Prologue

INTRODUCTION

In the summer of 2003, I finished work on a book entitled *Parasites, People and Places: Essays on Field Parasitology*. My wife, Ann, and I were in our cabin in Green Mountain Falls, Colorado, and I was trying to tell her the story from the book that had to do with the discovery by William Walter Cort of the cause of swimmer's itch back in 1927. At the same time, she knew I was sort of lamenting the absence of a new project. She must have been impressed by my tale, because out of the blue, she said, "Why don't you write a book about discovery in parasitology?"

This started me thinking about the possibility of doing something along that line. Gradually, over the next several months, I put together an idea. Stories regarding the discovery of the transmission of malaria or sleeping sickness have been told many times over the years, so they are sort of 'old hat'. But, then I thought, are they really?

I recalled the way I teach my own general parasitology course to undergraduates. I know that I mention Ronald Ross and David Bruce, among others, but I really do not get into much detail about how Ross and Bruce did their work regarding malaria or African sleeping sickness, respectively. Then, I began thinking about some of the new discoveries regarding malaria (*Plasmodium* spp.) and sleeping sickness (*Trypanosoma* spp.) that have been made since their life cycles, and those of other parasites, first were resolved. For example, consider the variant surface glycoproteins of the trypanosomes. Who did this research, and what led them to do it? Since this is definitely not my area of expertise, I honestly did not know for certain who did what until after I began researching the background information necessary to write this series of essays. So, I thought, why not briefly retell some of the old stories

regarding discovery in the nineteenth and early twentieth centuries, and link these historical accounts, where relevant, to some of the newer work that has been done in the last 50 years. In a few essays, I have simply gone to a prominent parasitologist and asked them to tell me about their lifetime of research.

Another idea emerged when I began thinking about this approach. I became intrigued by the possible role of serendipity in all of these parasitological discoveries. My *Random House* dictionary defines serendipity as "the faculty for making desirable discovery by accident." Then, I began to wonder, do some folks have a faculty for making "desirable discovery by accident"? Was Louis Pasteur correct when he said, "In the field of observation, chance only favors the mind which is prepared"? What about the life cycles of *Plasmodium* spp. and *Trypanosoma* spp.? A number of investigators were looking for the way in which the malarial parasite was transmitted, not just Ross. Was Ross endowed with a 'special' faculty for discovery? Why did he 'hit the jackpot' sooner than the others? In the case of sleeping sickness, Aldo Castellani first saw tryps in the cerebrospinal fluid of humans, but he thought initially the disease was caused by a streptococcus infection of the heart. It was David Bruce, however, who is generally given credit for identifying the etiological agent of sleeping sickness. Why not Castellani?

I also began thinking about something else. Ross, Bruce, and the other giants of their era have been dead for many years. But, what about those individuals who made important discoveries in the past fifty to sixty years? It dawned on me that many of these parasitologists were either retired, or were close to it, and some have even died. They have important stories to tell, but they are generally not being told. I think these stories need to be out there as well, in full view. The new parasitology students need to know who these people were/are and they need to know why these folks, or what I call the 'middle generation' of parasitologists, did what they did.

Who would I choose to talk about and why would I select certain ones to focus upon? I realized early that this proposition could become rather 'dicey'. Whenever anyone makes a selection of this kind, some folks will be annoyed because one of their favorite people was left out. On the other hand, since I am the one doing the writing, it must be my choice. So, that's what I did, I made some hard choices. I considered a long list of ideas and possibilities. I then proceeded to choose my favorite 'discoveries', my favorite parasites, and my favorite people (at least some of them). As it turned out, it is a very eclectic group, in

all three categories. In a few cases, I could not conduct an interview because the person is dead. So, I had to rely on someone else to tell the story for them, but I was lucky because I had some very good sources.

Another point, I am writing these 'stories' as essays because I think this format gives me freedom to roam. I am not bound by a particular style, and can pretty much go where I want and take a particular topic as far as I want. I also decided to place in a Prologue at least some of the biographical information regarding each person that I have interviewed, or that I talk about extensively in the specific essay. Each of the interviews begins the same way. Where did you go to school, first as an undergraduate, and then as a graduate student? How did you get into parasitology? When did you graduate? Then, I wanted to use fairly standard questions in an effort to get some sort of idea about how they think, where they might have traveled to do their research, why their work went the way it did, etc. In obtaining information like this, I was able to generate some useful comparisons of some very good parasitologists.

It was fun!

DICK SEED

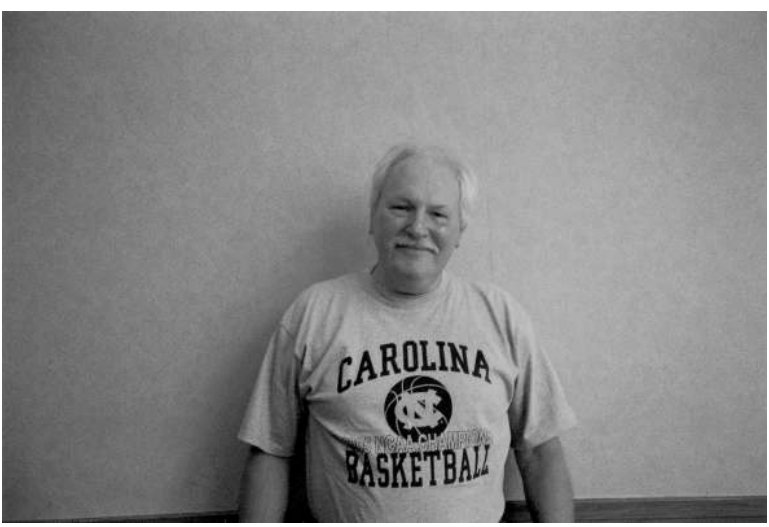

Figure 1. J. Richard Seed, retired Professor, Department of Epidemiology, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina

While thinking about discoveries in parasitology over the past fifty years, it occurred to me that the research on variant surface glycoproteins (VSG) would be of interest in connection with the story of how the life cycle of the African trypanosomes *Trypanosoma brucei brucei* was worked out by David Bruce. After doing some 'snooping' around in the appropriate literature, two names, J. Richard Seed and Keith Vickerman, F.R.S., recurred with some frequency. I decided to interview both of them and ask about their contributions to the VSG tale. Dick Seed was just down the road in Chapel Hill, North Carolina, an easy drive from Wake Forest and Winston-Salem, and Keith Vickerman was at the Glasgow University in Scotland, so I went there to see him as well, an easy trip by plane and train via London.

In May of 2004, I drove to Chapel Hill and spent the morning drinking tea and visiting with my friend Dick Seed. I have known Dick for nearly thirty years, having met him the first time at an American Society of Parasitologists meeting in San Antonio, Texas, in 1976. That was the year he received the H. B. Ward Medal for his contributions to the immunology and biology of the African trypanosomes.

Dick's undergraduate days in the mid 1950s were spent at Lafayette College in Pennnsylvania. He said that his interest in biology was already present when he entered Lafayette. While there, his enthusiasm for microbiology was 'tweaked' by Professor Willis ("Bugsy") Hunt, a 'Yaley', who then encouraged him to follow his lead and also head for Yale and his Ph.D., which he completed in just three years, working in the lab of David Weinman. According to Dick, "The latter was an M.D., and had spent much of his life . . . doing parasitology all over the world." Weinman was working on the African trypanosomes and this is where Dick focused his graduate research as well. While Dick's experience at Yale was a good one, he lamented that it was too short, just three years, and that there were many techniques, etc., he felt he should have learned, but did not have the time. For any young person reading this book, this is very good advice. Along the way, someone may advise you to skip the Master's degree and go straight for the Ph.D. I disagree. I strongly believe the Master's degree is excellent preparation for pursuing the Ph.D. degree. It presents you with an element of practice for what is to come.

I was interested to learn that, as a youngster, Dick had read Paul de Kruif's (1926) *The Microbe Hunters*, and that this is what stimulated his interest in infectious disease and, subsequently, in parasitology and trypanosomiasis. Another book, Geoffrey Beale's (1954)

The Genetics of Paramecium aurelia, had also caught his attention. Among other things, the latter book detailed the phenomenon of antigenic variation, which ultimately led him to a postdoc with Irving Finger at Haverford College in Pennsylvania. His thinking was that "antigenic variation among the African trypanosomes was similar to what occurred in the mobilization antigen on *Paramecium*. If I learned about the latter, then I could use the tools of the *Paramecium* geneticist to understand the African tryps." (When you read on, you will discover that the same two books had a huge influence on the career of Keith Vickerman too, another veteran of the antigenic variation effort, plus several others that I interviewed for the present book.)

As I will detail in my essay on African trypanosomiasis and VSGs, Dick did not really follow up on any of his Ph.D. research after he finished at Yale. In 1960, Jacob and Monod won a Nobel Prize for their discoveries regarding the regulatory processes associated with β-galactosidase in *Escherichia coli*. Dick's mission for most of his post-Ph.D. professional life was to search for what turned out to be an elusive regulatory process in trypanosomes. In graduate school and throughout his career, he made several important discoveries, but not the one for which he was ultimately searching. As will be seen from the trypanosome essay, however, the absence of 'ultimate' success was not for a lack of trying.

Dick's stay at Haverford was brief since 'Uncle Sam' decided to 'hire' him as a Medical Service Officer for the U.S. army. He was assigned to Fort Baker, just north of San Francisco, where he spent the next two years running a parasitology diagnostic laboratory. It was not a wasted time as he had two very good technicians from whom he learned a "lot about parasitology and diagnostic procedures." Following Fort Baker, Dick traveled to New Orleans where he became an Assistant Professor at Tulane University, advancing to the rank of Professor over the next eight years. After that came five years at College Station, Texas, and Texas A&M University, where he served as Chairman of the Biology Department. It was then on to Chapel Hill, North Carolina, where he became Head of the Department of Parasitology in their School of Public Health. He serves there as Professor of Epidemiology, although this (2006) is his last year before retirement.

I really enjoyed that morning in Chapel Hill with Dick. My stay was greatly enhanced by the presence of Dick's lovely wife, Judy, who provided tea and pleasant conversation during our breaks.

KEITH VICKERMAN

Figure 2. Keith Vickerman, FRS, retired Professor, University of Glasgow, Glasgow, Scotland

In late May 2004, my wife, Ann, and I drove to Charlotte, North Carolina, and boarded a flight for Gatwick Airport, near London. After a couple of days of getting our body clocks reset, we took a train to Glasgow where I was to interview Professor Emeritus Keith R. Vickerman, F.R.S. We arrived at Central Station around 2:30 P.M. and checked into our hotel. Ann suggested we take the underground out to the campus of Glasgow University and scout out Keith's office, so I wouldn't be late for my appointment the next morning. We not only found it, but also actually met and spoke with Keith for a few minutes that afternoon. Ann then wanted to visit the wonderful Hunterian Museum on the University's campus, which we did. We did not see much because they ran us out at 5:00. As we were leaving, we were caught in a classic thunderstorm. By the time we made it back to the tube station, we were drenched (no umbrellas – great planning!). When we emerged from the tube station at the other end, it was still pouring. So, she suggested we make at dash for a nearby 'Boots' (a chain drugstore in the U.K.) and buy a couple of cheap umbrellas. We came out with our new protection and walked back to the hotel, 'singing and dancing', in the rain. (By the way, as I could have predicted, we did not use the umbrellas over the next two weeks of our stay in the U.K.)

The interview the next morning went really well. Keith had even prepared a written autobiography and a full CV for me to take home.

He said it was part of an 'obituary' he was required to write when he was elected Fellow in the Royal Society. I don't know if he was 'pulling my leg' or not, but the written information did come in handy while preparing the essay on trypanosomiasis.

He told me that his entry into the biological realm was triggered by a serendipitous event, one that occurred early in his life. As a twelve-year-old in grammar school, he was enrolled in a second year science course devoted to the history of microbiology. With the sudden departure of his instructor, a mathematician with absolutely no training in biology was recruited as a replacement. Not knowing what to teach, the teacher, Keith said, "read to us from Paul de Kruif's *The Microbe Hunters*. I was spellbound," and a brilliant career began.

Keith went on to say that Elie Metchnikoff, the legendary Russian zoologist, was to become his idol. It was Metchnikoff who deduced that phagocytic cells in mammals may be involved as a defense against intruding pathogens while he watched similar-type cells attack thorns experimentally introduced into the bodies of larval starfish. Keith said he realized "later that it [Metchnikoff's idea] represents a perfect example of Popper's view of the scientific method – that a single observation inspires a flash of intuition that leads to a fashioned hypothesis that can be tested by further observation and experiment with a view to falsification or corroboration." What a great description of the scientific method!

Keith's undergraduate academic career began at University College London (UCL) in 1952, under the tutelage of Peter Medawar (who was to become a Nobel Laureate in 1960 for his work on skin graft rejection). While he enjoyed his relationship with Medawar, he considered him to be somewhat 'baronial'. When Keith announced his interest in parasitology for graduate work, Medawar was rather scornful, referring to parasitology, "as a somewhat philistine pursuit, far too long cut off from the advances of mainstream fundamental biology." In our interview, he said that Medawar considered the discipline as "impenetratively deaf to all the advances in biology for the past 50 years." (Keith told me he thought at the time, "Well, there must be an awful lot of catching up to do – all the more reason for getting into it.") However, for Medawar, protozoology was another matter. He was very impressed with the great American ciliatologist and geneticist, Tracy Sonneborne, and said to Keith, "The Research Councils are very concerned about the dwindling population of protozoologists, so why not become a protozoologist," and Keith responded, "I will." Keith actually became a protozoan parasitologist,

with an early, and then a long-term, research focus on the African trypanosomes.

In fact, because he wanted to work on trypanosomes, doing his Ph.D. presented some difficulty because he could not settle on someone with whom to study or who would take him on as a student. He finally ended up at the University College of the South West, in Exeter, with R. S. J. Hawes, working with protozoans of soil and soil-dwelling insects: "not exactly what I had envisaged, but I did manage to find a trypanosomatid in tipulid (crane fly) larvae." He was not entirely pleased with his experience there, although he did manage to spend a "term" working at "Edinburgh University in Michael Swann's thriving cell biology group." It wasn't totally bad at Exeter because he also met F. E. G. (Frank) Cox, a fortuitous event. Keith said that, "Frank was in a class I had demonstrated to and he had been a technician with P. C. C. Garnham" at the London School of Hygiene and Tropical Medicine. Keith and Frank were to become life-long friends and colleagues.

When Keith finished at Exeter, he went back to UCL and Peter Medawar's immunology lab, where he was offered the opportunity to work on any protozoan he wanted. He naturally went to the African trypanosomes. He also chose to focus his efforts on antigenic variation because of a book by Geoffrey Beale, *The Genetics of* Paramecium aurelia (the same one that Dick Seed had read). When I returned from London/Glasgow, I phoned Seed to tell him about my interview with Keith and then sent him a copy of the information that Keith had prepared for me. A few days later, Dick returned my phone call and excitedly described for me how many parallels there were between his early biological experiences and those of Vickerman. Both were to have huge successes in their work on antigenic variation in the African trypanosomes.

Keith's "fascination with life cycle changes and their relation to survival in changing environments" began as a student and stayed with him throughout his career. His research on the African trypanosomes actually focused on two areas, both of which were tied to life cycle changes and changing environments. Thus, for example, he spent a great deal of time attempting to understand the energy metabolism of the organisms, discovering in the process that in the tsetse fly gut, the amino acid proline is the main energy source. In the vertebrate, the trypanosomes switch to an aerobic glycerophosphate oxidase system. He was able to correlate these metabolic differences with significant morphological changes in the mitochondria as the parasite moves from the fly to the vertebrate host and back. It was while working on

these changes using electron microscopy that he made his second really important discovery. That was the physical presence of an antigen coat, the VSG, on the surface of the metacyclic form of the trypomastigote in the salivary glands of the fly. This was a significant event and one that was serendipitous – he was not looking for it. But, when he saw it, he knew about the significance of the coat, and he went after it. He made a huge discovery and a really momentous research contribution as a result.

Keith had a marvelous career at Glasgow University, retiring in 1993. He continues to write and do research in spite of a serious back injury recently suffered in a fall at his home.

BOB DESOWITZ

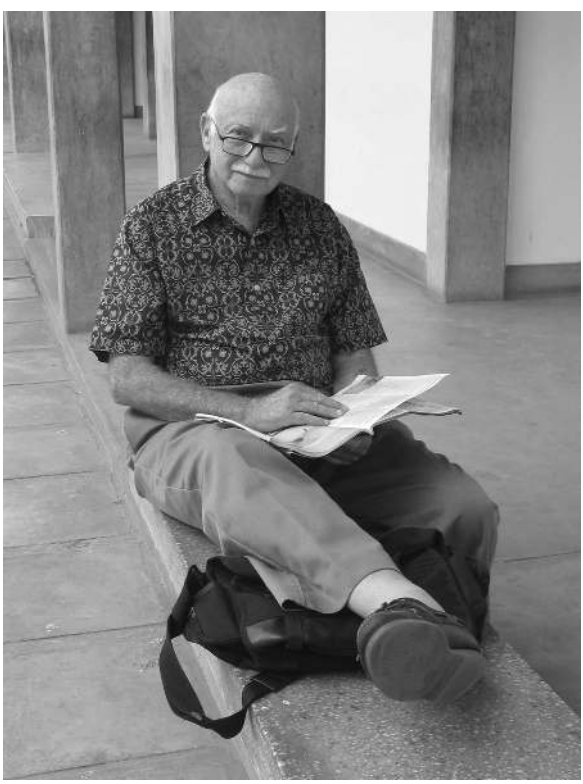

Figure 3. Bob Desowitz, retired Professor, University of Hawaii, Southern Pines, North Carolina

Bob Desowitz completed his undergraduate work at the University of Buffalo, in New York, with a two-year interruption by service in the U.S. Army right after WWII. He had become interested in microbiology and parasitology and decided to pursue the topics at the next level, graduate school. He asked his advisor at Buffalo where he should go and his mentor suggested the London School of Hygiene and Tropical Medicine. So, he applied and was accepted.

In the fall of 1948, Bob arrived at the London School of Hygiene and Tropical Medicine (LSHTM), ready to pursue his Ph.D. degree in protozoology with Henry Shortt, a former Colonel in the British Colonial Service. Fortuitously, Bob was in place to witness one of the great dramas of discovery in parasitology. Henry Shortt and P. C. C. Garnham were about to take the final step in pursuit of the *Plasmodium* spp. life cycle and solve a mystery that had been around for nearly 50 years. It seems that Fritz Schaudinn had reported in 1903 that the sporozoites of *Plasmodium* spp., on being inoculated into the blood of their vertebrate hosts by mosquito vectors, disappeared after about 30 minutes – correct! But, he also said that the sporozoites then penetrated red blood cells directly – incorrect! When Bob arrived, Shortt and Garnham had just finished the first effort to purge this assertion using *P. cynomolgi* and monkeys. I'll write more about this huge discovery later.

During my interview with Desowitz, he described Henry Shortt as a "truly wonderful man, and was marvelous to work for." Bob also explained, "Shortt was big on lineages. He [Shortt] was taught by Sir Rickard Christophers, and Christophers was taught by Sir Ronald Ross, so I'm a direct descendant of Ronald Ross!" Bob's Ph.D. research was on *Histomonas meleagridis*, the causative agent of 'turkey blackhead'. He told me that he kept all of his turkeys up on the roof of the building housing the LSHTM. It was soon after the war and there were still food shortages in the U.K. Each year, at Christmas time, Bob said, "Shortt and Garnham would show up at his lab space and inquire as to the availability of a control turkey."

When he completed his dissertation research, he was searching for a place to publish his work. Shortt persuaded him to submit it to *Nature* where it appeared as his first publication ("not a bad place to start," he proudly remarked during our interview). With his Ph.D. in hand, he was about to take a position in the local poultry industry when a monacled Englishman showed up in his office. He