Keyvan Nazerian

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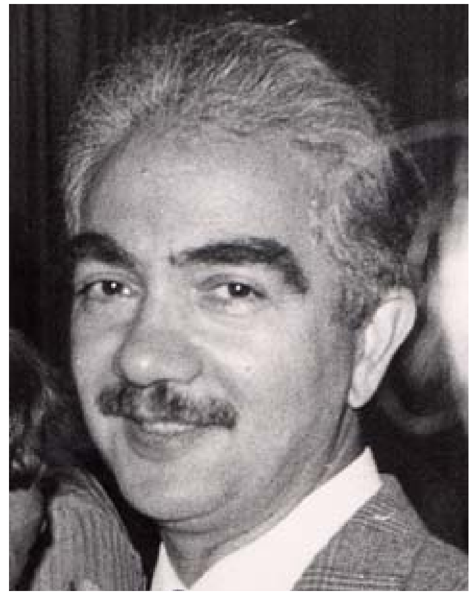

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Reflections

I intended to go to the medical school in Tehran, my home town but, as back ups, also took entrance examinations to a number of other colleges including the college of veterinary medicine. I was accepted to all except the medical school and decided to go to the veterinary school since it seemed to be very close to the medical field which I was interested in. I found it very fascinating and just as challenging as the medical field. I enjoyed my studies and did very well in all subjects including anatomy, physiology, genetics, parasitology, microbiology, infectious diseases and surgery. I found the study of the animal body and infectious diseases and how microorganisms caused diseases very fascinating. Upon my graduation in 1958, I took a competition examination and was offered an opportunity to come to the United States for graduate studies. I was accepted to Michigan State University and shortly after my arrival decided to join the virology laboratory of Prof. Charles H. Cunningham in the department of Microbiology. Charlie was working with avian infectious bronchitis virus and this started my work in the avian field. After finishing my MS degree at Michigan State University in June of 1960 my wife Farzaneh and I went to Italy to volunteer our services to the Baha'i Faith which was just developing its roots there. Meanwhile, I attended the Public Health Institute of the University of Padova as a visiting scientist while we were in Italy. When our Baha'i

service in Italy was finished in mid 1963 we returned to the US with our newly born son, Michael, and I went back again to Charlie's lab to finish a PhD program.

In June of 1965 I received my PhD and joined the virology department headed by Ray Dutcher at the South Jersey Medical Research Foundation in Camden, New Jersey to investigate the cause of bovine leukemia. At that time there was a herd of cattle at the University of Pennsylvania, New Bolten Center with high incidence of leukemia/lymphoma. Ray Dutcher and Bob Marshak from the Veterinary School at the University of Pennsylvania had received large grants and contracts from the National Institute of Health for these studies. It was there that I became familiar with the field of viral oncology. In those days, the story of Epstein-Barr virus as the possible cause of human Burkitt's lymphoma was just out. It captured my imagination and gave me some good leads in herpesviruses as possible causes of cancer. My wife and I were not too happy living in highly populated New Jersey and wanted to move away. I learned of a position at the Regional Poultry Research Laboratory in East Lansing and wrote to Ben Burmester who was the director of the Lab and whom I had met before and had a great deal of respect for. He was very pleased and favorable to my application. Shortly he offered me the job without having even interviewed me. So we came back to East Lansing in the summer of 1966 and I started setting up the electron microscopy laboratory and at the same time started a new project on Marek's disease (MD). Looking back retrospectively, it is clear to me that I came back to East Lansing to join the right group of scientists and at the right time. The stage was set for a systematic study and discovery of the cause of MD. Experimental transmission of MD had been accomplished and Dick Witter had worked out a short and reliable in vivo assay for MD allowing us to do quick transmission experiments. Expectations for an infectious viral agent were high. It was about two months after I joined the lab, in October 96, that I first observed herpesvirus particles in the gonad and nerves of a couple of birds with MD. I was very excited about this finding and showed these micrographs to my colleagues in the lab who did not seem to be impressed. At that time everybody was expecting an RNA virus similar to the leukosis viruses as the cause of MD and talking about a DNA herpesvirus was near to being a fool! A couple of months later John Solomon who was working in Dick Witter's lab detected some cytopathology (cpe) in cultures of duck embryo fibroblasts (DEF) that he had inoculated with blood from MD chickens. Both Dick Witter and John had been working on this project for some time. Colleagues at the lab felt that he had some contamination with Rous sarcoma virus (RSV) and those foci were RSV "pocks". John gave me a culture and I examined it with the electron microscope and found many herpesvirus particles. I became really ecstatic and went around the lab and showed those pictures to everybody. John seemed unable to repeat his experiment for a while and I tried to isolate the herpesvirus in culture. Every culture that was inoculated with MD blood in my lab showed the cpe and had herpesvirus. An important aspect of all of this was a suggestion by Bart Rispens**,** from the Netherlands who was doing a sabbatical in our lab, to use DEF. John had used DEF in his initial isolation and it turned out to be very effective. All cultures having cpe and the herpesvirus were infectious and caused MD in chickens but cultures without the cpe and the herpesvirus failed to do so. With all this evidence, skeptics were still strong until Peter Biggs from Houghton Poultry Research Station near Cambridge in England visited our lab just before going to the

AVMA meeting in Dallas in July 1967. Ben Burmester told him about our findings and Peter also shared his findings with us. His observations were quite similar to ours. That year I was not scheduled to go to the AVMA meeting but Burmester asked me to go and present my work. Both Peter and I gave essentially similar findings to the Leukosis Committee and the AAAP session. Many of the colleagues were skeptical about these findings but the public press was very interested and a number of reporters interviewed us. The news came out in public press including the New York Times and many local and poultry industry oriented publications. This was really the turning point in our MD research and from then on the entire group in our laboratory joined us in working on the new herpesvirus.

Tony Churchill and Peter Biggs' paper on this discovery was submitted to the weekly journal, Nature, and came out in 1967 but our paper was submitted to the Proceedings of the American Society of Biology and Medicine, a slower journal, and was published in January 1968. Later in the summer of that year I traveled to Europe with my wife and our two sons Michael and Alan to attend her brother's wedding in Padova. Italy and participate in an international Baha'i conference in Palermo. Sicily. On our way home we stopped in England and visited Peter Biggs and his colleagues at the Houghton Poultry Station. Tony Churchill, Jim Payne, Bill Baxendale and Peter Biggs and I exchanged our recent findings and talked about things to come. Shortly after my return to the US, I received an invitation from Peter Biggs and Guy deThe who was at the International Agency against Cancer in Lyon, France to the First International Symposium on Herpesviruses and Neoplasia to be held in Cambridge, England the following year. I was asked to give the opening paper on the virology and immunology of MD. That was the most exciting scientific meeting I ever attended. Researchers from all fields of herpes virology and cancer were in attendance and many scientific breakthroughs were presented at that meeting. I met many prominent researchers at that meeting including Professor George Klein of the Karolinska Institute in Sweden. He was very keen about our findings and was very much impressed with the progress. I spoke to him about the possibility of spending a year in his tumor biology department in Stockholm. He was delighted to hear that and encouraged me to start the process. He became a good friend and significantly influenced my future research on MD. Even though he was not working with MD and his concern was human cancer, yet he was extremely enthusiastic and very supportive of our work. I spent a year of sabbatical (1972-73) with my family, which was now larger by arrival of Lily a couple of years ago, in Stockholm and worked with George and his colleagues at the Tumor Biology department of the Karolinska Institute. This experience opened a new chapter in my career and gave me a wider perspective in tumor biology and immunology.

The puzzling thing of course was the mode of MD virus replication in the chicken and the mystery of the infectious nature of MD which was not compatible with a cell associated herpesvirus we had in culture. A report was just out that Joe Beasley had successfully transmitted MD through the use of contaminated dander. Bart Rispens and I had been talking about human chickenpox virus, a herpesvirus, and that skin lesions (vesicles) were the source of infectious chickenpox virus and spoke of the possibility that we may have a similar situation with MD virus. After learning of Beasley's findings I collected

some dander from isolators with MD chickens and prepared them for electron microscopy. This was a hard job since dander is not a typical sample one can use for electron microscopy. However, when I looked at the samples with the electron microscope I found an abundance of herpesvirus particles. Marius Ianconescu from Israel who was visiting our lab had just attended the Northeast Regional Poultry Conference in Minneapolis, and came back with news from Bruce Calnek of Cornell University that they had detected MD specific antigens similar to those Graham Purchase had seen in MDV infected cell cultures, in the base of the feather follicles of MD infected birds. This encouraged me to immediately look at the feather follicle epithelium with the electron microscope and try to extract cell free virus from this source. Results came beautifully and Dick Witter and I run a number of experiments showing cell free transmission of MD and electron microscopic evidence of the in vivo replication of the virus. The paper was shortly accepted in the Journal of Virology and was published in 1970. In the meantime Bruce Calnek and his group continued their work and published a similar paper in Avian Disease the same year. By now the etiology of MD was clearly established and work on development of vaccines from MDV was underway.

Tony Churchill and Peter Biggs in England showed in 1969 that attenuated MDV could protect against challenge with the field virus. Dick Witter in our lab had isolated a virus from turkeys suspected of round-heart disease. We worked together and found that the virus was a herpesvirus and that it was antigenic ally related to MDV. Ben Burmester called for a meeting to discuss the possibility of using the turkey herpesvirus for vaccine against MD. We all agreed and Bill Okazaki and Graham Purchase initiated a research project on this topic. Results were highly successful. Soon the turkey virus vaccine became the most frequently used vaccine against MD in the US and elsewhere.

By now a great deal of research had been conducted on the etiology and immunology of MD. After my return from Stockholm, I shifted my studies to more fundamental aspect of MD and with collaboration with Lucy Lee in our lab worked on transformation of lymphocytes by MDV and the status of MDV DNA in transformed cells. By 1980-811 reduced my work on MDV and started a new project on turkey hemorrhagic enteritis. Jagdev Sharma in our lab had succeeded to produce MD tumors in turkeys inoculated with virulent MDV. I developed a number of cell lines from these turkey tumors. These cell lines failed to produce MDV. I used these virus free cell lines to see if they can support the growth of hemorrhagic enteritis virus (HEV). Soon we found out that both HEV and marble spleen disease virus (MSDV) grew in one of the cell lines and we were able to obtain large liters of the virus. An effective cell culture propagated MSDV vaccine was developed against hemorrhagic enteritis and with collaboration with Aly Fadly in our lab we conducted the field vaccination studies. This work was patented and soon APHIS approved the vaccine for turkeys. Shortly it was accepted by the industry and became the predominant vaccine used in the field.

By 1984 when an effective vaccine was developed against hemorrhagic enteritis of turkeys, I shifted my research again back to MDV. By this time a number of new virulent MDV strains were isolated that were not well protected against by conventional vaccines. We decided to start two new projects on developing recombinant vaccines against MD.

One project was to use the herpesvirus to construct a recombinant virus and the other one was to use fowl pox virus (FPV). We knew quite a bit about the molecular biology of herpesviruses but nothing about fowl pox virus. Bob Silva was assigned to the herpesvirus work and I was to work with FPV. There were two problems: One was to develop FPV constructs for insertion of MDV genes and the other one was to identify and clone immunogenic genes from MDV. Lucy Lee was working on MDV genes and I was planning to use those genes as they became available. It took us nearly 4 years to do the work. Initially we constructed a few model recombinants using expression of bacterial genes but our huge success came when we collaborated with Nippon Zeon. of Tokyo, Japan and invited their scientists Noburo Yanagida and Rhyo Ogawa to visit our lab and work with us on constructing candidate recombinant vaccines. Finally in 1991 we constructed and tested recombinant FPV vaccines that expressed genes from MDV and indeed protected against MD. Soon, Lucy Lee cloned additional MDV genes and we constructed over a dozen recombinant FPVs expressing a number of MDV genes from different serotypes. Dick Witter worked with us and we showed that not all these recombinant viruses were protective but we certainly had several candidate vaccines. In addition we developed recombinant FPVs that expressed envelope antigens of avian leukosis virus, avian reticuloendotheliosis virus and laryngotracheitis virus.

Throughout my scientific career two major factors significantly contributed to my success. One was my association with competent, imaginative and cooperative colleagues both in our own laboratories and elsewhere; a few are mentioned here but there were many more who could not. They were internationally recognized research scientists, many of whom have received outstanding recognition and awards including the Noble Prize in medicine and physiology. This confirmed my strong belief that all major human achievements are the product of direct and indirect interaction and cooperation between scientists from diverse cultures, races and nationalities. Most of my publications and patents are clear reflections of this observation. To all these colleagues I owe a great debt of gratitude. The second factor was my ability to quickly identify, in most projects that I started, the most important and practical aspect of the problem we were trying to solve and then pressed on fully until the goal was achieved. This allowed me to see the light at the end of the tunnel and press on until I got there without loosing sight of the real goal and without being sidetracked by other perhaps minor and less important issues. Some details were missed in this process, but usually follow-up studies were conducted soon after these initial findings. My professional career gave me a great opportunity to repeatedly travel to countries like England. France. Germany, Italy, the Netherlands, Denmark. Sweden, Austria, Hungary, Israel, Iran, Switzerland, Japan, Canada and to many places in the US and gave me the opportunity to interact and directly collaborate with scientists and colleagues from many places and diverse cultures. Experiences I gained in this process have given me a broad perspective in science, personal career and life in general that I will cherish for a long time.

Biography solicited by the Committee on the History of Avian Medicine, American Association of Avian Pathologists.

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