Krishna R. Dronamraju
Clair A. Francomano *Editors*

Victor McKusick and the History of Medical Genetics

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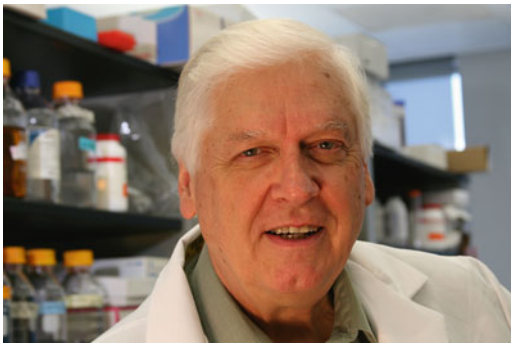
ISBN 978-1-4614-1676-0 e-ISBN 978-1-4614-1677-7 (eBook)
DOI 10.1007/978-1-4614-1677-7
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2012938639

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword



Hamilton O. Smith received an A.B. degree in mathematics at the University of California, Berkeley in 1952 and the M.D. degree from Johns Hopkins University in 1956. After 6 years of clinical work in medicine (1956–1962), he carried out research on Salmonella phage P22 lysogeny at the University of Michigan, Ann Arbor (1962–1967). In 1967, he joined the Microbiology Department at Johns Hopkins. In 1968, he discovered the first TypeII restriction enzyme (HindII) and determined the sequence of its cleavage site. In, 1978 he was a co-recipient (with D. Nathans and W. Arber) of the Nobel Prize in Medicine for this discovery. Subsequently, he studied DNA methylases and nucleases in *Haemophilus influenzae* Rd and discovered this organism's sequence-specific DNA uptake during genetic transformation. In 1994–1995 he collaborated with J. Craig Venter at The Institute for Genomic Research (TIGR) to sequence *H. influenzae* by whole genome shotgun sequencing and assembly. In July 1998, he joined Celera Genomics Corporation where he participated in the sequencing of the *Drosophila* and human genomes. In November 2002, he left Celera to join the new Institute for Biological Energy Alternatives formed by J. Craig Venter. In 2005, this Institute merged with TIGR to form the J. Craig Venter Institute where he is currently leading the synthetic biology group in an effort to make a synthetic bacterial cell.

I first met Victor McKusick in 1954 when I was a medical student at Hopkins. Among my many teachers, he stands out in my mind because he was young, enthusiastic, and high tech. I remember particularly one of his lectures in which he described the latest diagnostic tools being developed and used in cardiology, including if my memory serves me correctly, electro phonocardiograms. This application of new technologies to medical diagnosis was exciting to me. It was through his lectures that I developed a deep interest in cardiology which led to my subsequently taking electives in EKG interpretation and a one-quarter course with Helen Taussig on auscultation in the diagnosis of congenital and valvular heart disease.

It was not until the 1960s, when I began my research career in genetics and molecular biology that I learned of Victor's rise as an authority on human genetic diseases. He had become world famous for his encyclopedic compilation of all known human genes and genetic disorders, published as a series of volumes under the title, *Mendelian Inheritance in Man (MIM)*. The database was religiously kept up to date as new diseases were discovered. When he spoke at meetings or seminars, he would proudly show slides displaying the ever-growing number of volumes of MIM. When the human genome project started in earnest around 1990, I recall attending a dinner party with Victor and we began speculating about the number of human genes. We decided to make a bet and the winner would get a free dinner. I guessed 100,000 genes, but Victor thought there would be much fewer, around 50,000. It turned out that we were both wrong, but he was much closer. The real number was about 25,000. Unfortunately, I never had the opportunity to pay off the bet.

It was because of Victor's preeminence in medical genetics that our paths crossed again when I joined with Craig Venter at Celera Genomics in 1998 to sequence the human genome. Victor was a strong supporter of our efforts, and I saw him frequently at meetings of the Celera Scientific Advisory Board, and also later as a member of the Venter Institute Board of Trustees in Rockville, MD. Victor was a gentle human being who lent his vast knowledge, wisdom, good judgment, and prestige to our meetings. We were all very saddened by his passing.

Hamilton O. Smith, M.D.

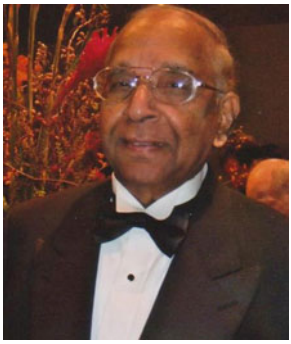
Acknowledgements

I express my gratitude to Dr. Anne McKusick for her kind cooperation in putting this book together. In addition to contributing a fine chapter, Anne generously provided much help in obtaining additional material and photographs. I am also grateful to Judge Vincent McKusick for his fine contribution about the McKusick twins, as well as helping with the identification of family photographs from their childhood. I am appreciative of the Foreword provided by Hamilton Smith, who knew Victor well as a student and later as a colleague.

I am appreciative of all the contributors, especially Kenneth and Victor McKusick, for kindly permitting me to reproduce their eulogies. Dr. Clair A. Francomano not only contributed two finely written chapters and a eulogy but also provided much assistance in preparing the book for publication. I thank Melanie Tucker at Springer for her cooperation and assistance in publishing this book.

Houston, TX, USA Krishna R. Dronamraju

Editor Biographies



Krishna R. Dronamraju is President of the Foundation for Genetic Research, Houston, and a Visiting Professor of the University of Paris. He was a student and close associate of J.B.S. Haldane, receiving his Ph.D. in human genetics from the Indian Statistical Institute, and later worked with Dr. Victor McKusick at the Johns Hopkins University School of Medicine. Dr. Dronamraju is the author of 20 books and over 200 papers in genetics and biotechnology. He was an Advisor to President Bill Clinton's administration and was a member of the United States Presidential delegation to India in 2000. He served on the Recombinant DNA Advisory Committee of the U.S. National Institutes of Health, Washington, D.C.

Clair A. Francomano attended Yale College as an undergraduate and received her M.D. from Johns Hopkins University School of Medicine. She worked with Dr. McKusick as a student, doing research among the Lancaster County Amish, and trained in Internal Medicine and Medical Genetics at Johns Hopkins from 1980 to 1984. She joined the full-time Hopkins faculty in 1984. In 1994 she became Chief of the Medical Genetics Branch at the National Human Genome Research Institute, National Institutes of Health, where she served as Clinical Director from 1996 to 2001. From 2001 to 2005 she was Chief of the Human Genetics and Integrative Medicine Section in the Laboratory of Genetics, National Institute on Aging. She joined the Greater Baltimore Medical Center faculty in 2005 as Director of Adult Genetics at the Harvey Institute of Human Genetics. Her research interests over the years have centered on Hereditary Disorders of Connective Tissue and Skeletal Dysplasias, areas to which she was introduced by Victor McKusick in the early days of her career.

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*Unfortunately, Dr. Rimoin passed away while the book is in press

Chapter 1
Victor McKusick

Krishna R. Dronamraju

Victor receiving the National Medal of Science, June 13, 2002

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K.R. Dronamraju and C.A. Francomano (eds.), *Victor McKusick and the History of Medical Genetics*, DOI 10.1007/978-1-4614-1677-7_1,

Introduction

I am grateful to Victor's twin, Vincent, for providing information about family history and background. Victor was the first physician/scientist in the family.

The McKusick twins were born and raised in Parkman, Maine, which stands almost exactly at the geographical center of the state, some 50-plus highway miles northwest of Bangor. Their ancestral line has been identified with Parkman since 1840. Their father was Carroll L. McKusick (1882–1969), and their mother was Ethel May Buzzell (1882–1944). Both parents were in the teaching profession and encouraged their children's education. In their direct ancestral line, the twins had no forebear who attended college before their father Carroll went to Bates College in the year 1900. All received a basic education in Parkman one-room schoolhouses and little beyond. Yet all the twins' direct forebears are remembered as outstanding citizens, active in the public affairs of their community, including support of local education.

In an autobiographical note written on the occasion of the Lasker Award, Victor recalled that he was first exposed to science (and to genetics) when he went up to Tufts to take premed studies in 1940. Victor and Vincent split up when they went to college, Vincent to Bates and Victor to Tufts, partly to avoid competing with each other for scholarship support but also because of diverging career goals.

Victor's desire to take up medicine was the result of a 10-week stay at the Massachusetts General Hospital, at the age of 15, when he developed an abscess of the left axilla and a superficial spreading ulcer of the right elbow that would not heal. Eventually, he was treated with sulfanilamide which had become available the year before, and the lesions healed and stayed healed. Victor later wrote that during that process, he saw much of medicine and decided that was the field for him.

Johns Hopkins

In 2006, Victor described himself as an "autodidact" in genetics, a quality he shared with many gifted scientists. He first came to know genetics in his last semester at Tufts when he took an elective course in genetics with Professor Paul A. Warren, "an inspiring teacher, who made the topic of classic Mendelism exciting." He finished up his third academic year at Tufts by January 1943. He would have continued there except for the fact that, in the fall of 1942, he learned that Johns Hopkins Medical School was accepting applications from undergraduate students who had not yet received a college degree, for an entering class in March 1943. This was a sudden shift for Johns Hopkins, brought on by the wartime exigencies, waiving their usual requirement of a bachelor's degree that had been strictly followed since its opening in 1893. Furthermore, he was strongly attracted to Johns Hopkins since a cover story appeared in *Time* magazine in January 1939, which focused on the Hopkins Professor of the History of Medicine, Henry Sigerist, and his views on socialized medicine. It also contained an account of the early history

of Johns Hopkins and of its Institute of the History of Medicine. That was the only medical school application he had ever made and was accepted to matriculate in March 1943.

Victor completed four academic years of medical school in three calendar years, graduating in March 1946. He continued at Hopkins with an internship in internal medicine and fully expected, after some postdoctoral training, to return to Maine to enter the general practice of medicine. However, his ambitions for the internship on the prestigious Osler Medical Service proved stronger, which led him to academic medicine.

Medical Genetics

Victor's interest in medical genetics began in June 1947, when a teenager named Harold Parker became his patient near the end of his Osler internship. That was his introduction to the polyps-and-spots syndrome. In the next 2 years, four additional cases of this kind came to his attention. Three of them were members of the same family, indicating an autosomal dominant inheritance. When he found out that Harold Jeghers in Boston also had five cases, Victor collaborated with him in writing up these ten cases in two papers in successive issues of the *New England Journal of Medicine* [1]. This syndrome, consisting of jejunal and other intestinal polyps and melanin spots of the lips, buccal mucosa, and digits, was later called the Peutz-Jeghers syndrome, in a paper from the Mayo clinic in 1954 [2]. However, Victor pointed out that Jonathan Hutchinson in London first described the pigmentary changes in identical twins in 1896 [3].

Pleiotropism

For the genetic interpretation of the polyps-and-spots syndrome, Victor sought the advice of Bentley Glass, who was then a member of the Biology Faculty of Johns Hopkins University. It was Glass who impressed upon Victor that pleiotropism of a single mutant gene was a more likely explanation for the association between polyps and spots rather than genetic linkage.

Victor's early work in cardiology is well known. Early in his career, his training in cardiology included reading electrocardiograms in the Johns Hopkins Heart Section under the direction of Elliott V. Newman. Later, from 1948 to 1950, he worked in a cardiovascular unit at the US Marine Hospital in Baltimore under Luther L. Terry, who subsequently became famous as the US Surgeon General who blamed cigarette smoking for lung cancer and other ailments. Victor was involved in several other studies in cardiology, especially of heart sounds and murmurs by the method of sound spectrography, which had been developed at the Bell Telephone Laboratory for analyzing speech sound. These studies resulted in a monograph entitled *Cardiovascular Sound in Health and Disease* [4].

Victor was greatly interested in historical studies in genetics; his writings include the initial chapter of successive editions of Emery and Rimoin's *Principles and Practice of Medical Genetics* [5], biographical articles on Jonathan Hutchinson, Frederick Parkes Weber, Walter Stanborough Sutton, and Marcella O'Grady Boveri. Victor was especially eloquent on the contributions of the London multispecialist, Jonathan Hutchinson, dedicating two volumes of *Clinical Delineation of Birth Defects* to the memory of Hutchinson.

Marfan Syndrome

While still on the junior faculty of Johns Hopkins, Victor pursued a detailed study of Marfan syndrome as well as four others, grouped under the category (I) "heritable disorders of connective tissue": Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and Hurler syndrome (the prototype of the mucopolysaccharidoses). This work was ultimately published as a book entitled *Heritable Disorders of Connective Tissue* [6]. Victor was greatly impressed by the multiple organ systems that were affected by the pleiotropic action of the mutation involved. He focused attention on all the Marfan patients he could, fully realizing that Johns Hopkins was a "superb site" for such studies because of its excellent departments of ophthalmology, pediatric and adult cardiology, orthopedics, and other specialties. Victor preferred to say "the Marfan syndrome" (rather than Marfan syndrome) because it makes it clear that the surname is merely a tag. He wrote, "After all, Marfan described the skeletal features only" [7, p. 29].

Because of the autodidactic nature of his genetic knowledge, Victor found it helpful to associate himself, as a junior faculty member at Hopkins, with other like-minded individuals which included Bentley Glass, Barton Childs, Abraham Lilienfield, and others, forming what was informally called the "Galton-Garrod Society."

Division of Medical Genetics

Medical genetics was formally institutionalized at Johns Hopkins on July 1, 1957, when Victor was invited by the Chairman of the Department of Medicine, A. McGehee Harvey, to take over the direction of a multifaceted chronic disease clinic that was initially developed by J. Earle Moore in 1952. Victor set out to develop a Division of Medical Genetics, within the Department of Medicine, based in that clinic which was renamed in honor of Dr. Moore. Victor justified this process by pointing out that genetic disease is the ultimate in chronic disease.

Victor later wrote that some of his colleagues were surprised when he switched from cardiology to genetics. There was a gradual transition. The Moore Clinic was earlier involved in a study of the genetics of heart disease and the initial support was provided by the National Heart Institute until the National Institute of General Medical Sciences was founded in the early 1960s. Victor continued to be involved in the Heart Sound Laboratory until 1962. Victor found that certain facilities of the

old Moore Clinic, such as long-term follow-up mechanisms for studying the late manifestations of syphilis, and its close links to the Johns Hopkins School of Hygiene and Public Health, with its statistics and epidemiology departments, were ideally suited for the new medical genetics unit as well. Paradoxically, he also found that carrying out research, teaching, and patient care in a cramped space was ideally suited for fostering collaborations among the staff and fellows with multiple research interests in cytogenetics and biochemical aspects, as well as other disciplines in relation to genetic disease.

The Division of Medical Genetics was a beehive of activity. Victor's energy and enthusiasm were infectious. Many fellows came from Great Britain, which was mainly due to Victor's close friendship with Cyril Clarke in Liverpool. In his obituary of Cyril Clarke, Victor wrote, "The passing … of Cyril Clarke brought back memories of pleasant and productive interchanges between Liverpool and the Johns Hopkins Hospital over a 20 year period or more beginning in 1957. Cyril was a central figure in those transatlantic collaborations in training and clinical research …. We at Johns Hopkins are much indebted to Cyril for the able protégés he sent to Baltimore in the formative years of medical genetics here" [8]. Among the Liverpudlians, who came to the Moore Clinic, were David A. Price Evans, Peter Brunt, J. Michael Connor, Brian Hanley, Peter S. Harper, F. Michael Pope, Brian Walker, David Weatherall, J.C. Woodrow, and Ronald Finn (the latter worked with Julius R. Krevens). Malcolm Ferguson-Smith came down from Glasgow to establish the cytogenetics laboratory. Weatherall, Harper, and Ferguson-Smith are contributors to this book. These are listed in the chapter by Weatherall.

Victor was ably assisted by two colleagues in the Division of Medical Genetics; one was Edmond A. (Tony) Murphy in statistical genetics and Samuel H. ("Ned") Boyer in biochemical genetics. David Weatherall worked first with Ned Boyer in the Biochemical Genetics section of the Moore Clinic and later with C. Lockart Conley in the study of hemoglobinopathies and with others in the Department of Biophysics directed by Howard Dintzis.

Victor's Publications

Victor's major research contributions and their publications are described and discussed in this book by several colleagues. These include his work on Marfan syndrome and related disorders, his extensive work with the Amish populations [9], contributions to genetic nosology, his great interest in gene mapping, his massive compilation of Mendelian disorders and the online version (OMIM), his role in founding and guiding the Human Genome Organization (HUGO), his contribution to education and training in medical genetics through a series of summer courses in Bar Harbor (USA), Bologna (Italy), and Beijing (China), and his most valuable studies in the history of science and medicine.

Victor was a prolific writer (see Table 1.1). During his lifetime, he published an enormous output of 772 research papers, books, reviews, and miscellaneous reports, which are listed in the Appendix. During the years 1949–1973, he published 538.

Table 1.1 Publications of Victor McKusick

Years	Number of all publications
1949–53	37
1954–58	112
1959–63	125
1964–68	122
1969–73	142
1974–78	74
1979–83	38
1984–88	32
1989–93	25
1994–98	29
1999–03	23
2004–08	13
Total	772

He published fewer (234) but still a large number in the remaining years 1974–2008. Once he became chairman of the department of medicine in 1973, there was a sharp drop in the number of publications. For example, in the five preceding years (1969–73), his publications numbered 142, as compared to 74 during the years 1974–78. This is understandable because of additional administrative work and other responsibilities which he assumed in 1973. Also, the work on the catalogs of Mendelian Inheritance in Man, Human Gene Mapping, and HUGO took up more and more time in later years. He was publishing until the very end; during the last 2 years, 2007–2008, there were nine publications, altogether, an impressive record of lifetime performance.

A scientist's penetrating insights and perceptions are not always found in his major works but in reviews of the works of others, in brief reports, and in correspondence, as well as personal conversations. Victor is no exception.

I start with a minor publication, an early review [10], of *Human Heredity* by the French biologist, Jean Rostand, (translated from French) which was published in 1961. Rostand was the son of Edmond Rostand, creator of *Cyrano de Bergerac*. Victor's review opens with the sentence "For a small book, this one packs a powerful lot of misinformation and misconception." He points out that the responsibility rests with the author, translator, and the Philosophical Library whose bad judgment it was to produce an English edition. It was first published in 1952, and the book translated in 1961 did not take into account the advances that took place during the intervening years. Victor contrasted this book with Penrose's "beautiful little" *Outline of Human Genetics* [11]. Rostand's book falls short of its avowed objective: "to introduce the greatest number of people into the sovereign dignity of knowledge," whereas Penrose's little book fulfilled that purpose "quite satisfactorily." Victor goes on to make other penetrating (and amusing) comments: "Men with many daughters will be intuitively suspicious of the view repeated on page 126 that 'there is probably a correlation between the tendency to produce boys and the virility of the father.'" "And the so-called simple inheritance of rare hereditary disease traits is misleading because it misses the important concept of heterogeneity of entities which phenotypically appear to be homogeneous."

Health of the Presidents

One amusing book, which caught Victor's attention because of his historic interest, was "The Health of the Presidents" by Rudolph Marx, a Los Angeles surgeon. Victor's comment, "His book undoubtedly makes entertaining light reading" [12]. Almost all presidents seemed to have had serious psychologic problems which led to other health problems: two examples are Taft's overeating and obesity, and the alcoholism of Franklin Pearce, as well as many others. Victor commented that "such collections of information about the health and illnesses of famous persons serve a useful mnemonic purpose in clinical teaching and practice: Cerebral thrombosis may occur in the 40s with survival for as many as 20 years thereafter, as in the case of Mrs. William Howard Taft." Another comment about a well-known scientist, Louis Pasteur had a stroke at 46, yet made his greatest contributions in the following 27 years.

Victor took the opportunity to make several corrections while making medical and historic observations of his own. Virginia was *not* the southernmost of the original 13 colonies. The reviewer was not aware that alcohol can be incriminated as an allergen in causing chronic bronchitis. "Habituation to whiskey" is meant, not "habitation to whisky," although the latter expression has interesting imagery. About Taft, the author wrote that he "developed the 'effort syndrome' – pain in the chest, shortness of breath, and heart consciousness after physical exertion, typical for angina pectoris." Victor's comment, "It was true angina pectoris from which Taft suffered. 'The effort syndrome,' which indeed has the mentioned symptoms as features, is a synonym for neurocirculatory asthenia (also called Da Costa's syndrome, cardiac neurosis, soldier's heart, etc.). Marx makes no mention of Taft's auricular fibrillation." Victor's conclusion, "Both the author's history and his medicine are thin in many places. However, he has produced a book that tells an absorbing series of stories without dispensing too much or too serious misinformation."

Misconceptions in Human Genetics

Writing in 1971 [13], Victor found it necessary to list 14 genetic misconceptions. His article has a timeless quality. This was extremely useful then (and still is today) as we come across these false ideas. Certain fundamental truths need to be repeated often.

1. "Congenital is synonymous with genetic." Congenital merely means present at birth. Exceptions are found in both directions. Some genetic disorders are not congenital in the usual sense, and many congenital malformations do not have a predominantly genetic cause. For instance, Huntington's chorea is genetic but not congenital, whereas rubella embryopathy is congenital but not genetic.
2. "If a disorder is inherited, a chromosome analysis will show abnormality." Most Mendelian disorders have no chromosome abnormality which can be demonstrated with existing techniques.

3. “A buccal smear provides full information on the chromosomes.” The buccal smear only tells the maximal number of X chromosomes per cell.
4. “If a genetic disorder is dominant, all children of an affected person will be affected; conversely, if all children of normal parents are affected by a genetic disorder, this is evidence of dominant inheritance.” This indicates ignorance of Mendel’s laws and the meaning of “dominance.”
5. “When individuals of only one sex are affected in a family, it indicates sex-linkage of the disorder.” Once again, this indicates ignorance of basic principles of genetic transmission.
6. “A disorder that occurs in multiple siblings with normal parents is not hereditary.” Recessive inheritance is characterized by affected sibs with normal parents, and a recessive disorder is as genuinely hereditary as a dominant one.
7. “Consanguinity brings out sex-linked disorders, for instance, hemophilia was frequent in the inbred royal families of Europe.” Consanguinity increases the occurrence of homozygous affected females but has no effect on the frequency of affected males.
8. “The occurrence of a hereditary syndrome composed of two or more manifestations is the result of close linkage on the same chromosome of separate genes, each resulting in one of the individual manifestations.” All “mendelizing” syndromes studied in full detail to date have been found to have their basis in the pleiotropic effect of a single mutant gene. Linkage produces no permanent association of traits because even closely linked genes become separated through the process of crossing-over.
9. “Dominantly inherited disorders tend to increase in severity with transmission from generation to generation, a process called anticipation. For example, age of onset, an expression of severity, tends to be lower in affected children than in their affected parents.” Ascertainment bias is responsible for apparent anticipation. On the average, only in milder cases of many dominant disorders, the offspring are expected to be more severely affected than their parents.
10. “Dominant disorders are common; recessive disorders are rare.” There is no correlation between the frequency of a disorder and its mode of inheritance.
11. “Inbreeding causes a build-up of ‘bad genes’ in populations.” Inbreeding does not directly change the gene frequencies. It does change genotype frequency; it increases the frequency of homozygotes. If the homozygote is at a disadvantage, inbreeding actually results in a decrease in the deleterious genes.
12. “Dominant disorders are more severe than recessive disorders.” As a general rule, just the opposite is the case; however, severity may be associated with either type.
13. “If a couple has had three children born with a given recessive disorder, the chance that the fourth child will also be affected is vanishingly small.” The risk of an affected child from two carrier parents remains 1 in 4, regardless of previous family history.
14. “Genetic disease is not treatable”: False. Many genetic diseases are treatable.

Genetic Nosology: On Lumpers and Splitters

Victor believed that certain fundamental facts are worth repeating. He emphasized the concepts of pleiotropism and genetic heterogeneity in his now classic paper, "On lumpers and splitters, or the nosology of genetic disease," which appeared in the *Birth Defects, Original Article Series*, in 1969 [7]. This paper is noted for delineating several fundamental problems, for instance, what constitutes a "genetic entity," what is the impact of inbreeding on nosology, and what are the problems in naming genetic entities. He mentioned examples from his own work, pleiotropism as a leading concern with respect to Marfan syndrome, whereas genetic heterogeneity became increasingly the focus in studies of the genetic mucopolysaccharidoses and the separation of homocystinuria from the Marfan syndrome. This became evident in successive editions of *Heritable Disorders of Connective Tissue* [6].

Victor compared the classification of disease with the taxonomy of plants and animals. Taxonomists like nosologists can be either lumpers or splitters. But there is one important difference. The nosologist's major concern is whether syndromes A and B are one and the same entity or distinct entities. The taxonomist, on the other hand, constructs a branching classification based on the phylogeny, the components in his classification bearing varying degrees of genetic relationship to each other, based on their descent from a common ancestor.

The fundamental questions tackled by Victor include the following: What constitutes a genetic entity? How does one identify genetic heterogeneity (including clinical, genetic, and biochemical methods)? Practical difficulties include rarity of the phenotype in the population, and small size of the families, and the naming of genetic entities. The phenotype resulting primarily from a specific and unitary factor is an entity. He wrote that delineation of genetic entities is on safe ground if a fundamental biochemical defect or a specific chromosomal anomaly is identified.

Inbreeding in the Amish

Victor discussed nosology in relation to inbreeding, for instance, the delineation of "new" genetic entities with recessive inheritance is enhanced in inbred communities. It was, in fact, his interest in inbreeding in the Amish populations which brought us together because of my research on inbreeding in India with J.B.S. Haldane [14–18]. In his genetic studies of the Amish, Victor combined multiple research interests. He wrote, "in the 1960s, skeletal dysplasias became an area of both clinical and research nosologic interest because of their relationship to the heritable disorders of connective tissue, because of studies of dwarfism in the Amish … which we initiated in 1963, and because of collaboration with Little People of America, Inc., which began in 1965 when I first attended the annual national convention of this fraternal organization of persons of short stature. Skeletal dysplasias became a major interest of many who were my fellows in that period including David Rimoin, Judith G. Hall, and Charles Scott, who like me became honorary life members of Little People of America." [19].