February 7, 1991

CAREERS IN VIROLOGY: A GOOD BEGINNING IS USUALLY REQUIRED FOR A GOOD ENDING

I have been asked to comment upon the future of virology and predict the most important advances we can expect within the next decade. This is an assignment I did not seek because long range predictions of the course and direction of science most often end up being quite far off the mark. I am somewhat more comfortable about discussing factors that are essential to the strength of virology and that must be nurtured and sustained in order to maintain the health of this enterprise. I will defer my role as a prognosticator but I am certain that Nostrodamus has nothing to fear.

The earliest phase of a new investigator’s training is undoubtedly the most critical period in his or her scientific career. A failure of the young scientist or a failure on the part of the research establishment during this interval usually removes that person from the system. Potential difficulties abound so that it is remarkable that so many young scientists manage this journey successfully and emerge as independent investigators. As I think back to my beginnings it is difficult to escape the conclusion that good fortune played an extraordinarily large role in my successful transit through the birthing event and early infancy as a laboratory trainee. This set me to examine the possibility that the invisible hand of a powerful deity had been at work. Because these events occurred during periods of great strife such as World War II and the Korean War, I felt that the single god defined by Judeo-Christian belief would have had more pressing and important problems to deal
with than the career of an embryonic scientist. For this reason I pondered the possibility that a more specialized god with a more circumscribed job description might have been responsible. I was able to identify such a god who had been active two to three millennia ago but who was granted early retirement after the advent of Christianity.

His name was Janus and he was a Roman god often listed in prayer ahead of Jupiter. Janus was the god of a good beginning which was certain to result in a good ending. His chief temple was in Rome and extended from east to west to mark where the day begins and ends. The temple had two doors between which stood his statue which had two faces that looked in opposite directions. One face was young and one face was old. Janus presided over all doors, gateways, good beginnings, the first hour of the day and the first day of the month. The first month was named after him. It was believed that because he simultaneously faced backward and forward he knew the past and was able to use this knowledge to ensure a successful passage into the future. In this capacity he undoubtedly served as the gatekeeper of Roman science and it is possible that he continues to function in this manner in our contemporary Temple of Science, specifically that domain devoted to virology.

Janus, or another equally beneficent influence, led me to the University of Chicago School of Medicine where Dr. Howell Wright was Chairman of Pediatrics. He quickly became my role model for an academic biomedical scientist. I was not alone because a disproportionately large number of my classmates also chose a career in pediatrics for the same reason. Howell Wright was a pediatrician's pediatrician and he was also sought out by most of the faculty of the University of Chicago. After finishing his clinical training he
had been a research fellow at the Rockefeller Institute with Dr. Leslie Webster. His research interests included the flaviviruses which brought him into contact with Dr. Albert Sabin, who was studying similar viruses in the neighboring laboratory of Dr. Peter Olitsky. As I was completing my clinical training in pediatrics, Howell Wright suggested I consider a fellowship with Albert Sabin who was then at the University of Cincinnati. He told me that Albert would bring order and discipline into my life, something he felt was needed at that time. As usual Howell was right on the mark.

When I joined Albert Sabin's laboratory in 1950 as a research fellow, he was the apotheosis of the solitary scientific giant. While a medical student he had recovered and characterized B virus, a simian herpes virus of considerable interest. He also developed rapid tests for identification of pneumococci that gained him an international reputation. Subsequently, during his post graduate research at Rockefeller Institute he began his study of poliomyelitis. He also quickly assumed a dominant position in several other disparate areas of research, for example, the pathogenesis of neurotropic virus infections and the role of murine mycoplasmas in diseases of the joints and central nervous system of the mouse. During World War II he served as a colonel in the Army Medical Corps assigned to the Surgeon General's office. He seemed to be everywhere, Cincinnati, Princeton, Cairo, and the Pacific Islands. The result: the first isolation and characterization of the dengue viruses (work done with Walter Schlesinger) and similar achievements with Sandfly fever viruses. In addition he developed a Japanese B encephalitis virus vaccine that was used extensively preceding the invasion of Okinawa. After the war his pioneering studies of toxoplasma infection provided much of the basic information about this important cause of congenital
defects in the central nervous system.

It is hard to believe but Albert actually did have a mentor at the beginning of his career. Dr. W.H. Park, a leading bacteriologist, made it possible for Albert to do research while in medical school. Albert probably only needed a quick jump start and he was off and running. Most of us, however, require considerable nurturing before we are ready to set an independent course.

Albert's great strength was and continues to be his ability to resolve a research problem into a series of clearly formulated questions and to attack each question with precision and simplicity. I can assure you that when Albert is moving upon a research objective there is little wasted motion. He moves like a master fencer, avoiding the shot gun approach favored by so many others. Finally, his ability to analyze and synthesize complex data is legendary. What a role model!

He kept his laboratory quite small so that he could perform most procedures himself or closely supervise those tests he assigned to junior scientists or technical support staff. This meant that Albert was almost always in the laboratory and accessible.

When I was redrafted into the Army during the Korean War, Albert arranged for me to be assigned to the Virology Section of the 406 Medical General Laboratory in Tokyo. There I worked with Edward Buescher, later to become Commandant of Walter Reed Army Institute of Research (WRAIR), and Bob McCollum, later to be Dean of Dartmouth Medical School. In this setting there was close and continuous collegial interchange that catalyzed my scientific growth and independence. A most wonderful experience that forged close and long lasting friendships.
During the two years I was in the Army, Albert developed his successful strategy for characterization and selection of live poliovirus vaccine strains. In addition, a number of promising candidate strains had been identified and were under study. On my return Albert was confident that the poliovirus vaccine program was moving rapidly towards a successful conclusion. Because of the increasing momentum of the program, there was an urgent need to expand the laboratory staff. Despite this need, Albert insisted that I develop an independent research program. Even though many years have passed, I am still impressed and appreciative when I consider Albert's generosity toward me at that time. Fortunately, this part of the story had a happy ending because my initial solo research effort yielded the first human parainfluenza virus. This propitious event represented my graduation from fellowship status. I owe this important transition to Albert who judged me to be ready and then provided the resources needed for an independent program.

A mentor is defined as a friend and sage advisor. In my case both Howell Wright and Albert Sabin exceeded this job description because they did more than give advice. They intervened in a most positive and favorable manner. Being a scientific mentor also carries the responsibility for weaning a young scientist from training status at just the right time and providing a scientific environment that favors early success during initial independent research. Prematurity and postmaturity are to be avoided at all costs. I must say Albert's timing was perfect.

Against Albert's strong admonitions I transferred to the Johns Hopkins School of Hygiene and Public Health in 1956. My year in Baltimore was a banner time as regards scientific discovery, but except for Bernard Roizman, who was a doctoral candidate, there
was very little opportunity for interaction with peers. Fortunately, several years earlier, Albert had set the stage for my next and final move. This occurred when I was in the Army being trained at Walter Reed Army Institute of Research (WRAIR) in preparation for assignment to the Far East. Albert visited me in Washington and suggested that I should meet Bob Huebner. There were not very many microbiologists Albert held in high regard, but Bob was one of the select few. Albert arranged a meeting with Bob and the circumstances of this encounter were certainly in keeping with the free and open spirit of this man I came to respect and admire greatly. We met Bob in a supermarket parking lot near my apartment and we sat in his car in animated conversation for over 2 hours. Bob had to cut short our discussions because he had to meet a group of Angus cattle breeders to negotiate the sale of one of his cows.

The next time I saw Bob was 4 years later when I was on the staff at Hopkins. During a conference in New York, Bob came up to me and without any preparation asked whether I would consider joining his laboratory at NIH. Within a few milliseconds I blurted out Yes, absolutely Yes. One of the fastest and most decisive recruiting actions in history.

At that time, i.e., 1957, Bob Huebner was Chief of the Laboratory of Infectious Diseases, NIAID, NIH. He had already isolated the agent of rickettsialpox and defined its role in disease, established the role of certain Coxsackie A viruses in herpangina as well as the role of Coxsackie B viruses in pleurodynia and together with Wallace Rowe he had recovered the first human adenoviruses and established their importance in acute febrile respiratory tract disease as well as conjunctivitis and keratitis. Bob Huebner and Joseph Bell had the foresight and imagination to establish a longitudinal surveillance of the
microbial experience of infants and young children in a welfare nursery (Junior Village) during intervals of health as well as disease. This study proved to be a veritable cornucopia of new viruses and epidemiologic insights. Wally Rowe, who had co-discovered the human cytomegaloviruses, defined many important aspects of their natural history during the Junior Village Study. Leon Rosen discovered new reovirus serotypes, numerous higher type adenoviruses and new enteroviruses in specimens collected from Junior Village. Together with Joe Bell, Leon Rosen described the epidemiology of these viruses and their relationship to disease.

Bob Huebner assigned me the responsibility for investigation of acute respiratory tract diseases, while he, Wally Rowe and Jan Hartley re-directed their efforts towards tumor viruses and persistent virus infections. Wally and Bob demonstrated that, under natural conditions, polyoma virus, a DNA tumor virus, did not cause tumors in its normal host, the mouse. Bob Huebner predicted the presence of oncogenes in host chromosomal DNA, while Wally and Jan demonstrated that murine leukemia viruses are present in the host genome and are inherited as other host genes. Bob Huebner was also the first to identify and characterize non-structural tumor (T) antigens coded by DNA tumor viruses. In 1968, Bob Huebner left NIAID for NCI and the LID was split into two laboratories, LVD and LID. Wally Rowe was appointed chief of LVD, while I was appointed chief of LID.

The early years in LID were extraordinarily exciting and productive. Laboratory staff rarely turned over when Bob Huebner was chief. With a rangy grace he listened carefully to each member of the staff and those individuals remained deeply loyal to him. Bob Huebner realized far better than most of his contemporaries that scientific teams would replace
solitary giants in many areas of microbiological research. This trend, which he helped to create, did not bother his ego. His gift of sharing the haunting doubts and the thrilling possibilities of the work with others was more infectious than the viruses that were under study. Bob's enormous spirit found the planning of massive studies easy. Projects with a twist or a dimension unlikely to occur to other scientists came tumbling out of his head. The Junior Village comprehensive prospective surveillance of microbial experience of infants and young children during intervals of health as well as disease is such an example. Also, Bob initiated and fueled a number of large collaborative studies involving major laboratories throughout the US. One of these collaborations was enlarged to become the NCI Tumor Virus Program. This program has been much maligned because it did not yield a human tumor virus. What this program did do was provide us with a fairly comprehensive understanding of retroviruses as well as certain DNA viruses that cause tumors in animals under specific experimental conditions. These insights were critical to the identification of the oncogenes that had been predicted by Bob Huebner. Probably equally important was the fact the Tumor Virus Program provided a scientific infrastructure of retrovirus biology and genetics that allowed the scientific community to respond rapidly and effectively to the emergence of AIDS. Where would we be now if we had not understood basic retrovirus structure and function 8 years ago.

My 34 years in NIAID have been stimulating, rewarding, productive and a source of joy beyond any expectation I had when I entered the Public Health Service in July 1957. My career has spanned the adolescent growth spurts and the maturity of this complex research center. Administrators who understood the need for appropriate expansion carved
a place where Huebner and Rowe could let their imaginations soar just as Carleton Gajdusek did in the Neurology Institute.

Capable young scientists in LID were eager to be part of a team. Many received a substantial grounding in LID and then moved on. Those who have stayed clearly reflect the challenge and exchange that occurs when talented investigators coalesce to create strong teams. Witness the considerable successes of Bob Purcell, Sue Emerson and Roger Miller and their colleagues in hepatitis virus research, Al Kapikian, Jorge Flores, Taka Hoshino, Mario Gorziglia and their associates in rotavirus research, Brian Murphy, Peter Collins and their colleagues in respiratory virus research, Ching-Juh Lai and his group in flavivirus research and most recently, Phil Johnson, Vanessa Hirsch and Bob Olmsted in animal lentivirus research. I am a daily witness to the encouragement these scientists give to their junior colleagues. The role of mentor appears to have been transformed to a democratic interaction between senior and junior investigators. Perhaps it is only by chance that our institute is populated with an abundance of good listeners and quick learners. However, somewhere a thread of the parenting process remains.

As for that young face of Janus that is facing forward, the work of our junior scientists assures me that the future is in good hands. And on a personal note I still feel my head is young despite the grey hair. A few more adventures in virology may still lie ahead.