Introductory Speech for Hal Dietz*

Victor A. McKusick

Victor A. McKusick and Hal Dietz

For two reasons, I take special pleasure in presenting the Curt Stern Award to Hal Dietz. In the first place, Dr. Stern was an important tutor in my self-education in genetics. In the second place, Hal has solved many of the mysteries of a genetic disorder I began studying in the early 1950s: mysteries of etiology (the mutational basis), mysteries of pathogenesis (the role of the transforming-growth-factor β–signaling pathway), and, perhaps (we certainly hope so), mysteries of effective pharmacotherapy. That disorder is, of course, Marfan syndrome.

Curt Stern was born in Germany and got a Ph.D. in Berlin at the tender age of 21. He worked at the Kaiser Wilhelm Institute with Richard Goldschmidt, who sent him to Columbia University to work for 2 years, 1924–1926, with Thomas Hunt Morgan in the famous "fly room." In 1933, Stern moved to the United States to escape Nazi anti-Semitism. He first taught and researched at the University of Rochester. His research was in classic aspects of genetics, using *Drosophila* as his experimental organism. While at Rochester, Stern developed a pioneer course in human genetics. That course was the basis of his classic *Principles of Human Genetics,* first published in 1949. Its influence can be gauged by the facts that the three English editions sold a total of more than 62,000 copies and that the book was translated into six other languages. In 1947, Stern moved to U. of California–Berkeley and finished his career there. He was president of this society in 1957 and received its Allan Award in 1974.

Stern's legacy to education in human genetics may be as important as his research contributions. Stern was important to the development of medical genetics at Johns Hopkins and to my personal development in the field. I recently found detailed notes I made in 1953 outlining the entirety of the 1949 edition of Stern's text book. In the early days of the Division of Medical Genetics, based in the Moore Clinic of the Johns Hopkins Hospital, Stern spent the month of January 1959 at the Hospital as lecturer in residence, residing literally "under the Dome," and giving 12 lectures, one each Monday, Wednesday, and Friday for those 4 weeks. Given in the Hospital's main auditorium, Hurd Hall, all 12 lectures were well attended. As in his textbook, Stern illustrated these lectures on the "principles of human genetics" with examples from classic genetics, in which he was rooted. Personally, from Stern's visit, I derived most from his perspective on linkage gene mapping and the fundamental importance of the gene map to the understanding of the genetics of any species. He pointed out that the arrangement of genes on our chromosomes is part of our anatomy, the implication being that it is information fundamental to the understanding of genetic disease. Stern's anatomic metaphor is one I have used extensively.

More ancient history: I first published on the Marfan syndrome in *Circulation* in March 1955, in an article entitled "The cardiovascular aspects of Marfan's syndrome, a heritable disorder of connective tissue." (Parenthetically, that was the first time I used the expression "heritable disorders of connective tissue" in print and the last time I used the possessive form of the eponym, Marfan's.) After Marfan syndrome, I looked around for other pleiotropic disorders that might be heritable disorders of connective tissue and settled on four others: Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and

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* Previously presented at the annual meeting of The American Society of Human Genetics, in New Orleans, on October 13, 2006.

Am. J. Hum. Genet. 2007;81:660–661. 0002-9297/2007/8104-0008$15.00
DOI: 10.1086/521408

Hurler syndrome (the prototype of the mucopolysaccharidoses). I studied in great detail, as I had done for Marfan syndrome, all patients and families in these other four categories seen at the Johns Hopkins Hospital. These five disorders, with the Marfan syndrome as queen, were the subjects of separate chapters in my monograph *Heritable Disorders of Connective Tissue,* first published just 50 years ago, in 1956.

I dedicated the book to Archibald Garrod and to all who believe, as he did, that clinical investigation of hereditary disorders can shed light on normal developmental and biochemical mechanisms. Garrod had made that point explicitly in "The lessons of rare maladies," published in *Lancet* in 1928, which I cited in my preface. In that paper, Garrod quoted William Harvey, who had made the same observation in 1657:

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.

Hal Dietz has powerfully validated that Harveian-Garrodian principle by his studies of Marfan syndrome and related disorders. Hal graduated from Syracuse Medical School summa cum laude and valedictorian in 1984. He came to Johns Hopkins for residency in pediatrics and in critical-care medicine, capped off by a 4th year as chief resident in pediatrics. In 1988, Hal embarked on a fellowship in pediatric cardiology and in genetics. In the course of that, he took to research like a duck to water. His first two papers, both published in 1991, were, one, confirming the mapping of the Marfan locus to chromosome 15 and, the second, his well-known paper using the positional candidate-gene approach to identify the first mutation in fibrillin-1 in Marfan syndrome—not a bad start for a new investigator. Hal's devotion to Marfan syndrome, both in the clinic and in the laboratory, has continued unabated in the 15 years since 1991, with description and molecular characterization of the Marfan-like disorder that bears his name, Loeys-Dietz syndrome, and with his work on the pathogenesis and rational treatment of Marfan syndrome. On the way, Hal has also done groundbreaking work on the significance of nonsense-mediated mRNA decay in genetic diseases.

Three general points about Hal and his work:

1. Whereas Hal's work has corroborated the Harvey-Garrod principle, it illustrates that clinical investigation of hereditary disorders by "standard" methods of clinical study, although a fundamental and indispensable starting point, is not sufficient for learning "the lessons of rare maladies." Special methods and technology are required. Hal's work has turned on its head the idea we had in 1956 that Marfan syndrome represents simply an innate weakness of a structural element of connective tissue. His work has shown that the pathogenesis of Marfan syndrome is more complex but at the same time, paradoxically, more amenable to pharmacotherapy.
2. Hal's work has always been close to the clinic. You can call it "patient-oriented research"; you can call it "translational research." It is both. You could say Hal is a scientist who takes care of patients or is a clinician who does research. I would say that he is an academic triathlete; he engages in the strenuous academic triathlon of research, teaching, and patient care—an integrated equitripartite career. He takes both competence and empathy to the clinic, from which he derives inspiration and intellectual challenge. He teaches in both the clinic and the laboratory.
3. There is a special quality about the Dietz laboratory. It has an excitement and enthusiasm that makes it a magnet for the brightest and best who want to work with Hal. He is a supportive mentor. He is a generous colleague and collaborator.

Hal, it is with personal pleasure that I represent the American Society of Human Genetics in presenting you with this award named in honor of a pioneer in human genetics education, Curt Stern.