Interview with Dr. Pittman in her office at the National Institutes of Health.

December 8, 1988

Interviewer: Dr. Victoria Harden, Director, Office of NIH History

Background: The daughter of a physician in Prairie Grove, Arkansas, Dr. Pittman was born in 1901. She excelled in mathematics and biology at Hendrix College, a Methodist institution in Conway, Arkansas. After serving for two years as teacher and principal in the academy of a girls' college, she enrolled in the University of Chicago, where she obtained M.S. (1926) and Ph.D. (1929) degrees in bacteriology. Because of the interest in medicine sparked by working with her father, she also took available courses in immunology and a minor in pathology along with the medical students. In 1928 she accepted a position at the Rockefeller Institute of Medical Research in New York City (now Rockefeller University) to work with Dr. Rufus Cole, Director of the hospital. There she addressed the question, "Does *Haemophilus influenzae* cause influenza?" Her focus changed, however, when she found two strains of the organism that were encapsulated--a "first" demonstration that earned her international respect before she was thirty years old. Four other capulsular types were identified, but it was type "b" that caused highly fatal meningitis in young children. Preparation of the first type specific *H. influenzae* antiserum for therapy led her into life-long work on the control of biologics, largely bacterial antisera and vaccines. In 1936 she came to NIH and remained on the staff until retirement from the Division of Biologics Standards in 1971. Since that time, she has been a Guest Worker in the Division.

Harden: What impressed you most when you first began work at the NIH?

Pittman: I was much impressed by the number of studies that were directly applicable to public health. There was a great deal of collaboration. I worked with Drs. F. J. Daft, H. F. Frazier, and W. H. Sebrell (later a Director of NIH). They were interested in nutrition. We treated dogs with severe black tongue (a disease in dogs equivalent to pellagra in humans) with codehydrogenase, a growth requirement of *H. influenzae*.

Harden: Who were some of the other people here at that time?

Pittman: Edward Francis, who worked on tularemia, Rolla Dyer, who became director of NIH. Trendley Dean was also just beginning to work on fluoride prevention of dental caries. There were three pioneer women microbiologists before I came. Ida Bengtson was the first. She did beautiful work on standardization of gas gangrene antitoxins for the League of Nations. Alice C. Evans was famous for her work on brucellosis. I worked with Sara E. Branham, who had been one of my teachers at the University of Chicago, in the development of a potency assay for antimeningococcus serum.

Harden: You arrived shortly before Dr. George W. McCoy retired as NIH Director. Could you comment on his work?

Pittman: It impressed me that Dr. McCoy did all inspections of licensed manufacturers of biologics personally. Of course, there were not so many then. You see, all the

establishments producing biologics had to be inspected each year. Dr. McCoy assumed responsibility for all the inspections personally.

Harden: And for the inspection, he had to go out there personally and take samples?

Pittman: He didn't bring in many samples. We didn't have many ways of testing these products at that time. He looked for cleanliness in production facilities.

Harden: The things that had to be tested were the purity and potency of the products, right?

Pittman: Well, we didn't have much potency testing. That was something we had to develop.

Harden: You were involved in introducing the Reed-Münch test, the first statistical method in biologics testing.

Pittman: Yes.

Harden: Explain to me what had been done before and why this was an important advance because it obviously was.

Pittman: As far as I recollect, at the time, quantitative tests were not being done. But when we tried to get a standard value for antimeningococcal serum, we had no method to establish a minimum lethal dose. So I used the plain Reed-Münch method which was a quick way of calculating, and so it was the first test that was introduced for the evaluation of the potency of products.

Harden: And, of course, I presume it expanded rapidly.

Pittman: Well, there were not so many products.

Harden: At the end of the 'thirties and during the early 'forties, NIH moved to Bethesda from downtown D.C.

Pittman: Yes. We moved out in the spring of '41, the last ones to come out. In Bethesda, the Divisions with larger staffs were located in separate buildings. Since people were separated, there was a decrease in intellectual cross-fertilization.

Harden: At about the same time, World War II started. How was your work redirected toward wartime problems?

Pittman: It was directed largely to the safety and purity of plasma and whole blood for the armed services. I will speak about the plasma first. We had no requirement for pyrogen testing although pyrogenicity of plasma had been observed back in the twenties. And the armed services were having a great deal of difficulty with fever following administration of plasma. Now the problem was that the plasma had to contain the plasma of not less than a thousand people in order to counteract the blood grouping substances. It was initially stored in the refrigerator, then filtered. Then, when it was administered to a patient, the patient would sometimes go into a severe febrile shock. I was called in, and I made an inspection in one of the establishments trying to locate the source of the contamination. I came back with about fifty contaminants. I was asked to work with Mr. Thomas Probey, Chief of the Section on Pharmacology, to determine how many bacteria can be in plasma before it is filtered to ensure that it wouldn't cause fever. And so we developed a rabbit assay for presence of pyrogens and tested the pyrogenicity of different concentrations of representative contaminants that I brought back from this establishment. We found that there could not be more than 5,000 organisms per

ml before the material was filtered. You see, they had been filtering and the organisms had been removed, but the pyrogen was still there.

Whole blood reactions likewise were caused by bacteria that grew during refrigerator storage. In other cases, the unit of blood was contaminated with air bacteria by withdrawing a sample for sterility testing. This led to the requirement that a sample of blood in a test tube be attached to the blood container. This sample is used to test for sterility, blood group, hepatitis, and now for AIDS. The blood container is never entered for a sample.

The failure of some contaminants to grow at 37° C. prompted the requirement that the sterility test be incubated at two temperatures. After a study of each ingredient in the sterility test medium, the formula was revised and has remained unchanged in the U.S.A. and internationally.

During these studies there was excellent cooperation with the manufacturers of biologics. The manufacturers were interested in the development of standards from a public health standpoint. We had very close cooperation with them until the lawyers took over. No, I take that back. Don't say lawyers--let's say management. Management made their yearly inventory and they did not want to carry things on. They wanted to cut down the inventory. And that is one change that took place. They were trying to make money instead of putting an emphasis was on public health. There was a big change here.

Harden: How did you get into pertussis research?

Pittman: In 1943, Dr. Milton Veldee, director of the Biologics Control Laboratory, handed me a small piece of paper, handwritten because we had only one secretary: "Develop a standard of potency for pertussis vaccine," it said. Others who had tried to develop a potency assay for pertussis had failed. Dr. Pearl Kendrick and Dr. Grace Eldering in the Michigan Department of Health Laboratories had successfully pioneered the development of a pertussis vaccine that provided significant protection against whooping cough. But even they had failed to develop a potency assay.

About this time, Dr. John Foote Norton, one of my professors at the University of Chicago who was then at Upjohn Company, and Dr. John Dingle were working on a potency assay for typhoid vaccine. They tried intracerebral (IC) challenge of mice. Dr. Norton observed that pertussis vaccinated mice were protected against lethal IC challenge with *Bordetella pertussis*. He reported this observation to Dr. Kendrick and me. At that time the dose of vaccine was expressed in millions of bacteria. We developed an opacity standard; then we exchanged information during the development of an IC challenge potency assay. U.S. Requirements for Pertussis Vaccine were prescribed in 1949. Potency of the bacteria was determined relative to the bacteria in a reference vaccine. In 1953 the U.S. promulgated a standard of 12 units per total immunizing dose. This requirement became the basis of the international potency requirement of the World Health Organization.

Harden: Pertussis vaccine, of course, has a greater number of toxic side-effects than some other vaccines. When did you become involved in studying the pertussis toxin?

Pittman: From the beginning, I was concerned about the toxicity of pertussis vaccine. A mouse test was specified in the first Requirements in 1949. Eventually, at least four toxins were described. But it was not until I was a guest scientist at the University of Glasgow in 1976 that it suddenly came to me that pertussis had a true exotoxin, like diphtheria or cholera toxin, that caused the harmful effects and the prolonged immunity of whooping cough. I was supposed to give a lecture at an epidemiological meeting on a very peculiar subject: "What were the specific antigens of the bacteria that you worked with?" Well, the pneumococcus has a capsule. *Hemophilus influenzae* has a capsule; meningicoccus, tetanus, diphthera, cholera have toxins. What was the specific added enzyme of pertussis vaccine? And I walked the floor. Suddenly, it hit me: we are dealing with a true toxin. But no one paid any attention. I was invited to present to laboratories in London that were paying the expenses for my animals' testing, but they were not interested in the pertussis vaccine. There was also a workshop here at NIH on pertussis and I got up and indicated that the pertussis had a toxin like that of cholera. The chairman said they were not interested in cholera, and I sat down. So I had presented the idea three times but no one had heard it.

But then, at the Third International Symposium on Pertussis Vaccine in '78, I asked Dr. Perkins [Frank T. Perkins, Ph.D.] if I could present the subject during the discussion and he gave me permission. I had my slides ready and when

I presented it, Dr. Emil C. Gottschlick was sitting next to John Robbins [John B. Robbins, M.D.] and said: "That is it. It is a toxin." And that was the first thing Dr. Robbins mentioned when he gave a summary of the Symposium. Then I published the paper about this, which was already in press at that time. It had been delayed because the *Journal of Infectious Diseases* wanted to put it in the first volume of the *Review of Infectious Diseases.* It came out in 1979. I ordered 200 reprints and they went like hotcakes. I ordered 200 more. I don't have a single copy left. So many requests came from all over the world. Reprints of the paper then in press went like hotcakes. I don't have a single copy left. You see, the mind has to be prepared to receive a new idea. It is satisfying to have changed the direction of work on pertussis vaccine.

Harden: When people tell you "It's not important; we're not interested in it," how do you keep the faith, and keep saying it until somebody is prepared to hear it?

Pittman: I knew it was true, and the paper was already in press at that time. Pertussis fitted all the definitions and requirements for a toxin. The same year my paper was published, a paper from Japan and showed that the pertussis toxin was of two parts: Two molecules--The active and the binding part, an A and a B part.

Harden: Would you talk a bit about your involvement with the Southeast Asia Treaty Organization (SEATO) cholera project?

Pittman: Yes. Dr. Joseph Smadel, an eminent research scientist, after serving four years as Associated Director of NIH, elected to come to the Division of Biologics Standards. SEATO had effected an improvement in smallpox vaccine and wanted

to do something else beneficial for the health of the people of Southeast Asia. They decided to focus on cholera and selected Dacca as the target city. It was in East Pakistan at that time, which is now Bangladesh. Dr. John C. Feeley and I were brought in to help design the laboratories and equipment in the Pakistan-SEATO Cholera Research Laboratory, a Public Health Service building that had already been built in Dacca but not occupied. Another laboratory was established, first in a tent, at the bazaar Matlab, East Pakistan, which is accessible only by boat.

NIH was in charge of the funds from SEATO and other sources. Dr. Smaldel, of course, was the power behind the study. The study was to cover the total field of cholera--from epidemiology to clinical. And they had many beds for bringing in cholera patients to observe. It really was the most extensive study of an infectious disease up to that time. I put Dr. Feeley on the project. He attended the first meeting that was held. This was just about that time an epidemic of the El Tor strain of cholera started. And I worked closely with Dr. Feeley but he was actually out of the country when I carried out the first test in the El Tor study that we did. Together, Dr. Feeley and I developed standards for cholera vaccine.

The high fatality of cholera is due to very rapid loss of fluid. The most important thing to come out of this project was the studies that verified the value of IV restorative fluid in treating cholera. This was the culmination of Dr. Robert A. Phillips's work of many years on. And later, with cooperation of others, oral

rehydration therapy, an oral formula for fluid with ingredients that are available in developing countries. It is now used worldwide for all kinds of dysenteries.

The SEATO Cholera Research Laboratory has been succeeded by the International Centre for Diarrheal Disease Research in Bangladesh.

Harden: I have seen Dr. John Seal's history of the program [W. E. van Heyningen and John R. Seal, *Cholera: The American Scientific Experience, 1947-1980*. Westview Press, 1983].

Pittman: There are some things lacking in that book, but that always happens. Dr. Smadel was really the director or the work. He was so nice to work with. He liked people.

Harden: He was quite a colorful character and appears in a lot of different NIH history stories people have told me. I first ran across him when he was working on rickettsial diseases when he was still at Walter Reed.

Pittman: Yes. Then he died in '65. I was asked to take over as Project Officer--as the Director--but I refused it at first. I did become Project Officer but John Seal was working and I didn't have too much to do. He was the director after that--from the NIH standpoint, Imean. We had to keep track of all the money. I got all the monthly reports, approved the budget, and things like that.

Harden: Since you retired, the honors have been heaped upon you, and as they say, you have slowed down to forty hours a week, only forty hours a week. I want you to make a broad sweep and speculate for me now. You've been associated with NIH for more than fifty years now.

Pittman: Fifty-two years in January.

Harden: This gives you the right, I think, to look back and make some evaluations. How have things changed, and what has being associated with NIH meant to you?

What do you think the contribution of the place is to the United States, to the world?

Pittman: Well, of course, I've seen a tremendous change and an expansion of programs. NIH has been and still is a leader in medical research throughout the world. Many countries have benefitted. Of course, smallpox has now come under control. It was pioneer work here that made that possible because we developed standards of potency for the vaccine. It was one of the first products that ever licensed. There was a lot a work here in regard to evaluation of contamination and then the evaluation of the potency of the material and also the drying of the products which made it possible for these worldwide controls.

Harden: For you as a person, how would you judge spending your career at a government institution, doing what you have done, with, say, some of your contemporaries in academia or elsewhere?

Pittman: I think it was a golden opportunity. I felt I was being able to obtain the best information about the control of biologic products, and it was very exciting and challenging to see the improvement in a product--even for the people who considered the things they did on the sterility tests mundane. But all these links that make the whole. Who ever thought of a test to be that tested for sterility? I was on the U.S. Pharmacopaeia Committee in regard to sterility testing and methods of sterilization. I learned a lot. I think one of the most important things I learned was that in sterilization, if they start with super steam, it doesn't sterilize as well as if you start and work up to steam. Some of the participants on the committee tested for us. We had spores form--spores that are indicators of insterility. Some found that spores would be killed in their autoclave in about a minute and in another autoclave it was about thirty minutes. And those were where they used the super steam. So that added to the requirements and

regulation--general regulations--manufacturers' regulations. And it was these little details that interested me, how they affected manufacturing to produce sterile products.

Harden: Certainly, it has always been an intellectual challenge.

Pittman: Oh, definitely. And the need to see something worked out and applied. There were very great satisfactions from that.

Harden: Do you care to make any comments on how the people have changed over the years? What do you see in young people coming to NIH today compared to years ago?

Pittman: I may not be in a position to judge, but this is my impression. Today, there is a greater interest in self-promotion than in public health and its application. Now, this may be due to pressure from universities that scientists publish or perish. And so many people--a dozen or more people--may have their names on a paper; they could not all possibly have had the heart of the problem at interest. Not all of them. We were so small that we were responsible for everything that happened. I think the attitude of young people today is different. It is to make a name for themselves. And I'm afraid that's being shown in the fraud cases that are coming out, being reported in *Science* now.

Harden: Do you think there is more fraud now than there used to be?

Pittman: Well, I don't know. But, there's something wrong. Ethical standards have changed.

Harden: At least for some people.

Pittman: Yes. And I think there are too many people, and, dare I say, too many grants.

Harden: That's a very interesting point. Where there is money, there will be more people involved. There wasn't so much money before the NIH grants program expanded. There was a smaller group of investigators.

Pittman: It was a smaller group and they had to succeed in their work.

Harden: Is there anything else you would like to say before we end this interview?

Pittman: Since I've retired, I've had a most interesting and satisfying time, making contacts with international laboratories. There have been some publications that have come out of that, especially the work that was done with the University of Glasgow. I introduced some work that changed the direction of the work on pertussis vaccine. And in a number of instances--one of my greatest pleasures has been of stimulating other people to do projects. That is the most satisfying when new people come into the work. In fact, just the other day, Dr. Rita Caldwell [Rita R. Caldwell, Ph.D.] said, "Why, you were my model." I didn't know that.

Harden: It's surprising sometimes to feel you are indeed the role model.

Pittman: Well, there were so many people who came to me in my later years before I retired. There was Dr. David Smith [David H. Smith, M.D.], who founded Praxis Biologics when it seemed like the older laboratories didn't have the "umph" to go on. He developed the *H. influenzae* type B (Hib) polysaccharide vaccine to protect children age two and older against Hib infection. And another was Dr. Marcello Gottshalk, who came to me when he came from Austria working on the meningococcus. And Dr. Rita Caldwell came when she first came to Washington for advice on "What organisms should I work on?" And I said, "Well, cholera right now is a hot subject." That led her into all that work that she's done on the Chesapeake Bay, as she was saying the other day. These are the things from which I get the most pleasure--stimulating people, talking about their problems. I used to call myself "Miss Information"—you can term it "Ms" if you want to. Somehow, people knew my name. I would have so many requests for information.

Harden: Thank you very much, Dr. Pittman, for talking with me.