A  How remote in November, 1946 seemed the possibility of getting polio virus to grow in tissue culture, to be able to do the many things that were done later. And this is a real indication of the tremendous importance of the developments of the tissue culture. I wouldn't say the discovery, but the development of the tissue culture technique by Enders, Weller and Roberts.

Q  You know, when that first report came out, you wrote a very hot letter to the foundation because apparently the foundation publicity suggested that this technique would allow for the production of enough viruses to make vaccine. And you wrote a three-page letter to O'Connor and to Harry Weaver excoriating the foundation for it.

A  Since this is a digression, I don't know what I wrote at the time. But the first report which was merely one type of virus which could be grown in suspended bits of tissue and which then you could determine again, only by titration in mice, was hardly the kind of thing on which to base great promises that were made. This was a constant problem. I don't know what I said in that letter.

Q  I brought the letter. I think it would be interesting.

A  Yes, I would like to see it because it bears on an important issue. The foundation, in trying to arouse public support, going beyond the facts. One step at a time. This is an important finding, and you have got to go further, but at that time, on the first report, the mere fact that you could
get some strains of virus to multiply in non-nervous tissue was not--that was not the real breakthrough. The real breakthrough came when tissues were first grown in large quantities which came really subsequently. And when, Robbins, who was then just a youngster working in Enders laboratory, discovered the cytopathic effect because in the first report, the only way that you could tell that it multiplied was to take it back to the mouse. And it wasn't just the development of tissue culture. It was the development of the specific cytopathic effect. It is very interesting Fred Robbins tells me that the first paper he submitted on this to the proceedings of experimental biology in medicine was turned back. So that there are a number of factors, and at one stage it was immature and constantly the foundation was guilty from that point on. I think that was in '49 or whenever that was.

Q Yes.

A Constantly of going beyond the facts, making promises that could not be based. And I think this was the problem that became even greater in later years.

Alright. Now the third point, the third approach.

Q Yes.

A To determine whether or not correlation can be found between the pattern of antibody development with age, particularly in the period of six months to five years, in countries with and without epidemics of poliomyelitis--both as regards such standard strains of virus as the MV or Armstrong which are apparently immunologically identical as well as certain other
immunologically distinct epidemic strains. This study is intended to help answer the question whether the absence of epidemics in certain countries may be due to the fact that wide-spread immunities acquired between six months and eighteen months of age with very little paralysis, either because at that age the virus is more readily held in check by the host or because--(and here is the real precedence)--or because viruses of low invasiveness predominated in those countries. [This turned out to be the crux--the crux of the situation. This is the point that I made before. The concept that not all polio viruses are the same in their capacity to produce disease--not because of the host, not because of the environment but because of the inherent genetic characteristics of the virus.] There is the crucial sentence.

[Then I go on after proposing these three approaches.] A program such as this is obviously not a one or two-man job but would require a team consisting of at least three experienced virus workers, each of whom, with an appropriate number of assistants could devote himself entirely to one of the three lines of attack just outlined. In addition, it might call for a geneticist whose job it would be to supply special genetic types of mice which would be required at this point. [You've always got to work with the bird in the hand before something else turns up, and that was an important potential approach.] While it is not possible to estimate the exact duration of such a program, one can at least predict that it will require persistence. And that is when
I go on to quote my favorite sentence. I say a sentence from the writings of Sir Francis Drake, recently pointed out to me by Dr. S. Ba~ne-Jones might well become the motto for such a program, "Grant us to know that it is not the beginning but the continuing of the same until it is thoroughly finished which yieldeth the true glory."

This motto, incidentally, has been one which I have had framed in my mind, namely the importance of not giving up too soon. You've got to know when to stop, but you've also got to know when not to stop.

Q Well, it is interesting that after sending this letter to Harry Weaver that in 1947 you had proposed a program to the National Foundation, which was an interesting program.

A I think, perhaps if you will permit the interjection, the interval was just a few weeks, and obviously what is not contained in correspondence are many telephone calls and personal discussions of what to do. Go ahead.

Q Yes. But you suggested a tripartite program, first to study the propagation of polio virus of human origin, especially those differing from Lansing in mice of different genetic constitution. Second, you would like to study the immune response of patients to virus recovered from their own tract which was obviously a study in antibody response and third was a question--could the absence of epidemics among natives in the Far East be correlated with the development of immunity at an earlier age in children than in the United States?
A Well I see here in front of me this application which was submitted in January of 1947--

Q Essentially a few weeks--

A There is a lot more to it than this but it shows the step by step thing that must be done before you can begin to deal with the larger question. In other words, it was necessary to have certain information before we could go ahead. And that we could do then, right away.

Q Okay. So I thought we might discuss each of these central problems and how they developed. You can take them in any order.

A Well, the first one, really, had to do with the immunological classification of poliomyelitis viruses.

Q Yes.

A This developed into a very large program in which I was one of the participants, and I think Harry Weaver, of course, this all--Harry Weaver was the umbilical cord between the investigators and the advisory council of the national foundation, and this was built up into an activity which has been duly reported now, and constantly under the scrutiny of a special committee that the national foundation established of which I was a member, we met repeatedly to discuss the design of the work before it was done, rather than letting individuals doing to work by themselves and then have to come up four, five years later, and say, oh, too bad you didn't do it this way because now we can't compare your results with
the results obtained in the other laboratory and we have to go back. We can't draw conclusions.

Q But you yourself didn't do any of the typing, did you.

A I was very much involved in the isolation of polio viruses from different kinds of disease. I was involved actually in providing an infra-structure of knowledge of cross immunity between different viruses that were isolated. I was very much a part of this. And as a matter of fact, I wrote the final I think it was Dave Bodean and I--I forget now which part I wrote--just to synthesize the whole thing. But I was very much involved in it. And this was I think one of the cooperative, collaborative efforts that were organized by the national foundation. However, much work that involved was very, very important. I know Salk was involved in it. Weiner was involved.

Q And Gebhart.

A Gebhart was involved in it, and it was well coordinated so that the data could be put together. It was not so much--you see in those days, I don't want to go into the details. We could talk for hours about the details. But you just don't take knowledge off the shelf and go and get an answer so the work had to be divided up so that one group would do one thing and another group would do another and then things would be exchanged because it was necessary to prepare antisera against a number of individual viruses and then cross them. It is a tremendous task of sort of work, but it is an inescapable one.
And let me apply to this again the major question, could you know how it would turn out before it started, and the answer was no. It could have turned out in a way that would have made any practical approach to control of poliomyelitis absolutely impossible by virtue of the fact that you could find that a strain of virus that you isolate in one year is already totally different from that in the preceding year, that there is constant variation because of what we know now of molecular biology of certain virus—but it didn't. It turned out that by and large, when you had recovered all the types—hundreds of strains from different patients, different parts of the world, different times, ultimately they fell into three major types. That was a very important discovery. Reagents were then developed so when the 

cytotoxic effect and tissue cultures became established, my God the work would really go into high gear. It couldn't have made any progress without this, and it was a collaborative effort that did this, in which I was glad to have had a part.

Q You know, somehow or other, sometimes you jump over things that you have done, mostly because you regard it as an important feature of things. Now, it so happens that you supplied any number of strains to be examined, strains that you got because you went into the field—

A Of another study.

Q That's right.

A Because I was trying to determine the response of the individual patient to his own virus. That is something we didn't have before. You see, and so this added up. And it
already was possible by work that we had done in our laboratory in

to show that when you had one outbreak isolated a number of
strains that they were similar, and that they were different
from others.

Q One of the things that I had in mind, was not quite
that. For example, in 1947, you went to Berlin during a fierce--

A The biggest epidemic in the history of Germany, I think,
not just of Berlin--2000 paralytic cases within two months.

Q Can you tell me about your experiences in Berlin?

A Well, that is another interesting story because I was
asked by the National Foundation to go there because the
commanding general there, there was an outbreak that began
in the Soviet sector in September and it very quickly spread
from the Soviet sector to other sectors and before you'd know
it, early in October there were already a thousand cases of
tremendous, ultimately just burned itself out by the end of
November, early December. But there are a number of aspects
to it. But I would take too long to tell there was really
nothing which you could do. There weren't even enough
respirators to provide for patients who were struggling for
air and to me it was a really first traumatic experience.
Because, while I had seen polio in large numbers in New York
City in 1931 it was much more children at that time. But
here in Berlin there were many young adults, and adults, and
they were all together in this huge hospitals. Several hospitals,
and just lined up. Some of them with bulbar polio whose
breathing was irregular and others who just with paralysis
of their intercostal muscles and the diaphragm, and there
weren't enough respirators, even though the national foundation was flying them in by military planes, and they were just lying there gasping for breath. It was really a terrific picture. The other point, of course, I took back a number of specimens with me to study the particular qualities of this virus—properties of this virus. But also because I was interested in environmental factors. I was interested in the problem of flies. Actually, although Berlin is so far north, there was a problem with, earlier, the year before, of transmission of malaria in Berlin by mosquitoes that were locally available. But with returned prisoners and other German soldiers. And so, Berlin at that time was divided, ruled, you see, one part was Soviet. The other part was American, French, British they were not united. So in the non-Soviet zones, it was decided early in the spring, actually, early summer, to spray, to remove mosquitoes. DDT was of course at the time. And the remarkable thing was that there was an effect, not only on mosquitoes but on flies. So that, relatively speaking, flies have only a one mile or so flying distance while the borders were in charge, the Soviet sector had much more flies. Moreover, because things were really tough, people were using their feces to fertilize little garden patches, even flower pots were growing tomatoes rather than flowers, and vegetables. So human feces were all over the place and it did appear as if the initial, larger spread—and I developed maps for that and published it—initial, larger spread in the Soviet sector where it started was influenced at least to some extent by the flies which helped
to spread it. But ultimately, it spread to the other sectors. So, these are some of the special interesting.

There were a number of other factors. Of course, Berlin was still in rubbles at the time, 1947. It was also the year in which Britain had its first big polio epidemic. It happened shortly after an international congress in Copenhagen at which Christopher Andrews came walking in one morning. He held a telegraph that he had just been notified, received notice from Britain in which he said, "Ladies and Gentlemen, I regret to inform you that the United Kingdom has just joined the ranks of civilized nations with polio epidemics. We are having" --this was '47--"we are having a most extensive polio epidemic that we ever have had in Great Britain." Nothing yet in Berlin. I attended that conference. I flew back to the United States. Within two weeks, I had a call to go to Berlin, and they really didn't know. They were starving for knowledge. What was there to tell, the latest knowledge. And I remember addressing a group--being asked to address a group on what is the present status of our knowledge about poliomyelitis. Mind you this is '47. We already knew something from our experimental studies, a little more about the nature of the disease, and there were more than 3000 people who turned out and they had to have loud speakers outside. I had my talk translated from English to German. I gave it in German. There were many unforgettable experiences in relation to that. But, the Berlin strains became among the strains to be studied subsequently. Of
course the Soviets during that period, 1947, were gloating both at international conferences and in Berlin. They said, of course, in the Soviet Union with our socialist system of preventive medicine, we don't have polio as a problem. This is a capitalist problem. And sure enough, in 1954, as they became a little more developed, up came the big epidemics in the Soviet Union also. It is an interesting fact that epidemics developed at such--huge epidemics--at such different rates even in different European countries.

Q  This different rate of development I find fascinating because this is one of the fascinating--

A  In studying it subsequently I have come among the many factors that are involved to place particular stress on movement of populations. As one experience that I cannot forget is what happened in Africa after World War II, when, in the Belgian Congo--the old Belgian Congo, the discovery of uranium led to extraordinary new development projects in which whole families were brought in from rural areas in the hills from all around where they lived for generations with hardly any noticeable polio and then when they all came together, a most extraordinary severe epidemic of poliomyelitis broke out. But, and here is the crucial point--the age distribution was practically all under two years--showing that the children and the adults who had lived in the areas where they weren't getting any significant amount of paralytic polio, were nevertheless immune when this epidemic strain, as I call it now, at that time we couldn't be sure what it was due to. But this age distribution
showed that there were other strains of polio, under certain conditions which could give rise to immunity with a very low price in paralysis under natural conditions. But when people were moving together, an epidemic strain from somewhere, coming in with a large number of susceptibles so it spread very quickly. And I think this was partly the factor also in Britain, and partially also in Germany. It is the movement of populations. We see it with meningitis epidemics in development areas. And I think that what happened in the Soviet Union also is that people began to move from more isolated areas in which they had lived almost within a five mile radius of where they were born, because don't forget the amount of destruction in the Soviet Union after World War II, was tremendous, and there had to be tremendous movements of population, and I think the movements of populations play a very, very important role in bringing special epidemic strains to bear on a population.

Q Now, when you started propagating polio viruses of human origin, in mice, did you run into any particular problems?

A Well, the problem was that actually, what we did, first of all, was isolate viruses in monkeys. We had to do it the old way. But without submitting it to the numerous passages to which the old MV strain, or the standard laboratory strains had been submitted and modified by passage. And the attempts to do it directly in mice, also, we had to do when we were waiting for ultracentrifugation techniques in order to be able to get enough from the stools that could not lead to very much success.
I mean, subsequently there were other procedures of adaptation by intraspinal. It was an uphill struggle. There were also problems with getting a special inbred strains from the Jackson Laboratories with the fire. There were all kinds of problems which did not really ultimately turn out well, except, that subsequently this became one of the early ways of determining the different capacity of virus that had been propagated in mice from virus that had been propagated in the nervous system of monkeys to infect by the oral route. This came later because the first studies on the different capabilities that it was not just a paralytogenic difference. And paralytogenic capabilities of the virus but in capabilities to multiply at the portal of entry in the intestinal tract when we shifted from rhesus monkeys to cynamologous monkeys and so it became another important fact that came out later is that the genetics of the virus were such that different genes, as we can use the expression now in a later era—we wouldn't dare use that expression then. Different genes coded for the capacity to multiply in the intestinal tract and different genes coded for the capacity to multiply in the cerebral cortex, to multiply in the spinal cord, to multiply in rhesus monkeys, to multiply in chimpanzees and probably also to multiply in man that all these different factors were determined by different genes, in the virus, which varied.

Q One of the reasons I raised this is, I really wanted an expression of the kind of difficulties that one had to work with being limited before tissue cultures to mice and monkeys.
For example, did you have, you know, there is a special virus of mice--Titler's virus--did that cause any interference in that?

A Well of course that was a problem because, when you study propagation, when you are trying to study propagation of virus as it occurs, let us say, in human feces, to propagate then in the intestinal tract of mice, you run into a problem that they have a polio-like virus themselves. A spontaneous one. And that then had to lead to a study, you see, you had to do all kinds of studies along the way of what is the natural history of this virus in mice. And I think somewhere in my reports we found how it is present at a certain age and is absent at another age, and how it is transmitted. So this was a problem also that limited the use of the intestinal tract in mice very very much. But again, you see, you can't move in a straight line. You may know where you want to get to, but you've got to stop on the way to get incidental information that blocks your path. So I did lots of things which ultimately were way off the path. But it seemed to be like the thing that had to be done next.

Q Now, certainly one of the problems was the immune response of patients to virus recovered from their own tract. Where did you collect your virus from?

A Well, obviously, we didn't limit ourselves to paralytic patients or patients with so-called non-paralytic polio only in Cincinnati. We worked in a radius around. We would go to Cleveland. We would go to Toledo. I mean, mostly Ohio but we would also go to Indiana. And we had to work with different people. Then we would have to be sure that we were able to
collect sequential serum specimens. Another man who came to work with me was Dr. Windsor from Holland. He worked with me on that. Some patients we were able to follow up for three years to study this. Because there was no use waiting until something might turn up. We had to do it in monkeys, and we had to do it at that time. And we had to develop procedures for measuring antibodies quantitatively and not just try to get away with a few monkeys. If it took hundreds of monkeys to quantitate the virus, to do it quantitatively with the sera in order to get meaningful results, that is what we had to do.

And so, there was a lot of work that was done on the immune response of patients to their own virus at different times, to related viruses, to complement fixing antigens that were something that was being done by LeSalle at the Rockefeller Institute. We worked together, so that this of course is fundamental unless you know the natural history of the infection in man, you cannot try to reproduce something which takes control away from nature and gives it to you. And therefore this can almost be a dictum which is applicable to the study of any disease that you are trying to control. Whether it is caused by infectious agents or not. You have to do the utmost to learn about its natural history. Which means all the factors that are involved for its various manifestations. Until you do that you can't have--certainly when it comes to a disease that might be controlled by vaccination--you cannot build a proper strategy for vaccine control
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until you know more of the natural history.

Q One of the interesting studies--
A Now that to me is basic research.

Q Alright. One of the interesting studies in the natural history of the disease was a study which you had done in Cincinnati in 1946--'47 I guess--on inapparent polio.

Examples of a summer grip

A Yes, at that time, yes.
Q that was at that time in Cincinnati.
A Yes. I wonder if you would finish your question.
Q No, I wonder--
A You see, again we were in search of understanding. At that time we knew nothing about other enteric viruses like akasacky and echo viruses. They only came out later. You see, when we were inoculating viruses that we were isolating into mice, newborn mice, after the work of Dölldorf and others, but in 1946, '47, we had--it was just assumed. You know, the large figures of the polio incidents are all inflated because everything that was an aseptic meningitis was called non-paralytic polio. It just so happened that in the study we carried out then, we did isolate polio viruses from so-called non-paralytic polio or border polio and also so-called summer grip that had no neuronal rigidity had no evidence of involvement of involvement of the central nervous system at all. And occasionally of course we'd got out but rarely a virus from so-called summer grip we got out
polio virus much more frequently from the mild cases of--which were not paralytic--non-paralytic polio. But as I look at the results now, we had very interesting results because some of the viruses--and this was done by inoculation of monkeys produced either some very mild or transitory paralysis or no paralysis at all but typical lesions that we could recognize on histologic examination. And at that time, with our limited knowledge, I called them polio viruses of low virulence. Now they might have been, but we had no way of testing for it because unless you could get a virus to produce paralytic disease you had no way of identifying it serologically as polio. And if you are reduced to, let us say, challenging with polio virus, monkeys that recovered, you had no way of knowing whether or not that monkey had had any lesions. So, I think now, that much of what I called at that time probably viruses of low virulence that produced non-paralytic manifestations in monkeys could very well have been certain echo viruses or coxsackieviruses because since that time we have learned that certain echo viruses and certain coxsackieviruses can produce polio-like disease in monkeys. We had no way of knowing. But at least there was a distinction that was growing. Of course, a much earlier study when Dr. Robert Ward came to work with me that we did in the winter of 1940

We wanted to know whether the paralytic disease that you encountered in the winter was really caused by polio. I mean, where was the virus--what happened during the winter months. And we found, sure enough, we could isolate typical
polio virus from patients in the wintertime. So, I mean, gradually the picture would have to be pieced together--that there wasn't some sort of wintering over place that the dissemination probably continued at a low level, you see, and then picked up. And that occasionally some became paralyzed also in the winter. You see, there is a period of ignorance when you just don't have all the pieces to make up a meaningful pattern. But you accumulate them bit by bit. You may misinterpret them in the beginning but ultimately they form a pattern when you have enough.

Q One of the things that was found is that your non-paralytic patients had no antibody to their own viruses during the acute phase and the paralytic patients had considerable antibody during an acute phase.

A Well, you see, this was during a period when we obviously couldn't test them against their own virus. I mean, if it was polio--some of them we could. What ultimately turned out is when there was no antibody at all demonstrable during the acute phase we were using the wrong strain of virus to test it.

Q The whole antibody response is interesting—that you were interested in this kind of problem. It seems to me that there was a belief at that time that the antibody response in polio was going to be different than the antibody response in--

A It was. It was for the following reasons. It was partially technical. Because the numbers of monkeys were always too small even when they were only seven dollars apiece,
when I worked at the Rockefeller Institute. Then they went up to $25, then $35. People tried to cut corners. And those who think you can learn more from one animal that costs $35.00 than you can let's say from one mouse that might cost 25¢, are wrong. And so the way of measuring antibody of just taking the patient's undiluted serum and seeing how much virus it would neutralize, it was the wrong way because by that technique, as we showed subsequently, you had one of two situations. Either you found that the patient already had antibody, just at the earliest time after onset, and that he also had antibody later. Or he had no antibody at the time of onset and he had no antibody later. Well. It was wrong both ways because the proper way to test, to really find changes in concentration of antibodies is to keep the virus constant and to dilute the serum and find how much antibody there is. How far can you dilute out the serum because when we did that we found that in patients who had antibody at the onset and who had antibody later that the amounts were quite different. There was very little to begin with and much more later. And when they didn't develop any antibody at all, it was because they were infected with a type of virus which we didn't use in the testing. So you see the pieces had to fall together by very laborious experiences.

Q  Well, I was just interested in that. I am also interested in the fact that when you sent your letter to Harry Weaver you play down the therapeutic approach, yet two years later, you become very much concerned with therapeutic--
A Let me explain that as far as I can remember the situation now. One of the people—-one of the colleagues in Cincinnati whom I admired very much and who headed the medical research institute in Christ Hospital is Dr. Herbert Schmidt. H. L. Schmidt or Herb Schmidt. It was Leon H. Leon. Alright. He was doing magnificent work on chemotherapy with malaria during World War II. He was one of the really most wonderful workers in my judgment that I have known. Methodical, wonderful. His wife was a neuro anatomist, and at that time they were studying the amino quinolines in malaria. We used to meet quite often and they found in studying the effects, in studying the pharmacology of some of these compounds that they could find effects on neurons. So I thought that substances that would have a special affinity for neurons could affect perhaps the course of the natural history of poliomyelitis.

Now, why did I go even and try to do anything about it, when my previous rational projections of what is possible indicated that therapeutic approach would have probably no real impact on the control of the disease. The point was that at that time we had no other. And there is a certain thing. First, let's learn. Let's find out. Not be entirely influenced by preconceived notions. And because there was also a wonderful group involved in chemotherapy with malaria, a wonderful group of chemists who were synthesizing different compounds just a slight change in the slight change would influence considerably—-I undertook to study this. And there were findings that, while
one compound with one kind of chemical configuration actually accelerated the course of polio. This is on intracerebral injection of the virus in monkeys and feeding them the drug, that another one, with a different kind of side chain, and one which was in fact used in the treatment of malaria was able not only to delay the onset but ultimately something like 40% of the animals didn't even develop paralysis.

This naturally, if you can get 40% protected--and in these I used large numbers of monkeys--these weren't five monkeys apiece where statistically it might have no significance. I don't want to summarize the details of it now.

Q  No no, go ahead.

A  So that the question was whether this nice group of synthetic organic chemists who were working with malaria program could be brought to bear on this and perhaps synthesize compounds that might be able to protect better. Well, it was a lot of work. I remember I had a visit from MacFarland Burnet at that time in the laboratory and I was all excited because some of those manifestations were really striking. Well, the upshot of it was that of course, to answer your question why did I do it. Because there was a phenomenon there to study which could develop somehow. That if you had compounds with a specific affinity for nerve cells that wouldn't destroy them et cetera. But the real denouement came that when finally I had the best compound by intracerebral inoculation and I was then of course starting--because I realized
that to go on working just by the intracerebral routes would get me nowhere and because already from the work at the end of '39 and '40, the work done before World War II, I was convinced that the natural route of infection was the oral route, the intestinal route, and I developed techniques for getting infection with high regularity in cynomolgous monkeys by the oral route, to get paralysis. So I said alright, now let's do it by a more natural route, comparable to what happens in man. When I fed the virus instead of giving it intracerebrally, the compound that exerted a very definite effect on virus given intracerebrally had no effect at all. So I dropped it, but not until after. It was a hell of a lot of work.

Q That was two years--

A And hundreds of monkeys were done. It was too foul an observation because we had nothing else. Now this has more general implications which people sometimes do not understand in the larger scene. You know, I am more interested in broader health research problems and health care problems now than I was previously.

As for example the problem of the tremendous increase in health care costs. In 1950, just 25 years ago or so, the total expenditure in the United States for everything that is called the health care industry was 12 billion dollars. Twenty five years later it was 116 billion dollars. From 12 million to 116 billion. The population didn't increase that much and we didn't get all that knowledge. People say,
why the devil—I mean, how long can we go on. And actually we can't. Now there are many factors involved in that, but one of them is that while medical research has not yet provided the knowledge to prevent cardiovascular disease, the various degenerative diseases, malignancies, it has provided information for therapy to fall. For trying to at least mitigate the situation, which you cannot deny to a patient. So that not until we learn to prevent these diseases that make the end of our life very miserable are we likely to make a big impact in the cost of medical care. And that will continue because we can't—who in our society will say that if we can't prevent it, for heaven's sake, let them die when next year, or two years from now something may be found that can really reverse the process. Who will do that. That applies to the same philosophy I had then.

Just because I postulate that the ultimate control of a problem must come from a means of complete prevention, not only prevention of disease in the individual but breaking the chain of transmission. I would not stop. If I thought, if I smelled that there could be something that could interrupt the progression to paralysis by some compound that could be given just because—and I was there and Herb Schmidt was there, and we had the possibility of doing it. So you take a gamble you see, and it didn't work out. But we learned an important lesson. I learned an important lesson, which is a lesson that many people who are working on chemotherapy still haven't learned—that it is quite non-productive, even counter productive
to carry out many tests on unnatural models. That if you want to find a chemotherapeutic or chemoprophylactic compound, you work on it under as close conditions of the natural history of the disease as you possibly can get. Because otherwise you are going to waste years of work and it will mean nothing. You come down the line to the natural model and it doesn't work.

Q I am glad you said that for a particular reason because I had previously heard that the work on isoplasmodid was discarded because isoplasmodid proved to be too toxic in its use, for use on human patients. Now the story you have told me has quite a different--

A I believe that this is contained in my last progress report on this study.

Q Yes.

A Of course it has a certain toxicity but in malaria also and in all chemotherapy, you weigh certain toxic side effects which occur in a certain proportion of the population, with what it's intended for use. You wouldn't want to use a toxic compound to shorten the duration of a common cold, let's say. A common--I'm not--a common cold. But, when you are dealing with a disease like crippling paralysis, or even malaria from which you may die, it is a different situation, so that you see, that kind of a thing you consider--of course you consider toxicity but it wasn't stopped because of toxicity. It was stopped because it didn't work on the natural route.

Q I think that is--

A Can you stop this a moment. I want to see my report.
Q Dr. Sabin, I just want to go over the point about toxicity of isoplasmodid and the reason why you finally dropped the work with the amino quinoline compounds.

A The main reason for stopping the work on amino quinoline compounds was that the least toxic compound which was effective in inhibiting the total number of infections of the development of polio in intracerebrally inoculated rhesus monkeys was ultimately tested for its effect on infection by the oral route in cynomologous monkeys because after all that is the natural route. We had to use another host to be sure. And the point was that in the very definitive tests it was not effective. So it turned out that it was not anything that was worth pursuing further because if it had no effect whatsoever by the natural route of infection, it is interesting that it has some modification of the effect when the virus is put in intracerebrally in a rhesus monkeys that—but there are too many other important questions to ask to pursue this, and this was the reason for stopping.

Q Now, you know, when one looks over this work, it goes on from 1949 to 1951. But the process of your work is also interesting because it again was halted sometimes because you didn't have the correct number of monkeys to work with it.

A Or the compound.

Q What?

A Or the compounds.
Q Or the compounds. Now, here you are working in a team situation where you are really dependent on someone who has particular pharmacological and biochemical knowledge, and really the research cannot go on until they make, synthesize, a compound. How did you take to that kind of work, you know, where you are really not dependent on your own--

A As you are asking me this question, I ask myself another one. Why didn't I do the critical experiment to use the procedure of testing it against orally administered virus instead of intracerebrally administered virus. Why didn't I do it in '49. Why did I knock myself out for several years and the answer to that question was not because I wasn't convinced that the oral route was the most important because of the work that I had already done, but rather that I didn't have a good model and a good strain with which to get sufficient paralytic disease in monkeys to be able to do a significant experiment. And it was only that while this work was going on with different amino quinoline compounds by the intra cerebral route that I was exploring other pathways of getting a good strain and a good way of having a high frequency of paralysis and infection after administration by the oral route. So I didn't have it in '49. And I would have had to reach the decision. Just because I don't have it, shouldn't I do it. Or should I go on and try to find out what is the relationship between compounds having an affect on the nervous system in some way and the behavior of a virus that is attacking the nervous system. And of course the decision was to go ahead, and not to wait for something that may not turn up.
That is point number one that comes to mind.

Point number two was that the finding that some of the compounds accelerated, made the disease worse, and other compounds inhibited, led to the hope, the constant hope that we had that if you can manipulate the structure of the compound, you might be able to develop a compound you see, that would have even a greater inhibitory activity and certainly no greater toxicity. For that you have to work with a team. The concept of teamwork on this was very well developed during World War II when teams of malariologists, organic chemists toxicologists were doing work on trying to find the best possible compounds against malaria. As a member of the Armed Forces Epidemiological Board it was just built in. And I worked with the same group. And so it was necessary to wait until they would synthesize new compounds that we could then test for activity. When things didn't come out on time, we weren't wasting our time. We had many other things to do when the compounds came along we went to work. And then when finally a good method was developed for getting paralysis with regularity after oral infection with cynamologous monkeys then we'd do the crucial experiment and it doesn't work. So we go on with something else.

Q But you know when you work with a team and people do particular jobs how do you keep up their interests?

A You must motivate them to begin with. Now these people were producing compounds of this sort for another purpose, in malarial studies. Dr. Schmidt was a researcher par excellence
and was not only a great toxicologist, a malariologist and so on, they had an interest in these compounds. I provided another motivation because at that time we said look we have nothing else. Wouldn't it be wonderful if a side dividend of this work on malaria could be the development of a compound which when given early after the first suggestion of central nervous system involvement could stop the further progression in the majority if not in all. Wouldn't be wonderful. This is the way you look at it. And there is their motivation. They are already working as a team. And this is not just one organic chemist. There were different organic chemists. There was Elderfield, and Drake and Knefley, they were the best organic chemists in the country, already working on the antimalaria program. I motivated them. Elderfield I knew. He worked at the Rockefeller Institute when I was there. Schmidt I knew. The others I got to know. You know this is in the community. What do you do, you motivate them. And you all work together.

Q Well the interesting thing is--
A They are doing other things also, mind you.
Q Sure. Because I discovered, looking through the reports, that you had meetings with these people to discuss should we go on, should we do this. And actually you do get a non-toxic isoplasmodial and then you try it out and it doesn't work through the oral route.
A That's the denouement
Q Now there is another de neumont as it were and that is an observation of Gregory Schwartzman's on cortisone. And I wonder if you would speak to that.

A Well using, certain strain of virus that was pathogenic for mice but was not very virulent, Schwartzman demonstrated that the administration of I forget whether he used mice or hamsters.

Q Hamsters.

A Alright. Hamsters. demonstrated that after a certain dosage of cortisone that the disease was more severe and many more hamsters were paralyzed. Now of course this had some similarity to the effect of some of these adjuvants, quineline compounds which were also making the disease more severe in mice and monkeys but what I became why I picked this up was not because I was still further interested in understanding at this particular stage for my major objective the relationship of certain hormonal factors in determining whether a polio infection shall be more severe or less severe. Of course I was always interested in that. But it was a question that was more directly related to my major objective. I wanted to get more human strains into small animals. Into mice, into hamsters. And so I had to know a little more because when we then tried to repeat Schwartzmann's first experiment it didn't work with the virus we had. And so we went into a rather extensive study. I had Dr. Fieldsteel working with me on this at the time to learn much of the details and we did demonstrate even in monkeys with strains of lower virulence that the effect was a real one, that cortisone could make
the disease more severe. But basically as a tool for making polio more effective against strains which wouldn't have an initial effect in mice or hamsters it just didn't work. In other words it was a technological observation that I tried to utilize— not a technological observation. It was an observation of somebody else that I tried to utilize to see if it would make easier my progression of the path to get polio viruses out of monkeys into something else, in order to be able to get out viruses with modified capacity for infection of higher primates, human beings. So again you have to take side paths to. It was a step in that direction not because we didn't have anything else to do.

Q Were other virologists working on that particular problem at that time, of getting a polio virus into a host?

A Yes. It was done by intra spinal inoculation. Type one was finally gotten into mice by intraspinal inoculation but it wasn't a very practical approach. And while this was going on, actually then the neuropathic effect was described by Robbins and that of course.

Q That is in tissue cultures.

A Yes in tissue culture and that made the other approaches so much less significant.

Q Okay. We have to stop now.

END OF TAPE