2014 Victor A. McKusick Leadership Award Introduction: David Valle[1]

Roderick R. McInnes[2,3,*]

It is indeed a great honor and personal pleasure to present the 2014 McKusick Leadership Award of The American Society of Human Genetics (ASHG) to David Valle, director of the McKusick-Nathans Institute of Genetic Medicine at The Johns Hopkins University School of Medicine. David has been an exceptional colleague and friend for more than 40 years. We first met when he visited the lab of Charles Scriver at McGill in the early 1970s, and his comfortable leadership style was evident even in those early days.

Great leaders beget other great leaders, and David's inborn leadership skills were epigenetically enhanced by some of the giants of human genetics. Victor McKusick, not one given to public displays of sentiment, would have been visibly delighted to witness David's receiving this recognition today. A triumvirate of role models including Victor, Charles Scriver, and especially Barton Childs had forceful imprints on David's career. In his obituary of Victor, published in *The American Journal of Human Genetics* in 2008, David noted Victor's life-long "romance with genetics, … intellectual honesty, clarity of thinking, a willingness to work hard, a dedication to education, and a wry sense of humor," all genetically complex traits that also capture the essence of this year's recipient of the McKusick Award.

David's research has placed him at the forefront of three disparate areas of human biology and genetics, an unusual achievement in modern science. His first research interest was the aminoacidopathies. In 1977 he reported his first major finding: that gyrate atrophy, an inherited retinal degeneration, is due to ornithine aminotransferase (OAT) deficiency. Many key publications on ornithine metabolism and its associated diseases followed over the subsequent decades. The most significant, undoubtedly, must be those demonstrating that gyrate atrophy was one of the very first treatable retinal degenerations, a milestone in the management of inherited disease.

David's second research direction, on disorders of peroxisome biogenesis, was announced by a period of remarkable productivity from 1995 to 1998. In collaboration with Hugo Moser and Stephen Gould, he identified 5 of the 12 genes known to be associated with these disorders. The genes were discovered by in silico screens for human homologs of known yeast peroxisomal genes, and their orthology was then established by functional complementation of human peroxisomal mutants. David's colleague Aravinda Chakravarti notes,

> His insight into the future of human genetics could be gauged by his championing studies of distant model systems to unravel human disease. The mouse is easy, but the meetings organized by [him] and Phil Hieter, on investigating human-yeast protein homologies to understand human disease, arose from his own work on peroxisomal disorders.

The comfortable and productive collaborations between Gould, Moser, Hieter, and David are typical of how he interacts with colleagues, interactions invariably characterized by his generosity in sharing ideas and credit.

In recent years, determined to identify genetic variants that contribute to psychiatric disorders, David has turned his attention to this third area of research. This transition, from monogenic to complex disorders, is a challenge few have taken up. Two beautiful recent papers illustrate the success of his team in this domain as well, first in identifying schizophrenia-associated variants in *DPYSL2* and *NRG3* and then, importantly, in presenting strong biological evidence that supports the functional significance of these variants—a substantial contribution to our understanding of this important condition.

Although David is an internationally respected research leader, perhaps his greatest passion has always been

[1]This article is based on the address given by the author at the meeting of The American Society of Human Genetics (ASHG) on October 20, 2014, in San Diego, CA, USA. The audio of the original address can be found at the ASHG website.

[2]Lady Davis Research Institute, Jewish General Hospital, McGill University, Montreal, QC H3T 1E2, Canada; [3]Departments of Human Genetics and Biochemistry, McGill University, Montreal, QC H3T 1E2, Canada
*Correspondence: rod.mcinnes@mcgill.ca

http://dx.doi.org/10.1016/j.ajhg.2015.01.018.

medical genetics education, both in research and in the clinic. In his lab, David has mentored more than 30 superbly trained biochemical geneticists, who now work in more than 20 academic medical centers throughout the world. Much of the research on OAT and gyrate atrophy was led by a postdoc, Grant Mitchell, who remembers,

> In the mid 1980s, Dave's lab was one of the few places where full-time lab training could be combined with intense clinical learning. When I arrived, Dave was fresh from his sabbatical with Nobel laureate Daniel Nathans. In the Molecular Biology Department at Hopkins, Dave's lab was unique because of its clinical focus. He was an unparalleled mentor who is still a thoughtful pillar of support and inspiration.

Another former trainee, Larry Brody, recalls, "The lab had very little hierarchy and continuous interaction. Anyone joining with an air of superiority soon realized that science was about what we do not yet know."

At Johns Hopkins, David has directed the Human Genetics Predoctoral Training Program for more than 25 years and has participated directly in the education of more than 400 graduate students, dozens of whom now have outstanding careers of their own. Graduates of this program are department chairs or hold important positions at the NIH and other government agencies, in big pharma, in law, and of course in teaching. David was an original co-chair of the Curriculum Reform Committee at Hopkins, and the impact of his educational philosophy will be felt for many years, given his key role in the conceptualization, development, and implementation of Genes to Society, the new Hopkins medical school curriculum for the 21st century.

In addition to playing leading roles in education at Hopkins, David has had great influence on medical genetics education both nationally and internationally. Since 1992, he has co-directed the annual Short Course in Medical and Experimental Mammalian Genetics—a venerable course started by Victor McKusick more than 50 years ago and organized by Johns Hopkins and The Jackson Laboratory. Since its inception in 1959, over 5,000 clinicians and scientists have attended the course to learn the foundations and the latest exciting science in human and mouse genetics. Patsy Nishina of The Jackson Laboratory, a co-organizer of the course with David, recalls,

> I learned from my interactions with David that he is a true Renaissance scientist, able to contribute both breadth and depth to any scientific discussion. Because of his deep well of knowledge, David was always able to pitch hit on only a moment's notice when speakers were unable to make it for their talk. The success of the Short Course for more than two decades can be largely placed at David's door.

In a second role of international significance, David was an editor of the classic reference book on human medical genetics *The Metabolic Basis of Inherited Disease* and, since 2001, has been editor in chief of its descendant online version *The Metabolic and Molecular Bases of Inherited Disease*. His encyclopedic knowledge of molecular genetics and metabolism, along with the input of the entire team of editors, helped transform that text, expanding it from biochemistry to the molecular basis of all medicine and ultimately bringing it to the Internet.

As a first-class clinician researcher whose contributions have been so well balanced between the lab and the clinic, David has few peers. He has trained many of the most prominent clinical geneticists of the US. Ada Hamosh recalls,

> At morning clinical rounds, Dave would use the Socratic method, prompting house staff with questions until they couldn't answer one. One day I decided to read every paper on the disorder affecting the child I had just admitted. The next morning, Dave asked me questions for a full 45 min until I got to one I couldn't answer! All clinical fellows were expected to develop the habits of rigorous thinking and knowledge of the literature and to apply that knowledge at the bedside.

David's intellectual, interpersonal, and leadership skills have placed him in a truly remarkable range of other important roles in American genetics and research. These include being president not only of the ASHG (2003) but also of the Society for Inherited Metabolic Disorders (1987–1989) and HUGO America (2004–2007). In addition, he has been chair of the Accreditation Committee of the American Board of Medical Genetics (1990), chair of the Board of Scientific Counselors of The Jackson Laboratory (2010–2014), a member of the Advisory Council for the NIH National Human Genome Research Institute (1995–1999 and 2006–2011), and a member of the NIH Council of Councils (2009–2012).

In closing, I want to point out that David's closest colleagues regard him with great affection. Larry Brody noted, "The worst lesson I learned from Dave was that many deadlines really aren't. He raised procrastination to a high art!" Similarly, Ada Hamosh recalls,

> His patients never minded his being late, because they knew that when they finally got to see Dr. Valle they would have his undivided attention for as long as needed. Of course, this commitment only made him later for the next appointment. For his 50th birthday, a long-term colleague gave him a watch in which the numbers said 1-ish, 2-ish, etc.

This trait has become legion and is perhaps most famously exemplified by stories of David's late-evening desperate drives to Bethesda—in the days before web-based submissions—to deliver a grant to the NIH, by hand, at least three min before the midnight deadline!

Please join me in welcoming David Valle as the 2014 recipient of the ASHG's Victor A. McKusick Leadership Award.

2014 Victor A. McKusick Leadership Award[1]

David Valle[2,*]

Thank you, Rod. It is a genuine pleasure to be introduced by a longtime friend and respected colleague.

I will start by admitting that I am honored, humbled, and amazed to be the tenth recipient of the McKusick Leadership Award.

I'm honored because the recognition comes from The Society, which has been my intellectual and spiritual home for more than 40 years. As is the case for most of you, our annual meeting is a real homecoming for me, a time to see old friends and re-charge my intellectual batteries.

I'm humbled because the previous nine recipients—David Rimoin, Walter Nance, Victor McKusick, Arno Motulsky, Charles Epstein, Lee Rosenberg, Francis Collins, and Rochelle and Kurt Hirschhorn—are all my heroes. How could it be that I am in their company? And, of course, I'm especially humbled because Victor McKusick was a friend and colleague for the nearly 40 years that our careers overlapped at Johns Hopkins.

And finally, I'm amazed because I think of this award as something given to the more senior members of our society…and then I realized that I *am* "more senior."

I know precisely when I first met Victor: on July 3, 1969, exactly 3 days into my year as an intern on the Harriet Lane Home service in the Department of Pediatrics at The Johns Hopkins Hospital. My senior resident instructed me to call Victor's office to place a consult on a dysmorphic infant I had inherited on July 1. I had some trepidation placing the call because I was well aware of Victor's reputation as a preeminent medical geneticist, and my anxiety increased when Victor himself answered the phone and told me he would be there in 15 min! And he was—walking down the hallway, he led an entourage of about 20, including Margaret Abbot, Tony Murphy, and many others. Looking for an answer for my patient, I quickly presented the case, and Victor and I examined the baby together. After a minute or two, he looked at me and said, "I don't know" and departed as quickly as he had come. Initially, I was disappointed to be left without a diagnosis, but later I realized that Victor was being completely honest and recognized that any suggestion he might make, no matter how tenuous, would immediately lock the child into the suggested diagnosis and inhibit future critical thinking about the problem. This intellectual honesty was the first of many lessons I learned from Victor.

Over the next several years, I saw more and more of Victor at Johns Hopkins and especially at his annual Short Course held every summer at The Jackson Laboratory in Bar Harbor, Maine. We became good friends and worked on many common problems. I greatly valued his friendship, his many contributions to genetics and medicine, his judgment, and his dedication to education and to this field, genetics, which has dominated both of our lives. One of the great pleasures of receiving this award was the chance to share the news with Anne McKusick.

So, how did I get into genetics? My career has been greatly influenced by a life-long fascination with biology and by the great good fortune to be influenced by many mentors and role models.

I grew up in rural upstate New York, where I spent all my free time roaming the woods and fields surrounding our house, often with my dog as my sole companion. I always had tubs of frogs, snakes, turtles—you name it—in the garage and in my room. I went to a central school in Baldwinsville, NY, and one of my earliest memories is the excitement I experienced when, in fourth grade, I learned that you actually got to take a course on biology in seventh grade! My first mentor was my seventh grade biology teacher, Phyllis Mangano; she gave me many opportunities to explore biology beyond the boundaries of the

[1]This article is based on the address given by the author at the meeting of The American Society of Human Genetics (ASHG) on October 20, 2014, in San Diego, CA, USA. The audio of the original address can be found at the ASHG website.

[2]McKusick-Nathans Institute of Genetic Medicine, School of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA
*Correspondence: dvalle@jhmi.edu

http://dx.doi.org/10.1016/j.ajhg.2015.02.001.

class room, including sending a loaner microscope home with me for the year and showing me how to do experiments with planaria, the amazing flatworm that can be induced to grow two heads. Later, my family moved to Kansas City, where, in my junior year of high school, I was able to take an advanced biology course. We did a lot of field biology, and my teacher and second mentor, Jerry Wilhelm, convinced me to go to Duke, where he had spent time and where they had a strong biology department.

My freshman year at Duke, 1961, was momentous for me on three accounts. First, I met Calvin Ward, a fly geneticist, and began 4 years of working in his lab—this was my entry into genetics. Second, walking home from the lab late one night, I decided on a career in medicine because it gave me the opportunity to stay in touch with biology while at the same time providing the opportunity to help others directly. And third, I had a blind date with Susan Twigg, who was to become my wife, companion, and lover for the ensuing 53 years and counting. All in all a pretty good year!

I stayed on at Duke for medical school, where I worked my entire 4 years with James B. Sidbury, Jr., a pediatrician and biochemical geneticist. Jim was great—unassuming, smart, funny, and treasured by patients and colleagues alike. Jim had a tremor, a hazard in the lab, where he was forever spilling acid on his clothes. For this reason, his wife, Alice, made him wear acid-resistant pants designed for gas-station attendants. He only wore ties when he was called to the dean's office, and he always dressed in thin white shirts with splayed open collars. One day, we went to see a young patient whose family had just arrived from out of state to see the great Dr. Sidbury. When we walked in to the patient's room for the first time, the father took one look at us and asked in a deep Southern drawl, "Are you boys here to fix the air conditioner?" Of course, when they experienced Jim in action, they realized they had entrusted their child to the best.

When I finished at Duke, Jim sent me to Johns Hopkins for pediatrics and genetics. During my residency years at Hopkins, I learned how to be a doctor and loved every minute of it. At the completion of my residency, John Littlefield hired me directly as an assistant professor charged with running the Pediatric Genetics clinic—something I did for my first 12 years on the faculty. During those early years as a resident and junior faculty member, I got to know many great Hopkins doctors and colleagues—Bill Zinkham, Saul Brusilow, Mike Kaback, George Thomas, and most importantly, Barton Childs, whose influence on me was and continues to be profound. Barton both challenged and nurtured me. He opened my eyes to the consequences of genetics and genetic thinking for all of medicine. What amazing good fortune to be able to work with him for more than 25 years!

I should mention two additional scientific experiences of note. After the second year of my residency, I spent 3 years in the Metabolism Branch of the National Cancer Institute, where I worked in the lab of James Phang on the metabolism of proline and ornithine. Jim continues to be a close friend and advisor to this day. A few years later, as a Hopkins faculty member with support from the Howard Hughes Medical Institute, I had the chance to do an on-site sabbatical in Dan Nathans's lab, where I learned molecular biology and was exposed to Dan's calm wisdom and acute scientific insight.

My first exposure to ASHG was the 1975 meeting in Baltimore. Already committed to genetics, I can remember the exciting science I heard and the personalities I met. From that point forward, I continued to be active in ASHG in virtually every possible capacity. I urge young people here for the first time to follow this same path. I guarantee that you will learn from the experiences and treasure them.

In any event, these were some of the experiences and mentors that molded me and brought me to this podium today.

Here are some final thoughts before my closing remarks:

1. As our president, Cynthia Morton, told us in her address, we are privileged to be in genetics at this time and place. Our field is leading a revolution in medicine that will result in a more informed and individualized activity—one that will enhance care and improve prevention. It is our responsibility to lead the integration of genetics into medicine. We should be rigorous in assessing what we do and do not know and continue to push for progress across all fronts from basic science to social concerns. We should not be paralyzed by uncertainty; rather, we must consider all possibilities, make an informed plan, move forward, monitor our progress, and be willing to change course depending on the results and new knowledge as it appears.
2. We have much yet to learn. We should continue to reach out and interact with our scientific colleagues in other fields—engineering, computer science, computation, and especially, all of biology. To paraphrase Max Delbruck, all living beings have a common ancestry. We should continue to take full advantage of this fact. Last night, too few of us heard the wonderful story of the discovery of miRNAs at the Gruber award ceremony. The enthusiasm and excitement of the awardees, Victor Ambros, Gary Ruvkan, and David Baulcombe, was palpable. Their transformative discovery came from work on plants, worms, and eventually, vertebrates. ASHG should continue to promote interactions across biology to speed our scientific progress and broaden our horizons.
3. I emphasize the value of participating in the education of others. The secret, of course, is that the teacher always learns more than the student. I urge all of you to drink from this fountain. It is essential for achieving the goal of integrating genetics into all of medicine.

4. Finally, regardless of the area of genetics that occupies you, get excited! Do not be complacent; be rigorous, be skeptical, do the experiment, test the hypothesis, and learn from it. And, like Victor, don't be afraid to say "I don't know."

In closing, I have many to thank. First, to my colleagues here at ASHG and at Johns Hopkins, as well as my many students and trainees, you have enriched my life and continue to keep me on my toes, up to date, and ready for the next challenge. Second, I have been blessed by having a stellar and dedicated core support team. My two lab technicians, Gary Steel and Cassandra Obie, and my administrative assistant, Sandy Muscelli, keep the lab running and me on track. In aggregate, our team has been together for more than 100 years!

Last, and most importantly, I thank my family. My parents, Joy and Bob Valle, are still healthy and have always supported me and let me follow my interests, even when they did not completely understand what I was doing. I thank my son, Josh, a teacher who makes me proud, my daughter-in-law, Mary, and my granddaughter, Margaret, who, I can tell you from a completely unbiased point of view, is truly exceptional! Lastly, and most importantly, I thank my wife, Susan, who has been with me through thick and thin since that blind date in 1961. Your love, support, and patience have made my life exciting and worthwhile. Nothing would have been possible without you.