Q Dr. Sabin, Today I would like to begin from the time that we inadvertently stopped last time and I wish you would search your mind and tell me the significance of the experiments done at Willowbrook by Saul Krugman.

A The experiments were not done by Saul Krugman. Saul Krugman was a and his associates were very important partners. The reason for doing that was that it was necessary to find children whom we knew to have been free of previous evidence of infection with polio virus and then to vaccinate them with the best available Salk vaccine and give them the maximum number of doses to see not only the kind of response that you had in them but also then to determine what the influence of that response would be on their reaction to an administration of Type 1, Type 2 and Type 3 polio vaccine, the strains which we had in my laboratory. The important thing was in Willowbrook also that my good cousin Saul Krugman had a wonderful facility there for studying all sorts of things and these children who were selected for these studies, once they had been screened, were kept in certain groups, in certain facilities, away from contact with the innumerable others because it was practically full as we discovered later of all sorts of viruses. Alright we did that and what we learned basically from this when we finally came to challenge them was first of all we learned a good deal about the response and what happened to the antibody and the high avidity antibody and low avidity antibody. It is
all contained in the data although I never, we never had time to publish it in detail. But we also learned that even those who responded well with higher levels of antibody when subsequently fed the vaccine strains that there is no influence on the multiplication of virus at all. So that all of the statements that have been thrown about that if you have a high enough level of antibody you will not get multiplication in the tract were completely disproved in that Willowbrook study. That was number one.

But an unexpected development in the Willowbrook study was the fact that the children however they were isolated, many of them, not all, many of them had all kinds of other enteric viruses. So we had an opportunity with the wonderful collaboration of Saul Krugman and his other associates of and with the innumerable specimens of stools and sera that were obtained that we could then, that we then studied quantitatively in our laboratory to determine the effect of the presence of other kinds of enteric viruses in a population that was under control. And so we learned a great deal about the basic information of what happens when there is a struggle for territoriality in the intestinal tract among different viruses inhabiting the intestinal tract. We learned about the nature of interference. We learned about how a virus multiplication let's say of polio viruses could be held down and then how it would come back again. And how for example if a certain virus was multiplying at the time we fed and then let's say when polio took over later you couldn't find any evidence of that virus activity at all. And this had a bearing on interpreting
subsequent field events in which we were still dealing with a world in which highly paralytic strains of polio were still spreading and occurring and it was evident that you could have an infection with one virus at a certain time and then when you gave the vaccine virus you could get multiplication of the vaccine strain and you wouldn't be able to detect necessarily unless you knew the patterns we learned that ten days before another virus was operating. So we learned many things in that Willowbrook experiment that went beyond the basic question of the influence of vaccine acquired antibody on the subsequent multiplication of the polio vaccine strains in the intestinal tract and presumably also in the paralytic polio vaccine strains. And it was a very, very important experience all around.

Q You know I am a novice. You have mentioned this on several occasions. High avidity, low avidity. I wonder if you would explain that to me.

A Alright. There is a much more modern terminology in the type of antibody that develops after the first stimulation of the antibody forming system. Different kinds of gamma globulins come in and they have a different avidity for the agent, for the antigen with inducements. And that can be demonstrated by various techniques. Now what happens is that you may get a very high titer of antibody originally of low avidity antibody but then it disappears and it is replaced by high avidity anti--which is much lower. So that we had a very simple way of measuring it because we could tell for example in a neutralization test that when we read the test at a certain
time let's say two, three days after the virus and antibody were put in the tissue cultures, that we had neutralization, a high antibody titer. But if you kept the tubes, two, three more days it broke through because it was a low avidity antibody which apparently dissociated from the virus and the virus was then able to multiply. There was another test, for example which became much more useful because it was simpler. The so-called metabolic inhibition test. And that tested only low avidity antibody because you read it fast at a certain time and from that you would have pooled, very high levels of antibody. But in the first place the high avidity antibody would be low and all of these things came out because they bear, they have an important bearing on what that antibody does in the body. This is a general phenomenon which is now interpreted in terms of the different classes of immuno globulins that are formed during the course of a primary response to antigen whether it be a defined virus, live virus or an antigen material.

Q Was this a concept that people accepted at that time in '59.

A Well it was not a new concept. There were already high avidity and low avidity antibodies it was known in other systems but it came out very obviously during the course of our tests you see here we had a very high antibody titer and you keep the tubes for two or more days and the neutralization disappears. But it is nevertheless important.

Q Now there was one other series of tests if you will, or field tests on one of the most important is that which occurred
at Taluca Mexico. And I wonder if you would tell me how those field tests got underway, what their purpose was and what you generally found.

A It was carried out in 1958. One of the important questions we learned about this kind of a vaccine which is totally different from other live vaccines: small pox, yellow fever and so on because they are given to people who don't have other viruses in their place. We were dealing with a totally new situation in which we were vaccinating at the portal of entry, which happened to be the intestinal tract and which by that time already the work of many people including ourselves showed was full of all kinds of viruses and particularly in certain populations and particularly in populations in subtropical and tropical areas with poor sanitation and hygiene. So it became necessary to know what would happen in an area in which there were such viruses when you fed polio virus. Not when you fed it individually, ten children now and a hundred children the next day and maybe a thousand children the third day but I had the concept that in order to achieve elimination of the circulation of a certain kind of virus it was not just mass vaccination to get that virus in, the vaccine virus into a large mass so that you would hopefully displace the paralyzing viruses that have been occurring in nature for eons of years. Maybe not eons but certainly for a long time. But rather what was the strategy required to do it. And my hypothesis was that unless you did it rapidly in a short time you would just allow the regular viruses to
continue a chain of transmission and those who didn't have resistance, who didn't develop resistance in the intestinal tract or at least enough resistance for a challenge with the paralyzing virus, with an infection. We use the word challenge. So it was necessary to do it not in a few children the way we did it for example in Willowbrook and studied it in great detail but to go out in the field and that is where my former associate, Dr. Mauelo Romolus Alvarez who worked with me until 1956 and then went to his own laboratories in Mexico City and carried out studies there on smaller groups, thousands. The idea was that we would try to go into a city. Taluca was a capital of a district, about 100,000 population and feed the vaccine in a well-organized campaign simultaneously to the whole child population. Simultaneously meaning within about a day. But you see this was a different--it was not just mass but mass plus time. People sometimes look upon this kind of research as if it were just a matter of taking knowledge off a shelf. You have to test hypotheses. This kind of field experiment on mass populations is as much a biological experiment as anything you can conceive in fundamental research. It is fundamental research on mass populations. You can see I am sensitive to the people who call one thing fundamental and another thing--but don't let me digress now. So it was possible to arrange this for the summer of 1958 but it was not merely a question of putting it in. You also had to find out what was happening so that we had to do thousands of cultures. We had to take samples of a population and first
of all bleed them beforehand so we know what they had beforehand. What kind of antibody they had. We had to take swabs, rectal swabs on hundreds really of, subsequently though it turned out to be thousands of children beforehand so we would know exactly what did they have in sufficient numbers so that the rectal swab would then reveal it in our tissue cultures. And then feed them. And then continue to take cultures from them to see what happens. Which virus is dominated. And this was an extraordinarily well organized study. We ended up by doing 5500 to 6000 cultures on specimens we obtained from the children because we took them at intervals. And we learned many, many things which I presented in a ten minute summary during the meeting of the American Association of Physicians in 1959.

Q Now, how did you feed your vaccine? Did you give it monovalently or trivalently?

A It was done because by that time the concept arose you see that in certain communities you would have to use a trivalent vaccine and we knew of the interference so we also had to study what happened after a single dose of trivalent vaccine and what happened then when we took a selected portion of the population and gave them another dose of trivalent vaccine. Well, it would take too long to summarize but we learned a tremendous amount that was new. We learned for example and it is all documented in print. It was published on this. That within a very short time the polio viruses that we fed took over, became dominant. That they displaced the other viruses that were spreading. Of course there were already
polio viruses spreading in the community too, naturally occurring. They displaced the other viruses for a period of about two months and then we also learned. When I say displaced it is not completely. It is quantitative. And we also learned that many of the children who were carrying other viruses at the time because of this mass vaccination who originally in whose intestinal tract the vaccine strains didn't take. There was no evidence of multiplication that after about two weeks, sometimes three weeks, sometimes even four weeks they picked it up from somebody else. This is what came to be called the ping pong effect that doing a whole community en masse in a short time resulted in spread of the virus in the community so those who might have had interference at the time you fed them the virus were able to pick it up from somebody else and become immunized later. And then we found the extent of the response, the extent of interference let's say of type 2, type 3 with type 1 and also subsequently after a number of months we came back, and to a selected group gave a second dose of trivalent vaccine and found how this brought up the immunity very well. This became the basis really of the concept which still is terribly important and which subsequently has been tested in several countries but still isn't being applied in countries that need it the most of how to actually achieve the best results in the use of this kind of a vaccine in communities in which you have a warm climate all around the year you have children just playing together in huge numbers and the problem of meeting the interference of other viruses. I will talk later when we come to discuss the
problems of eradication of polio in different parts of the world how the things that we learned in Taluca became fundamental for ultimate application in practice.

Q Now, this is all the period of developing the vaccine.

A Let me add one more point. I want to make it clear the logistics that were involved because these thousands of specimens had to be sent frozen from Mexico, from Taluca Mexico to the Cincinnati laboratory and I had a huge staff working up all of their specimens, testing them, we had to not only identify what we isolated, whether it was polio or not polio. But what type of polio and then very often what kind of virus. And we had to use not just one tissue culture. We had to use several kinds of tissue culture because we also wanted to isolate adenal viruses and not only echo and coxsacki viruses. It was a monumental job and all of those specimens were sent to the laboratory. I had a big staff working on them and this collection of specimens became also subsequently a bank from which still new kinds of echo viruses were isolated subsequently. But that is a monumental effort. I want to make one more interesting little aside on this.

I presented these data at a meeting of the American Association of Physicians which as you know is the elite group of university professors of medicine. They still do and they had been meeting for years in Atlantic City and had attendance of about 5000, usually huge. And I was given just ten minutes because those are the rules. And it was a period when there was much discussion in the country as well as in the world.
still. This was 1959, just at the beginning of the summer before the wide, tremendous field trials involving millions of children in the Soviet Union and elsewhere were carried out and Salk vaccine, my vaccine was very much under discussion. When I got through presenting, compact, solid, you know, one lantern slide after another summarizing the data showing the soliquilibrium (?) this viral equilibrium in the intestinal tract, its nature and quickly and the impact that it had in as few words as possible. Something happened which was recorded in the annals of the Association of American Physicians that never happened before. I had a standing ovation. When I walked back to my seat and they had a separate place set off. The members—I had been a member of the Association—and I was sitting next to my good old friend John Paul and when I came back and this standing ovation he said to me. He turned to me and he said Albert, don't let it go to your head. You know it's not a very critical audience. That is not in the proceedings of the American, in the history of the American Association of Physicians. But that remark I never forgot. And of course he was right. It is a very nice little—

Q It is a very nice anecdote about Paul and I think it leads into my next question. There were a number of ancillary studies which were done not in your laboratory but again Saul Krugman and Robbins undertook an interesting piece of work on when to feed the virus.

A Saul, would you excuse me.

Q Yes. Sure.
A This was a post hoc thing. This was after the vaccine had been adopted for use. There were many more important things as a guide to what to do which has not been covered. I have my notes here. Because one of them, very important studies, and a quite a different population was done in Czechoslovakia because Taluca was quite a different setting, population setting than obtained in Czechoslovakia. Because one of the main discussions was because it was such a different, revolutionary type of vaccine, how would it work in different population groups. It was a very urgent and necessary question. And actually when the special advisory committee of the World Health Organization in 1957 recommended that there should be tests on growing, increasingly larger numbers, there were various people to whom I distributed the vaccine in the world and tests were made in many places. Some were made in Sweden and England. Many tests were done in Holland by Professor Verlinda and the whole faculty of the University of Leiden. There were many tests done. But, there was also a big test done in Singapore for example, earlier, in 1958 when they had a big epidemic which was Type 1 and they wanted to test because there had been no mass use yet of this vaccine. And I had the two millions doses of each type that was prepared by Merck and so in Singapore they decided to determine whether the feeding of type 2 during a type 1 epidemic would have an impact on the course of the epidemic. So there was really. I forget how many now it's in the data but I think a couple of hundred thousand children were fed type 2 vaccine in the course of the
epidemic and certain studies were carried out by Dr. Ail, (?) by others who were stationed there and the data strongly suggested that it interfered. It is not the best way to fight an epidemic because subsequently you see after the vaccine was approved, its main use first in the United States was come in during epidemic periods but nevertheless it was the first time that it had been fed to a couple hundred thousand, a very large numbers. So the next thing that happened and this was all done through W.H.O. W.H.O. received a request from the Ministry of Health in Czechoslovakia. Could they have 200,000 doses of each type of the vaccine. They would like to test it children up to about 14 years of age. They had a very good epidemiological unit. They had a very good institute for doing laboratory work and they wanted to see what would happen if they would vaccinate. They started. They aimed at about 200,000. Ultimately it was about 145,000 in different areas of Czechoslovakia. Very carefully followed with laboratory study. Czechoslovakia was particularly interested because the year before they had quite an epidemic of paralytic polio even though they had had a mass vaccination, extensive vaccination with killed virus vaccine. So they wanted to see what this would do. And they really carried out a magnificent study which showed exactly what happened, the kind of sera conversion, in other words those without antibody developed antibody and furthermore, the safety, what you encounter. And since they didn't treat everybody you also had an opportunity to see a spread to family members. And Czechoslovakia was not a country
in which let's say all of the adults already had immunity. They knew they didn't. So that when they fed only children up to 14 years of age there were not only older children in the schools with whom they mixed but there were also fathers and mothers and other children so that there was an opportunity of the second phase of spread from the vaccinated to the unvaccinated. And it was a tremendously important study which established not only the high effectiveness of the vaccine. They did not feed trivalent. They gave type 1 and then type 3 and then type 2 and very, very important data came out of that and I visited, and I worked with them and I had tremendous respect not only for the organization that went into it but the extraordinarily good follow up, the studies on isolation of virus, antibody development before and after. That was done at the end of 1958 and extended over to 1959 and provided tremendously important studies because when Czechoslovakia started on that Chumakov had already whose efforts in Moscow were entirely devoted to this whole institute for making enough killed virus vaccine to vaccinate the polio. They were having a lot of paralytic polio. He turned and he also got several hundred thousand doses from me to begin to plan the experiments on millions in 1959 because what he did, first of all—and he was a much better organizer, much more reliable than Smoradinsov who did studies in various—very important studies that were helpful in thousands in Leningrad. He then organized studies in countries where again many of the adults were not already immune. Countries like Latvia you see and Lithuania and Histonia and these were already mass things and furthermore he
did something else. He used this vaccine that he got from me to make enough for some millions so that in 1959 before the Ministry of Health and the advisory councils and the Soviet Academy of Medical Sciences made their final decision at the end of '59, he had a field trial not only even material that I supplied him but with material that he made from material that I supplied him, enough for about ten to fifteen million you see. All that was backed up by what was happening in Czechoslovakia because with the experience of Czechoslovakia he had a much better basis for going out then to Histonia, to Latvia, to Lithuania as well as to places in Moscow so the impact of the work done in Czechoslovakia was very, very great in setting the stage for tremendous extension in the studies to other countries which let's say would be more comparable to a country like the United States from the point of view of the proportions of population, different age groups there were, and did have or did not have immunity. So you see Toluca was important for one part of the world. Czechoslovakia was important for another part of the world and I still have a wonderful photograph that was taken at one of the international meetings in Washington on live polio virus vaccine in which all the people--because we formed our own consortium. It was a period when there was no governmental involvement at all. There were no treaties, no exchanges. I did everything on a person to person basis. I did it with Czechoslovakia. I did it with Singapore. I did it with Holland, with Professor Verlinda. I did it with my good friend and former associate Manuleo Romolus from Mexico and we all came together and we had a photograph taken
before a globe. It was a person to person consortium and it represented a kind of activity which if you in my judgement now if you would get involved in formal governmental relations you would never get done. The public health service played no part. W.H.O. played no part except to be an intermediary and having supplied its good services of an advisory committee. It was an extraordinarily exciting and important period in this work.

Q Now let me ask you. Isn't it true that previous to your, to the Czechoslovakians feeding live virus, they had had courses of Salk.

A Well I just got through saying that the year before, one of the things that impelled them to do it is that they had a very, very sharp outbreak of paralytic polio in Czechoslovakia after having used killed virus vaccine.

Q I didn't--

A That is already on the record. And this is one of the thing that led Czechoslovakia to do it. But Czechoslovakia really had a superb organization in its Ministry of Public Health. Superb organization in the Institute of Epidemiology.

Q They had well trained--their people were well trained.

A Oh great virologists and epidemiologists and they had the organizational capability. They were really superb.

Q You know one thing that I wonder whether Dorothy Horstman played a very significant role in the acceptance of Chumokov's experiments and Histonia, Latvia and Lithuania because as you know part of the criticism was that no one knew how to check the Russian data.
A Let me comment on this. There was no question that polio and politics were not inseparable and that there were during the many meetings, and there was a strong feeling. Well, you can't rely on the Russians. Well of course, unfortunately a large part of it is true because with all the dedication and everything they have not developed a critical approach to evaluation of data that one would have liked and would obtain elsewhere and that would fit American standards. So it was not without reason and there was always this question. It came to a head which I may or may not have related before. At one of the conferences and I forget just at what point but it was already after the Soviets had done things on a large scale. We had a meeting, a sort of work shop. It was arranged at the National Institute of Health and of course the Soviets were there to report their data. Ishdanov was still I think Deputy Minister of Health. He was a great virologist. He himself didn't do the work. So he was a critical evaluator and good old Dr. Charles Armstrong who certainly made wonderful contributions to polio actually got up there in that meeting and he said in public he said he did not think that the Soviets had a very great regard for life and he personally was not prepared. Maybe I am not using the exact words. Prepared to accept Russian observations on safety. And Ishdanov who was not as volatile as Chumokov. Chumokov was sitting by and merely getting a translation. At international conferences Chumokov also controls himself. Ishdanov merely said very quietly to Armstrong. He said Doctor Armstrong I would like for you to know that the regard we have, the feeling
for the well being of our children in the Soviet Union is no less than the feeling which you have for your own children. He said if you think that we who have the responsibility for the public health in the Soviet Union would purposely mislead ourselves with a vaccine that came from the United States. It was developed in the United States, would mislead ourselves as regards the safety for our own children, Dr. Armstrong, you are wrong. Nevertheless this continued as a very important factor and what happened after these extensive studies was I also had my doubts about the reliability for example of many things that Smoradinsov reported and still has. But I developed a tremendous respect for the integrity of Chumokov and his associates. Nevertheless I could be considered biased. He was right. So I think under auspices if I remember correctly of W.H.O. Dorothy Horstman was asked to go to the Soviet Union and make a very careful analysis of the way they were working, whether the data were correct, work and studies (?) and she wrote a report which I don't think was published but was circulated to the National Foundation, to the U.S. Public Health Service, to the World Health Organization and that had an impact. But actually the impact ultimately was of the mass vaccination that occurred in 1959 in the Soviet Union which preceded the very careful analysis of the data by the Academy of Medical Sciences and they are not above criticizing Chumokov though subsequently they picked (?) kicked (?) him out for something else. I think wrongly. They went over those data with a fine tooth comb, and a special scientific advisory council to the Ministry of Health in the Soviet Union. And this was all done
very quickly in November, December, 1959 after the summer experience. And it was in December I think of 1959 that after this study the Soviet Union was the first one to come out to say that from now on this shall be the vaccine, vaccine produced from these strains shall be the vaccine used in the Soviet Union. Now mind you, at that stage there was still no other government that had accepted this vaccine as a public health policy. But with this recommendation, Chumokov turned and I think he did it before because he was always in advance. But he said well if I wait for the bureaucratic decisions necessary, it may be too late because he wanted to tool up in advance of the 1960 polio season. So he began. He turned his institute that before was a place where they were making killed virus vaccine. He just stopped almost everything and turned it into mass production of the oral vaccine from these strains. Now whether or not there were all the fine checks that were subsequently written into the regulations doesn't matter because the point was that in January, February 1960 he was ready to give vaccine to 70 thousand persons in the Soviet Union under twenty years of age.

Q You want to say millions or thousands.

A Million. I am sorry. Million. Seventy. Seven oh. To millions in East Germany, to millions in Czechoslovakia, to millions in Hungary, in Bulgaria in Rumania, all of the satellites. Yugoslavia was not a satellite. Poland was super-nationalistic. It is another chapter which will come in later. But before the season began, the polio season began,
about 100,000,000 persons had received the vaccine before the summer of 1960. And I mean, there was a tremendous mass use before any other government had made a decision. And then there were conferences. There was a conference in Moscow before the beginning of the summer. There was an international conference in Copenhagen. There were conferences and there were all of these things. How much can we trust the Russians. And so on and so on. But the impact of this because it stopped polio in Czechoslovakia just. And it was done on a mass scale. East Germany, everywhere the Soviet Union to a large extent although the Soviet Union is a big country and there are many places where they couldn't reach. The Soviet Union isn't now in 1976, hasn't achieved the record of the United States you see with almost comparable populations. I mean we are dealing only with small numbers but quite a different expanse of land. Well at any rate it was that impact with all of the things that ultimately led other governments to reach a decision. And actually it was the impact not only of the field trials in 1959 but of the use in 100,000,000 persons behind the iron curtain that led ultimately with all of the discussions about the Russians, and there were commissions sent over ultimately there for the United States division of biologics to reach a decision. What are we going to do about this. So you see there was all of this background and of course while this was going on again in 1960 other countries, Yugoslavia for example which in polio and politics were separate from the Soviet Union and I was invited there and I gave them my vaccine and they
carried out their own field trials in their own cities and then they set up the vaccine right away. I mean it is a long, involved chapter but those are the things that led up to the acceptance of polio vaccine. These strains, for live polio vaccine. But when you then had to go the difference between acceptance and production that was a totally new concept. It presented all kinds of difficulties.

Q Now, before you jump ahead because I have a tendency to go back to things, what is happening in the outside world. In the United States there is in essence other work that is going on and I want to come back at least to get some comment from you as to the significance of tests or trials, trials would be a better word that John Paul and Dorothy Horstman did in Connecticut, that Saul Krugman and John Fox. That Saul Krugman and Fred Robbins did and a study--

A I am not sure now whether I know the tests on small groups that John Paul and Dorothy Horstman did were very important. Tests in families, that Fox did. The groups were all small groups. This is the tiny thing before you get into the thousands and as far as I know Fred Robbins and Saul Krugman didn't come into this till later. Besides whatever Saul Krugman did we did together subsequently. That came after, after acceptance in the United States because there is also a period of important history between the time the decision to use it in the United States, or approval by the public health service and what was happening between approval and availability and all the epidemics that occurred in the
United States and the things that happened. I mean this is another chapter. So what you are referring to, there were many small studies within in the United States, in England, in Holland as I said.

Q I know. But.
A They were very different from the mass field trial.
Q That is true. But what I wanted to get at even in a word is what the purpose of these small studies were.
A Again they were to study how the virus multiplied, the response and things like that. But again you see this is a very long chapter of a tremendous amount of work. We have spent months, more than a year getting up to actually the most intense period of activity and we don't have the time to go into many details because there were many other important problems. Because the small studies are on record. They contributed little bits of information which all had to enter into the total effort but this is all prior to the mass studies that then occurred in the United States, elsewhere before manufacturing began.

Q Alright. Then let us turn to something else. I think one of the first community studies that you did was a community study in Cincinnati.

A Yes. But let me. I don't have the exact dates in front of me. It would take too long. So let me just take it off the top of my head.
Q Okay.
A The various aspects that were involved. We had two problems in the United States. Maybe there were more than two or three with relation to the introduction of the live polio virus vaccine. First was the problem of the acceptance by the public health service. Because as you know we discussed previously strains that had been used by Koprowski and Cox. It was the same business actually except that they parted ways. And an independent determination in neural virulence and so on by the public health service which showed in their own way that the strains that I had developed were more acceptable from the point of view of neural virulence and of course there were studies carried out by Lederly. A considerable--at considerable expense. Lederly had spent 13 million dollars trying to push through without a study of different strains what they happened to have. Studies in South America and so on and the records of the international conferences on this are full of data. So, but finally after use on more than a hundred million in nineteen hundred and--

END OF TAPE