In the organization of the dengue research unit, there were two basic guidelines of principals for its organization that were apparent from the beginning. One, that no satisfactory work could be done without a constant fairly large supply of human volunteers located within a relatively short distance from the laboratory. And secondly, that it was better to carry on the work in a dengue-free area within the United States—bringing the viruses to the research unit, than to bring the research unit to an area where dengue was occurring in our troops. Now it was with this in mind that the work first started in Cincinnati and then moved to the Longview State Hospital. The human volunteers in Jersey were white Americans who were serving sentences for civilian offenses at the New Jersey State Prison at Trenton. The authorities in the prison donated a hospital unit of seventeen beds which was mosquito proofed and used for housing the volunteers during the specified periods of environmentation. We had two nurses, one day, one at night. A clinical laboratory technician, who always assisted in the work at the hospital unit. The laboratory facilities at the Rockefeller Institute for medical research at Princeton was approximately fifteen miles from the hospital unit at Trenton. And, Lieutenant, later he was Captain William G. James, J-A-H-N-E-S, sanitary corps was assigned to the unit as the entomological associate.
And Lieutenant, now Captain Walter Schlessinger, of the medical corps joined the unit as a virologic associate. Several civilians technical aides were made available by the Rockefeller Institute. Now this association with the Rockefeller is a bridge, not only of myself, but Jahynes had worked with the yellow fever group from the Rockefeller Foundation and was trained as an entomologist. Dr. Schlessinger had worked with my former mentor, Dr. Oletsky. at the Rockefeller. So we had this unit. Now, the interesting thing. Of course there were many things that helped. It wasn't all that simple. But the fact that one of the pioneers of dengue research was General James S. Simmons who happened to be chief of preventive medicine service in a certain general's office--certainly didn't hurt because he was extraordinarily interested after all the years of important study on this disease that he had done about ten years earlier in the Phillipines. Suddenly, and certainly made it a lot easier to get things moving through. He was very anxious to see that we had all the help that we needed.

Now, when we started to work at the Rockefeller, we were getting serum transported to us in dry ice from overseas. I have already mentioned I think that first strain of virus that we isolated was from Hawaii, at Longview State Hospital. But subsequently, interesting problems arose in the field which created problems of identity of the
infectious diseases that were occurring in New Guinea, in Australia all the way down in the Pacific because there were fevers there—many fevers which did not have the typical clinical course of dengue. Some of them lasted one or two days. They didn't have rash. And all sorts of questions arose as to what they were. And they were sent to us. And when we inoculated sera from patients with such atypical fevers, into volunteers in Trenton, Americans who had never been out of the country, these sera reproduced typical dengue. And so we isolated several different strains from New Guinea. A strain is an isolate from a single patient who had a certain clinical disease. Now the question arose, why was it and what was the significance of the fact that in New Guinea the patient had a disease of only twenty-four, forty eight hours without rash, and when we inoculated it into volunteers, we get the typical disease five, seven days with rash of different kinds, and so on. Well, the possibility was considered that maybe it was, maybe it wasn't dengue. But that was done by Waters. So, one had to establish first of all that it was transmitted by *Aedes aegypti* mosquitoes. Of course we had a big insectory at the Rockefeller Institute at Princeton. Captain Jahynes was maintaining this, and we proved that this was indeed transmitted. That it had all the properties of dengue. And then, however, we began to study as we did in others, other volunteers, the resistance to reinfection. And we found that although
volunteers who had been infected with the Hawaii strain were resistant to dengue. That if somebody had Hawaii first, and at the time when he was completely resistant to it, if we gave him one of the New Guinea strains, he was not resistant. And it depended pretty much what the interval was between his infection with the Hawaii strain and the other strains as to what kind of clinical manifestations he would have. If the interval was long enough, he could get it completely. So we realized that there were different immunological strains, types of dengue which could be either documented in full. And furthermore, the question also then came up whether those peculiar manifestations in the field were due a) to previous exposure to real dengue and then reinfection, getting a modified disease. And also, the possibility that because by then we were already thinking of a relationship between yellow fever and dengue whether the immunization that all American troops had gotten the yellow fever vaccine could somehow modify the course of events on natural exposure to dengue.

Well, this isn't something you can study in the field very well. So, we had to set up experiments in which we vaccinated volunteers with yellow fever—as they were in the army. I got the yellow fever vaccine from Dr. Max Tyler, in New York. And, then a different intervals, challenged them with dengue. That means inoculated them with dengue. And we found that within a week after getting
yellow fever vaccine, there was indeed interference, so that you did not get the typical dengue. And this was entirely during the period when yellow fever vaccine apparently was multiplying in the body. Then it interfered with the multiplication of dengue virus and could give rise to a three day fever without rash. Or in other words, modified. But after seven days, when antibodies for yellow fever appeared, and it stopped multiplying, then there was no resistance whatsoever. Typical dengue appeared. Which made it clear that what we were seeing in the field apparently was not so much related to yellow fever vaccination because they didn't get it weeks before. But it was probably interference or partial immunity from immunologically different types of dengue.

Well this then of course led to a whole series of other studies on immunity. We tried to find a host. We tried eggs of course. We didn't get anywhere. But we had our first success in adaptation in young mice. You see, yellow fever grows very easily in mice. Very virulent or otherwise. That is the basis of the vaccine. But dengue did not. But we finally got dengue adapted to mice.

Q What was the initial difficulty? Why didn't it go?
A Well, because when it--when something doesn't grow initially, something you must understand the population of genetics, in viruses. Not all viruses particles have the same capacity to multiply in certain cells. So when you have
a population of virus particles or infectious doses, let us say ten million or so. And you put them in a host for which the majority of the virus particles don't have a capacity to multiply, you may get nothing. But let us say one mouse may come down. And then it has to be a young one. Because in the older ones it didn't go very well. Then you take that mouse, it takes a long time before let's say it shows any manifestations, and you pass that, and what you do is enrich because you can get some multiplication which will not be pathogenic and some of the virus particles that are. So that gradually as you pass, you eliminate the slower-multiplying non-pathogenic virus particles for the mouse, and you pick out the pathogenic ones so that after a number of passages, that is called—their's called—that's the adaptation process. Actually the selection of the virus particles with the capacity of the most rapid multiplication in the brain of mice, and then you have a virus which will multiply more rapidly.

Well, in carrying out such studies, we also then carried out to determine what was happening to the virus in relation to virulence for man. And we showed that as we selected out the virus particles that were most virulent for the mouse, it lost pathogenicity for man. That was the first vaccine you see. This—

Q Alright, so you adapted the virus to mice. And then the same thing that happens in yellow fever, you get a mutant.
We don't get a mutant. We select out the virus particle which has properties that prevent it from multiplying in let us say not prevent it from multiplying. It multiplies, but it produces a basically inapparent infection although at different stages, it was still pathogenic. You see, during early passages. But as we went beyond a certain number of passages, it lost its capacity to produce disease but it still immunized against the challenge of the original human virulent virus. And then of course we had to do many studies with mosquitoes to make sure that a vaccinated--what would mosquitoes do if they fed on a vaccinated individual at different times. Would they pick up virus which on, when put on human beings who were completely susceptible, would they pick up virus that would change in them and become virulent. It would be a danger. I mean there were many many questions that had to be investigated, and were investigated. And it was this that led to the ultimate tests on a vaccine for dengue that were carried out again in time before the staging of large numbers of Americans in the Phillipines. Because we were afraid that what would happen is that when we began to move the armed forces after the war was finished, in Europe, and began to move in on the Phillipines, and MacArthur came back and took back the Phillipines, that we would get dengue epidemics. And therefore, I had prepared with the help of
then commercial company after I worked things out. I don't know, it was a million doses or something like that. Again, from mouse brain vaccine. Of course, these studies were carried out in monkeys. It is a long story. If I were to tell the whole story of dengue--

Q I shutter when you say it's a long story and then you don't tell it.

A Each of these is enough for a book. So let me hit some of the high spots. Let me—some of the high spots before we get into the problem of dengue vaccination, and the establishment of new tests by which you could make a diagnosis of dengue without having to inoculate a human beings. Well one of the things obviously we were interested in would be to see whether we could see the virus of dengue under the electron microscope. Because the electron microscophy was not yet developed at the time which was '44, and '45. But Dr. Wendell Stanley at the Rockefeller Institute at Princeton had an electro microscope in which he did some very basic studies on tobacco mosaic and he offered very kindly to have a look at concentrates prepared from the serum of volunteers in which the virus was present in a concentration of ten million infectious doses for a cubic formula. Well we saw infectious experiments on some very extraordinary bodies, and I don't remember the details now but I think we had some serum from the same volunteers before they were infected.
At any rate, there came out most unusual structures. Many of them were dumb bell shaped, elongated bodies, with a diameter of about forty millimicrons or so. And this was much bigger than the size of the virus as we measured it by passage through membranes which were used for measuring the size of the virus. Of course another reason for using those membranes very early was to make sure we didn't have a mixed trachetzial infection there that--because of homorrhage, the petecii bothered us.

Now, the question was whether to pursue this very interesting observation by finding out whether other persons with fever might have similar structures within them, we couldn't absolutely say that the structures we saw from these was necessarily the dengue virus. Nor did we undertake very careful studies in time relationships. Because there were other priorities. But in the light of findings in the last few years with the hepatitis b virus and the so called Australia antigen part of it, which is part of the hepatitis b virus. And the kind of pictures we would get from electron microscope with that, I have a feeling that what we saw was not dengue virus. That we saw in effect, probably hepatitis b virus that was contaminated. But that is one aspect of the story.

Another very interesting serendipity discovery that came out of this work with volunteers in the work at Princeton was connected with the attempt to determine the role of yellow
fever vaccine in possible protection and modification of dengue. As I said before, I received a vaccine from Dr. Max Tyler which produced in New York, at the Rockefeller Foundation was the only group producing yellow fever vaccine for the army at that time. And although Dr. Tyler told me that just before he sent me the vaccine, that it was potent vaccine, as a matter of routine I out of the same vials that I used for inoculating the human volunteers, I wanted to test the potency of it and so I inoculated and titrated it in mice, white mice. From the Princeton breeding colony. This is the way you tighten the potency of yellow fever vaccine. You determine the smallest amount that will produce a fatal encephalitic death in mice. And lo and behold none of the mice—those inoculated with the larger quantity undiluted vaccine or any of the—none of the mice showed anything. And I called up Max Tyler, I said Max, for heavens sake, I relied on you. I inoculated this yellow fever vaccine into human volunteers, and I very carefully screened and set up for a whole series of experiments, and the mice I inoculated here at Princeton don't show anything at all. You sent me an inactive vaccine, it got inactivated somehow, and you spoiled now, Max, how could you do this to me? Max Tyler says, Albert, you know me well enough how I operate. On the day that I sent you this live flies vaccine I took an alequot and ampule, and I resuspended it and titrated in mice here. It had the full potency. So since I had
the greatest respect and admiration for Max Tyler, whom as you know, I subsequently nominated for the Nobel Prize, I thought there was something fishy here. And I began to look into the history of the mice I was using at the Rockefeller Institute at Princeton. Now there were already some observations years before that when yellow fever virus as the original virulent virus that is also a very active in mice, it isn't just that—it is only the vaccine strain that infectious for mice. That when such tests were done in different breeds of mice in Webster's had done some. There was great irregularity. There was not an all or none effect as here. There was irregularity. Some mice were more susceptible than others. Some showed some resistance, but when you took his particular breeds of mice, and you know Webster was doing work on genetics of mice in relations to resistance to bacteria in the virus.

So I thought, let me see what the story of the mice at the Rockefeller Institute, to Princeton. I said are these the same mice you are—that are being used at the Rockefeller Institute in New York? Oh, yes, they are swiss mice. But they said, we started our own breeding colony about twenty some odd years ago. And we use only the mice that have been inbred here. They come from the same swiss variety as those at the Rockefeller Institute, but we have been inbreeding them. So I said to myself, is it possible that this inbreeding for twenty years has produced a variety of mice that might
be different from--. I went to the Rockefeller Institute in New York. I said Max let me have some, the same swiss mice you used here. I am going to take them back with me to Princeton. And I took an alequet of the vaccine that I used, yellow fever vaccine to inoculate the human volunteers, and inoculated swiss mice from the Rockefeller Institute at New York and the swiss mice that were outbred for twenty some odd years at Princeton. They were both swiss mice. And loaand behold, in this controlled experiment, Max Tyler was right. And I was wrong. The Princeton mice didn't come down in the second experiment, and all the Rockefeller swiss mice came down. But furthermore they came down in a most extraordinary way. It was a hundred percent. A hundred percent resistant in the Princeton mice, a hundred percent susceptible in the swiss mice. Well this was a terrific thing. I had no time to get into the genetics of it except that I established this, and then later when I returned to Cincinnati, it started me off on a line of study on the inheritance of resistance to certain viruses. And I was able for the first time to do a typical mendellian experiment, in which I bred Princeton swiss mice with Rockefeller Institute swiss mice, and got the equeine generation, and then back crossing and they had two generations, and I found that the inheritance followed a typical Mendellian formula for inheritance determined by a single gene.
And this became the basis of a new line of studies that I carried out because it was never possible to do it that way before. Because there were never mice 100% susceptible and 100% resistant. And then it turned out that the factor, that the gene that was responsible for this resistance was the gene that controlled viral multiplication. It held it down. That the mice in which which showed no signs of illness at all, the Princeton mice, nevertheless seemed inoculated those that were inoculated with the smallest amount of yellow fever vaccine developed antibodies for yellow fever. And then when I determined, when I did experiments to determine the level of multiplication, I found that while in the swiss mice, they multiplied let us say to a level of at ten million. But in the Princeton mice it also multiplied, and way down, inoculated in the smallest amount, but it never got above 100 or 1000. So that the differential was 10/thousandth, 100/thousandth times less multiplication in the resistant mice. So the gene for resistance was a multiplication controlling gene, to prove it more, we went on with transplanting tumors. That was the story of my research later on. But then since yellow fever is related to a number of other viruses, in a group relationship like dengue, Russian spring summer encephalitis I was able to show that the mice that were resistant to yellow fever also had a resistance to dengue, to Russian
spring summer, they were not resistant to others. In other words, that this gene was very specific for a certain group of viruses. And this was actually the study on the genetics, the mechanism of inheritance of resistance was the report that I gave after my election to the National Academy of Sciences in 1951 I think it was. Well, this was a side issue of this, a serendipity out of these studies at Princeton. There were a number of other things. Of course we did many mosquito studies because one of the questions was out of the many species in New Jersey, and New Jersey was well known, is still well known for its mosquitoes, biting mosquitoes. We tested them and in our volunteers. Because first it was an absolute necessity to make sure whether by chance a mosquito getting into our ward could get out and then infect somebody and then start an epidemic. Well, we proved that none of these Jersey mosquitoes could transmit dengue.

Q Did you find any other transmitters besides alapictus, and--

A No. At the present time, this is still basically a Haiti egypti, Haiti alapictus. I think there is some related species in the Pacific. But all of these studies, and the studies on immunity and resistance and properties of the virus and so on were a prelude to the post-war story that we heard about dengue and what happened in Japan. And I don't think we have time for that but that is a story
that has to be told.

Q Oh, yes. Well we will next--

A In Japan. Let me just put down for the record here before we stop that Japan had epidemics of dengue in its population affecting several million. And this became the study

Q We will take up the study. One last thing before we leave, when I look at these mission-oriented studies, one of the things that I find absolutely amazing is literally the amount of time to find solution to a problem. Within a year all of these studies are done.

A Well it wasn't within a year. It was a little longer.

Q Well, let us say fifteen months. But still a very short period of time for that kind of productivity. And as a matter of fact, you must admit that if one looks through the literature, one finds that you really didn't publish much on these dengue studies.

A If I were to publish this in detail, I would have five monographs, and I didn't have the time. I published the basic factors because if I had stopped to publish in detail everything we were doing, I wouldn't have time to do the work. So I had to make the choice. Was I in the business to write papers, and increase my bibliography, or was I in the business to do work. Urgent work. And when the war was over, it was a question of preparing vaccines and going on. You see, so that actually I put productivity
ahead of paper writing. And then, when the war was over, and I went back to polio and went back to all sorts of other studies, I never had the time to write up completely, the same thing that you just mentioned on my dengue work, is true of my polio work.

If I would have written up in detail all the stuff I did in polio I would have six monographs. Which I could still do if I would take the time out to do it. But I didn't.

Q Alright. Now, the rapidity of the work is the thing that I find interesting.
A Concentration of effort, my friend.
Q Is that just in concentration?
A Yes sir.
Q of effort?
A Concentration of effort. Not working on a thousand things at one time. For example, I could have very easily gone off on studying this fascinating phenomenon of genetic resistance to virus, but I postponed it. I said that is not my major problem now. And of course I also had problems holding Schlessinger back from doing all sorts of little side things he was working with me. He was a good worker. Keep your eye on the ball. What is our mission. Our mission is to find a way if at all possible to have a vaccine ready in time to protect American troops when they begin to move and operate in dengue infested areas. That
was mission number one. And therefore, immunologic relationships were essential. Adaptation modifications were essential. The danger in the potential transmission by mosquitoes of persons receiving the vaccine and not showing signs of disease was essential. And there were all sorts of setting priorities. This is a disciplined way of working, which unfortunately most of—majority of scientists do not work in a disciplined way in relation to an objective they set for themselves. They are—there is a little too much philandering. Let me say.

Q It is the wrong word for this kind of—
A The wrong word. But it is philandering
Q Okay, I think—
A As you look at the mistress on the side, you think she will be better. So you go off with her.
Q Well, at any rate, this is really very good. I like that. I will stop here.

END OF TAPE.