Q Polio in what amounts to underdeveloped countries.

A Well, not only underdeveloped countries because I wouldn't call Japan an underdeveloped country. But I would like to say something about the problems, some problems, some aspects in Asia. In the first place, Japan is a remarkable example of an Asian country in which shortly after very severe epidemic in 1961 they decided to shift to oral polio virus vaccine because the evidence of the effect on the epidemic was so good. And they have achieved now, within a short time, a status comparable to that of the best in Europe. But there is also an interesting period there of political decisions that had to be made, and one of them was that prior to the '61 epidemic they had six different pharamaceutical companies each of them making Salk vaccine, each of them selling it to the government. And when the government decided--it was the government that made the decision that there shall be a shift over to oral polio vaccine and now. Each of them applied to me, asking me for the strains. I said I am very sorry. It is none of my business how Japan does its business but for a country like Japan to make the small amount of vaccine that would be needed, small or even large, to have six different companies do it, it is not only counterproductive, it is uneconomical; it is unreasonable. This is not killed virus vaccine. One cc is equivalent to a hundred times as much coverage as the killed virus vaccine. I said I will not do it. Whatever you decide, because I was thinking that it was going to be trouble. I said I will give it to one.
But I won't give it to six. So, it seemed reasonable to the minister of health besides what was there to turn to. And so the Japanese who very quickly, very quickly adapt, you see, to such situations, and the six companies formed a consortium in which they formed one what they called live polio virus vaccine laboratory except in Japanese it is pronounced rive. Rive porio virus raboratory. And they very quickly got together a very good staff and they got together a testing agency in the ministry of health that would be equivalent to the bureau of biologics in our country. And a surveyance committee. They also kept on surveying. And pretty soon they made quite acceptable vaccine and mass vaccinations were carried out and they maintained it and they have had an excellent record right down the line. So it can be done that with a good organization, quite by different methods than I described a little while ago, in countries in which there is a great deal of dissemination of enteric viruses, so it can be done. But they have a very superbly organized health service administration.

On the other hand if we take a big country like India I was first in India in 1961 in the Kafkan (?) and the Institute in Bombay asked me for the strains and I came with the strains, a certain amount that I would give to all other manufacturers. Certainly not thinking that they would already be set up but having every confidence that they would be able to go ahead and modify or get a certain structure together to produce vaccine. I had had visitors from India and so on. But they didn't get very far and of course India has many other
more important problems than polio. But, they continued to have outbreaks here and there with many paralytic cases and the pressure continued. And finally, in 1963 I was asked to come to India by the Ministry of Health as a W.H.O. consultant because the rabies vaccine laboratory in the state of Madras in Kohnur (?) a beautiful, beautiful place high in the mountains had managed to get money from Nehru to build a special facility for oral polio virus vaccine production and already then when India was turning much more to the Soviet Union they had a man who had spent a year with Chumokov and presumably they were all ready to go.

When I visited Bombay two years after I had been there before almost, they hadn't gotten anywhere. In Kohnur on the other hand they already had the building practically completed. I made certain recommendations for modification. I thought the man who trained with Chumokov would probably be able to get a proper staff together. I was highly gratified and the question was of course they needed equipment which they didn't have. Equipment like oh autoclaves, tissue culture bottles, you know the sort of thing you need for mass production. And so the question was again well you don't have very much money, and I was invited to lunch with the American ambassador, Galbraith was at the time. He asked me about this, why I was there and I said that I thought that while the Kafkan Institute wasn't really set up that things looked good. That if they could get a number of proper systems going at it, if they could get the
equipment in a short time, that as far as I can see they ought to be able to get started on production of seed and other things in six months.

He said, well how much do you think it would cost? I said I would doubt very much if it would even cost a million dollars. He said a million dollars. Why that is pocket money for me. He said you can, on my behalf at your next meeting with the minister of health of India say that if he wants this equipment, just to pick up the telephone and he can have it tomorrow. I transmitted this information the very next day. But what happened was that the Russians got wind of it and they offered of course. And like the proverbial donkey, starving to death because it can't make up its mind from which bale of hay to eat, years went by before they made a decision. And really years went by before they ever got into production. And they still aren't any good. And years later they, and I said why do you need two production places in India. You have already got a building, a structure concentrate on one for heaven's sake and get it done. But they didn't. The state of Maharashdra Bombay has its own status, still bold, and therefore we also got to do it here. The end result they weren't making it in one or the other.

Q Wouldn't it have been more reasonable for them to buy the vaccine?

A You know it is very easy to say reasonable. The Russians charged the equivalent of ten kopeks even out of Egypt. I will come to Egypt later, you see. The Russians didn't give away the vaccine. They didn't give it to Japan during the epidemic.
They charged them a hell of a lot of money, and when it comes to foreign exchange when you have it. With some countries yes, but for a big country like India it was reasonable to make it. I could never figure out why Japan has never produced it for export. I don't know of any places that Japan has exported to. Actually, if Japan wanted to, it could make vaccine for all of Asia. But why they never did, I don't know. Well, at any rate, India has never gotten anywhere just like it hasn't gotten anywhere with many other things. It has gotten somewhere with some things but with many other things of lesser priority they just can't make the decision. Now let me--

Q  Is it only the decision. Or do they have people?

A  It is the lack of discipline. It is the incapacity to be systematic about anything that prevails over most of India. Anything would be wrong. A lack, a basic incapacity almost inherited from the British civil service which left them with a very disorganized way of doing things. This is the real problem. You've got a government in India with very, very great idealistic intentions but just getting nowhere with the basic problems. There are parts of India where things have more or less developed but basically this is a real problem here.

Now what is going on in China I don't know except that they have gotten the strains originally about 1960 from Chumakov and personal work for a year and a half, who apparently went back Peking. I have indirect information that polio is pretty much under control. There is no polio in China but they have
absolutely refused to discuss this or show this to any of the missions that have gone over. And even though I had years ago established some very good friends I have never had. I have not had an invitation since the establishment of relations to find out. I am curious but no word. But then there is a very interesting situation in Viet Nam that I came to hear about.

Several years ago a W.H.O. mission had come back with a report that during the Viet Nam war despite all the difficulties that public health had made extraordinary progress in North Viet Nam but South Viet Nam was a shambles. Word also came that--well I knew that South Viet Nam continued to have a great deal of polio because at one point I received a direct appeal during a period when for some reason production had stopped. There was a problem of a certain bad virus that was introduced and there was a sort of temporary halt in the importation and so on.

And the Minister of Health of South Vietnam appealed to me. Could I get him a million doses of vaccine? Get it. Couldn't Could pay. So I began to go around to the different makers and I said, well, this situation--there is a lot of polio in South Vietnam and nobody came up with any vaccine and I was of course in touch with the State Department. The State Department said don't worry about the money. He said we will pay for it. If you can find we will pay for it. And finally I got in touch with my friends in Italy at the Scalala Institute and they offered a million doses free. That was their contribution.

It was an expressed of good faith. And the United States supplied provided air transportation. It was flown over to South Vietnam.
I probably got into hands--I am guessing now--I have no direct information because I never--I didn't receive a letter of thanks from the Ministry of Health. I received absolutely no report how it was used. And my guess is that it went into the hands of private speculators who probably sold it to people who didn't need it. And it had no impact. On the other hand, the report of the W.H.O. mission in North Vietnam was that polio had been eliminated. And it was I think as late as 1959, in '59 and so on, Hanoi had an epidemic with about 6,000 paralytic cases of polio so it wasn't that it wasn't a problem there. But

But when I was in Cuba in 1967 the professor of surgery at the University of Havana who had just come back from a mission to North Vietnam, and when we were at a reception and we were introduced, he says, it is very odd that I should meet you because one of the many things they showed me while I visited in North Vietnam was how they were making your vaccine underground among the many underground factories that they had established, they took me to one special separate pharamaceutical unit where they were making their vaccine by themselves. I would have thought that among all the other troubles under the bombardment and under the war that they would get it from the Soviets, but they were making their own.

Q That is just--

A This is incredible. I have had no other information but this is the information I had already in 1967 when everything was done underground. But there was the information from the W.H.O. mission that went over while the war was still on in
Vietnam saying that public health in Vietnam despite everything had made great advances and they mentioned that among the things that eliminated was polio. So, this is how the situation stands. You have a proper organization the way Japan had it can be done. Probably North Vietnam by some ways did it a little bit like Cuba. I don't know what they did. It shows again that when you have no organization as India has no organization, there is no use having a vaccine just like there is lots of other good technology available that would help with the problems in India if but there is lack of organization, there is no achievement.

We go to Africa, Egypt presents an interesting aspect again of relations because obviously through the break with the Soviets where Egypt was getting all its vaccine from the Soviet Union. Now I was on a political mission to Egypt in 1968 and I met at the time quite aside from my meeting with the ministers and relating to the problem of war and peace in the Middle East, I had a session with people from the hospitals and gave seminars and also I met some of the people that I knew when I was in Egypt in 1943. And the hospitals were full of cases of paralytic polio. And I said to them -- this was '68 -- the Soviet dominance was very great. And I said aren't you vaccinating. Oh, yes. We are vaccinating by using Russian vaccine and they would whisper on the side. Some of it is really very good. It did its job in Cuba. However, whatever the problems may have been, but it was quite obvious that again, poor application, poor use doesn't stop the chain of transmissions in such countries and there is probably no question that a certain number were immunized but it didn't stop the chain of transmission
and paralytic polio continued but it is also very interesting that long before, not too long before, there was a final break in relations between the Soviets and Egypt, Egypt as I said before, applied to W.H.O. and said they wanted to make their own vaccine. But it is certainly not under control and it still isn't and it cannot possibly be without the type of annual program of vaccinations in which you have a well organized effort and I think it can be done in underdeveloped countries, under certain leadership and if the W.H.O. is going to play a role, if it is merely going to supply vaccine, it will be worthless. It just won't achieve very much. Because what is needed even more is the method of its use and its availability. However certain other problems have arisen in Africa and that is again and it has to do with the method of use. That when small groups of children are tested for so called sera conversions. How many that are negative will become positive, the conversion rate which has been demonstrated first by me in Chicago, in Cincinnati, and then subsequent studies which were done with trivalent vaccine for example in Chicago in the poor areas of Chicago, for two doses of trivalent vaccine given a certain period apart, resulted in sera conversion rates in a range of 95% or 95 to a 100% so we knew that even when used in poor populations there could be circulation of other viruses but not as much as in Africa that it had an effect that nevertheless it was always less. It was a question. And so the thing arose, well, this kind of a vaccine is not effective in countries with a lot of enteric organisms and it is really not with--well there
were many interesting ways when I examine the data. Some of them are due to the fact that resistance to infection to multiplication in the intestinal tract can already be acquired during the first month of life when the children are protected by maternal antibody and at a certain time of life as subsequent studies that I carried out with Krugman and those associates in New York showed that when they get it very early in life they may not develop antibody and yet may have resistance to intestinal tract. Then there were also some other indications that when it was used en masse without reference to conversion that it was effective you see in stopping. I think the real issue is that certainly if you just take it in small groups as in a clinic here and there, you do have unquestionably the interfering effect of the other enteric viruses. But, when you give it en masse and you eliminate as the studies at Taluca showed for a period of weeks, six weeks, eight weeks, the dominant role of the other enteric viruses, you set up a chain of transmission of the polio viruses, you would get good coverage.

And furthermore, if you repeated year after year in a certain age group, those who haven't been protected the first year get more intestinal resistance the second year and finally you create a situation where you have intestinal tracts that are not as susceptible except those that are newborn come in but they are picked up every year. So that the real problem in Africa and some other countries with many enteric viruses is the system of use. The need for mass campaigns, repeated every year which I believe should consist of first a dose of
type 1 to allow it to spread to the maximal extent possible followed not less than two months later by a dose of trivalent vaccine and done every year so that the public health activities are not tied up all year round with this. You have a certain basic program development but again it is like many other things that can't be done because lack of organization.

Q Well, not only lack of organization. Certainly one of the problems in Bombay at the Kafkhan Institute, was a lack of personnel.

A You see, if W.H.O. now which has taken on the responsibility for seeing that areas of the world that need vaccine and can't get it, will get it. This is no problem. The problem of producing vaccine is no problem. It is a cheap vaccine. It is easily produced in mass quantities. It keeps for years. Very recently a modifications in production which, if they really come into being soon it may be possible for one pharmaceutical company to work with six months and make enough vaccine for the world or for a region of the world for ten years and then forget about it. So that I would say the real obstacle to the ultimate elimination of poliomyelitis in the world is the same obstacle as it is the obstacle to the conquest of poverty, of hunger and other things: organization, discipline and so we are going to continue to have polio in many parts of the world as long as we continue to have the other much more serious problems than polio existing. This is my feeling about the matter.

Q Now is there anything else that we have to talk about on the polio?
I think not. I think this would be a good time and I would hope very much that we could spend a couple of hours now—

at least a couple of hours to cover, not in detail but my transition from work predominantly on infectious diseases and the virology of various diseases to the problem of viruses and human cancer which is a chapter that began in 1962 and it did not end until twelve years later and perhaps what I would regard one of the most dramatic experiences in my entire scientific life.

Q Alright, then why don't we go to that subject now and let me give you a general question to begin. How does one make a choice—how does one let go of something that you have been doing for thirty years and how do you then go about choosing the problem that you are going to—

A Well, actually by about 1962 I had made most of my decisions about actual laboratory work with polio. I was still involved in some policy decisions but not in lab work and not so much enteric viruses and although I think most of the effort was already gone by that time on dengue and arthropod borne viruses and so on, there was a real issue of, in which direction to go. I had many many thoughts in my mind at that time. For example since 1947 I was serving on the study section of the National Institutes of Health dealing with tropical diseases. I was very much influenced also by the fact that during this period prior to 1962 I was chairman of the special group, the national academy of sciences to evaluate the problem of public health and the need for research not only the application of existing knowledge but the need for new knowledge so I was very much involved in that and the various problems in tropical public health.
has interested me a great deal particularly since I saw problems there. I was in part parasitologically oriented from my work on toxoplasma but I saw the kind of operational procedures used in virology they were quite foreign to parasitologists, and I saw new potentials particularly of vaccination against tropanosurmiscosis

African tripanosurmiscosis which I was tending perhaps to shift away from virology. But this was the period also partly because of my involvement with polio vaccine production when SV40 emerged into, into prominence as a virus that could produce certain experimental cancers in hampsters. A good deal of work had already been done on adenal viruses. And it was quite evident that some of not the types of cancer viruses that we had known since the times of Rouse, you know, leukemia viruses and so on. And the work that Gross, Ludwig Gross had done which were with viruses that were quite unique. You could call them uncogenic viruses. They produced nothing but apparently malignencies. They were ordinary viruses, adenal viruses, tumor and others which experimentally could transform normal cells into malignant cells, could produce experimental cancers. And here was a perfectly harmless virus for monkeys, no evidence of it producing any disease under certain very special experimental conditions it produced this cancer. And there was a big move on at that time and one of the people who is a great arm twister was Joe Smardell who was at that time I think an associate director of the National Institutes of Health and very much involved in the Cancer Institute. They were out canvassing the field particularly of polio virologists who were about to
do something else to see if they could entice them to studies on the role of viruses and cancer. Well, I was one of those. And as I was thinking I thought well, here are certain disciplines, techniques that I have, there certainly are many, many unanswered questions. Was there a special little niche where I could operate where let us say that was not already very well tilled, where the soil was not tilled by others. And as usual I saw a very great concentration on model systems. And from my experience with polio I knew the importance of model systems, that it was necessary to have them to gain basic information. But even in model systems you could devise experiments of the sort that would be able to answer the ultimate question in human beings. That I was not the kind of person who was satisfied to work for years on a model system regardless of whether the experiment I did had a bearing on the human problem. The real question was not only to me but to everyone can one, what kind of information, what kind of technology has to be developed to be able to answer the question whether any human cancer is caused by a virus. And more especially, whether or not the DNA viruses like the adenal viruses, human adenal virus, and SV40 is a DNA virus. Viruses which are not encountered in nature but specifically associated with cancer but are associated either with completely inapparent infection or very mild manifestations—could they also be responsible for human cancer. So, I decided that that's the field that I wanted to get into. And I got into it in 1962 but with the idea that ultimately, ultimately I would try to study in model systems, try to find ways of getting indirectly
to the human problem. Well, I have I wandered around a good bit. First there was an attempt to determine whether or not it would be possible to really find the code for transformation in the DNA of virus transformed tumors because there was already the experience with polyomide I mentioned only adenoviruses because that was also in humans but polyomide came first. A virus in mice that didn't cause any disease yet was able experimentally to cause such extraordinary malignancies and already work you know, it was beginning to pick up tremendous momentum, many, many people were coming into the field. And there was already an indication that there were polyoma viruses. Polyoma virus induced cancers in hampsters in which you couldn't isolate the virus, and one of the first things we attempted that failed was to see whether or not DNA extracted from such cancers, virus free cancers would be able to transform normal hampster cells. It was a lot of work but it was a blind alley. There were many blind alleys.

I decided to work with SV40 tumors. Dr. Koff was associated with me in this and we carried out many studies that I don't want to go into details but it was primarily in order to determine whether or not in tumors it seemed to that were originally induced. You knew they were induced by one of these DNA viruses, polyomide, SV40. And where the virus had disappeared. Presumably leaving no fingerprints. What were the means of finding such fingerprints. Was it a perfect crime. In other words was it a completely hit and run thing where the criminal gets away and you have no way of tracing it. So there was a lot of work involved on the nature of so called cancer antigen, tumor
specific, tumor antigen that was produced. And the response to that tumor antigen. And then what was the source of the code for the tumor antigen. Was it merely the expression of information that the normal cell already had or could it be shown that the virus was responsible for virus DNA, the virus inheritable material itself was responsible for it. And also there were studies originally with tumors in which the tumor cells only occasionally gave off a little bit of infectious virus. Something that was very similar to a lysargony in bacteria farge in which the bacteria farge transforms a bacterium and it retains the information of the original farge, that is the genetic information. Occasionally it gives off spontaneously a little bit of farge but mostly not. And therefore it is called lysogenic. And under certain conditions of stimulation, X-ray, ultra violet radiation and other things you can sort of bring the virus genetic material back to synthesize a lot of farge. In other words the evidence was, under those conditions that the whole viral genome remained in a suppressed state. Occasionally giving off little bits of virus but being suppressed. But it was there as a complete genon, total information capable of synthesizing the whole bacteria farge. And as I was studying one line particularly of SV40 hampster tumor it seemed to exhibit all of these manifestations comparable to bacteria farge. And many experiments were done really which ultimately showed because there was a big argument going on particularly at that time between Bill Beckow and myself and others as to whether or not because Bill Beckow didn't give in till quite late. He said oh, it merely meant that
there was a little bit of the virus left over. But in view of the other manifestations that I was able to show without going into detail. It was comparable to farge, one would have to postulate that the information if it was not a contaminant was contained in each and every tumor cell even though only a trace of virus under certain conditions could be isolated. And so we carried out what I regard as perhaps the first demonstration and that has been overlooked by many of the colleagues who think that that was done in too simple a way.

The first demonstration that in an experimentally induced cancer by a DNA virus like SV40 in which the tumor cells no longer produce virus except very rarely, I was able to demonstrate that the information for producing such virus was contained in each and every cell of that tumor and not only an occasional one. And this was done by very simple technique. A simple technique was because it was a highly malignant tumor, that it was possible to produce tumor cells, tumors growing progressively, with single cells. You see there is a spectrum among experimentally produced cancers where you may need with some a million cells to give, to grow progressively. With others, 10,000 cells. It was almost a little bit like my neural virulence studies except in another way. But here I had a tumor in my hand that I got originally from Dr. Eddy at the DNIH in which I was able to show that when you diluted the thing way out to a point where you would have only one or at most two cells, and you inoculated large numbers of hamsters you would get progressively growing tumors, growing with almost every tumor cell. And then I studied the capacity of tumors that had been derived from one cell or two cells by
comparison with tumors that grew out when you put in a million or ten million cells, the capacity to give off a little bit of virus and there was no difference. And this provided for the first time that the code for the capacity to occasionally produce the little bit of virus was contained in each and every cell and this was a very important basic bit of information which was not yet available from other more sophisticated molecular biological techniques.

And then came the study of the nature of the course of events in still other lines of SV40, some which I made myself at Cincinnati with SV40 and others which I got from other laboratories because I was never one to limit myself to working with one tumor line, with one virus variant. And there was a whole number of other SV40 tumors in which you could do everything. You could stand on your head the things that I was doing, multiplication in vitro and exposure to X-ray and all sorts of tricks. You could never make them to produce any virus at all. In other words there was no evidence that they had retained any or certainly not complete genetic material but since it was possible to show that even those tumors from which you couldn't get back a little bit of virus occasionally, nevertheless had an antigen that was very specific for those tumors. It was not the same as the antigen produced by tumors induced by polyoma virus or by tumors produced by adenovirus so it was an antigen that was specific for a virus. You still couldn't be sure that it wasn't some sort of specific effect turning on the cell that the virus coated it. So the question was whether this antigen was due to virus genetic information or host genetic information.
And merely doing absorption tests was no good because it was already a pretty good, like the laws of thermodynamics, a pretty good law, that many genes exist that aren't turned on, and they may make products under certain conditions for example in embryonic life which then they don't make any more so merely using normal tissue for absorption as a test wouldn't do.

Then of course there had to be a very careful study of the antibodies that these specific tumors produced in tumor bearing hampsters. Where there was no antibody against the virus at all but there was antibody against the specific antigen. And then of course during the course of very careful studies I also found there were certain cross reactioning antigens. There are all these complications that I won't go into now but at any rate it was possible from the work that I was doing with Koff to show that this so called specific tumor antigen which was actually produced in each and every cell. We first demonstrated it by complement fixation but others working about concurrently. You know it was like certain work in physics, where certain things come out fast, simultaneously. Others using the immuno-fluorescence technique for SV40 could actually show that each and every tumor cell had it you see. That it was in my laboratory that it was first shown, work that Culp and I did together, that it wasn't necessary for a cell to be transformed to have this antigen. That during the course of an ordinary, destructive infection of monkey cells by the SV40 virus, that early in the course of the various events that happened, there was produced a material that would react with the sera of hampsters that were carrying the non virus producing SV40
tumors but not those that were carry polyoma or adenal or others. And then by absorption test it was possible to show that this was a function of the viral genetic material and had nothing to do with transformation. That it was very specific. This then also led to a whole collection of information which was also supported by work that others were doing on polyoma and adenal viruses. That indicated that perhaps one approach to the human problem would be to find out whether or not human beings carrying certain cancers had in their serum antibodies for certain specific tumor antigens that were produced by adenal viruses. At that time we didn't yet have a system that would tell us whether or not herpes viruses were capable of producing malignancy in vitro. But adenal viruses certainly. And we organized a group, the business was a collaborative group to so called DNA collaborative group which consisted of Huebner, Melnick, myself, Lynette, to develop some sort of program in which one could test the situation in human beings. And the problem--then we set up a program to collect sera from patients with different kinds of cancers and match controls. And determine whether they had antibodies for let's say certain adenal virus, tumor antigens which could be produced, and not let's say that the controls wouldn't have because antibody was infected with herpes. There were many other model systems studies in monkeys and so on that I can't go in. I don't want to go in at this stage because they are not relevant to the ultimate direction of the work but after I had done all of this orienting work on when these antibodies are produced, under specificity of those antibodies, and what all sorts of details that may be involved, to be able to use it in
human beings I decided that since there were lots of people already working with the adenal viruses I had to choose something else. And so one of the questions that was occurring was that well, herpes simplex virus, both ordinary what was, came to be called type 1, that around the face and mouth, and the genital herpes which by that time came to be called--