Written Review With: Abner Louis Notkins, M.D.

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Introduction: This memoir (partly oral and partly prewritten) is being conducted by E. Gordon Margolin, MD, volunteer in the Office of NIH History and Stetten Museum, in Dr. Notkins' office. He is the chief, Experimental Medicine Section, National Institute of Dental and Craniofacial Research and will relate his relationship with NIH as we go along. He is the author of over 425 scientific papers, editor of five books and recipient of three patents. Thank you, Dr. Notkins, for your willingness to record your information.

Margolin: To begin with, tell me a little of your family history and early years.

Notkins: I was born in New Haven, Connecticut. My father was a physician and my mother was the first or one of the very first female real-estate brokers in the New Haven area and an investor.

My parents had a beach house on Long Island Sound. I spent the summers swimming, fishing, and building sand castles. During World War II, I had permission from my father to turn part of his flower garden into a "Victory Garden" to grow vegetables. It was located only 50 yards from the high water mark but my corn, tomatoes, radishes, and string beans prospered. It was a small plot of land so I spent time figuring out how to rotate crops by reading plant books and drawing charts to determine how and where to place my plants. It was great fun and gave me something to do every day.

I went to the local high school where I turned out to be a good student. I was involved in many extra-curricular activities and in my senior year I was appointed editor-in-chief of the class year book and was elected president of my class.

Margolin: How about your college education?

Notkins: In terms of colleges I was accepted at both Yale and Dartmouth. Being a little rebellious I wanted to go to Dartmouth because my dad and my uncles all went to Yale. After much consultation I asked my English teacher who I highly respected. He put it this way: "At Dartmouth they read the books, but at Yale they write the books." I chose Yale and only years later did I realize I had been tricked, because my English teacher was a Yale graduate.

Upon entering Yale I soon realized that everybody was editor of their year book, president of their class, and much more. It was a very competitive environment, but discussion with my classmates was enormously stimulating. I took a divisional major entitled "Evolution, Culture, and Behavior" and the required courses for entrance into medical school.

Margolin: I'd like to learn a bit more about this enticing course. How may it have influenced you in your later life in science?

Notkins: The divisional major in evolution, culture, and behavior had a major impact on my thinking about the world. It showed me that one area in life, which at first seemed self-contained, in fact, interacted with many other areas and did not stand alone. This knowledge served me well in my research career where I was always looking for how one scientific area interacted with other scientific areas. When I first began, my research career in was in the area of virology and that rapidly moved me into the interaction between viruses and the immune system. From immunology I moved into molecular biology and genetics and more recently into genomics. All of these areas and the techniques involved are related to the basic problems that I have been and am continuing to study.

Margolin: Now tell me about your medical school and residency training.

Notkins: I received my M.D. in 1958 from New York University-Bellevue Hospital, where I spent all my elective time in research, which I enjoyed far more than much of the formal course work. I then did an internship and residency in internal medicine at Johns Hopkins.

Margolin: How then did you get to NIH?

Notkins: Immediately after Hopkins, in 1960, I had the good fortune of being accepted at one of the research laboratories at the NIH as a Public Health Service Officer. This served two functions. It satisfied my military requirement during the Vietnam War and gave me the opportunity to see whether research was what I wanted to do. The answer turned out to be yes and I now have been at NIH for over 56 years. My research has been interdisciplinary and focused in the areas of virology, immunology, and autoimmune diseases.

I will always remember my first day at the National Cancer Institute (NCI). My mentor, Dr. Maurice Landy, took me down one of the long corridors in Bldg. 10 and we entered a laboratory of about 250 sq. ft. He said, "Dr. Notkins, this is your laboratory, the young lady at the bench is your technician and this is the order book for you to get whatever you need." Upon leaving the lab, almost as an after-thought, he said, "Oh, Dr. Notkins, do something interesting." I was totally overwhelmed and for the next few weeks I took home more journals than I could carry and read furiously.

Margolin: What an interesting introduction for you to this fabulous facility. My guess is that techniques for indoctrination of new arrivals these days are a lot different. Right?

Notkins: Yes, but this is a story beyond what I want to get into. Anyone who reads what I said will immediately recognize how different it is today.

Margolin: I noticed in your bibliography that your early studies were with Lactate Dehydrogenase Virus (LDV) and Persistent Viral Infections. Could you elaborate about that?

Notkins: During my first few weeks at NCI I visited one of the labs that was studying the effect of different drugs on the growth of sarcomas in mice. I noticed that to evaluate drug effectiveness the investigators would sacrifice the mice and score by histology the degree of tumor necrosis. When I was doing clinical medicine before joining NIH, to measure acute tissue damage, we would obtain serum from the patient and evaluate the level of a number of enzymes, such as lactate dehydrogenase (LDH). I thought the same technique should work on sarcoma-treated mice and would not require histology and animal sacrifice. I obtained sera from these mice and observed an enormous increase in LDH. Most intriguing, this increase occurred several days after transplantation of the sarcomas into mice, long before the sarcomas had a chance to significantly grow. This suggested we were transferring an infectious agent that was associated with these tumors which we initially called the LDH agent. In-depth studies proved that the LDH agent was, in fact, a virus and that most of the transplantable tumors being studied at NIH were contaminated with this virus (LDV). Almost every experiment we did provided new information and LDV became my research teacher. Ultimately we learned that LDV produced a life-long viremia by infecting macrophages and thereby inhibiting the clearance of certain enzymes. Of particular interest, we found that the LDV persisted in the circulation in the form of infectious virus-antibody complexes which could be neutralized by anti-immunoglobulins. Many other viral infections now have been shown to persist in this form. At the same time we were studying LDV, Dr. Michael Oldstone at Scripps Research Institute was studying Lymphocytic Choriomeningitis Virus (LCM) which also produced a persistent infection. Taken together these studies helped to open up the field of persistent viral infections and viral immunopathology. I continued working in this area for many years by studying herpes simplex virus, human immunodeficiency virus, and cytomegalovirus.

Margolin: Then, I gather, your studies turned to natural antibodies and their behavior and properties. Tell us about that phase and about polyreactive antibodies.

Notkins: It was known for over 100 years that unimmunized normal mouse sera, in the absence of antigenic stimulation, could bind to a variety of self and foreign antigens including viruses and bacteria. These antibodies were known as natural antibodies, but little was known about their properties. We decided to study the properties of these antibodies by hybridoma technology. Using this technique we succeeded in isolating a number of monoclonal antibodies that to our surprise were not monoreactive but instead reacted with a variety of different and totally unrelated antigens. We referred to these antibodies as "polyreactive" and found that about 50% of the B cells in the human umbilical cord and about 20% of the B cells in the mature adult circulation were polyreactive. Further studies revealed that many of these polyreactive antibodies had germ-line or near germ-line sequences. Moreover, we found that these polyreactive antibodies could bind a variety of different bacteria and are now thought to be an important component of the innate immune system and a first line of defense before the adaptive immune system kicks in. Further studies showed that polyreactive antibodies were important in the phagocytosis of the millions of cells that undergo apoptosis each day. What makes polyreactive antibodies polyreactive has not been definitively demonstrated but it is generally thought that the flexibility of the antigen-binding pocket of polyreactive antibodies is more flexible than the antigen-binding pocket of monoreactive antibodies.

Margolin: You were on the cusp of very basic physiology in the area of immunity. I assume this led to questions that could be applied to disease-states. I know your first interest was in type 1 diabetes and viruses**.**

Notkins: My colleagues and I then asked whether other viruses could produce human disease equivalents in mice, such as type 1 diabetes. Dr. John Craighead of the

University of Vermont had just shown that encephalomyocarditis virus (EMC virus) could infect pancreatic beta cells. In our laboratory we studied this virus at both the histopathologic and molecular levels and found the onset of diabetes was dose and mouse-strain dependent. Studies at the human level were hard to perform because of the difficulty in obtaining viable beta cells. However, in one case that we studied of a child who died of acute onset type 1 diabetes we did succeed in isolating a Coxsackievirus from pancreatic beta cells. Furthermore, we found that this virus could produce type 1 diabetes when injected into mice. The role of viruses in type 1 diabetes is now actively being studied in many laboratories throughout the world, especially in Europe and Japan.

Margolin: And how did these findings lead you in relating type 1 diabetes and autoantibodies?

Notkins: An alternative possibility to viruses as a trigger of type 1 diabetes is autoimmunity. In the mid-1990s we succeeded in isolating a gene which encoded a protein that we called Islet Associated-2 (IA-2). Examination of sera for autoantibodies to IA-2 revealed that this autoantibody often appeared years before the onset of type 1 diabetes, and in combination with other autoantibodies is now widely used to predict which children are at high risk of developing type 1 diabetes. Studies on the molecular properties of IA-2 revealed that it is a trans-membrane protein of dense core vesicles that secrete insulin. Over expression of IA-2 increases insulin secretion, whereas deletion of IA-2 decreases the secretion of insulin. Further studies revealed that IA-2 is present in many different types of neuroendocrine cells and can also regulate their secretion, resulting in a variety of phenotypic alterations such as changes in behavior and circadian rhythm. Over the last few years the emphasis in our laboratory has been on the role of micro-RNAs in regulating the expression of IA-2 and other genes associated with insulin mRNA.

Margolin: I see that other major studies followed these discoveries. I am interested in hearing about the relationship of interferon and autoimmune diseases.

Notkins: Still other studies on autoimmune diseases in our laboratory led to the discovery of immune interferon in the circulation of patients with diseases such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma and Sjogren's syndrome. In certain of these diseases, particularly lupus, we found a good correlation between interferon levels and disease activity. These findings played an important role in opening the field of lymphokines in autoimmune diseases.

Margolin: These creative and signal studies certainly led to your having received multiple honors and recognition. Which ones do you consider the most outstanding?

Notkins: Based on various aspects of my research I have given a number of honorary lectures and received a number of awards, but there are four awards that I am most proud of. The first is the Distinguished Service Medal from Public Health Service (HEW) in 1981; the second, the 1986 Paul Ehrlich Prize from Frankfurt, Germany; the third, the 1989 Solomon Berson Award in basic science from my medical school; and the fourth, an honorary doctorate in 2007 from the University of Athens in Greece.

Because of my interdisciplinary approach to research, perhaps stemming from my background as a physician, I was invited to serve on the advisory committees of a number of organizations such as the Multiple Sclerosis Society, the March of Dimes, the Juvenile Diabetes Association, and the National Disease Research Interchange. I found my involvement with these organizations very enlightening and useful in thinking about my own research.

But the most significant recognition that I received, while living as a bachelor in Georgetown in Washington, DC, was meeting a young architect named Susan Woodward who agreed to become my wife. We have been married for 47 years.

Susan has her own architectural firm and has been my strongest supporter. Without her understanding and help I would not have been able to devote nearly full-time on my research. Architecture and collecting paintings has become our hobby.

Margolin: I commented at the outset that you have three patents in your name. Would you care to elaborate briefly on these accomplishments also?

Notkins: The patents don't add anything to my story. They just involved a lot of paper work with very little return.

Margolin: There have obviously been many changes in your role here at NIH over these years. What are some of the administrative issues you can recall?

Notkins: After spending a couple of exciting years at NCI in the early 1960's, I moved to a new laboratory in the building of the National Institute of Dental Craniofacial Research which had just opened with the commitment from the Institute that I would have a free-hand to work on whatever basic research project I found interesting and of potential importance. After about 20 years as a principle investigator at NIDCR, I was appointed Scientific Director (SD) of the Institute. At that time most SDs gave up their laboratories when they become an SD, but I insisted on keeping my laboratory. For approximately seven years I had the dual responsibility of managing the Institute and running my laboratory. Now it is very unusual for SDs not to have a laboratory. The advantage of being SD was that I had interaction with SDs from all the other Institutes and could discuss a variety of scientific, administrative, and philosophic issues. At one of the meetings I commented that the different Institutes were like silos and that we should have more interaction among the Institutes. I was told to come back with a suggestion. I proposed what is now known as the NIH Research Festival and the idea was accepted by the SDs. The Festival now lasts for two to three days. There are major symposia, workshops, and poster sessions on topics that involve individuals

from the different Institutes who are working in the same or overlapping scientific areas. The Festival turned out to be a great success with as many as 2000 people attending the various sessions each year. We will be celebrating its 30th anniversary this coming fall.

Margolin: What technological changes have you observed over these years that you consider some of the most important contributions to the rapid increase in scientific knowledge in general?

Notkins: Over the years there have been an enormous number of technological changes such as the MRI in clinical medicine, and genomics at both the clinical and basic research levels. But what I believe has produced the greatest number of changes for the greatest number of clinicians and basic research scientists is the computer and the associated internet. When I first came to NIH, secretaries would type manuscripts and make copies by using sheets of carbon paper. Each week I would spend hours in the NIH library to read the latest journals and search the stacks for appropriate references. The communication with colleagues in the United States and Europe was by "snail mail" and often would require many days to receive a response. There was no such thing as data bases or bioinformatics. This has now all changed with the computer and in my view this has led to the most dramatic changes as to how we do science, communicate, and administrate. There are no longer just "wet labs" but a combination of "wet lab" scientists with "in silico" scientists.

Margolin: What technology enabled you to do your work, specifically? Did you produce your own instruments?

Notkins: We used state of the art technology and added new technology when it became available. We did not make our own instruments.

Margolin: How about giving us an overview of your experience as a research scientist at the NIH.

Notkins: I never thought that being a research scientist at NIH was a job; it was more like having a hobby in which I was totally immersed. NIH allowed me to explore my own ideas which in most cases were curiosity driven. I didn't have to constantly apply for grants or teach courses. It allowed me to spend most of my time in the laboratory, interact with my fellows and with colleagues at NIH, who were interesting and intellectually provocative. NIH was not Camelot; there were up and downs, but I can't think of a better place to do research and I loved it.

Margolin: And what is this about the Notkins Research Foundation?

Notkins: During the early part of my career I was fortunate enough to have been invited to a number of small focused meetings in Europe involving 20 to 30 people. These meetings allowed me to meet some of the top scientists from around the world and to spend several days with them interacting and discussing in depth specific scientific topics. These small meetings contrast to the large professional association meetings at which there are often 10,000 or more people. I found the small meetings, which are still rare in the United States, far more satisfying and important in my development as a scientist. To give other scientists this opportunity I now have established "The Notkins Research Foundation" with similar purposes and goals. The Foundation will be funded in stages over the coming years and I hope it will have a positive impact on science and scientists and further our understanding of biology and the pathogenesis of disease.

Margolin: Thank you so much, Dr. Notkins.

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