This is an oral history with Dr. Louis Howard Miller on January 13th and February 10, 2020, at the National Institutes of Health, about his career in the National Institute of Allergy and Infectious Diseases (NIAID). The interviewer is Victoria A. Harden, Founding Director, Emerita, Office of NIH History and Stetten Museum, National Institutes of Health (NIH).

Harden: Dr. Miller, would you please state your full name and that you know we are recording this interview and that you give permission for the recording.

Miller: My name is Louis Howard Miller. I'm in the NIAID Laboratory of Malaria and Vector Research. And I give permission to do anything you want with this. I don't even have to see it.

Harden: Thank you. You were born February 4th, 1935, in Baltimore, Maryland, and you grew up in Baltimore. Would you tell me about your family, your early life through high school, especially about anyone who might have inspired or nudged you towards a career in medicine or science?

Miller: There was none. My mother was one of the first to go to school beyond high school, and she did art at the Art Institute in Baltimore. She wanted me to go there and work, but she did not influence me. My influences came later.

Harden: Nothing in high school, then, teachers.

Miller: No, I was sent away to school because my mother was worried I'd get in trouble, and so she sent me away to a private school. It was Mercersburg Academy, a place where I was put away for four years.

Harden: Is it in Maryland?

Miller: No, Mercersburg Academy is in Mercersburg, Pennsylvania.

Harden: Oh, I'm sorry. I misunderstood. Who were your heroes as a boy?

Miller: I don't remember any. It's an interesting question, because it doesn't ring a bell. You know, some people talk about the book about microbiology, the very famous one that a lot of people were influenced by [Paul de Kruif, *Microbe Hunters*], but I wasn't. My influences came later.

Harden: Okay, you chose Haverford College for your undergraduate work. I understand that you were a wrestler there as well as a scholar. Why did you choose Haverford, and what did you major in?

Miller: I very much liked their Quaker philosophy. It appealed to me. In fact, since you are asking about people who might have influenced me, in that period, Albert Schweitzer would be one I would mention. He grew up in the terrible period of Europe during the '20s, when Europe was a mess, and he decided he didn't want to stay there. He moved to Africa. First he had to go to medical school, and then he went there as a physician to work on things there. When I was at Haverford, he came to visit after he won

the Nobel Peace Prize for his work in Africa. He was quite a scholar and an organ player, and he wrote a book called *Out of My Life and Thought*. One chapter of it explained how to fix an organ, because he had to do it himself. He was an internationally recognized scholar. When he came to Haverford, everything about him influenced me to want to go to Lambaréné in Gabon where he was, but it never happened.

Harden: Were you thinking about going into medicine at that point?

Miller: Yes.

Harden: What nudged you in that direction?

Miller: I don't know, actually, what influenced me, but I think Albert Schweitzer was a great influence on my plans. There was one interesting thing I noted when I reread the book recently. It was very strange to me that although he was a great intellectual in Europe, a world famous organ player, he never talked about an African friend. That just struck me as bizarre. How could you be out there all those years, working as a physician, saving children and adults who were dying from whatever they were dying from, and not develop any individual friendships? When I read his book, which was written after his time there, it was all about things that he was involved in in Europe, and nothing about an African colleague. I've grown very close to African colleagues, and so to me, it was a very strange thing to realize that a guy I had been drawn to, when I read his book, that he had taken a

direction which—. Maybe it would be different today. Maybe in those days, it was the way people acted or did. For me, I worked for many years in Mali, and it was just completely different. I mean, I had so many friends, one of whom was a leader in Mali, who recently died. It was quite different. I was surprised at that, but Schweitzer is who influenced me. I've never been to Gabon, never been to Lambaréné. I want to go there, and the guy who works there, a German scientist, has always been trying to get me to go and visit, but I've just never gotten around to it.

Harden: Well, I take it that it was your interest in the Quaker philosophy, and your interest in medicine, that made Albert Schweitzer such an influence on you, as opposed, say, to Selman Waksman, Hans Krebs, or Fritz Allan Lipmann, all of whom won Nobel Prizes at about the same time. They were Ph.D. scientists, so it was medicine more than science that seems to have captured you.

Miller: Yes, I think so, and it very much influenced what I chose to do and where I chose to go for my internship. I went to Mount Sinai because it gave me the ability to train in all areas. For most internships in medicine, you only work on medicine. At Mount Sinai, you do gynecology and surgery as well, and I wanted to train to be able to go out to Lambaréné or someplace like that, where I would need to be able to do all the different medical disciplines.

Harden: All right, well, let's drop back before your internship and talk about your medical education at Washington University Medical School. Did you do any kind of special research, or gain any particular clinical experience in tropical medicine as a medical student?

Miller: Not really. The first year, they didn't have a lot of money for medical students to work in research. I built a road in Baltimore, so I was not involved in research at all then. But my second year, I got very interested in going abroad to study tropical diseases, and I went to Puerto Rico, where there are very interesting people. What I went out there for turned out not to be very interesting. I was sent out from the Hematology Department at Washington University to work with a person who believed he had found something in worms that would induce hematopoiesis, and so they wanted me to look at it. It was just terrible work.

Harden: Were these hookworms, or other kinds? Do you remember?

Miller: No, they were *Ascaris*, but anyway, it doesn't matter. Hookworm is a natural one, but you don't think about it, because hookworm is a severe cause of anemia. One of the previous major donors in medicine and other fields was John D. Rockefeller, and you know, he acted very different than did Bill Gates. Rockefeller built many things. He had an advisor who was from a particular religion who believed that you make people better if you make them healthy and educate them. That led him to support black schools in the South. People were also very sick, both blacks and whites,

from hookworm disease and severe anemia, so he decided to eliminate it, and the way to do this was to build privies, because hookworms can't crawl up greater than six feet, so he built a six-foot privy. The other thing, of course, was teaching people to wear shoes or some kind of foot covering so the hookworm can't invade the feet. He did that, and it was fantastic.

Harden: Indeed.

Miller: Those two things made me realize how special the Rockefeller Foundation was. Then, of course, he created the Rockefeller Institute of Medical Research, which became Rockefeller University. There are so many things Rockefeller did--such a diverse group of contributions.

Harden: Coming back to your internship and residency in New York, was there anything else special, in terms of moving your career along?

Miller: The most important thing was that I talked to this person whom I was going to go to work for--whom I was very interested in working for—at Columbia University, Harold Brown [Dr. Harold W. Brown]. Everyone called him “Stooly” Brown. He worked on stools, but he had a lot of character, a lot of interests, and people were very interested in him. He's the one who told me that I should do research, not to practice medicine in Africa. It's very frustrating to practice medicine in these countries where there are so many problems, so little gain, and so Harold Brown was the

person who influenced my decision not to continue the line I was taking but to move towards research in medicine.

Harden: This brings me to the question I ask every physician. Dr. Brown's advice was part of it, obviously, but what made you decide that research was for you, as opposed to clinical practice or public health?

Miller: It's an interesting question, because I didn't think about it. Why did I go into research? I don't know. Most of the people, like Harold Varmus and these people, who came to the NIH instead of going into the Army—this was the time of the Vietnam War—came here to do research. I was very naïve in those days, so I didn't know anything about the NIH and that program. The head of the Department of Cardiology here at NIH tried to get me out of the Army and into his group, but it didn't work. When I went through basic training, they asked me where I wanted to go, and I said Southeast Asia. They had no problem with my request because the war in Vietnam was just starting. It was 1965, and so I wanted to go to Southeast Asia.

Harden: It's interesting to me, because apparently the Army wanted you initially to go to WRAIR, to the Walter Reed Army Institute for Research.

Miller: Yes, that's right.

Harden: Somebody said, "This guy is very bright and can do research." They wouldn't have sent somebody to do research that they didn't think was suited for it.

Miller: My first experience in interacting with research people was when I was doing a fellowship in California. I got to go out to Hawaii for a meeting. I met all the top people in research in renal research and other fields, and the guy who really influenced me there was Colin MacLeod [Dr. Colin MacLeod], the guy who should have won a Nobel Prize for his work. He and Oswald Avery [Dr. Oswald T. Avery] and Maclyn McCarty [Dr. Maclyn McCarty] at the Rockefeller Institute discovered that our DNA is the basis of gene expression, but because they did the work in bacteria, and people didn't think bacteria were organisms, they never gave them the Nobel Prize.

They missed it completely. The Nobel committee was wrong. MacLeod, Avery, and McCarty had indeed worked on an organism to show that DNA was the genetic mechanism by which proteins are made. It was interesting. Dr. MacLeod came into the restaurant where we were eating in Hawaii, and he immediately sat down with me and just talked about things. I was really taken by him. Here I was nobody, and here he was, already a great scientist, and I thought, "My God, that's wonderful." It didn't influence me in terms of going into science, but it did make me

realize how there are people out there who are spectacular human beings, and he was one of them.

Harden: Interesting.

Miller: They may have found out through this meeting that I was there and involved in research, and interested in research. My research at that time was not very good. I was doing pretty mediocre research at the place I went to in Los Angeles.

Harden: That brings me to the question of why you decided to become a renal metabolism fellow. Why suddenly renal studies on top of internal medicine?

Miller: My reason for entering this was all screwed up. I got very interested in tropical sprue. It was a big problem. In India, there are a lot of sprue cases. In Puerto Rico, there's sprue, and it is also found all over the world. I became interested in the etiology of sprue. I thought I wanted to study and understand metabolic research so that I could go out and study tropical sprue. As it turned out, metabolic research was not probably the right training. And to this day, no one has figured out the cause of tropical sprue. Is it caused by a virus? Is it caused by a bacterium? I wasn't trained in any of these things. When I look back on it, I wonder why in the world? I went into the Army and to Southeast Asia to work on sprue. We would go to a hospital there where they had diarrhea patients, looking for sprue.

We thought, "That's a natural place to look for chronic diarrhea," which is characteristic of sprue. They are chronic diarrhea patients. Only one patient had sprue, so it essentially didn't exist in Thailand. For whatever reason, it was not there. That was what was driving me in renal metabolism. I should have been going into virology or bacteriology, but I didn't.

Harden: If we may drop back in time for one more question, I would like to know more about the master's degree you took in parasitology with Dr. Brown. You were posted in Central America. Tell me about that.

Miller: It was a wonderful place. The outstanding place in nutrition research in that time was Guatemala. The program was run by Moisés Béhar [Dr. Moisés Béhar], a very famous scientist there, and Nevin S. Scrimshaw [Dr. Nevin S. Scrimshaw], a scientist from MIT [Massachusetts Institute of Technology]. It was a wonderful experience to learn about nutrition and what the problem was with nutrition. They had developed a drink called Incaparina. INCAP [Institute of Nutrition of Central America and Panama] was the name of the place where I was working, and Incaparina was cheap to make and included all the foods that were local, and it could be used to correct nutritional diseases. Unfortunately, it didn't work out because the people would rather drink Coca-Cola than Incaparina. They thought the reason might be just the way you sell something. They tried to use the techniques of Coca-Cola, but it didn't work out.

Harden: Was Incaparina more like the smoothies that people mix up today in the blender? Was it made of vegetables, or something like that?

Miller: Yes, that's right. It included vegetables and fruit, and it was mixed up to supply the necessary mix of amino acids that are missing in a corn or corn and beans diet.

Harden: But it wasn't sweet like Coca-Cola.

Miller: No, but that wasn't the point of it. The point of it was to enhance nutrition, but the children wouldn't drink it. The children in Guatemala were getting terrible malnutrition diseases at that time the same way they occurred in Africa. If you ever see a child who is skin and bones, or has edema of the feet, you know it's an awful disease. It was called kwashiorkor in Africa, and Guatemala had its own kwashiorkor. It was a terrible disease, but the inexpensive drink they had developed to treat it was not accepted in Guatemala.

Harden: They still prefered Coca-Cola.

Miller: I'm afraid so. I did too.

Harden: Coming back to your time in the military, as I understand it, it was while you were in Bangkok and had decided that tropical sprue was not going to give you much to work on that you made your decision to move into malaria research. Would you tell me more about that?

Miller: At that time, there was a very good scientist there named Bob Desowitz [Dr. Robert S. Desowitz], who's written many books on tropical diseases and parasitology. He was quite an influence on me, but I don't think that he was the major reason I changed focus. For some reason, we realized that malaria was a big problem in Thailand and in Southeast Asia, and that realization probably influenced me more than anything else. I knew almost nothing about malaria, so I had to go to the library for a month. They had a very good library at one of the university medical schools there, and I spent a month in the library developing what I wanted to work on. My first work, since I was a clinician then, was to work on things like renal failure. We took care of renal failure patients there, and also, when I went to Vietnam, we had renal failure patients.

What happened was that when soldiers went into renal failure with malaria, the standard procedure was to send them to Japan or to the Philippines, but they would die on the plane. Finally, they realized that they couldn't evacuate people with malaria and renal failure, so they sent a renal unit to Vietnam. The head of the unit got hepatitis, which is very common in people who work with renal patients. He handled a lot of blood, and it's not unusual for people who handle blood to get hepatitis B. The guy who was under him was a good scientist, but he wanted no part of Vietnam. He wanted out. So here they had a whole unit to handle renal failure in Vietnam but no one to run it. A friend of mine and I took it

over. For about a month or two, we took care of patients. One of them was a young guy who got malaria and would have died from renal failure.

Harden: This was in Vietnam. You went into Vietnam?

Miller: Yes, we were running the dialysis unit, Craig Canfield [Col. Dr. Craig J. Canfield] and I.

Harden: Where were you?

Miller: We were in what's now Ho Chi Minh City, which was Saigon at that time. We were doing our dialysis there. I'd finish working late at night, because these patients were very sick, and I worked very long hours by myself. The MPs wanted to drive me back, because I lived in the community, in a back street alley. I needed to walk outdoors, so at 3:00 am I would take off on my own and walk back. I would tell the MPs that I didn't want a ride to my place. It was just the way I was.

Harden: Did you ever have a problem with somebody trying to hurt you?

Miller: No. I always believed I was born under a star. I never believed anything would ever happen to me, so I never worried about it. The biggest worry I had was my roommate. We were doing the work on renal failure together, Craig Canfield and I. He had a gun that shot .45 caliber. He'd sleep with it, and I was always terrified that he'd shoot me in the night by mistake, so I kept a bottle by my bed, because I didn't want to walk to the bathroom and

wake him up. He was the only one I was afraid of. I got invited by one of the technicians to visit her home in Chợ Lớn, which is where the Tet Offensive started in Saigon in 1968. It's the Chinese part of Saigon, and so I went there. Everyone said, "You can't go there." I got into one of these little motor scooters. They drive, you sit in the back. I went there. It's just the way I was. There were very few things I was afraid of. That wasn't one of them.

Harden: Did you wear a white coat or anything that identified you as a physician or medical person?

Miller: No. I had military clothes, of course. I also had civilian. I can't remember if I wore my military clothes or civilian clothes to Chợ Lớn, but I never was worried about anything. In fact, when Craig Canfield and I drove around in a Jeep, I sat on the right hand side. Craig said to me, "If someone throws hand grenades at us, what are we going to do?" He gave me a tennis racket. What he didn't know is that my backhand was terrible. It was just awful. How could I protect us? But anyway. He ended up being very important in discovering a drug that people use today for malaria, and he was head of the malaria research unit at WRAIR when he came back.

Harden: What drug is that?

Miller: It's Malarone. Malarone is a combination of two drugs, and he found out that one of them, proguanil, was an anti-folic acid metabolism substance,

but it didn't work that way. He realized it was working another way—they still haven't worked out how it works—but he did all the work to make GlaxoSmithKline take over the project and produce the drug. Today, anyone who travels to Africa takes this drug once a day.

Harden: While you were in Thailand, you also did some research with Dr. Desowitz on deep vascular schizogony. If I understand it correctly, schizogony refers to a replication process in which the malaria parasite undergoes nuclear division without cytoplasmic division. It is followed by a budding, or segmentation, to form progeny. "Deep vascular" refers to the site where this takes place.

Miller: Schizogony refers to the action of a mature malaria parasite you don't find in the peripheral blood, and that was known for a long time. In *P. falciparum* malaria, it was characteristically stuck to the endothelium and various organs. No one knew how it stuck there. When I came back from Southeast Asia, I got two monkeys from Craig Canfield at Walter Reed to study *P. falciparum* in them. These *Aotus* monkeys are the ones out of Colombia, South America. On the red cell were these knobs that were attached to the endothelium, and that was really a wonderful discovery.

Harden: That was one of your first major discoveries, I believe, and you were only in your 30s.

Miller: It's not like today. These poor guys are in their 40s before they get their own labs, but in those days, while I was about Columbia, I had grants to do research, but also a grant that paid my full salary. It was just easy to get funded in those days.

Harden: Were these NIH grants?

Miller: Yes, NIH.

Harden: You were on the faculty at Columbia University College of Physicians and Surgeons from 1967 to '71. You were rising from assistant to associate professor, and then this discovery that you made and published brought you to the attention of Frank Neva [Dr. Frank Neva] at NIH.

Miller: One thing we should talk about for a second is Frank Neva.

Harden: Yes, that's where I'm going, so tell me.

Miller: He was one of the nicest people and leaders I've ever encountered. Tony [Dr. Anthony S. Fauci] knew him, because he had him take over the NIAID intramural program for one year. Frank was just a wonderful human being, and a supportive person. He brought me here. He also brought Alan Sher [Dr. Alan Sher] here. Frank was a really wonderful human being, and very thoughtful about his people. We miss him. The way he chose me was this: a very famous English malariologist, P.C.C. Garnham [Dr. P.C.C. Garnham] came over as an advisor to the head of the

intramural program, and they asked him whether he thought I would be a good person for the Laboratory of Parasitic Diseases [LPD]. He was the person who decided to bring me. The other thing you should know is that Frank was very upset with the people in malaria down at the CDC [Centers for Disease Control and Prevention]. There was a big malaria component there, and Frank was unhappy with it. Here was Frank, who was an expert in schistosomiasis and virology, not malaria, criticizing them. They said, "What do you know about malaria? We have 100 years of experience. How much do you have?" Frank was just so angry, and so he asked me to come to set up a malaria research program. Before I came, I had asked everyone, "Is NIH heavy in research?" I was ignorant.

Harden: Ted Nash [Dr. Theodore Nash] told me that hiring you was the very first thing Frank Neva did when he was charged with revitalizing the Laboratory of Parasitic Diseases.

Miller: There is one other thing you should know before we talk about that. There was another intramural NIAID research area that was very weak: immunology. To strengthen that program, John Seal [Dr. John R. Seal], who was head of the intramural program, brought in Benacerraf [Dr. Baruj Benacerraf] and Bill Paul [Dr. William E. Paul].

Harden: So at that time, NIAID was trying to beef up different programs.

Miller: Immunology was thought to be very weak, and parasitology was the other one, and to remedy the weakness in parasitology they brought Frank Neva down from Harvard. He had worked with Tom Weller [Dr. Thomas H. Weller], who had done a lot of work with John Enders [Dr. John F. Enders] and Fred Robins [Dr. Frederick C. Robbins]. The three of them won a Nobel prize for discovering how to culture the polio virus. That discovery had made development of the polio vaccine possible. Frank Neva and Tom Weller had identified the rubella virus, which can cause birth defects in infants born to a mother who develops rubella during the first twenty weeks of pregnancy. Despite Frank's achievement, the people in malaria at the CDC gave him a hard time. It was just terrible, so when Frank brought me here in 1971, he turned over the whole malaria program to me.

Harden: I want to step a bit sideways now, away from research, and talk more about this reorganization in LPD. I would like you to describe the situation when you arrived. With respect to your section, Bob Coatney [Dr. G. Robert Coatney] had retired in 1966 and Geoff Jeffery [Dr. Geoffrey Jeffery] in '69, so those very distinguished people were gone.

Miller: When Bob Coatney retired, he took over clocks. He became head of that society [National Association of Watch & Clock Collectors]. He was very aggressive. He would tell me, "You know, if I were to take over malaria research today, give me two young people and I would beat them all up." He was one of these guys like that. There was another NIAID guy, Don

Eyles [Dr. Donald E. Eyles], who discovered that if you used sulfur and pyrimethamine together, they synergize. He was out in Southeast Asia, and he wanted P.C.C. Garnham to come to Malaysia, where Eyles was working. but Coatney would not let him. He said, "Garnham can't go there. You can't have him in Malaysia," because Garnham and Coatney were competitive with each other.

Bob Desowitz was the last student of the great scientist H. E. Shortt [Dr. Henry E. Shortt], who discovered, with Garnham, the third cycle of malaria. There's one in the mosquito, one in the human. The third one's in the liver. They discovered that in about 1949 or so, and Bob was in there studying under Shortt, and he felt that Shortt was the leader of that group. I never knew Shortt, but I did know Garnham, and he was pretty special. He brought me to NIH.

Harden: Tell me who was here, who was in Bethesda and who was in Atlanta—Chamblee, actually—when you arrived?

Miller: Most of the people, positions—let's talk about positions—were in Chamblee, Georgia. They had a primate unit, and they had a very good scientist named William—Bill—Collins [Dr. William E. Collins]. He was head of that unit, and he was a very good scientist. He had worked with Jeffery and Coatney. Collins and Coatney wrote a book together on primate malarias. When I got here, the people at the NIH were very weak scientists. One of them wanted to get tenure here, but Frank Neva refused

to give him tenure. This scientist knew people like those at Rockefeller, who said, "Wow, he thought he was going to get a position here," and Frank said, "He's not good enough," and he was right.

Now I'll jump ahead to 1975. What happened is that Nixon [President Richard M. Nixon] cut the NIH by 25%, and that was very traumatic. All my people were down in Chamblee. To build a new unit, I had to bring them up to NIH, but they all decided to stay in Chamblee and work for the CDC.

Harden: Weren't there studies using prisoners as subjects by this group in Chamblee, and hadn't there been questions after the Tuskegee syphilis experiment scandal was exposed in 1972 about whether prisoners could actually give informed consent? Didn't that stop most research on prisoners?

Miller: Yes, research on prisoners had stopped. I was head of the unit in Atlanta, at a federal penitentiary, running the studies there. I wanted to get out of there, but Nixon cut NIH 25% just as I was going to move all these slots to NIH in Bethesda. John Seal, the Director of Intramural Research at NIAID, saved the unit. He thought malaria research was so important and poorly handled that no matter all the pressure he was under—he had to reduce by 25% positions in the NIAID intramural program—he did not take one position from me. He allowed me to bring all the positions to NIH to build the unit.

Harden: So you got to keep all those people and positions or Dr. Seal had to get you new positions.

Miller: The people all went to CDC, but Dr. Seal gave me the positions to rebuild. That's when I started rebuilding the unit with new people. There were two outstanding people I should mention. One was Richard Carter [Dr. Richard Carter], who developed a transmission blocking vaccine and discovered other things. He was really a good scientist, and he had worked with Garnham before that. The other person was Russell Howard [Dr. Russell Howard], who has since gone into biotechnology. Russell did beautiful work. He and Carter are the two people I made as the leaders under me. I had one group, and they had two other groups. These three groups really made a difference. There was one more person who made a difference. Bob Gwadz [Dr. Robert Gwadz], who was in entomology, made a difference because he helped me develop the research in Mali with Ogobara Doumbo [Dr. Ogobara Doumbo] and Yeya Touré [Dr. Yeya Tiemoko Touré]. Our goal was to develop entomology research there, but as it turned out, that didn't work out very well initially, and it's only now that good research there is being performed.

Harden: I want to come back to that.

Miller: Later, Yeya got a job at WHO [World Health Organization] as the director of the Special Programme for Research and Training in Tropical Diseases (TDR). What made a difference and what I really was dreaming about is

now happening. A guy named Tovi Lehmann [Dr. Tovi Lehmann], who is in our lab now, is running a research lab in Mali on entomology and doing a wonderful job of it. It's happened, but it was not through the way I had hoped it would go. In the 1990s, I got to working with Ogobara Doumbo in medicine, not in entomology.

Harden: I also have the name David Wyler [Dr. David J. Wyler]. Did he come to Bethesda, or did he stay in Chamblee?

Miller: He did come to Bethesda, but he also was down there working at the prison. He never really made much of an impact. Actually, down there, the biggest impact was made by W. A. Krotoski [Dr. Wojciech A. Krotoski], who figured out how to find malaria parasites in the liver. He used antibodies against the asexual blood stages that cross-reacted with parasites in the liver. He had beautiful pictures, working with Garnham on that. I wasn't involved, but these were nice studies.

Harden: Let’s come back now to your personal research. In 1971, you apparently went to a conference at WRAIR that threw you into working with Sydney Cohen [Dr. Sydney Cohen], trying to figure out why some parasites didn't affect—

Miller: You've done your homework.

Harden: Yes, I've done my homework.

Miller: Those conferences were held by Elvio Sadun [Dr. Elvio H. Sadun] at Walter Reed, and he brought Sydney Cohen. I was impressed with the work in which he took a monkey malaria, *P. knowlesi,* and studied how it invades red cells That really turned me onto looking for the receptor used for invasion. What I did was take all the negative and null red cells I could get my hands on, trying to find the receptor, if there was a receptor, for invasion. Only one type of red cell was not invaded, and it was one that was Duffy blood group negative. When I went to the library that night, I discovered that the Duffy negative blood type was only found in Africa where people are resistant to *P. vivax*. Thus the work on *P. knowlesi* led to the discovery of why Africans are resistant to *P. vivax.* Everyone know that Africans were resistant to *P. vivax*, but no one connected it to Duffy negative blood group.

What I had found, even though I was studying monkey malaria, was the cause of why *P. vivax* would not "take." I looked up the frequencies. There were huge frequencies of Africans missing this gene, and it was probably selected for because it protected them from *P. vivax*. It didn't cause any problems for them medically. Then I got to work with David Clyde [Dr. David F. Clyde] from the University of Maryland, where we conducted research on a group of volunteers who were prisoners and who were black. We Duffy typed them, and we studied their susceptibility to *P. vivax*. My collaborator at Maryland had *P. vivax* sporozoites that he could inject, and volunteers who were Duffy negative could not be

infected. That broke the whole thing open. We had already shown this in previous work with *P. knowlesi*, but it was during the following year that it became known that we had identified the red cell receptor for invasion by *P. vivax*.

Harden: And that year-

Miller: 1975.

Harden: Over the next decade or so, you focused on the theme of Duffy receptors and the invasion of red cells and started working things out. Would you tell me about additional findings from the work, and who worked with you?

Miller: There were other fellows who worked with me, and we were able to identify Duffy on the red cell, as a protein, and what it's like, and we were able to study it and try to get a fix on why the parasite could not invade. It was very evident that what we'd found was the red cell receptor, and without that receptor, the parasite couldn't invade. Our paper in the *New England Journal of Medicine* was published in August, 1976, and for this discovery, I got into *Time* magazine. They realized this was an important finding, and in 1976, they had an article about it in *Time* magazine.

Harden: I have some names, and I wondered what you might have done in particular work with these folks. I have John Adams, Chetan Chitnis—

Miller: Okay. John Adams [Dr. John H. Adams] was working on identifying the ligand molecule that bound the Duffy receptor. He did a lot of things and now is a major worker in *P. vivax*. First he was at Notre Dame, and then he went down to Florida. The real breakthroughs came with Chetan Chitnis [Dr. Chetan E. Chitnis]. He had done his undergraduate work in India. His father was a physicist who was doing all the international satellites for India, and his mother was a biochemist, so he started in physics, and he went to—I think it was someplace in Texas, to study quantum mechanics in physics. He decided he didn't like it, and so he went to Berkeley to do a PhD in biology. At that time, I believe it was in fungi, but then he came to work with me. He was the person responsible for the discovery that Duffy was a chemokine receptor and for so many other things about it. We purified the ligand from the parasite that bound to the Duffy blood group. He did so many things like that. He really was seminal in many studies on Duffy. He is now head of the Malaria Parasite Biology and Vaccines Unit at the Institut Pasteur in Paris.

Harden: As you have begun talking about chemokines and other things, you are moving along in time. The entrance of molecular biology into laboratory practice increased dramatically in the '70s and the '80s. Several people have told me about how they had to retrain themselves to do molecular work. Did you have to retrain yourself?

Miller: Oh yes. I was very lucky. I got to go to Cold Spring Harbor in 1981 to train. They had a fantastic lab there, and the person at the head of it,

Joseph Sambrook, had just written a book on molecular cloning from Cold Spring Harbor [[T. Maniatis, E. F. Fritsch, and J. Sambrook, eds., *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory Press, 1982)]. Those three weeks were wonderful. As I learned later, they weren't going to take me at first because I was so old, but they finally decided to take me. I had a letter of support from Bill Paul to get me into the course, and maybe that was the reason I was accepted. I don't know, but what I can tell you is that the course was wonderful. We worked day and night. If any experiment went wrong, even though things were moving quickly, you had to repeat it and get it right before you could go on, so we were working day and night, seven days a week, for three weeks. It was just wonderful! I remember going to the first lecture by a very famous molecular biologist who was a co-author on the *Molecular Cloning* laboratory manual. His name was Tom Maniatis [Dr. Thomas Maniatis], and he had done hemoglobin typing.

I didn't understand a word he said, but each day I gained a new group, and it was just amazing. Barbara McClintock [Dr. Barbara McClintock] was there at that time, and when she came in, the young scientists were crazy about her. She was an idol because she had worked out all the genetic moving, jumping of genes, in corn, and she had insights into it that were amazing. Just by looking at corn and studying its genetics, she was able to work all that out. This gives you a feeling for the variety of people with whom I got to interact—at the level of listening to those

lectures and reading enough to be able to understand a little bit of what they were talking about. I had no background in bacterial genetics, in phase genetics, in any of these fields, or in molecular biology, DNA biology. I had to learn everything in three weeks, and that was fantastic. That was very special for me.

Harden: But it gave you the kind of background you needed, then, to come back and transform your own work.

Miller: Absolutely. It's funny. We were looking for someone to head up a group to take over the molecular biology of malaria, and the first guy I interviewed was a student of the guy who had discovered a lot of restriction enzymes at Hopkins, and who won a Nobel Prize. This young man came to me and said, "Give me the literature." I said, "There is none." He said, "I'm not interested. If there's no literature, I don't want to work on it." I thought, "This guy, I don't want him to work with me." Any guy that said that, it's like a dog in a butcher shop. You got all this meat, and it's nighttime, and you grab any piece you want, and he decided he couldn't do any of it. Quite amazing, but anyway, we finally got someone. His name was Tom McCutchan [Dr. Thomas F. McCutchan], and then later, Tom Wellems [Dr. Thomas Wellems] came, and this was the building of the whole molecular program.

Harden: Really interesting. As you became convinced in the mid '70s, that malaria could not be addressed without addressing the transmitting mosquito itself,

you collaborated with Bob Gwadz and started a medical entomology program at the NIH. Would you tell me about this?

Miller: We also started a program in Mali, using Rockefeller Foundation money and WHO money, but the program here was built because Bob was able to attract really fantastic people. He had trained with George Craig [Dr. George B. Craig Jr.], who was at Notre Dame and was the leader in medical entomology at the time, in molecular studies. Bob brought Fred Nijhout [Dr. H. Frederik Nijhout] to NIH. In a year and a half, Fred did so much, so much. We had a mosquito that wouldn't mate, that you have to force it to mate by putting its things on to female mosquitoes, take their head off, ejaculates into the female. He wanted to know why they wouldn't mate, so what he showed was that males have hairs on their antennae that come out for mating and that attract them to a female. He studied the physiology of what brings these hairs out, why they come out. He did all these beautiful studies. I tried to keep him, but he wouldn't stay.

By the way, Fred's wife Mary [Dr. Mary Nijhout] worked with Richard Carter on the factors that allow exflagellation in parasite mating in the mosquito, and the factors that led to that.

The next person who came to the lab was this amazing guy, Ron Rosenberg [Dr. Ronald Rosenberg]. I'll never forget, I was interviewing a secretary, and she kept complaining about being bitten by mosquitoes, and I thought, "Here's a crazy one. I don't want her to come," so I let her out

and thanked her for coming, and then I discovered that Ron Rosenberg had dropped a gallon of mosquitoes, and they were everywhere. What Ron discovered, which is still a fascinating thing today, is that the reason *P. knowlesi* could only be transmitted by a group of *Anopheles* mosquitoes called *Leucosphyrus* mosquitoes. One of them was *A. balabacensis*. There are a number of others. They're all in Southeast Asia, and that's why *P. knowlesi* can't come out of Southeast Asia, because the mosquitoes in other parts of the world can't transmit it.

Ron showed was if you took the salivary glands from *A. balabacensis* and put them into another mosquito that you can't infect, their salivary glands would be infected. Then he put the other mosquito's salivary glands into *A. balabacensis*, and it did not get infected, meaning there's something in the mosquito salivary gland that had the receptors for invasion. It's really beautiful work. After that, he found something that would change my whole research history. He found that Duffy negative people in Kenya were being infected by *P. vivax*. Remember, I had found that *P. vivax* doesn't infect Africans. He was finding Duffy negative Africans were infected, and since then, there have been a whole bunch of papers on that. It turns out they do get infected. It's never as strong as a Duffy positive. We don't know, to this day, what the receptors are on the red cell that allow it to get infected, and what the parasite ligands are that allow it to get infected.

Harden: But it's just in Kenya?

Miller: No, no, no. This is all over Africa. It was just missed before. The assays are much better today. We have a PCR assay, because infections with *P. vivax* are extremely low, and when we found them in Mali, we found 25 infected. We had the slides wrong. We could only find the parasites in 10 of them. We had proven they had *P. vivax* by PCR, but we couldn't find the parasites. They were that low in parasitemia. In places like in Mali, the population is almost exclusively Duffy negative. There are no Duffy positives near them that could have brought in *P. vivax*, and then infected the Duffy negatives. But in a number of places, like in Madagascar and Ethiopia, the Duffy positive and negative Africans live side-by-side, so the *P. vivax* in Duffy positive ends up going into Duffy negative. The Duffy positive people have fever and all the symptoms you see in malaria. In Duffy negative Africans, infection was so low, they were asymptomatic.

Harden: Interesting.

Miller: Yeah, so it's not a perfect match without Duffy. Now, there are a lot of possibilities, and we don't know why they're getting it, and that's part of our research today, getting back into Duffy and *P. vivax* to try and solve that mystery. Ronald Rosenberg did one other thing when he went back to Walter Reed. He was the first and only person to ever grow *P. vivax* in vitro. No one's ever grown it since then, and he wrote a paper on it with Bill Trager [Dr. William Trager], who was the first to grow *P. falciparum*. For some reason, Trager never picked it up after that. The question

remains why no one has ever been able to repeat it or reproduce it. *P. vivax* culture is something I'm working on now.

Harden: How do you culture these things?

Miller: They grow in red cells, and *P. vivax* is difficult because it only invades young red cells, reticulocytes. The reason may be that the enzymes in the young red cell have more active antioxidant enzymes, and those allow the parasite to develop. Bill Trager grew *P. falciparum* in 1977 or '8. He published a paper in *Science* on growing *P. falciparum*. He then went around the world training people to do this. It was spectacular, but Ron Rosenberg, when he cultured *P. vivax*, he never did it again, and never tried to build on that. Other people have tried using their techniques but have been unable to grow *P. vivax*.

Harden: Another of your colleagues was Frank Collins [Dr. Frank H. Collins], who worked on the genetics of encapsulation. Would you talk about that?

Miller: Yes. That's interesting work. What Frank found was that certain mosquitoes could encapsulate parasites and kill them, and others could not. What he then found was published in *Science*, a very nice paper. The important point was that refractory mosquitoes were not refractory to all malarias, just to certain ones. One of the ones that they were refractory to was *P. falciparum*, which is the main parasite around the world. What happened after that is Carolina Barillas-Mury [Dr. Carolina V. Barillas-

Mury], who now is senior scientist at NIAID, discovered the molecular mechanism for that in her lab. This finding, that the parasite was resistant or susceptible, or could grow in certain mosquitoes, was all related to a gene, Pfs47, that led to its encapsulation. That was Frank Collins' work. It was quite a healthy group of scientists.

Harden: It was indeed. Moving into the 1980s, you yourself began to work in medical entomology, which you have talked a bit about. This was with Musa Touray [Dr. Musa G. Touray] and Alon Warburg [Alon Warburg]. Is there more to tell me here?

Miller: Well, my goal—and they were doing basic studies—was to freeze mosquitoes. Think about it. You have to maintain these colonies of mosquitoes. It's so cumbersome and so difficult that I decided to try to freeze them. The other thing I tried was putting a gene into mosquitoes that would allow a transformation, so I tried to develop methods of transforming mosquitoes.

Harden: Transforming them how and why?

Miller: You put DNA in using a vector, and it gets introduced into the genome.

Harden: What will this do? What does this accomplish?

Miller: You select a gene you can follow, like an insecticide-resistant gene, and then you see if it goes. We got one in, but it turned out to not go in by the

vector we gave, but it was a random introduction. All that work was injecting mosquitoes every day, larvae, and trying to freeze them. It was a whole new thing that I've never followed up on, and as for the freezing, they still haven't really accomplished it very well.

Harden: And then revive them, I presume, for later study?

Miller: Now they have techniques like CRISPR/ Cas9 for putting genes into mosquitoes, so now it's quite a bit easier.

Harden: Okay.

Miller: In those days, we didn't have these tools that were found recently, which recently won a Nobel Prize.

Harden: Would you talk a bit about your work on what happens as the malaria parasite passes through the mid-gut in its development? You were working with Klaus Sieber [Dr. Klaus-Peter Sieber] and Marcel Huber [Dr. Marcel Huber] on this, I believe.

Miller: Yes. There, we were looking at a particular gene that led to encapsulation, and we worked out what that was related to. The mosquito has a peritrophic membrane that covers blood, so any bacteria in there are inside, and then the epithelium that the parasite has to go through is outside this. What we discovered was a gene that the parasite had called chitinase that would go through the peritrophic membrane and be able to

invade. We showed that chitinase was critical for invasion of the peritrophic membrane.

Harden: You've talked a little bit about the Malaria Research Center in Mali, but I understand that the person who was in charge of it eventually left and went to the World Health Organization's Tropical Disease Research Center. Tell me more about that, and what's happened to it since then.

Miller: The person who stayed on was Ogobara Doumbo, with whom I was working, but the critical thing that happened at that time was related to Tom Wellems, who thought he had discovered the gene for resistance to chloroquine. It was a complicated area, and the guy in his lab who had done all the molecular biology at that time was Su—Xin-zhuan Su [Dr. Xin-zhuan Su]. Su had showed where it was approximately. You often don't have an exact fix on which gene it is. There are a lot of genes, one after the other. They probably found the wrong gene in the first study. It was only when they went out to Africa and followed the presence of this gene and whether people were resistant or sensitive to chloroquine, they discovered the gene on which they had focused was wrong. They came back into the lab, and they did the laboratory work again. Tom Wellems, along with other people, eventually discovered the chloroquine-resistant gene. This was feedback between Africa and Tom Wellems' lab. It was beautiful work.

My work at that time was more on, as we talked about before, cytoadherence in infected red cells to the endothelium, and that's an area I went into, describing the molecular basis for it, and more about the molecule itself. Three labs identified the molecule. At that time, a lot of people didn't believe antigenic variation had anything to do with *Plasmodium*. They were wrong. Tom Wellems found it in his lab, I found it in my lab using very different techniques, and then the third lab was one that Russell Howard out in California, found. Three of us published back-to-back in *Cell*, three papers, and because everyone trusted me, I sent the papers in. It was amazing, because the guy who ran *Cell* at that time, who started it, was an amazing scientist, and he came back to me with questions within an hour after he received these three papers. I couldn't believe anyone could read them that fast and come back with questions. His name was Benjamin Lewin [Dr. Benjamin Lewin]. He was the person who started *Cell*, and just came back with questions that were right on. It was wonderful.

Harden: What has become of the center in Mali since 2004? Is it still there? Is it still working?

Miller: Oh yes. Ogo died, I believe, a year or two ago, and one of his younger students took over and is running it now. I haven't been over there recently because we're trying to study the *P. vivax* in Duffy negative red cells over there, and their team can't go up to Bandiagara where the *P. vivax* was

because of the risk of attack by terrorists. There is so much fighting going on up there right now that it's not an ideal place.

Harden: During the 1980s, you also played a major role, as I understand it, in establishing molecular entomology at the World Health Organization. Would you tell me about consulting with them?

Miller: I worked very closely with the leader there, who was a fantastic human being, Tore Godal [Dr. Tore Godal], a Norwegian who took over TDR and had great insight into where to go. He was the one who started the use of drugs and bed nets, and he did the studies for them. He did so much, and that's why he brought Yeya Touré there to run that program. There was a French entomologist who was very famous. I can't remember his name now, but I was set up to talk to him, and convince him of the importance of malaria research, entomologic research, molecular research, and he said, "You know," this is the guy from France, "If I was still over there, I could eliminate malaria in Africa, but because I'm not, we may have to use other techniques." He had a lot of ego, but that was the start of the program, the Molecular Program in Entomology at WHO.

Harden: Is it still going on?

Miller: Yes.

Harden: The MacArthur Foundation played a role in this and in rejuvenating medical entomology in the United States as well. Is it still very active in

this field? Has the Gates Foundation [Bill & Melinda Gates Foundation] taken over? Do you know what the situation is?

Miller: As you said, MacArthur played a huge role for 10 years, and the person who was really a leader there was Fotis Kafatos [Dr. Fotis Kafatos]. After he left Harvard, he was in the Bio Labs. He was the youngest professor, 28, to become a full professor at Harvard. He was a bright guy, and he went to the European molecular biology lab to head it up in Heidelberg. While he was there, he set up his entomology group, and one of the people he trained was Carolina Barillas-Mury, who's come here, whom I was telling you about.

Harden: In another line of research in the '80s, you were using molecular techniques to pursue your interest in why *P. falciparum* does not circulate, but stays attached to blood vessel walls.

Miller: And I told you that the molecule involved, we identified in 1985. Three labs identified, my lab, Tom Wellems' lab, and then independently, Russell Howard's lab. Since then, a lot of things have gone on. For one thing—and this was discovered by others who had been at NIH, Patrick Duffy [Dr. Patrick E. Duffy] and Michal Fried [Dr. Michal Fried]. They discovered that the parasite bound to heparan sulfate in the placenta. This was a major breakthrough when they were at Walter Reed out in Uganda.

Harden: In 1989, you served as President of the America Society for Tropical Medicine and Hygiene, and in your presidential address, you asked the rhetorical question, "Why don't we have a program in basic research on mosquito biology, and why do we have to sell malaria vaccines as something we can produce next year?" “Very quickly” was the message you were highlighting as something that should not be the focus of malaria research. I go back to the very early years when I was here at NIH, when the basic versus applied research arguments were very strong, and that's what I think I am hearing you say. It's almost plaintive, to a certain extent, but tell me about your philosophy.

Miller: In 2007, the Gates Foundation came out with this statement: "We have to eliminate malaria." Once they came out with that, they wouldn't support blood stage vaccines, which is what I work on. That was decided. You had to do vaccines that would prevent infection through the liver, through pre-erythrocytic vaccines, or transmission within the mosquito. You couldn't work on blood stage. I feel that it would be wonderful if we could eliminate malaria from Africa, but right now, we have to protect the kids. Kids are dying of malaria. They're getting terrible diseases, and we must protect them. I think these blood stage vaccines will be able to protect them.

Harden: Did you ever think that were going to be able to convince the United States, which doesn't have but a little bit of malaria, to fund this kind of work?

Miller: I think the driving force there will be Tony Fauci, who as NIAID director must continue to advocate for work on things like vaccines and will support the research.

Harden: All right, we're coming to 5:30 pm. Let's stop here for today.

SECOND INTERVIEW

This is the second interview in the oral history with Dr. Louis Miller, on February 10th, 2020, at the National Institutes of Health. The interviewer is Victoria Harden.

Harden: Dr. Miller, I understand there are a couple more comments you would like to make relating to entomology in in malaria research.

Miller: I remembered that Bob Gwadz, who worked for me, brought fantastic people to the lab. He had worked with the greatest entomologist of that period, George Craig, who was at Notre Dame. When you visit Notre Dame and you're at the hotel there, what do they talk about? Not the football team. They talk about George Craig. He died but he was fantastic, and a lot of these people came through George Craig. And that's how Bob was able to capture fantastic people. You remember Ron Rosenberg,

Frank Collins. Fred Nijhout worked on how our mosquitoes would not mate in captivity. He figured out that was because the males couldn't hear the females. They have hairs on the antennae and the hairs have to come out for the males to hear the wing beat of the female. The hairs would stay flat against the shaft, and after he worked out the problem, he would pull those little hairs off, put them on a drop of liquid, with all kind of adrenergic and different things to find exactly what the impulse was that lead to their coming out. He showed there was a thing below the hair that would expand in size while these stimuli were bringing the hairs out. It's just spectacular work. He then went to Duke, and I tried to get him back to run the department but he wouldn't come. He had become interested in the wings of butterflies. The wings of some butterflies have these things that look like eyes on them so birds won't eat them. I told someone when I was in Nepal about that, and he said, "You know that butterfly that was here and had the big eyes? A bird just ate it." Life is that way.

But anyway, what you brought back to mind were these people Bob Gwadz brought here who were really fantastic. The one he brought more recently was Tovi Lehmann, who is running a big entomology program in Mali. The reason I went to Mali was to develop medical entomology, and although I didn't do very much, to be honest, he did. What he did was collect mosquitoes in the villages to see, for a particular mosquito, how long it lasts, and he showed that one of them lasted for nine months in the village, seven or nine months in the village. And then he

decided to see why another group of mosquitoes would come in later and how they got from the River Niger to the village, which was about 50 kilometers away. He put up balloons with sticky tape all over them and collected all the insects he could, including things that attack crops. It was quite a collection he made over the last few years. At any rate, Bob Gwadz was the person who brought him here.

Harden: Let's move sideways for a moment to ask some organizational questions about NIAID. In 1985, you received the Paul Ehrlich and Ludwig Darmstaedter prize. In 1990 you were elected to the National Academy of Sciences, and throughout the '90s, you were getting more and more awards and honors. In 1992, you became chief of the Laboratory of Malaria Research, and I'm assuming that laboratory was created specifically for you. In 1995, Frank Neva retired, and you then took over as chief of the Laboratory of Parasitic Diseases. Can you tell me about all this, the transitions that were going one in the '90s?

Miller: To begin, Frank Neva was the nicest human being I've ever worked with. Just spectacular. Very thoughtful, full of ideas. He is the person who, with Tom Weller, isolated the rubella virus. Rubella was the disease that caused congenital problems. His was one of two labs that actually isolated rubella, and he did other things of course. But he was just a nice person and really looked out for people. I'm one of the people he looked out for, but he looked out for everyone. The other person at NIAID who was very

useful was the director at the time, Richard Krause [Dr. Richard M. Krause], who was so supportive of me. He was the person who put me up for the National Academy and he did many other things for me during that period. He was there before Tony took over. He was just very positive. And then there was John Seal, the head of our intramural program.

Harden: John Seal, yes.

Miller: He was an authority on cholera, and he wrote a book about it. He was very supportive. He brought up our work and praised it to all the PIs [Principal Investigators]—not PIs but heads of NIAID labs. I had just started then—1971, but John looked out for me and his other people. And then in 1975, when President Nixon cut the lab by 25%--he actually cut the whole NIH across the board. I had a whole group of people in Chamblee, where a big part of my lab was located. They went over to the CDC. We're talking about 15 people. But John Seale thought malaria was important, so he allowed me to keep those positions and rehire a new group, even though he was under great pressure to find 25% savings.

Harden: So you could hire people then and bring them to Bethesda?

Miller: Yeah, that's right. And that was just because John Seale appreciated malaria research, which was not well funded in the US at that time. He believed that it was important to maintain the quality of the NIH. It was that type of thing that made it possible for me to bring in people like Russell Howard, a great biochemist, and Richard Carter, who started the

whole program in transmission blocking and immunity vaccines that's still going on today. So this is how you bring in these top people to head up research programs. And Frank Neva would make people leave who thought they could stay forever because they weren't very good. Although he was a nice person, he still made judgments. He brought in Alan Sher around the same time who's still here. He became chief of LPD.

My lab at that time was the Laboratory of Malaria Research. Then I took over as chief of LPD. Later, LPD was divided into the Laboratory of Malaria and Vector Research (LMVR) and the Laboratory of Parasitic Diseases. Alan Sher was the head of LPD, and Tom Wellems took over LMVR. Although the powers that be never assigned them to these positions for about five years--you know how it is—I thought it was obvious they should take over. Finally, after much pressure from me and from others, they finally took over. At that time, I was head of the malaria vaccine program.

Harden: Okay, now, tell me about that. How did the malaria vaccine program differ from the Laboratory of Malarial Research?

Miller: So early on, David Kaslow [Dr. David Kaslow] decided that he didn't want to make new discoveries, he wanted to apply them to what was a problem in Africa. And so he started the the program for vaccine development and got the first commitment from NIAID. We got money from various sources and slowly built a vaccine unit that still exists today.

Harden: This is separate from the larger vaccine center or no?

Miller: The larger one you're talking about is the NIAID Vaccine Research Center. It's under John Mascola [Dr. John R. Mascola]. But it was originally under Gary Nabel [Dr. Gary J. Nabel]. Gary did a great job in building it—it cost a lot of money, it has a whole building, and they're doing important things.

Harden: But not malaria?

Miller: No. They didn't have malaria. They were supposed to be focused mainly on HIV, which is not an easy subject. I don't know if you heard recently they had to stop the trial on South Africa in HIV because it was not working.

Harden: Yes, I did know about that.

Miller: And so I guess you'd say, malaria is sort of low hanging fruit. It's a lot easier, not easy, but a lot easier than HIV or TB. And speaking of tuberculosis, there has been a recent breakthrough in a candidate TB vaccine produced by GSK pharmaceutical firm [M72/AS01E]. The practice has been to give BCG vaccine to all children in the developing world to protect them against malaria and tuberculosis. But it doesn't work completely, it has a lot of problems. The new candidate vaccine was given IV to rhesus monkeys, and they were protected. In humans, the GSK vaccine provided about 50% protection with only two shots, one month

apart. It's amazing. I was very excited about that. And that's a recent publication.

But for me, I'm interested in blood stage malaria. So that's one of the goals of my work now is to see this vaccine happen.

Harden: You've been working for a long time on these transmission blocking malaria vaccines, I believe.

Miller: That was Richard Carter. I did some studies with him but it was mainly Richard Carter who was under me but who did all this exploratory and discovery work in transmission blocking. We continued it somewhat but now Patrick Duffy is taking it on as the new chief of the Laboratory of Malaria Immunology and Vaccinology. He's continuing this work in transmission blocking.

Harden: So what are you working on then?

Miller: I'm trying to develop a blood stage vaccine. As a preface, I'll tell you that malaria is a bad disease. And with cerebral malaria, it has a 20% to 25% death rate. And those who survive have about a 20% to 30% likelihood to develop neurological deficits, convulsions, a lot of other things. It's a very sad thing. And if they had a blood stage vaccine, it would control the blood stage of infection. It would be a big deal. And that's what we are trying to do. But the Gates Foundation has not supported that. In 2006 or 2007, they came out with a statement that they wanted to eliminate

malaria. And that's a nice goal but while we're waiting to eliminate malaria, it would be better to help protect these kids in Africa. And that was my goal.

Harden: How do you differentiate the kind of stage people are in between what would work with the transmission blocking vaccines and the blood stage vaccines?

Miller: It's completely different.

Harden: Tell me about it.

Miller: The blood stage vaccines block the mosquito from infecting people. The way they work is when a mosquito feeds on someone who has been vaccinated, it blocks the infection of that mosquito, and therefore they can't transmit. What we're trying to do is protect the children from malaria by giving them this material from the blood stage, and that's our goal.

Harden: Wow.

Miller: But the problem is there's something called “the Valley of Death,” which you've never heard of. But when you're developing new ideas, the Valley of Death is the place where good ideas die when you get to a certain point in the lab but need money to take them further. The money is hard to come by because the idea is still experimental. There are things you hope will happen, but you can't guarantee it, and it will cost money to test the idea.

And that money is pretty small in the larger scheme of monies spent. For example, the Gates Foundation spent, I think, almost a billion dollars along with GlaxoSmithKline to develop a vaccine that didn't make it. And that just tells you how difficult it is.

Harden: Malaria vaccines have traditionally just been extremely hard to develop. I remember a conversation that I had a very long time ago with Victor Haas [Dr. Victor Haas], whom you may know as head of NIAID's precursor institute after World War II. Dr. Haas said that he had tried to make a malaria vaccine from the eggs of mosquitoes, and, of course, that effort went nowhere. My sense is that people have tried all kinds of different approaches.

Miller: Sure. The approach that Richard Carter led in my lab was attacking the parasites in the mosquito makeup. The energies are very different on them than the blood stage. And so I think it has a chance but again it has to be very effective. You can imagine, you vaccinate today and in another year or two, antibodies go down. That's the problem with all these vaccines.

Harden: I see. So you have to revaccinate?

Miller: You can, but that's always difficult in a vaccine program. They have to revaccinate. It's easy to get people, for three or four months or five months, you get the whole population. BCG for tuberculosis is given at birth. That's easy. You have these children who were just delivered, and you give them BCG. But malaria is given at three to four months and they

have to have campaigns where they go out and give the children all the vaccines. So they give them measles and mumps and rubella—so many different vaccines are given at the same time. Along with, of course, vaccines against tetanus and diphtheria and pertussis which are bad diseases. And there are also other diseases to be vaccinated against, and some of the vaccines were worked out here. John Robbins [Dr. John B. Robbins] worked out the vaccine against *Hemophilus influenza*. It was a wonderful vaccine. And then he worked out one against typhoid fever that worked very well. This campus has had a lot of things going on. But unfortunately, for malaria so far it's very difficult.

My wife works on a treatment for cerebral malaria, which you give the child. And at least for the mice that are being tested—in mouse malaria, they go into coma on day six. You give this drug on day six and half the mice survive, wake up and are fine. It's amazing when you see a mouse in coma and see it wake up. But even that's hard to get money for. It's down there in the Valley of Death.

Harden: And your blood malaria vaccine, have you done animal experiments like those with the mice?

Miller: Oh sure. And with *Aotus* monkeys. It protected the monkeys quite well. But the problem we run into is that the adjuvant we use for the vaccine is no longer available. There's a company named Novavax that makes an

adjuvant that's very good, and we're trying to make contact with them and get their adjuvant to use for our vaccine trials.

Harden: So once you get that, you've done the monkeys and then the next step would be people, right?

Miller: Yes. Well, that would be for people. If we get that vaccine, we'll have to study it in animals, show if it makes good antibodies, but if it does, then we go into people and challenge them with malaria and see if they resist the infection. We watch them very closely, so it's not dangerous for the people infected. They may get bad headaches, but it's not a dangerous thing to give them malaria, because we have drugs that treat it right away as soon as we see parasites in their blood.

Harden: When you served as Chief of the Laboratory of Parasitic Diseases, did you make any major changes as lab chief?

Miller: Well, the biggest thing was to split the lab in two. And Frank Neva did not like that because he had always had this one lab. And people who work with helminths went one way, and that was under Alan Sher. Tom Wellems took over the malaria group, and we entered a new building. It had to be reorganized for everything we were doing there. Tom took on a lot of responsibility then.

Harden: Another focus of your work has been the binding of parasitized erythrocytes in the placenta. Would you talk about that?

Miller: We looked at various places they bind. But my work was more focused on the binding of infective red cells to endothelium. But the other thing I studied, of course, which opened up the *P. vivax* story was the finding that Africans don't get *P. vivax* because they have Duffy negative red cells. That doesn't seem to cause problems for them, but it did protect them from *P. viva*x. But now *P. vivax* is coming back to Africa and we're trying to figure out why.

So this was the discovery of a receptor on a red cell that we identified what from the parasite bound to. And the person who was in my lab at the time many years ago, Chetan Chitnis, has been trying since then to make a vaccine against the molecule—the part that binds to the red cell. And if he can make an antibody to it, he can block invasion, and that's what he's working on.

Harden: This brings up the larger question too about whether we really are at the stage of designer drugs with molecular biology—what you can see and mentally image, as to how the body works. Do you think we're there?

Miller: The biggest period for discovery for this type of thing was around 1940 when drugs started coming in. DDT came in then from a group in Switzerland. And a new drug, chloroquine, was developed by the Germans before the second world war and during the second world war. They developed this drug that eventually became chloroquine. And between DDT and chloroquine, you had the basis for the malaria eradication

program of the 1950s. By 1959, malaria had come back with a vengeance. And then it also, in Sri Lanka, it went from almost zero cases to a million cases. They again recently eliminated it. We'll see, I hope they can maintain that. In India in the '70s, there were no cases of *P. falciparum*, which is a worse malaria than *P. vivax*. And by '77, there was a huge recurrence of *P. falciparum*. That was the basis on which I went over to India. The head of their research council invited me over to go around and look at what was going on then. And it was not a very strong program at that time. But subsequently they built a very strong research program throughout many institutions in India.

Harden: In 2015, Dr. Youyou Tu won the Nobel Prize for the discovery of artemisinin therapy for malaria. Would you tell me the story about this discovery?

Miller: Well, there's a history behind it. I was always curious what the Indians in Peru told the Jesuits, because the Indians had this drug quinine. It's the greatest discovery of all drugs, medicinal drugs, ever. Saved more lives from malaria than any other. It still works—quinine still works today. I never could get anyone interested in going back in the Jesuit notes and their discussions with the Indians, because everyone thought, "What would the Indians know?" But now they know that there was pre-Columbian *P. vivax* probably in Peru and other places. And so the Indians did see malaria. The question is, did they develop the drug that the Jesuits brought back to Europe? It was called the Jesuit drug. And it's strange,

because when one of the top people in England got malaria, he wouldn't take the drug because it was from the Jesuits, and he died. Stupid, these things.

And then I found out that in Sweden, a very famous scientist, Carl Linnaeus, who is one of their great scientists and after whom many things are named, wanted to get married in 1710 or so or 1720, and the woman's father said, "You have to get your doctorate first before I let you marry my daughter." And he went to Holland and the thing he wrote was a paper on malaria. And he knew drugs in the area about treatment, quinine and *Artemisia annua*, which is the drug that Youyou Tu discovered, and it was the plant wormwood that carried the drug. He obviously had gotten it from the Chinese pharmacopeia that probably came in that time or a little before. Marco Polo and all these people coming back from Asia had brought the Chinese pharmacopeia, and that's how Linnaeus had it.

But when I went to a meeting in 2006 in Shanghai and asked them, "Who discovered artemisinin or Qinghaosu"—and this was a malaria meeting filled with Chinese malaria investigators—no one knew. And then I talked to Nick White [Dr. Nicholas White], who had gotten a big award for working with Qinghaosu, I asked, "Who discovered it?" He said, "I don't know." And I said, "This is not going to be like quinine with the Indians, I'm going to trace it down right now."

I got a friend of mine from LMVR who was down the hall from me, to help me, Xin-zhuan Su. I said, "I want to know who discovered

Qinghaosu." So we went to China and traced the origins of what had happened. We looked into the books, and we went to see Youyou Tu. The history is: During the Chinese Cultural Revolution, from 1966-1976, Ho Chi Minh came to Mao Zedong and said, "I have a big problem, we need antimalarials. We can't figure out how to do it." Mao turned the problem over to Zhou Enlai, who was a real intellectual. The first thing Zhou did was put the scientists under the Army, so the Red Guard kids couldn't touch them. And the Army brought the scientists back—one of them was cleaning toilets. And so this woman, Youyou Tu—the way they say it in China, they say the last name first, Tu Youyou. “Youyou” is her first name; it's two syllables. We went to talk to her, and it was obvious that they had not made any progress by 1969. Zhou En-Lai came to this institute she was in and talked to institute director. He turned it over to her, and she was a hard worker. She looked in all the literature.

Do you know how the literature is kept in China? It's on bamboo. Have you ever seen it tied together? There are libraries filled with these little rods of bamboo. And so she went back and looked through all the literature about people being treated for fever in malarious areas. In those days, malaria wasn't known, they knew they had fever. One of the therapies used by Ge Hong (284–346 CE) was Qinghaosu or artemisinin. Tu Youyou tried testing it in mouse malaria. At first it worked, and then it didn't work, so she went back to the original description of it by Ge Hong.

He described how the drug was extracted from plants in boiling water, but he said that for this drug, you had to put it in cold water.

So then Dr.Tu switched to using ether to extract it because you can get rid of the ether at low temperatures. And she suddenly had a compound that cured 100% of the people with malaria. She tried it first in mice, and then she went to humans. I put her up for the Lasker Award—it's called the pre-Nobel. I put her up for that, and right away, the Lasker people contacted me. The guy who contacted me was a Nobel laureate. He was very famous. I was in Sweden at the time he called. He said, "This nomination is coming up now." And he wanted to know whether she did the trials ethically, when she treated people. And I told him, "Yes." But it would take a while to get the data.

She won the Lasker one year after we put her up for it. That was amazing. It was appropriate but amazing. It was the first time I went to the Lasker Awards. It was a lot of fun to see her present her work. She was very spirited. And it was great fun for me to go there and to hear her talk at the Hotel Pierre. That's where they had their meetings.

Harden: And then the Nobel came after that?

Miller: Yes, but that was a little slower. I started nominating her for it, also. I was in Sweden for two months on a sabbatical in the parasitology and malaria group. And I told the story to everyone about her. But still, year after year passed. And then I was on another sabbatical in Denmark, when one day I

came into the lab, and someone said to me, "Did you hear that a Chinese woman won the Nobel Prize?" "Wow!" That was wonderful.

Harden: Indeed.

Miller: I'm sure she was also put up by other people, but it was interesting. There were other people fighting with her for it, saying that they'd done some things later. The Nobel prize is very interesting. When they gave the prize for discovery of HIV, they didn't give it to Gallo [Dr. Robert C. Gallo]. They gave the prize for HIV to two other people. Every year they give it to three people, so they could have given it Gallo, but for various reasons, as you probably know, they split the prize differently. The third person who won was Harald zur Hausen, who had discovered that human papilloma virus (HPV) causes cancer of the cervix. Which no one could argue with. I mean, what could you say about a guy who made that discovery?

And of course the NIH then made a vaccine against the human papilloma virus, the virus that causes cervical cancer. John Schiller [Dr. John T. Schiller] and Douglas Lowy [Dr. Douglas R. Lowy] at the National Cancer Institute (NCI) made the vaccine. It wasn't an NIAID vaccine.

For Dr. Tu's Nobel, the Nobel committee did a different thing. They didn't want to split it among all the people who had worked on malaria therapy. They gave it to her alone. The two other people they gave it that same year had developed ivermectin for river blindness. So

even though Qinghaosu was developed for treating the people in Vietnam, it never got there. Its impact has been in Africa.

It's interesting how these things have a way of developing. With respect to ivermectin, it's wonderful to have those two people get the Nobel prize with Tu. The Nobel committee had to choose something that was equally impressive to curing malaria. There are great areas of Africa where people had to leave because of river blindness. And ivermectin made such a difference. Originally they had insecticides because black flies transmit it. And they had satellites seeing if the rain increase increased the flow of water to decide on the amount of drug released. But of course, the insects became resistant to the insecticides. The big breakthrough was ivermectin. The drug was owned by Merck, but Merck gave it all away through the Carter Center in Atlanta. Merck could not give it through WHO because they weren't organized well enough. But the Carter Center was, and they implemented the whole ivermectin treatment plan.

Harden: Back to artemisinin, I saw an article in the *New York Times* about a debate as to whether Dr. Tu had used modern scientific methods in her work or had used solely traditional, ancient Chinese methods. I believe it was both.

Miller: Yes, of course.

Harden: But the Chinese government seemed to insist that only ancient techniques were used.

Miller: Because they wanted multiple people to get the Nobel prize.

Harden: Oh, did they?

Miller: Oh, yes. And you can't do that for the Nobel. She's the first person who was a Chinese scientist trained in China, educated in China who won the Nobel Prize because of her research *in China*. There have been no others yet. A lot of Chinese win the Nobel Prize but after working in Europe or the U.S., not when working in China. So of course, the Chinese government wants to hold her prize up to the poor people there. "She got it, why can't other Chinese scientists?"

Harden: Now, taking the really long view, would you comment on the overall state of malaria research in the world today and the prospect of reducing morbidity and mortality?

Miller: Kids with high parasitemia are running around and playing soccer. You don't know they're sick until they get very sick. One or two percent develop cerebral malaria or other complications. But until that moment, we never can predict which one's going to get sick. So that's why I feel a blood stage vaccine is so important. I'm not against eliminating malaria, but while we're waiting to eliminate it, it'd be better to help protect these kids. That's my view.

Harden: Indeed.

Miller: There's one other vaccine against blood stage malaria. It's being tested by an English group, and they have better support than I have. We'll see what comes of it.

Harden: Would you comment also on the value of the intramural and NIAID program in supporting your work? The basic question is, why did you study it NIAID when you must have had many other job offers?

Miller: Yes, that's true. And I'm glad I stayed. I had very nice offers, from Rockefeller, from Harvard. And I have no question that the environment I'm in is the best for me to do work. That doesn't mean there aren't fantastic groups around the US and in other countries doing wonderful work in malaria. There are. And to solve a problem like this, it takes a lot of work.

Harden: Yes it does.

Miller: A lot of groups. And money. Unfortunately, the Gates Foundation feels that they have to eliminate malaria, so they can't give money for a vaccine that will reduce disease.

Harden: But NIAID has been very supportive of your work over the years?

Miller: Yes, but now it's more difficult. Think about it. It doesn't cost much to get started. Two million dollars to get off the ground, or a million dollars,

million and a half. For a research lab, that's two or three research labs. It's a lot of money. It's peanuts for vaccine development. Absolute peanuts.

Harden: Is this a government wide problem that's causing the shortage?

Miller: It's the Valley of Death. Can you imagine supporting a vaccine when there are all kind of problems with knowing will it work or won't it work? And who's going to make it if it works? So it's not a simple thing. You have to work with industry. John Robbins, who died recently, developed not just the *Haemophilus influenza* vaccine, but also a typhoid vaccine. They tested it in Vietnam. It had a 94% efficacy in preventing typhoid. He did it all himself, that's the way he was. He didn't bring a company in, and today—it now must be 20, 25 years after he did this—there still isn't a typhoid vaccine available.

Harden: It hasn't ever been developed?

Miller: No, because you have to work with a company. If he'd have worked with a company instead of demonstrating hubris and saying he could do it all himself—

Harden: Interesting.

Miller: It's very sad.

Harden: These are all my questions but I want to know, is there anything else you want to talk about before we stop?

Miller: No, I think I've talked enough.

Harden: What does the future hold for you?

Miller: Oh, wow. I hope to keep working in the lab with a small number of people, post docs, who do all the work, as you know. And if I can keep going, I'll continue working on some things I'd love to solve. They've never been solved. How to culture *P. vivax*. *P. falciparum* was solved by Bill Trager, but that was in 1977 or 1978. Since that time, *P. vivax* has not been possible to grow. And I think we have good ideas and we're starting our experiments to grow *P. vivax*. So that's one thing. Another is this vaccine for blood stage. If I walk away from the lab, it won't happen. And another is the treatment for cerebral malaria my wife has developed.

So there are all these things that if I can keep going would be wonderful. I mean, I care about this. We're just starting a new program in Cameroon. And the area has a very unusual *P. vivax*. Working in a place, you have to build on the strength of the local scientists. You don't just walk in, take samples, not if you want long term impact. And of course, I want to have long term impact. The way I plan to do it is through training young scientists in the area to which I want to go, and building their infrastructure. That's what I'm thinking about.

Harden: Very interesting.

Miller: There are a lot of things I don't think would happen without me. Whether they'll happen with me, I don't know. And whether they'll work or not, I

don't know. And that's the problem but that's what research is. They just had a huge HIV vaccine trial in South Africa that failed. I don't know what it cost, but it would have been a lot of money. That's the way it works. You hope it'll work, you do your best to make it work, but it may not work.

Harden: Thank you so much for an excellent oral history.