VICTOR A. MCKUSICK, MD
October 21, 1921 – July 22, 2007

Victor A. McKusick died on July 22, 2008 at the age of 86. He was a University Professor of Medical Genetics at Johns Hopkins University, where he had spent his entire medical career. He was a legend in human genetics, respected and revered as the 'Father of Genetic Medicine,' and a master clinician, scientist, medical historian, writer, teacher and mentor. He was an identical twin and grew up on a dairy farm in Maine, attending a one-room schoolhouse for eight years.

McKusick was first and foremost a physician, and followed the Oslerian tradition of paying close attention to his patients, seeking insight into the cause and management of their disease.

Following his residency in Internal Medicine, he obtained training in cardiology. However, he claimed he "found genetics much more challenging, exciting and novel". When a method of analyzing speech sound that had been developed at the Bell Labs, called sound spectrography, was brought to his attention he felt that this would be useful for analyzing heart sounds. He developed a new method of studying heart sounds, which he called spectrocardiography. His cardiology text, *Cardiovascular Sound in Health and Disease*, was published in 1958.

Through his cardiology interests, he came across families with Marfan syndrome and aortic aneurysms. He conceived that this was a syndrome in which one could think of the pleiotropic effects of a single gene, which affected one element of connective tissue, wherever it was in the body. He became interested in the cardiac aspects of the heritable disorders of connective tissue – a term and concept that he introduced. He defined pleiotropism, genetic heterogeneity and variability in each of them and published his first book, entitled *Heritable Disorders of Connective Tissue* in 1956.

Over the years, he excelled in the clinical nosology of these and many other genetic disorders. Some of his colleagues viewed his research as the medical equivalent of stamp collecting and some wondered if it was even science. But Victor perceived that the future of medicine — and insight into the molecular gears and switches that are the science of life — lay in the direction he was heading. If getting there required going house to house, examining babies, asking about grandparents… he was more than happy to do it.

Victor did not limit himself to descriptive studies. Enlisting the help of many basic science colleagues, they were able to define the biochemical and molecular defects in many disorders. He was especially effective in crossing basic science and clinical lines and across specialties. He recently reached his ultimate working goal in Marfan syndrome after over 50 years of work, starting with description and natural history, to the exciting work of Hal Dietz, the first McKusick professor, of finding a potential pharmacologic therapy for the aortic disease that first attracted his attention. This is a classic example of clinical genetics at its best.

In 1957, Victor took over the syphilis clinic at Johns Hopkins and renamed it the Moore Clinic for its retired director, who had initiated its change into a multifaceted chronic

disease unit. As a general hospital division, this brought genetics into the mainstream of clinical medicine. At precisely the same time in Seattle, Arno Motulsky started a Division of Medical Genetics within the Department of Medicine.

Victor built a division of medical genetics with cytogenetics, biochemical genetics, population genetics, and immunogenetics components. Malcolm Ferguson- Smith, who came as a Fellow at that time, set up the first cytogenetics laboratory in the Moore Clinic in February of 1959. This was probably the earliest clinical cytogenetics laboratory in any large general hospital in this country.

Pharmacogenetics also got started in the Moore Clinic with the study of the genetics of metabolism of the antituberculosis drug, INH.

He recruited a very large number of Fellows, more of them from abroad at first, particularly from the UK. Soon he was flooded with fellows from throughout the US, Canada and Europe. He trained several hundred Fellows in medical genetics from around the world over the years, many of whom became international leaders in the field – he was a true pied piper.

Victor started a monthly journal club at his home where each fellow had to review six to seven medical journals and bring in a short description of any new papers on genetic disease, which led to the publication of an annual review of new findings in medical genetics. When he was studying the X chromosome in about 1960, he asked the question, what genes are on the X chromosome? One way of getting an answer to that was to make a list of all the traits that are X-linked and he published a catalogue of X-linked disorders. Studying the Amish in late 1962 he expected to find new recessive disorders. In order to know when they had a new disorder, they had to know what the old ones were, so he made a catalogue of the recessive disorders. These catalogues and his annual reviews of medical genetics lead to his classic *Mendelian Inheritance in Man (MIM)*, long considered the bible of medical genetics – a constantly updated catalogue of genetic diseases and the genes that caused them. This was before the day of the word processor. He put the catalogue on the computer in 1964 and then produced a computer printout book, which became one of the first computer-generated medical texts. He eventually stopped publishing a hard copy version of MIM and put it on the internet (OMIM). The transfer to the Internet made him one of the earlier users of that communication technology.

His involvement with the Amish was a fringe benefit of university committee work with the Johns Hopkins Press, when in the fall of 1962 he reviewed the manuscript for John Hostetler's book called Amish Society. His studies of inherited disorders in Amish were very useful for illustrating a number of genetic principles, particularly the Founder effect of consanguinity and in the delineation of new entities of which he discovered about a dozen previously unrecognized, inherited conditions. The Amish have served as a model for studies in similarly isolated populations elsewhere. He greatly enjoyed his contacts with the Amish and his farm background made him sympathetic and sensitive to their culture.

His involvement with the skeletal dysplasias was an outgrowth of the Amish studies. He was first invited to the National Convention of Little People of America (LPA) in 1965,

as a result of a story about their studies in dwarfism in the Amish in *Time Magazine*. He was later named an honorary life member of LPA. He was also an honorary fellow of the American Academy of Orthopedic Surgeons and he claimed that he was the only member of those two organizations who was more than six feet tall and didn't operate.

The pioneering observations that G6PD and color vision were closely linked on the X chromosome and that the Duffy blood group were located on chromosome #1 came from his unit. Victor was clearly a clairvoyant. At the birth defects meeting in 1969 in The Hague, he suggested that mapping the human genome would be the way to go to unravel the mysteries about lots of birth defects and genetic diseases. In 1973, together with Frank Ruddle, he began the International workshops on gene mapping in man and pioneered the use of computers for linkage work. He approached the genome as an organ and began writing about the morbid and functional anatomy of the human genome. With Jim Renwick, he pioneered the use of computers for linkage work.

The human genome project was strenuously debated, because many people thought it was a crazy and very expensive idea and/or that it really wasn't science but just brick counting. As a leading proponent of completely mapping the human genome, Victor served as an enthusiastic advocate, advisor and kibitzer of the Human Genome Project and served as the founding president of the International Human Genome Organization (HUGO). Victor was a true cartographer, whose efforts not only led to the mapping of the human genome, but also put genetics on the medical map.

Through his fellowship, courses, meetings and writings, Victor was an extremely effective teacher and salesman of medical genetics. His annual genetics course at Bar Harbor, Maine, first given in 1960, is widely credited with training generations of genetic medicine practitioners and scholars. Victor attended the course by computer streaming, even to his last day. This long-standing course attracted a large number of health science faculty members, including a fair collection of department chairs and deans. One of the major objectives of the course was to upgrade the teaching of genetics by teaching the teachers. Indeed, a large proportion of people in genetics in this country have attended the course at some stage of their careers. The multiplier effect of this "teaching of teachers" was a catalyst in the development of medical genetics as a specialty. Victor also created the annual Clinical Delineation of Birth Defects meetings – a yearly meeting dealing with nosology in clinical genetics.

From 1973 - 1985, Victor served as the prestigious Osler professor and chairman of medicine at Hopkins, which further strengthened the role of genetics in medicine. Thus, he became a direct descendant of William Osler, the master clinician of John Hopkins at the turn of the century. Osler's extensive consultative practice provided him with material for his descriptions of new or almost new disorders, as did Victor's. Like Osler, Victor stressed the importance of practical experience in learning the physician's art by extending clinical teaching from the textbook, laboratory, and classroom to the patient's bedside. Even at his large Clinical Delineation of Birth Defects meetings, Victor would present numerous patients in the flesh as a teaching tool.

Victor was instrumental in creating the independent American Board of Medical Genetics. A decade later, the American Board of Medical Specialties admitted the American Board of Medical Genetics as the first new fully independent medical Board in

20 years, and as a full specialty. We then formed the American College of Medical Genetics, which became the 24th recognized medical specialty by the Council of Medical Specialties. We instituted an annual meeting, and combined it with the ongoing March of Dimes (MOD) Meeting, which were originally Victor's Clinical Delineation meetings.

Victor was always one to two decades ahead of his time: creating a division of medical genetics, inventing spectophonocardiography, predicting the usefulness of linkage and gene mapping, pioneering the use of computers in publishing and medical use of the Internet. He made major contributions to biochemical, molecular and population genetics without being in a lab or getting formal training in mathematical genetics or computer technology. He considered his lab to be the clinic and the library.

Victor was the recipient of numerous awards, including the Allan Award of the American Society of Human Genetics, the Gairdner Award, the Lasker Award, the National Medal of Science and the Japan Prize.

His enormous energy, a rigorous work ethic, effective time management, the ability to foresee the use of multiple new technologies, rapid response to new findings, coupled with his warm and friendly personality inspired thousands of students, doctors and scientists around the globe. Almost every physician in the future will benefit directly or indirectly from his research, teaching and his persistent and successful championing of the Human Genome Project.

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