

This is an interview with Dr. Robert Anacker on October 26, 1984 at the Rocky Mountain Laboratory. The interviewer is Victoria Harden.

Harden: Dr. Anacker, will you begin by giving us some background information on yourself and tell us how you came to be at the RML?

Anacker: I was born in Minneapolis, Minnesota Sept 7, 1926. My father was in construction work so I did considerable moving around in my early years and I wound up in Montana in 1936 as a consequence of the earthquake in Helena and the reconstruction that was necessary at that time.

I attended the seventh and eight grade in Helena and a year of high school at Billings. I also had a year of high school at Butte Montana. At the outbreak of World War II, my father found employment in Iowa, so my third year of high school was spent in Iowa. The fourth year was back in Bozeman, Montana, and then we moved to the state of Washington. I entered the University of Washington in the fall of 1943, attended one semester, worked for awhile at Boeing Aircraft Company, and then entered military service.

I returned to school in September 1946 at the University of Washington, matriculating in forestry. I had always had an interest in biology and in science. This [forestry] seemed to fit in with those interests; however, after a year I felt this wasn't exactly suitable for me, so I switched to microbiology, and I have been in that field ever since. I received my Bachelor's degree at the University of Washington in March 1951. A friend of mine graduated in microbiology the previous December

and had found employment at the Rocky Mountain Laboratory. He wrote glowing letters to me and said there was an opening for a professional assistant with the new doctor, Charles Shepard.

Harden: Who was this friend?

Anacker: Dan Ritter. He got his degree in microbiology just a quarter before I did. He came in December. He liked the laboratory very much; he liked the environment very much; and, in fact, he found a girl he liked very much, and he was married in the first year that he was here to a fellow employee, Sally Stevens. His glowing letters plus the fact that I lived previously in Montana and had liked the area very much prompted me to apply for the position which I then received.

I came in March 1951 and remained here for a year and a half, working with Dr. Shepard and in part with Dr. Edgar Ribi. Dr. Ribi was a visiting scientist, at the time, from Switzerland.

I returned to graduate school [at the University of Washington] in September 1952 and finished my Ph.D. work in December 1956. I had hoped to come back to RML but there were no positions available at the time. I went to Kansas State College and spent approximately a year and a half there as an assistant professor. Then I became an assistant professor at the University of Montana. I worked with Dr. John Munoz in his department, doing part time research and part time teaching.

I was able to return to the RML in August 1960, and I have been here since that time. I worked with Dr. Ribi beginning in August 1960. As I mentioned earlier, Dr. Ribi, whom I first met in 1951, was a visiting scientist from Switzerland. He was permanently employed here in 1960, and was chief of the

biophysics section. He had a number of interests of the general type that I suppose would be classified under the heading "structure and function of microorganisms."

One of the projects that he had been working on, prior to my arrival, was rickettsiae. He asked me if I would like to work on rickettsiae. Since I had not worked with them before and since the laboratory was an outstanding center for rickettsial research, I decided this would be a good avenue for me to follow. I worked for the first several years on Q fever rickettsiae, following up some of the leads Dr. Ribi and associates had developed and then branched out a little bit.

We found that the protective antigen of the Q fever rickettsia resided in the cell wall of the microorganism, as one might expect. "Toxic" properties were also associated with the cell wall of the organism. The exact constituent was not identified at that time. We did determine that the phase I antigen of the rickettsiae could be extracted with trichloroacetic acid. This material, essentially polysaccharide in nature, reacted very well in a complement fixation test with serum containing phase I antibody. The trichloroacetic acid extract of the Q fever rickettsiae was not very protective compared to the cell wall.

One of Dr. Ribi's other projects was endotoxin. He had been involved for several years in attempting to determine the structure of endotoxin and that portion of the endotoxin which was responsible for endotoxicity. I assisted him in that project for several years. One of the areas in which I worked was the characterization of the substance called "native haptin."

Another of Dr. Ribí's interests at that time was tuberculosis research.

Harden: May I interrupt you before you get into a discussion of tuberculosis research? Am I correct that the Q fever rickettsia is intracellular--lives inside a cell--and produces an endotoxin that is released into the cell?

Anacker: Yes, Q fever rickettsiae are obligate intracellular parasites. Endotoxin is not a soluble product. It is firmly associated with the cell wall in microorganisms. The Q fever rickettsiae are reputed to have an endotoxin, but its activity is very different from the endotoxins that one normally studies, the endotoxins that have been characterized from organisms such as Salmonella enteritidis or Escherichia coli. The fever produced in experimental animals by this substance from Q fever rickettsiae has a very different character from that produced by known endotoxins. It does produce some fever. The material appears to be lipopolysaccharide in nature, but I think in time we will learn that these endotoxins, if they are such, will be quite different from the so called classic endotoxins.

One of Dr. Ribí's other interests was tuberculosis research. He had been collaborating with Dr. Carl Larson, the director of the RML at that time, in tuberculosis research. He asked me to join him in that project. Since tuberculosis has been a major public health problem throughout the whole world for many years, I felt that this was really a very deserving area of study. In addition, the tuberculosis organism has a number of very interesting components eliciting various immunologic reactions which are of great academic interest as well. One of Dr. Ribí's

principal goal was to develop an effective practical vaccine. This was a goal that was to elude us in the next several years.

We prepared cell walls from the the BCG strain (vaccine strain) of Mycobacterium tuberculosis. Dr. Ribi had already found that the cell walls induced protection in mice to aerosol challenge with virulent Mycobacterium tuberculosis. However, the vaccine was administered in oil and intravenously--features which could make a vaccine impractical for use in humans.

One of the projects that I worked on was to determine whether the vaccine could be administered by routes other than the intravenous one and still achieve protection. We tried subcutaneous, intramuscular, footpad and other routes and compared the results with the results obtained after intravenous immunization. Unfortunately, protection in those animals given cell walls in oil intravenously was far superior to the protection achieved when these materials were administered by other routes.

Second, we learned--this was really known before--that the lungs of animals inoculated intravenously were greatly enlarged. Dr. Bill Barclay from the University of Chicago was a frequent visitor during those years, and he embarked on a histopathologic study to characterize and quantify the granulomatous response of the lungs.

This lung enlargement was a constant companion to the intravenous immunization, and there was such gross enlargement of the lung that, certainly, this route would have been unacceptable for humans. Attempts to "detoxify" the vaccine so that the vaccine would still provide protection without changes in lung

structure were unsuccessful. We made a number of extracts of the BCG organisms, but the only kinds of preparations that protected well were those administered in oil intravenously.

We used guinea pigs, mice, and monkeys as experimental animals. There was a contract set up between RML and the Naval Biological Laboratory in Oakland, California, where the monkey experiments were carried out. In all cases these animals were challenged by the aerosol route--the route by which people are normally infected. We felt this was very important. One can demonstrate some protection by challenging by other routes, but this did not seem to be realistic.

Probably my most important contribution at this time was the finding that we could make protective vaccines from inactive extracts of the BCG organisms. Chloroform extracts and their residues, particularly after further treatment with sodium hydroxide, were not protective. When we recombined the chloroform extract of the organisms, containing substances such as Wax D, with the inactive residue, we obtained a protective combination. Perhaps Dr. Ribi will be interviewed later, if he hasn't been interviewed already, and perhaps he will say something about his use of some of these extracts of cell wall materials from tubercle bacilli and his regimen for chemotherapy of cancer in horses, and perhaps in other animals.

After we had worked approximately five years and were not making a great deal of progress towards our principal objective, I told Dr. Ribi that I wanted to return to rickettsial research. It is well known that RML has been the center for research on spotted fever rickettsiae. We are in an area where spotted fever

has been very important since white men came to the Bitterroot Valley. The mortality rate in the early 1900s approximated 80% in adult males. It was first studied here in the early 1900s by Dr. Ricketts. Spotted fever is caused by the rickettsia carried by the wood tick Dermacentor andersoni and can be transmitted in the laboratory from one experimental animal to another through an infected tick.

The vaccine was developed here. I am probably going into matters that others have already discussed, so maybe I will go on to my particular contribution or my particular areas of research.

Harden: It is certainly much easier to document this earlier period than the period from World War II to the present. I would like those of you who have been at RML for some years to tell me as much as you can about this period.

Anacker: Since World War II?

Harden: Since World War II.

Anacker: Since I came in 1951 and left in 1952 and returned in 1960, I don't have a lot of immediate experience in the early part of this period. When I was at the RML in 1951, there was a group still making typhus vaccine. I believe that this was phased out shortly after I left in 1952. A considerable amount of typhus vaccine was made at this laboratory during World War II, but I don't have direct knowledge of this.

Harden: When you came back in 1960 did you find that the lab had a different direction from when you were here the first time?

Anacker: Yes. I could say a few words about the change in direction from my particular viewpoint. Dr. Parker was the director of this laboratory from the late 1920s until 1949, the

year of his death. It is my understanding that during his tenure, most of the research conducted at the RML was focused on rickettsial research. First and foremost would have been research on Rocky Mountain spotted fever. I know that during the war, according to some of the information in the museum that used to be downstairs, there was some research being done on other rickettsial diseases. One disease in particular was scrub typhus, which is caused by Rickettsia tsutsugamushi.

A great diversification effort occurred when Dr. Carl Larson arrived, about 1950. Dr. Larson was instrumental in bringing a number of the researchers at NIH, Bethesda, to the RML. Among them was Dr. Shepard, with whom I worked first, and who had worked, at least during part of World War II, on typhus and Q fever at NIH. Others who came were Dr. William Hoyer who was interested in Brucella, Dr. Sam Salvin, who was interested in immunology and diseases caused by fungi, and Dr. Fritz Bell, who did much work with rabies. These are the ones I can think of right now.

About 1971 I started working again with rickettsiae, this time with Rickettsiae rickettsii. This was about the time that John Bell was going to retire. I received some very basic information from him about how to handle spotted fever rickettsiae. At the time I started working on this project there was not a completely satisfactory vaccine available. There was a commercial vaccine made of rickettsiae grown in eggs. The material was only partially purified so that the vaccine still contained a great deal of yolk sac material. It was my idea that

perhaps if we purified the spotted fever rickettsiae to a greater extent, we might achieve a better vaccine.

I spent some time learning how to cultivate the rickettsiae in tissue culture and yolk sacs of the embryonated egg. I applied the procedure of density gradient centrifugation to the purification of the spotted fever rickettsiae and did achieve a very pure product. We were able to analyze this product chemically, so we know the basic chemical composition of the spotted fever rickettsia.

This particular preparation was very effective in protecting mice and guinea pigs under laboratory conditions. At this time I thought possibly I had a candidate for a Rocky Mountain spotted fever vaccine for humans, and I started looking for help in getting a field trial going. I am a Ph.D., not an M.D., so I am not qualified to work with human subjects. It was necessary to get other help.

I wasn't able to enlist any help in my first attempt, and I found about the same time that a group at Ft. Detrick was involved in the same kind of research. There was a rather large group there. They had available a number of volunteers, whereas here I was working by myself. I was very happy that the Ft. Detrick group was interested in developing their product for human use. Their product was made similarly to the way I made the one here. I felt that this was a good candidate as a vaccine, so I switched to other aspects of rickettsial research at that time.

Harden: That was in the early 1970s?

Anacker: This would be about 1975-76. I think it would be pertinent to discuss some of the work of the Ft. Detrick group, because it has a bearing on what I might say later. The Ft. Detrick group first vaccinated some army personnel subcutaneously in low doses, monitored them very closely, and learned that there were not any major adverse reactions. A contract was then set up with the University of Maryland to inoculate human volunteers with the vaccine and to challenge them with a small dose of living rickettsiae. The results of this study were published in November of this past year, 1983. I believe the trial was actually started about 1980.

I probably should mention that there was another human vaccine trial in 1973. I said earlier that there was a commercial vaccine available, but it was not as effective as we would like, although I feel that it did some good. There were a number of instances in which people who had been vaccinated developed spotted fever.

There had been no direct human trials in the history of spotted fever vaccine before this time. The vaccine developed here had been administered, and Dr. Parker kept excellent records of the individuals who had been vaccinated by personnel at the RML in the first fifteen to twenty years of the vaccination program. This early vaccine was made up of ground-up infected ticks, and all the agents in the ticks were killed with formalin. Dr. Parker's records show that a few people got sick after administration of this vaccine, but their symptoms were certainly ameliorated, and there were few, if any, deaths among vaccinated individuals.

The first trial of which I am aware in which people were vaccinated and actually challenged with the organism was the trial by DuPont, et al. The results of this trial were published in 1973. They used two vaccines: 1) the yolk sac vaccine that was developed here by Dr. Herald R. Cox and commercially produced by Lederle Laboratories, and 2) the infected tick vaccine that was produced here.

I don't know the age of the tick vaccine they used. This was an important fact that was omitted from the DuPont, et al. publication. There is a very strong possibility, I think, that the tick vaccine which was administered was at least several years old at the time it was given to the vaccinees in that trial.

The results of the vaccine trial were quite disappointing, because all of the individuals who were vaccinated and then challenged developed symptoms of the disease. They were treated about twenty-four hours after the first appearance of symptoms. It's probable, I think, that the disease in these individuals would have been ameliorated, but it's really impossible to tell, because it is not desirable to allow an infection of this type to persist in humans without treatment.

Harden: Had the laboratory been producing tick vaccine through the years?

Anacker: I'm afraid I can't answer that. It had produced tick vaccine for a number of years--I would say at least fifteen years--but that vaccine was not disseminated after the commercial vaccine was produced. I think the vaccine used in the DuPont trial was at least several years old, and it may not have

provided a true test of the actual potency of a fresh vaccine. However, it was a very crude vaccine and probably would be unacceptable at this time.

The vaccine trial published in 1973 was disappointing, and it probably contributed to the decision of the Bureau of Biologics to remove the vaccine from the market. The trial conducted in the early 1980s was more successful but not 100% successful. Sixteen people were vaccinated and challenged: four were completely free of symptoms; twelve did develop symptoms and were treated with antibiotics almost immediately.

I don't know the current status of the vaccine, whether there is any movement afoot to produce it or whether there has been a decision to reject it. In my opinion, although probably not a perfect vaccine, it's the best thing that's available, and probably it is considerably better than the yolk sac vaccine.

Another of my interests has been the constituents of R. rickettsii which have biological activity. One of these substances is erythrocyte sensitizing substance. Dr. Shih-man Chang, at Harvard in the early 1950s, had a crude product which sensitized erythrocytes and was effective in diagnostic tests for Rocky Mountain spotted fever, although not completely specific. After I had developed a technique for purifying rickettsiae, I reinvestigated this problem and extracted the same type of product from purified rickettsiae instead of rickettsiae that were in a suspension consisting primarily of yolk sac material.

We probably rediscovered some things that Chang had already reported. In collaboration with Dr. Karim Hechemy at the New York State Department of Health, our material was tested again as

a diagnostic reagent. Dr. Hechemy adsorbed our product to latex particles, and this was sent to a number of state health laboratories. It showed some promise as a diagnostic reagent. We are continuing our study of erythrocyte sensitizing substance. We now have a monoclonal antibody which I think is specific for this material, and we are going to pursue this lead.

Harden: I'd like to ask you a question about developing a diagnostic test of this sort. One of the criticisms that the Grace Commission raised was that work of this type was overlapping the work of the CDC. Would you respond to this?

Anacker: I suppose there could be some overlapping in the mission but the truth of the matter is that the CDC was not pursuing this particular lead. It's my understanding that the mission of CDC is to develop diagnostic tests and to make epidemiologic studies of various diseases. So there is some conceivable overlap but as I just mentioned CDC was not engaged in working on this product. Our participation was limited to preparing the product. Dr. Hechemy forwarded the product, after making his modification, to the various state health laboratories.

I am also interested in the virulence of spotted fever rickettsiae. In investigating this, we have been comparing strains from different parts of the country--strains that have different degrees of virulence for experimental animals. At this point we do not have any hard leads, and this study is being continued with the use of monoclonal antibodies as one tool.

We are still engaged in attempting to determine which components in rickettsiae are involved in stimulating protection in humans. For this purpose we are making various extracts of

rickettsiae and are attempting to purify various components of our extracts by affinity chromatography. We are in the midst of this particular study. We are focusing on two substances which appear to have protective activity and conceivably might be useful as a subunit vaccine. But it is too early to tell whether these materials actually will be of practical value.

The laboratory has undergone several reorganizations since I have been here. Probably the first major reorganization, that I am aware of at least, is one that occurred about 1950. I actually came on the tail of that one. When Dr. Larson came, the research was greatly diversified. There was still a core here who did spotted fever research, studied the ticks which carried the spotted fever rickettsiae as well as the other rickettsiae, and did taxonomic studies of ticks and mites.

There has been in the last half-dozen years another fairly major reorganization. When a number of individuals retired, their programs were discontinued. As far as rickettsial research is concerned it appears there will be a change of direction. The people making these decisions have not confided in me so I can only comment on what I see happening.

There was a unit of rickettsiologists that existed prior to 1979. Dr. Burgdorfer was chief of that section. There were several of us in that section. When the Laboratory was reorganized into three Laboratories, the rickettsiologists were split into two groups. I personally objected to the decision but, again, the people making these decisions don't confide in me and did not ask my opinion. I think this has created certain administrative problems, and I would hope that sometime in the

future this could be rectified. Even in a small laboratory, people--the rickettsiologists in this case--can follow parallel lines of research and not really be aware that there is duplication of effort because of administrative separation.

Harden: Do you think that the reorganization was needed in general or do...?

Anacker: This is a very touchy subject.

Harden: I will let you say as much as you want to as little as you want.

Anacker: I've already said too much.

Harden: I know there were a number of strong feelings surrounding the reorganization. There were actually two things going on during this period. There was the reorganization from the administration in Bethesda and then there was the Grace Commission report, which one might see as being in opposition both to the RML and to the administration in Bethesda. So I have simply been asking people about the various charges and counter charges that were made here and there. My goal is not to tear down anyone's reputation but to sort out various decisions that were made and what people felt about them. Do you have any observations you think would be useful to add?

Anacker: The feeling here was that the individuals who came representing the Grace Commission did a very superficial job of studying the Laboratory. They talked to very few people. We're not sure--at least I'm not sure--what evidence they used in making their judgements. And we feel, or at least I feel, that we have been maligned unnecessarily, unfairly.

I think that there has been a great deal of excellent research conducted here. I think that there is excellent research being conducted now. Of course I am biased, but I feel that closing the Laboratory would be very unfortunate. It would not only affect the livelihood of a number of people--it would also affect scientific research because of the quality of research that has been done here.

There have been criticisms of the Laboratory mainly because we are isolated. But I think there are advantages to this apparent isolation, not real isolation. We are connected to other laboratories by telephone; we have various kinds of communication through computers, etc., with NIH and with MEDLINE. We can get information from the library. We get our bibliographies through MEDLINE as fast as anyone, I think, at NIH.

There are also advantages to living in a small community. Here, it is much easier for someone wanting to check an experiment at night to come a mile or two and check his experiment and make an adjustment, than it is to fight traffic in a metropolitan area. I think we are much more likely to do that sort of thing. Some of us originally came because we liked this type of environment. I think that those who were not familiar with this type of environment when they first came have grown to love the area. And I think that employee satisfaction makes for better quality work.

Of course I am prejudiced about the local area, and I would find it very difficult working in a metropolitan area. I think I would suffer from shock for some months if I had to work in a

large area--fight traffic, air pollution, crowds, etc.--and didn't have the release that I get in this kind of environment from all sorts of healthy activities.

So because of our instant communication with the outside world, the so-called outside world, and because of the very high quality of life that we experience here, I feel that the American public is probably getting more for its research dollar from RML than from NIH.