A This paragraph said, and this is following the proposal to prepare ten liters of each type, from each of the selected strains rather. Not only of each type but of each of the selected strains within a type. I say that because of the high titers which the strains yield in monkey kidney tissue culture, it is conceivable that the cultures could be diluted at least 20 to a hundredfold in human beings. This means accordingly I say, each cc of culture of fluid may be sufficient for twenty up to a hundred or more doses. So ten thousand cc would already, could already mean one million doses. And this was one of the important points of a live virus vaccine and of this particular one because unless from a, from ten liters which was a simple thing to prepare you can have a million doses of vaccine, you would have another practical impediment that would be very great.

Now the next paragraph deals with another subject. I won't read it into this because it deals with the present status of work in plans on chimpanzee rhinitis and c enteritic interitis viruses. Again one of the things that come along, a side revelation while you are working on something else. So this projects a plan of study now on polio up until—that is for 1956 as it appeared it would be on October 3, 1955.

Q Now I want to stop here. I want to refresh your memory about--.
A When we had already at the end of 1953 when Dr. Hennison worked with me that year, when we had for the first time each of the three types of attenuated viruses. Certainly with a remarkable loss of virulence by the intracerebral route, it became desirable to know whether or not and to what extent they might multiply in the human intestinal tract. Now, ultimately we knew that the final tests for multiplication in the human intestinal tract would have to be made in man because the many studies that we carried out most of which were published, not in detail but there is a statement shows this remarkable difference in the susceptibility of the intestinal tract of rhesus monkeys, cynamologous monkeys, chimpanzees, and the question was, where would the human fit in. It was quite evident that viruses that multiplied poorly in the intestinal tract of the rhesus monkey multiplied much better. That means that it took less to infect and the level of multiplication as measured by the amount of virus per gram of stool was greater in the cynamologous monkey. And we also found examples of viruses that multiplied very poorly. We would have said they are not very good. They are not useful because they didn't multiply well in the intestinal tract of cynamologous monkeys. Now mind you the original virulent viruses multiplied extensively and beautifully in the intestinal tract of cynamologous monkeys. And some of the more avirulent mutants that we found also did. But there were others which were desirable because of their greater neural virulence attenuation that multiplied very poorly in the cynamologous monkey and if we had used only that and we said well this is going to be the
basis of choice, we might have been stuck and just given up too soon. But then the experiment was carried out, and which viruses which didn't multiply very well. And I have already described that before, in cynomologous monkeys, when fed to chimpanzees did better. Very much better. Smaller amounts were required to initiate infection. The level and duration of multiplication was larger. So the question arose, is there a progression, an evolutionary progression in which the alimentary tract in primates becomes more and more susceptible to polio viruses while the central nervous system becomes less and less susceptible, more and more resistant. It is an advantage for the virus for survival in man because that is the only way it can survive. So obviously it was necessary to find out where in the scheme of things does the human being fit in. Now how do you start off? How can you tell what will happen in human beings. We don't. We have no basis. You have epidemiologic data which are all very nice for theory. But when it comes to giving virus to any one human being, you are stuck. The only information we had was we knew that Koprowski had fed mouse modified virus to some human beings. They had antibody, they didn't have antibody. But now we have all three types. So you start on this side. It so happened that the three people who at that time now, this was 1954, in the laboratory, who were working directly on this. Dr. Hennison had already left was myself, with my excellent associate, Dr. Romulus Alvarez, Manuel Romulus Alvarez and a technician called Harding. Now, in 1954 I was already what, 48 years old and the other two were no--too young either. So we tested
ourselves first as to what evidence we had for natural exposure. And apparently we all had some natural exposure. I forget now it doesn't matter how high the antibody levels were. So we thought it would be a good idea to start off to see what happens in people who have had natural exposure, who would have some low antibody levels. Because if virus—if there should be any virus multiplication in them, then obviously the particular virus would multiply in human beings that have had no previous—so that is why we selected ourselves. It was meaningful only in a sense that we got multiplication and really it didn't tell much else. I don't remember now what the level of multiplication was, how long it lasted. There was an antibody response. We also learned that. You learn step by step. You don't just jump in to completely susceptible people.

Q I want to ask you a question. Is it wise?

A Is it wise? There is no other way. You could do it the other way you could do it is to start right off on people who had no immunity at all. In the first place the decision that it had to be tested in man at some point was an inescapable one because it was intended for man. The fact that under natural conditions and particularly in certain countries with certain strains, nine hundred and ninety-nine out of a thousand or maybe even all but one out of a hundred thousand become infected with polio viruses that have not been selected the way we selected, and that they become immune, we knew. So we knew that the risk was not very great. But the point is not, is the risk great or small. But the question is, is there any risk. And therefore before you go on and test anything in
persons who have no antibody at all. And presumably you have
had no previous experience with the virus, it is prudent to see
what happens in people who let us say have some antibody for the
virus. Now I would like for you to stop your machine at this--

The first tests on any human beings with material or with
the attenuated strains that we had tested in monkeys and chimpanzees
were accordingly carried out on three people in the laboratory.
Myself, my associate from Mexico at the time, Dr. Manuel
Romulus Alvarez, and a technician, Mr. Hugh Harding. As it
turned out none of us was free of previous evidence of
infection. And the main purpose was to determine, nevertheless,
whether or not the chimpanzee avirulent strains that were being
tested by the oral route in chimpanzees could multiply in the
alimentary tract of human beings. Now, one of the volunteers--
volunteers--we all volunteered with a level of, with an initial
type 2 antibody titer of 1 to 32 swallowed ten to the 7.2
that would be 16 million tissue culture doses of the chimpanzee
and intracerebrally avirulent, monkey intracerebrally avirulent
virus. Now that is a very very big dose. It is a tremendous
dose. But the idea was to find out what was happening. He
excreted virus in his stool seven and ten days later. It
might have been there earlier. I didn't have all the specimens.
At levels of 100 to a thousand tissue culture infective doses
per gram of feces. Now whether that was high or low, whether
that was due to the fact that he did not, that he did have
previous infection with type 2, we didn't know. But at least
we knew it multiplied. As it turned out later this was quite
a low level. His antibody titer quickly rose. Now as a matter of fact that at two weeks it was already--before I go to the antibody titer. The virus was not detected in his stools beyond the tenth day. I see a record here which shows that it was tested at two weeks, three weeks, four weeks, five weeks, and it just wasn't there. It multiplied for a very short time, actually I also see from the record here that it wasn't there during the first 24 hours or 48 hours after feeding. It appeared later, and in these quantities. But, very quickly his antibody titer rose from one to 32 to one to 3200 and persisted for at least six months. So,

Q Now this is all three types or just one type. Just MEF\textsuperscript{1} or--

A In the first place I am going to ask you to forget all about MEF\textsuperscript{1}. I have already established that it was one of the viruses that was tested that would have to be left out. We are working here with chimpanzee avirulent virus. Actually the one that was fed here for the first strains that we had established, that we had selected out by the various procedures I described before. The Type 1 was Mahoney. The Type 2 was YSK. The Type 3 was Leon. We had not yet gone into an extensive program of finding which was the best. The purpose of this program was to determine in the meantime certain parameters of multiplication and behavior of viruses that we thought might be safe to try in human beings on the basis of the fact that they were completely avirulent on spinal inoculation in chimpanzees.
Q But all three viruses were fed.
A But always one fed only one type, you see because if you begin to feed all three, you see you have problems of interference and in analysis, you limit the things. So the type 2 that was fed was the type 2 YSK that had undergone all of the tests that I have previously described.
Q Alright.
A Now the interesting thing was that in this colleague of mine, Dr. Manuel Romulus Alvarez who received the type 2, and 16 million tissue culture doses of it in one swallow, that while he developed this hundredfold increase in the type 2 which was fed to him his type 1 and type 3 antibody did not significantly change during that period, maybe a little bit but not much. Now the remaining two, that is Mr. Hardy and myself, were fed type 3 virus, the Leon. We didn't--the type 1 antibody that was present was apparently we did not use the Mahoney virus. We just used the type 2 and type 3. And here was an interesting situation, Mr. Hardy also had a level of antibody of 1 to 32 for type 3. And he was fed 25 million tissue culture doses of type 3 virus from the Leon. The virus didn't multiply in him at all. There was no, if any significant change in his antibody titer, tested for a whole long period, and it didn't multiply. It failed to multiply because he had had this previous infection and his intestinal tract was completely resistant. It didn't multiply. Now, I swallowed the same dose, 25 million tissue culture doses of the Leon attenuated virus, Leon strain attenuated virus. My antibody
titer was lower. It fluctuated between let's see I have a record here. It fluctuated between 1 to 3 and 1 to 15. Now, this could have been due to a previous infection of type 3 virus or it could have been due to something else. So I didn't know. I was the only one with the lowest titer. Therefore I took the type 3, you see, and the interesting thing is that in my particular situation the virus did multiply. It didn't multiply in my technician who had a somewhat higher level. But it did multiply in me. Now, the--it multiplied, virus was excreted at seven days only at a level of 100 TCD\textsuperscript{50} per gram. And as I look at the record, it actually multiplied during the first week. Only one week because already it was positive at seven days, but the next specimen taken at ten days was negative, two weeks was negative, three four, five weeks, was negative. In other words, a short spurt of multiplication at a very low level, on the basis of subsequent well controlled experiments, it is obvious that I had a partial intestinal resistance to infection, but the virus multiplied a little bit and the antibody rose a hundredfold, but then it dropped down to 32 and remained at that level. Now, what did we learn. We were able to learn in the first place that it would multiply in some and not in others, who had antibody. But all that we knew was that when such huge amounts, it was only later that we realized that intestinal resistance was a quantitative thing, that you could overcome it, that let's say if an ordinary dose of ten thousand tissue culture doses would start up a multiplication easily in anybody without
previous experience. You could have resistance to ten thousand to a hundred thousand to a million. But then if you fed ten million tissue culture doses, you could break through that resistance, but even then it would multiply only for a little bit, and at very low level. And finally you could reach a point where no amount of virus that you fed would multiply. You would get complete intestinal resistance. But the additional thing that we learned was this. That the virus recovered from the alimentary tract of both Dr. Romulius Alvarez in whom there was excretion of the type 2 virus, and in myself in whom there was an excretion of the type 3 virus, that that virus remained intracerebrally avirulent for monkeys and even after it was allowed to propagate to high levels in monkey kidney culture etc. In other words, you see when we tested the stool directly we couldn't give more than a hundred to a thousand tissue culture doses intracerebrally so it was not so surprising that it was not virulent intracerebrally. But then when we multiplied this out to ten million to a hundred million and when we gave that to monkeys, it was still intracerebrally avirulent. Now that was a very important initial finding, because supposing that the reverse had happened. Supposing we had taken the stools from Dr. Romulus Alvarez and from myself and inoculated the original stuff before selection and culture in monkeys and the monkeys would come down paralyzed like a ton of bricks. It would have altered the whole course of our experiment. So you see this preliminary trial on three people who already have had experience with
previous infection taught us certain important things and made it possible to go on. Because it turned out this way the next step was obviously there was a need for larger numbers and not only for larger numbers. We had to go in to persons without evidence of previous infection. Now I think would be the time for me to reexamine those letters that you just mentioned because after this was finished about the middle of 1954 or not till later, till all the tests, the intracerebral tests in monkeys were not completed until the end of '54. We were looking around for places to do more human tests. Well there were several places where studies were going on. Studies were carried out on various problems on hepatitis at the Willow Brooks State Hospital; studies were carried out in some prisons for example, Dr. Huebner was at that time engaged in studying the disease producing properties in human volunteers of the various adenal viruses that were isolated.

Q You remember that.

A And he had an entree into this federal penitentiary in Chillicothe Ohio. So let me now start--

Q Before you stop I have one more question to put to you. And it bothers me because it is a kind of ethical question. Now, you look in retrospect at this and say look at all of the wonderful things we found out. You also said there was not too much risk in doing this. There was some risk but not too much. Now scientists who do research, who really do research don't know the answers beforehand.

A You know what they probably will be.
Q Alright. You know what probabilities are but you don't know the answers beforehand. I look back in the history of scientists who experiment on themselves, like John Hunter who is doing a study of syphilis and gonorrhea and he infects himself. And in essence what he does has shortened his own life by an experiment for the human good. What right does a scientist have to experiment with his life?

A Well, the same right as a person has to commit suicide. So let me look at the fish. For another facet. Let me examine another facet. The basic decision is whether or not in order to make progress at least this is my criterion. The information that needs to be obtained for human welfare, not curiosity now, when it comes to curiosity a scientist can do anything on himself that he likes as I said in the same way as a person is allowed to commit suicide. It wasn't the first time that I used myself for example. When I was looking, when I was working on pneumonia, pneumococcus pneumonia, and I was very much interested in the soluble specific substance in relation to immunity to pneumonia and the response after pneumonia and after I had studied it in rabbits, I wanted to see what would happen to myself, and I inoculated myself with anti pneumococci serum and then into the area I put insoluble specific substance. I was questioning the problem of sort of an antigen antibody reaction. And I had some of the worst trouble from that horse sera that I inoculated myself in different areas of the skin because I developed--it came after a certain time--I began to have hives. And they appeared and reappeared and reappeared so I studied on myself why is it that when I put in
one, I inject sera, a foreign serum in one place in my skin and alright after a week I forget what it was, I begin to get early carrier. Itches like the devil. It comes and it disappeared, but why did it keep on appearing and appearing and appearing. It would come and go and come and go and come and go. And so there were various hypotheses. One was that more than one antibody, more than one antigen is contained in horse serum and that as antibody for different antigens appeared at different times, each time a new antibody appears, you get another early carrier. And then the other possibility was that antibody appears in a small quantity and it gets tied up, it combines, and you get this local reaction. Then more antibody appears, and as long as there is antigen remaining in the area to combine with antibody, you are going to continue to get hives until it is all used up. So not being satisfied to watch what happens, I was curious. And this is pure curiosity. There was no need to do that really except for, to satisfy curiosity. So at certain stages I inoculated new areas now that there was antibody to see what would happen at new areas because if the reactions, the multiplicity of reactions, various other things would occur in the same way in the new areas, certain explanations would not hold. The question was, after it all stopped, after no more early carrier appeared, if I would inoculate a new spot with serum, I asked myself what would happen. Would I again get repeated bouts of early carrier or would I get it once and disappear. Well I experimented on myself not for a necessary step in order to be helpful to somebody but in search of understanding. So that when you describe what a scientist does
in search of understanding that is his prerogative. He can do
with his body as he likes. But when you come to the larger
question of the ethical problem of let's say using himself first
and then others, using human volunteers in general, to me the
overriding question always was, number one, is this experiment
necessary. Is this knowledge that can be gained this way and
cannot be gained in any other way, have I exhausted every
possibility. Let's take for granted for a moment that you do
everything from the point of view of safety, extraneous agents
that you know of. And in this particular instance, this was
indeed the question. All of this work was not merely to gain
understanding of a biological phenomenon. But to develop
something that would have to go into human beings and as I
explained before because there was this problem of changes in
the evolution of primates as regards the reaction of their
intestinal tract, the viruses, polio viruses that had undergone
different selective mechanisms, and had different properties.
There was no alternative. And that was the time to get started.
So in order to get started, to learn anything before I go out
and ask anybody to do it, I must say that yes, I will do it
myself. And besides, there is another consideration that I
didn't mention before. We took monkey kidney cells and
fortunately at that time we didn't know certain things we
knew later about certain contaminating viruses for which we
couldn't test. We had polio virus multiply in monkeys. We
could titer the amount of polio virus in it. But how did we
know that something else may not have formed in there that
doesn't happen nature. That quite aside from immunity to
poliomyelitis virus there could be something in those cultures that could be harmful. If somebody would say to me, alright you are going to do this experiment. You are doing this experiment to learn more about polio. But how do you know there isn't something harmful in those cultures. Have you ever swallowed some of this culture fluid? And if I didn't do it I would have to say no. So this was also the reason for swallowing the large, a much larger amount than we would ever consider feeding to a human volunteer. We swallowed a whole cc of that culture fluid, measured by polio it was 16 thousand, 16 million to 25 million tissue culture doses. We would never figure--and the reason we did that was to at least make sure on ourselves that there wasn't something in the culture fluid as such that would be harmful. So you see all of these thoughts go into the decision making process.

Q Alright at this point. Dr. Sabin, one of the things that strikes me is really the rapidity of developments in your research toward the end of 1953 because early in the spring, almost just before the spring of 1954, it is clear that you were beginning to consider doing tests--certain tests, orienting tests in human beings, and could you tell me the development of your thinking along those lines and what you thought you might do.

A The preliminary studies which have already been gone into in considerable detail showing the differences in behavior of various attenuated strains when given by mouth and given by brain and given intraspinally etc. had led me to the conclusion that obviously the ultimate test of the suitability of any strain
by the oral route or some even, if the oral route should for some reason not be suitable, perhaps by perentral injection, led up basically to the question that—there was no question—I am backtracking that the experiments would have to be extended to human beings to get the ultimate answers. But the question was when. Now I had already decided after the various studies that had been carried out in '52 and '53 and after we had had at least a quite an attenuated strain of each of the three types, that the time had come for certain preliminary studies so the various candidates that were being checked out in monkeys, chimpanzees, ultimately would also have to be checked out in human beings, that it was necessary to obtain fundamental information on the behavior of various attenuated polio viruses in human beings before one could reach a decision on the selection of one that is optimum. So it was not a question of waiting until you had the best possible strain that you could get by studies on monkeys and chimpanzees before you would do any tests on human beings, but when would it be proper and also necessary. And I find that very early in 1954 I was thinking of the possibility of carrying out such a study hopefully in children among whom one would expect to find some that had no immunity at all. And therefore approach, with my old associate, Dr. Robert Ward, who was then professor of pediatric, at the New York University Medical School and together with my cousin, a member of that department, Dr. Saul Krugman, was carrying out studies on rubella and certain other problems, hepatitis, subsequently at the Willowbrook State School of
State Hospital for mentally defective children. And I made inquiries from him as to whether or not it would interfere with their own work there if we tried to set up a collaborative study with Ward, Krugman doing one part of the work and we doing another part of the work. And I had to justify to him. I had to tell him why I thought that the time was then, early in 1954. And in a letter in which I wrote him about this subsequent to a telephone conversation. I say that after giving this matter considerable thought, I have come to the conclusion that a poliomyelitis virus which does not produce paralysis after direct spinal inoculation in chimpanzees and is harmless in other respects may be regarded as safe for oriented studies in human beings. The orienting information which is now urgently needed and can be obtained only in human beings is concerned with the following (1) a quantitative determination and I stress here the word quantitative, of comparative, of the comparative infectivity and immunogenicity of the modified viruses by the oral and intramuscular routes. (2) the question of interference when all three living viruses are administered simultaneously. (3) the question of excretion of virus after oral and intramuscular administration. And finally (4) the pathogenic properties of the excreted virus. I would like to now I have finished reading from the letter because the rest of it goes into great details of what I would expect to do. I would like to--I am intrigued reading this letter now of March 1954, that at that time in my own mind I was still not certain whether one would have to use the oral route or let's say the
intramuscular route. There were possibilities that the optimum strain of attenuated virus from the point of view of loss of neural virulence might have little or no effect on feeding because we had found that our strains of virus that we had at that time were very poor from the point of view of producing immunity when they were fed to cynamologous monkeys, and they didn't multiply enough to be detected, at least in cynamologous monkeys in any case. Or cynamologous monkeys weren't good enough to test for that property. But there was a possibility that if after intramuscular inoculation the virus did multiply not merely there are a pre-existing dose of antigen--did multiply and if it would be possible to produce immunity with very small doses and if there would be resistance and all the other requirements for a good vaccine, that it could have an advantage, that it wouldn't be excreted. You would have to know, for example, would a virus given intramuscularly remain closed so to speak whereas a virus given orally would spread from person to person. So it was quite necessary to have no preconceived notions or not leave out studies on the intramuscular route.

Well, I pursued this to a point where finally the director of the--because Dr. Ward and Dr. Krugman were quite willing to collaborate or work out a protocol and then the director of the hospital, of the Willowbrook State Hospital wrote to the commissioner in Albany and instead of mentioning certain orienting studies. I don't know that that would have made any different at all, he wrote to the commissioner in Albany and asked permission for having a polio vaccine trial
carried out at Willowbrook State Hospital. And this permission was denied. The Commissioner incidentally was Dr. Brill. I don't have his initial here, or first name. And this permission was denied. The record also shows that I wrote a letter to Dr. Gilbert Dahldorf explaining to him my reasons for the necessity of making the transition. That it was not a question of a vaccine trial. That we were in the early stages of studying the behavior of polio viruses in the human intestinal tract, and that there were advantages to doing it in an institution where one could follow the children for a long period of time, there was no risk. They were being constantly exposed to polio viruses that were circulating in the Willowbrook State Hospital. Now that I think of it, it was probably the worst place in which to gain such information because unless you had such children in complete isolation you would never know what part of the effect was due to the vaccine strain, or potential vaccine strain that you fed, and what part was due to intercurrent infection. It was not a very good idea but at least there were no alternatives.

At any rate it was turned down. But I know--these are exploratory operations--I knew that in order to obtain funding for such work, permission to carry it out, I would have to have the approval of the Advisory Committee of the National Foundation for Infantile Paralysis. One way or another. Wherever I might do it. And so I made the request for such permission, projecting the kind of studies that would have to be done, and we have here a letter of March 29, 1954
that I wrote to Dr. Koom who was director for research for the Foundation and who would have to present the whole thing to the advisory committee. And there are a number of very interesting points that obviously he was asking that the advisory committee would very properly have to ask and that I would have to justify. I look upon it as a very necessary step in the whole process for an investigator to be given permission to carry out studies of any kind on human beings. That his own judgment cannot and should not be the final judgment in such things. Of course this was more than 20 years ago when the criteria for the use of human subjects in important tests were not being followed as rigorously as they are now. I wrote him on March 29 that as matters stand now, I don't know when or where it will be possible to carry out these studies. And then I went on to describe to him everything, giving him the summary of everything we had learned about the behavior of the viruses in cynamologous monkeys, in chimpanzees and why there was evidence for a difference in primates, at difference stages of their evolutionary development in relation to susceptibility of the intestinal tract and the susceptibility of the nervous system, and why it was absolutely necessary to move on to studies in human beings.

Now, I said for example also that I would not have considered extending my studies of the pathogenic and immunogenic spectrum of the modified type 1 Mahoney, type 2 YSK and type 3 Leon viruses to human beings if I had not found that in chimpanzees they produce neither paralysis nor lesions after direct spinal inoculation. And then I describe all the tests that were done on chimpanzees. I went on to say that the
demonstration that poliomyelitis viruses which possess only limited capacity for damaging the neurons of the monkey are apparently completely incapable of damaging neurons in the chimpanzee provides the basis for extending the studies on these variants to human beings. Then I reply to a certain number of questions that he posed to me on his own behalf. I presume. Questions that would be of importance to the advisory committee. And here I am now quoting from the lengthy letter that I wrote.

You asked, I say to him, quote, have preliminary tests of the excretion of virus after oral or intramuscular administration been carried out in monkeys. End quote. My reply is that this type of test is of little or no value in cynamologous monkeys since they excrete little or no virus even after administration of virulent virus. I personally kept normal monkeys for months with others which were receiving virulent YSK virus by mouth and not a single one of 20 developed antibodies. And yet this is an aside here now I think about 60% of the monkeys became paralyzed after oral administration of the, of this virulent virus and 100% developed antibody. Yet they were not excreting virus. Dr. Francis. I go on in my letter to Dr. Koom, to say, Dr. Francis informs me that he has obtained similar negative results in tests with virulent Mahoney virus. I personally fed very large doses of the modified Mahoney virus. That is the one that lost intracerebral virulence in monkeys to 20 cynamologous monkeys and only eight of those twenty developed antibodies. This is in line with the
demonstration that all three types of the modified virus, that is intracerebrally avirulent for monkeys, despite cultivation in cynamologous kidney tissue, were much less effective in initiating immunogenic infections after intramuscular injection in cynamologous monkeys than the parent virulent strain. The fact then, moreover. This is an aside here. This indicated that mere multiplication in an extra neural tissue in epithelial like cells from monkey kidney did not provide those viruses or retain in those viruses the capacity to multiply in extra neural tissues after intramuscular injection. You see the complex problem we have here. Simplicity thinking doesn't just--

Q Doesn't add.

A Doesn't hold. And I continue in the letter to say that the fact that an occasional monkey developed antibody after receiving as little as ten or a hundred tissue culture doses of virus makes it important to determine that the quantitative aspects and regularity of response in the more susceptible human beings. Second question here. I say you ask quote. Is it necessary to study interference in human beings now. Would it not be better to carry out initial orientating experiments on interference using monkeys or chimpanzees. End quote. And I answered. I have already carried out orientating experiments with the modified viruses in monkeys. Five groups of cynamologous monkeys were inoculated intracutaneously with approximately one million tissue culture doses. And neither type 1 alone, type 2 alone, type 3 alone, a mixture of all three given in the same sites, or each of the
types given in a separate limb in each monkey. Test for all three types of antibody were made in all. All of the monkeys which received the type 1 or type 2 viruses developed homotypic antibody, within about thirty days. And 80% of those which received type 3 virus developed antibody. In other words, more than after feeding. None of these monkeys developed heterotypic antibody. In the two groups which received all three types of virus, interference manifested itself by a delay in antibody development and by a failure of a small proportion of monkeys to develop type 1 antibody and a large proportion to develop type 3. There is no significant difference between those that received the three viruses as a mixture in one place or when they were inoculated separately in different places. It is possible that in more susceptible hosts like the chimpanzee and man, this interference may be less noticeable. On the other hand, I interject here it could have been even more noticeable because of even greater multiplication. But it is apparent that only direct tests on human beings can give the answer. Furthermore such tests that have to be done on human beings regardless of the outcome on chimpanzees. As regards interference by the oral route it would be useless to do any tests in cynamologous monkeys and tests—and the reason for that is that it doesn't multiply there, not even the virulent ones multiply there. And the tests in human beings would have to be done regardless of the results obtained in chimpanzees.

Then I continue. The main question therefore is, are these viruses safe to use for orienting studies in human beings. I base my own decision on the intraspinal tests in
chimpanzees. If these experimentally modified in viruses had produced paralysis even only after spinal inoculation in chimpanzees I would not have used them. I would not consider to use them. But since the chimpanzees exhibited neither paralysis nor lesions after an inoculation of approximately 2 million tissue culture doses, I thought that orienting studies in small groups of human beings could be undertaken. Then finally you asked. I am still reading from the letter in reply to the questions that he asked me. Quote. Since these three strains of experimentally modified poliomyelitis virus will presumably be grown on epithelial cells derived from normal in quotes monkey kidney tissue what steps will be taken to avoid the possible contamination of such normal kidney cells with live "B" virus, the virus of lymphatic poreal meningitis, or microbacterial tuberculosis and of course, in quotation, at that question.

My answer was that intracutaneous and subcutaneous injection in rabbits and guinea pigs and intracerebral injection of mice takes care of all these three possible contaminants. Of course "B" virus and microbacterial tuberculosis can also be eliminated by filtration. The intracerebral tests in large numbers of monkeys provide an additional safeguard. One more point that has a bearing on this problem may deserve a few words. My current grant provides funds for a study of the pathogenic spectrum of poliomyelitis viruses that may be recovered by tissue culture from healthy children who have no known contact with a clinically diagnosed case of poliomyelitis.
I think at this point here I can stop this because this deals with the question of pathogenicity of naturally occurring polio viruses in healthy children which I have already discussed.

Q  We discussed that.

A  And I merely mentioned this to indicate the need of searching for a still more highly attenuated virus in nature.

Now, this was written, this letter was transmitted on March 29. Perhaps as a background I should say that at this point in 1954 the National Foundation was about as fully occupied as it could be at the so-called Francis field trial of Salk vaccine. The intrusion of any other kind of activity, of any other kind of vaccine was something that they wished, like a bad dream, might go away. At any rate, I mean this, this is not without some potential significance. But I would like to make it clear that I regard the need for submitting the kind of proposal that I was submitting to an independent body for judgment for justification to go ahead. And to go ahead with the safety guidelines that I provided is an absolute inescapable necessity. It cannot and should never be circumvented. It is of interest therefore that there must have been a number of telephone discussions after that and I find here a letter of May 7, 1954. In other words, just about 5 weeks or so after I had written the previous one explaining all of these things, a letter that I wrote to Dr. Rivers who at that time who at that time, really, was heading up the scientific activity for the National Foundation for Infantile Paralysis, for polio foundation. I said this letter is being written to you. That is to Tom Rivers, as chairman of the NFIP vaccine committee
about my proposed studies on human beings. After our conversation in Atlantic City on April 12 which was just two weeks after I wrote to Henry Kooms I received a letter dated April 20, 1954 from Dr. Kooms in which he notified me that my proposal for studies on human beings has been referred to the vaccine committee. In other words, here is where the rub comes in.

I am making an aside remark here. My proposal had nothing to do with a vaccine. It was a proposal for studying certain fundamental properties of attenuated strains of polio virus to compare their behavior in human beings with their behavior in chimpanzees and monkeys and so on so we could establish certain guidelines for predicting the behavior of certain strains in the selection ultimately of an optimum candidate strain for a vaccine. I was not making a proposal for a vaccine. It should have been reviewed by the same committee, the advisory committee that gave out grants for all kinds of polio research, the same kind of advisory committee that was going over my work for years under the auspices of the National Foundation. But, as I pointed out in my preliminary, this was a special year. There was a special vaccine committee whose work actually at that time was concerned with working together with Francis and Salk about setting up and monitoring the field tests with killed virus vaccine that was going on extensively all over the country. That in my judgment was wrong. My proposal should not have been referred to the vaccine committee. It should have been referred to the research advisory committee on which Tom Rivers also served. The fact that it was referred to the vaccine committee showed a certain concern of not muddying the waters of vaccine trials with one vaccine with now considering
another one. And I wouldn't be surprised on the basis of what I had learned later that the very fact that the director of the Willowbrook State Hospital for mentally retarded children asked the New York State commissioner in March, 1954, the commissioner, Dr. Brill, for permission to do a vaccine trial. This would be a live virus vaccine, in the school, the fact that it was turned down--now I am guessing--my guess is that he called up the National Foundation, as I would have, if I had been the Commissioner of Health for the State of New York, and I received such a proposal, I would have called up the--and probably knowing some of the people. I won't use the vivid language. For God's sake, don't you dare mix up this vaccine trials that we have with the killed virus vaccine going on now with another live virus vaccine trial there. Don't. So, it was wrong to speak of the work that I was proposing at that time as a vaccine trial. It was not a vaccine trial. It was a fundamental study of properties of polio virus. At any rate, it was referred to the vaccine committee. And I am going back to my letter to Dr. Rivers.

And I say that Dr. Kuhlmann, in his letter of April 20 to me added the following, quote. Not all of the members of the Vaccine Committee being available. Incidentally that included many other people. It included public health officers, public health service, all sorts of other people who were not--whose judgement was not at all required on a basic study of this sort. At any rate, since they would not all be available, it was then suggested that a special meeting of the committee
would be arranged at which you yourself would have an opportunity to present your proposed--

END OF TAPE