, and he should have been able to tell the difference, or rather the similarity between the organism that he called *Leptospira icteroides* and the *Leptospira icterohæmorrhagiæ.* Plenty of other people were able to show that Noguchi's spirochete was one and the same with that which caused Weil's disease.

On the basis of Noguchi's claims, a vaccine was prepared against *Leptospira icteroides* and given experimentally to part of the Brazilian army. Later an article even came out in the *Journal of the American Medical Association* purporting to show that the vaccine was helpful against yellow fever. I have no explanation for how these results were obtained, but I will say that for a while many people believed it, with the possible exception of Hans Zinsser and several others who would

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*English he thought he heard, back to German which he knew better, then to Japanese; to respond in English the process was reversed, Japanese to German to English. The result was confusion and a jargon only he understood. Perhaps he wished to amuse Dr. Rivers with a Japanese type of jocularity rather than an antinomianism* (private communication).

Dr. Peyton Rous, the doyen of American virologists writes in a similar vein.

*I came to know Noguchi well during the years from 1909, when I came to the Institute, until he left for Africa. In 1909 his reputation was already so great from what he had done that he was pressured to do still larger things, not only by his fellow scientists, but by foundations and the lay public; yet he remained a modest, honest, and immensely serious scientist. It was as such that, wishing to check the findings of the Englishman Stokes about the cause of yellow fever, he went to Africa, though ailing, and risked and lost his life. A false person would never have acted in this way* (private communication).

never accept the spirochete as a cause of yellow fever. In 1927 Adrian Stokes, Johannes Bauer, and Paul Hudson went over to Africa to combat a yellow fever epidemic on behalf of the Rockefeller Foundation, and their initial reports cast doubt on the *Leptospira icteroides* as a cause of yellow fever.[16] Noguchi at the time thought that the yellow fever in Africa was entirely different from that which he found in South America and, supported by the Rockefeller Foundation, prepared to go on an expedition to West Africa to test his ideas. A week or two before he left, I met him in the illustration department of the Institute. He was getting some pictures taken of what looked like tissue cultures and he asked me at that time if I would accompany him to Africa. Well, knowing what I knew, I was very polite to Noguchi, thanked him for the invitation, and told him that I had a lot of things going that I couldn't leave, and that I couldn't go. It was on this expedition to Africa that Noguchi developed yellow fever and died. However, before he contracted the fever, he sent a long cable to Dr. Flexner, claiming that he had discovered the cause of yellow fever in Africa, and that it was a large positive spore-bearing bacillus. (I never saw the cable, but Francis Blake, who was on the Board of Scientific Directors told me about it.) When Noguchi's cultures were examined later, they contained nothing more than B-cereus, something you find most everywhere. Obviously Noguchi was still cockeyed as hell about yellow fever.

Q: Dr. Rivers, what you have told me is a savage indictment of Dr. Noguchi. Didn't he do some rather nice work on Bartonella?

*Rivers:* I didn't mean to imply by what I said that everything that Noguchi did was wrong or dishonest. As a matter of fact, you are quite right, his work on Oroya fever and *Verruga peruana* has stood the test of time and is a nice solid piece of work. It is when you weigh

[16] In 1925 a yellow-fever commission, under the leadership of Dr. Henry Beeuwkes, was sent to West Africa. There, work on 67 cases of yellow fever failed to reveal the Noguchi leptospira. In 1927 A. F. Mahaffy, a member of this commission, was first to transmit the disease to an animal (rhesus monkey) other than man. In 1927 the writers mentioned here by Rivers were first to confirm that the causative agent of yellow fever was a virus. For further information, see W. A. Sawyer, "A history of the activities of the Rockefeller Foundation in the investigation and control of yellow fever," *Amer. J. Trop. Med.*, vol. 17:35 (1937).

his accomplishments against his failings that you find him wanting. I don't think that Noguchi was an honest scientist, and I don't think that he was a great scientist, although his name was great at that time, and I will bet you right now that scientists all over the world will feel that I have been disrespectful in speaking of my elders in the way I have. But this is the way I felt, this is the way Hans Zinsser felt, and this is the way a number of other scientists in the world felt about Noguchi.[17]

*Q:* We have spoken now at some length about several of your colleagues at the Institute but little has been said of your colleagues at the hospital.

*Rivers:* When you speak of the hospital, almost the first name that comes to my mind is that of Oswald T. Avery. As I mentioned before, I first met Dr. Avery when I joined the Pneumonia Board during World War I to investigate an outbreak of pneumonia following a measles epidemic. Even at that time, Dr. Avery was one of the acknowledged experts on pneumonia in the United States. He was one of those who took a lead in typing pneumonia, and as early as 1913 had helped develop a serum therapy for treatment of pneumonia type 1. Dr. Avery worked at the Rockefeller Hospital and was directly responsible to Dr. Cole, who was also interested in pneumonia. As a matter of fact, one of the chief endeavors of the Rockefeller Hospital for the first thirty years of its existence was research in the field of pneumonia. Many of the early momentous discoveries in this field came from Avery's laboratory. In 1930, for example, Dr. Avery, in conjunction with one of his young workers, Dr. René Dubos, discovered a bacillus from the soil of a cranberry bog in New Jersey which was capable of dissolving the capsular polysaccharide surrounding the pneumococcus, thereby making it susceptible to phagocytosis. It was a discovery that not only revealed an important factor in the pathogenicity of pneumonia but also helped initiate one of the significant advances in pneumonia therapy prior to the advent of antibiotics. Actually it was Dubos's later work with tyrothricin and

[17] For another recent critical appraisal of Noguchi, see P. F. Clark, "Hideyo Noguchi 1876–1928," *Bull. Hist. Med.*, vol. 33:1 (1959).

gramicidin which helped lay the groundwork for the great breakthrough in antibiotics that came in the early forties.

Avery was one of the nicest people I ever knew, but he was rather shy and retiring. He was small of stature, and a lot of people seeing him for the first time might call him a sissy. He certainly had the outward marks of a sissy because he was small, gentle, and considerate. But if anyone pushed him, they would have found anything but a sissy. Avery was tough, or rather I should say, tough-minded, and you had to be pretty damned good to get anything by him. Actually I would say that he was not entirely familiar with what went on in other parts of the Institute. He only knew or cared about what was going on in his particular field. You couldn't sit with Avery for 15 minutes (and I don't care what you were talking about) but what he would have you talking about your own work as it related to the pneumococcus. Avery spoke and wrote beautifully, and his youngsters found that he wouldn't pass a paper for publication unless it met his standards of expression. He was peculiar in the way he conducted his department. If a man came to work in his department, he just left him alone for about two years, and the fellow just had to figure out his own reading and what experiments to do. It was only after the fellow was around for a year or two that Avery would begin to speak with him. Now, that kind of behavior was pretty tough on a youngster, but if he stuck it out it usually paid off. It was sink or swim, but it divided the good from the bad, the men from the boys. It was through this technique that Avery helped develop some of the leading bacteriologists and immunochemists in this country, among them Tommy Francis, Colin MacLeod, Walther Goebel and René Dubos.

*Q:* Some of your early papers have footnotes telling of the kindness of Dr. Avery in supplying material for given experiments.

*Rivers:* I was and am not a timid soul, and I have never been accused of that. If I needed any information that I thought Dr. Avery had, I never hesitated to ask him, and I was never turned away. Avery would give of his knowledge freely, and any material he had that was handy and that he didn't need himself he would gladly give me. Avery was just that kind of a person.

To me, Dr. Avery was one of the great men that I came in contact with at the Institute; yet I was never close to him—never—even after I became director of the hospital in 1937. I guess a lot of people at the Institute never became close friends with Avery, but the ones who knew him and had the privilege of being close to him were extremely fortunate, because he saw problems in a big way.

*Q:* Dr. Rivers, were workers at the Rockefeller Hospital only concerned with bacterial and virus diseases?

*Rivers:* Hell, no. There were workers at the hospital who had little or nothing to do with viral and bacterial diseases. For example, at the time I came to the Rockefeller Hospital, Donald Van Slyke was already hard at work on problems relating to kidney physiology. Carl Binger, who today has a reputation as a psychiatrist, was in those far off days interested in the physiology of the lungs and heart. The hospital, in addition, had a department that was solely devoted to problems of cardiology. That department was run by Dr. Alfred Cohn.

Dr. Cohn, was, in fact, one of the pioneers in this country on heart research. Before coming to the Rockefeller Institute, he had studied with Sir James MacKenzie and Sir Thomas Lewis in England (two of England's great cardiologists of the early twentieth century), and as early as 1909 had helped Sir Thomas set up a string galvanometer for the purpose of taking electrocardiograms at University Hospital in London. Cohn always used to stress that the use of the string galvanometer for taking electrocardiograms was first developed in Einthoven's laboratory in Leiden. As a matter of fact, when Cohn returned to the United States in the fall of 1909, he brought an Einthoven string galvanometer with him and set it up at the Mt. Sinai Hospital in New York. Strange as it may seem, he once told me that he wasn't the first in this country to publish on the use of the string galvanometer for electrocardiograms, and that that honor fell to Dr. Horatio B. Williams and Dr. Walter James of the College of Physicians and Surgeons at Columbia, who published the first paper on this subject in the *American Journal of Medical Science* in 1910.

By the time I took over the hospital in 1937, Cohn was still a member of the Rockefeller Institute although he was no longer en-

gaged in serious cardiological research. He had at this time actually become a philosopher and not a bad one at that. He was an extraordinarily well informed man, well read in a variety of fields, and with a passion for collecting rare books. His personal library was large and had books in it ranging from medicine to music. I know because Dr. Cohn left his library to the Institute, and today it is housed in a special room in the administration building for the benefit of Institute members and students. Still, all of this doesn't tell you what kind of a guy Cohn was. For me the spirit of Alfred Cohn is contained in a letter he once wrote to Dr. Flexner criticizing Dr. Francis Peabody of the Harvard Medical School. It was an exchange that came about as the result of a long letter that Dr. Peabody had written to Warfield Longcope, who at that time was chairman of the Board of Scientific Directors of the Rockefeller Institute. The letters in themselves are interesting because they are part and parcel of a debate that is still going on in American medicine relating to the role of research and clinical instruction. Because they are lengthy, I am going to read parts of them verbatim, so that in the future one can judge for himself the spirit of these two men. Before I do, I should perhaps say a few words about Francis Peabody.

Dr. Peabody has been dead a long time now—if memory doesn't fail me, I believe, he died sometime during the late spring of 1928—but I want to tell you that they still remember and talk about him in Boston today. To my mind, and I know that this is going to rile some people I know in Boston, Dr. Peabody more than either Harvey Cushing or Henry Christian, was the spirit of medicine in the Boston of his day. Originally he was a graduate of the Harvard Medical School, but after graduation he went to the Hopkins and worked with Dr. William Thayer. I don't know how long he spent at the Hopkins, but from there he went to Friedrich Muller's laboratory at Munich, and subsequently came to the Rockefeller Hospital in 1911. His work at the hospital was mainly concerned with pneumonia and poliomyelitis, and as a matter of fact in 1912, together with George Draper and Alphonse Dochez he wrote a monograph on poliomyelitis that to this day ranks as one of the best clinical descriptions of the disease. Dr. Peabody's stay at the Rockefeller Hospital was relatively brief, and in 1914 he returned to Boston to take a post at the then newly opened

Peter Bent Brigham Hospital. He was a superb clinician and teacher and quickly rose to be professor of medicine at the Harvard Medical School.

When the Thorndike laboratory was opened at the Boston City Hospital in 1922, Dr. Peabody was made its first director. Given the politics of Boston and Boston medicine, I don't think that anyone except Francis Peabody could have made that unit function in the wonderful way that it has. Peabody had everything going for him when he developed a cancer. Those boys at Harvard went wild trying to do something for him. Every possibility was explored. Dochez, a close friend of Peabody's, once told me that, when Dr. Blair Bell in England developed a so-called cure for cancer through use of lead therapy, Dr. Channing Frothingham dropped what he was doing and hopped a boat to England to investigate its possibilities. Needless to say, he returned empty handed and frustrated. Dr. Peabody carried himself well in that last illness, and in spite of great pain gave himself wholeheartedly to an examination of problems in medical education. Before he died, he gave a talk to assembled physicians and students of the Harvard Medical School on the role of the doctor. It was a masterpiece and was later reprinted in the *Journal of the American Medical Association*. The letter that he subsequently wrote to Dr. Longcope was a detailed exposition of his position. Later the letter was mimeographed and sent around to various people for comment. I believe that in this way it came to the attention of Dr. Cohn.

My dear Warfield:

Thank you so much for your good letter. Of course you are altogether too kind in what you say about the Clinic at the Boston City Hospital and the part I have played in its development, but you set me up and stimulate me to write you at some length about the problems that many of us who are teaching Clinical Medicine have on our minds,—whither are we tending and what ought our aim to be? I have tried recently, without much success, to formulate a very brief statement as to the type of Clinic I wanted to develop at the Boston City Hospital and I am glad to be encouraged to try my hand at the subject rather more in detail. First of all I do not think we can or should all aim at having the same type of Medical Clinic. This must depend in part on local conditions,—thus you, in a University Hospital, completely under your own control, have a very different problem and will produce something quite different from what I, a cog in a

great Municipal Hospital, can produce. Each has its advantages and its disadvantages. In part, moreover, the type of Clinic will reflect the personality and interests of the Chief, and the whole character of the Clinic may alter when a new Chief is put in charge of it. . . .

I believe that the primary function of a Department of Medicine is to teach students those things that will enable them to practice the best contemporary medicine and will give them a foundation on which to superimpose the advances that will come during their professional life. They must be taught medicine as a vital expanding subject, and must be stimulated to keep abreast of its growth. If it be true that preparation of students for a career in Clinical Medicine, and more specifically for the practice of medicine, is the first duty of a Department of Medicine, then it seems clear to me that the backbone of the Clinic is the General Ward and the Out Patient Department, for it is here that one finds or can readily create conditions which most closely resemble those which are found in actual practice. . . .

If the General Ward is the back-bone of the Clinic, then the Head of the Clinic must be close to it,—indeed it ought to be directly under him! The importance of the General Ward, and what it stands for as representing the general practice of medicine can only be impressed on the younger members of the Staff and on the students if the relation of the Chief to the ward is real and not fictitious. The whole atmosphere of the General Ward, and thus the attitude of the future practitioners to the profession of medicine is here set by the Chief of the Clinic for it must always be remembered that standards of thought, as well as of action, are set from above. . . .

What is to be expected of the Chief in the way of research? One hears a great deal about research ability as a qualification for the Professor of Medicine and about the necessity of his carrying on research personally while he occupies the position. Capacity for high grade research is so rare a quality in itself that it will always be almost impossible to find it combined with the other qualifications demanded of a Professor of Medicine. Ability to do good, conscientious, independent work, interest in stimulating and assisting others to carry on research, and an appreciation of the role that research plays in the Medical Clinic are more important than great personal research genius. The Professor must keep in close touch with the work of his Staff, guiding where he can, suggesting and encouraging, and he should always try to keep up some independent work if only for his own intellectual satisfaction so that he may set an example to the Staff and may have some little field in which he excels his assistants. Even if he had great ability as an investigator he could not expect to accomplish much as the multifarious demands on his time make it almost impossible to obtain the sense of leisure which thoughtful work requires. Indeed, I am inclined to

feel that if a man really has this rare gift he ought not to be the Head of a Department of Medicine lest his talent be wasted.

One may reasonably question whether the large proportion of the budget of the Department of Medicine that is devoted to research and the great stress that has been laid on research ability in the selection of teachers is entirely justified when one considers that much of the research output is of a routine nature and that really significant research is unusual. My personal feeling is that it is justified, although I think the pendulum has swung too far in the matter of choice of Professors. Here there is a very unfortunate tendency to pay too little attention to broad clinical experience, something that is acquired only by many years of hard work, and too much attention to research ability, or what is worse, to the possible development of research ability in some promising young man. The publication of a number of good papers does not really indicate any marked capacity for investigation and such papers certainly offer limited evidence of ability to run a Department of Medicine. Even in the preclinical laboratories and Research Institutes the proportion of research that is very noteworthy is not always particularly high, and when one considers all the other functions required of the men in the Department of Medicine, I think that on the whole, we may be rather proud of what they are accomplishing.

There is a common tendency to attempt to select Assistants in a Department of Medicine whose training represents the different preclinical sciences, physiology, organic chemistry, physical chemistry, physics, bacteriology, etc.,—so that one may have a well rounded Clinic. There is obviously much to be said in favor of such a plan as it helps to bring together an experienced group of "scientists", but there is also an inherent practical danger which I am sure we all have observed and to which more attention should be paid. These men, thoroughly trained in one direction, quite naturally look for their research problems in the fields in which they are trained. They seek the problems to suit their particular tools. This must necessarily be the attitude of workers in a fundamental science when they attempt to study a clinical problem, and this may explain why they often are not more successful in formulating and working out problems involving a knowledge of disease in man. The approach of the Internist to the study of disease in man should be quite different. He is, first of all, absorbed by an interest in the problem and then seeks the type of tools necessary to solve it. This is the intellectual, rather than the technical, method of approach. Once given an absorbing passion for the solution of a clinical problem, the man who has a good general scientific training can usually acquire in a few months or in a year or so, enough of any of the fundamental sciences to enable him to tackle it. The Clinical Investigator, with his knowledge of disease in man, thus finds the problem first and determines the practical way to study it, turning to his colleagues in the fundamental sci-

ence especially for technical experience. We often discuss what the difference is between the function and opportunity of the man who is primarily a "scientist" working on a clinical investigation, and the man who is primarily an "Internist" using methods of exactly the same highly refined nature, and also working on the same general type of investigation. The real difference is, I think, to be found in the point of view of approach. The Medical Clinic should encourage its staff to use methods of any sort, no matter how difficult or specialized, that are needed for the solution of their immediate problems, but their first interest should center about the general subject of disease in man. The first interest of the "scientist", on the other hand, is and should be in the development of his own particular field. Each has his proper and legitimate role, but in the Medical Clinic it is better to have an inspired "internist" than a skilled "chemist". . . .

In the last analysis, the whole problem resolves itself into what kind of men you select for the Hospital Staff. If they do the type of work they are expected to do, they can never see more than a very few private patients—fewer, indeed, than come now to the Private Wards of some "full-time" Clinics. If they want to see more patients they must be transferred to the Clinical Staff. Practically, the issue has seemed to me to solve itself without presenting any great difficulties and without resorting to an overorganization that limits the freedom of the individual. What we want is less of the system and law that kills and more of the Spirit that gives life.[18]

If the patient was the center of Peabody's medical universe, research was the heart of Cohn's world. It's an argument that still goes on in medicine today and perhaps with a little more intensity. The letter that follows is Dr. Cohn's criticism of Peabody's argument.[19]

*August 1st, 1928.*

Dear Doctor Flexner,

It was not my intention to permit so long a time to pass before replying to your letter of May 7th, 1928, concerning the opinion you formed on rereading Francis Peabody's long communication on the subject of the medical clinic. I too have reread it and have come to the conclusion that it is likely to remain harmful, not so much because it is actually harmful in itself, but because the close scrutiny of ideas is not an American habit. If thinking were as active and prevalent a function of the national character as action, the amount of damage that might be done would depend on the

[18] Francis Peabody to Warfield Longcope (undated mimeographed copy in unmarked folder, Rivers papers). This letter and two articles that Peabody wrote on the relationship of the physician to the patient appeared posthumously as a small book. F. W. Peabody, *Doctor and Patient.* Macmillan, New York, 1930.

[19] Alfred Cohn to Simon Flexner, August 1, 1928 (Flexner papers).

regard in which his opinions are held. And now his memory is a myth, and myths have influence. Recently an interesting side light on this episode has come to my attention. Governor Smith and certain of his advisers have become dissatisfied with the support of the Editorial page of the New York World. [This is naturally not for publication.] Its qualified, understanding attitude of certain crucial aspects of the political and social situation have inclined them to wonder whether their cause might not be better served if the World went over wholly to Mr. Hoover; its opinions then would be much easier to meet—without equivocation and without embarrassment. A political situation like this which requires immediate action, requires the immediate development of an attitude; people care; the meaning of the World's Editorials sinks in. But the meaning of Peabody's letter may on account of the national habit of indolence in the domain of reason escape analysis.

I thought at first that it would be profitable to analyze each of the thirteen or more points in "The Soul of the Clinic." That can in point of fact be done. The result would however be unsatisfactory and unclear because it would fail to be informed by the motives and ideas which underlie his letter as well as by those which are opposed to it. Sharper contrast between the two positions can be developed than simple statements which seem to disclose no striking differences. Pain and fever and glycosuria may exist for instance for more than one reason—it is *not* always by their fruits that you know them. It is the underlying ideas which are crucial. The difference between whether this life is the matter of main concern or some other one, is after all the real difference between the Renaissance and the Middle Ages.

The difference between Peabody and me is that to him the center of interest in medicine is practise and the care of the sick; to me it is the enlargement of the confines of Knowledge. His is not an unworthy object. But its center of gravity is not one which places the medical clinic in the heart of a University. His might be a preparatory or an apprentice school. It makes of the Professor the father of his children and of knowledge a decoration. But in a University knowledge is not a decoration but a passion and indeed life itself. The University does not neglect the care of the sick nor ignore teaching how this end may be accomplished—it has a function here just as it has assumed one in respect to engineering. At the same time though it cares for mathematics and physics. But to care only for engineering is to erect a Stevens Institute; to be concerned only or principally with the care of the sick is to found a school like the College of Physicians and Surgeons of the year of grace 1900. Very good objects these, but not the one to which I thought I was devoting my life. Perhaps I have been in error in believing that the meaning of our activities was not even remotely directed to making the Professor feel more comfortable and intimate with his patient when he had established a relation with him on the basis of the coin of the realm. Or has the doctrine of materialism so taken possession of

the puritan tradition that the meaning of noblesse oblige has completely departed from the belief of our society. But this is a trifling matter. It points however to an interest in action and in human relations rather than to one in knowing and in science. This is the interest which lies at the basis of Peabody's position.

You suggest that if the system cannot stand the criticism to which it has been subjected it must be either too young or too weak to survive. It is not so much that the system can or cannot stand criticism as that the system which is under criticism is *not* the system we are proposing. If there is any slaying to be done it makes a difference whether the victim is a goat or a sheep. Their swan songs sound different and may make a different appeal.

It seems unnecessary to analyze Peabody's letter in great detail. The error, foreseen by many of us at the beginning and still uncorrected, concerning the functions and choice of professors is an error of judgment, only of historical interest; it does not cut to the root of the issue nor invalidate our proper aims. Time and a deeper insight may be counted on to correct it—provided loyalty to the initial aims remains.

The wards are not "the backbone of the clinic"—at least of a University clinic. They represent merely one of the vertebrae. Whatever part of the argument depends on this assumption must go the way of all syllogisms based on incorrect premises. The description of "the head of the clinic" is trivial. This conception of the professor is more like that of a Y.M.C.A. secretary than of a person with vital purposes in life. I can find little compensation for intellectual curiosity in the excellence of his proposed manners or in his sartorial perfection. Much may be said of the other qualifications predicated of Peabody's professor, but I find it unprofitable to take what he says seriously when the image and example of personalities like Nothnagel come to my mind, unless it is necessary to admit that Europeans when transplanted to America become trivial.

On the subject of research it is possible to say much but in order to do so, Peabody's conception of research itself requires analysis for he does not seem to regard it as an integral function of the good society nor to comprehend its essential nature.

But I must stop. If I escape boring you I may be impaling myself on the other horn of the dilemma by being annoying. I wish an enemy rather than a friend had written that letter.

We send you our greetings, the more cordial now that we are cooled.

Sincerely yours,
ALFRED E. COHN

*Dr. Simon Flexner*
*South West Harbour*
*Maine*

*Rivers:* I think that this letter tells you more about the kind of guy Alfred Cohn was than anything I could say. He wrote beautifully, and he loved to argue either from the privacy of his study or at the lunch table at the Institute. To sit with Cohn at lunch was always an experience because the youngsters at the Institute have no respect for age and when Cohn threw rocks he always got some thrown back at him. Which is just the way I would have it—you bang at ideas and people as long as you are able to. When folks get too old to stand or do this they should quit.

*Q:* Dr. Osler said that scientists after the age of 40 had little to contribute.

*Rivers:* Osler was too tough. I know plenty of guys who were fruitful long after the retirement age of 65. Plenty of guys.

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