Judith G. Hall: a genetic journey

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At a certain point in life, it is interesting and rewarding to reflect on why and how life has taken you on such a unique journey. What were the bumps along the road, and what have you contributed? I always liked biology, perhaps because my mother loved pointing out the exceptional in everyday life: unusual bugs, colorful seeds, or deformed branches. By contrast, my father challenged me with high academic expectations. And, perhaps not surprisingly, I was determined to keep up with my older brother. But why genetics? My choice of genetics was clearly because of a comparative anatomy teacher at Wellesley College: she was dull as dust until she began talking about genetics. From my present vantage point, she was an old-fashioned spinster professor, but one very dedicated to her students. I remember that every summer she went to Indiana to study "information transfer" in bacteria. Her enthusiasm was infectious, even though very little was known about genetics back then.

Subsequently, and as a direct consequence, while in my first year at the University of Washington Medical School, I took a genetics elective. No one else in my class had "discovered" genetics yet—as a result, I had an hour a week to myself with one of the "fathers" of medical genetics, Dr Arno Motulsky. Over the year, we worked our way through Professor Curt Stern's book on human genetics. WOW! The future and the challenges became clear. Consequently, I spent an extra year in medical school getting a master's degree in genetics, studying fetal hemoglobin production under conditions of low oxygen. On the one hand, that experience made it clear that genetics was the field for me. On the other hand, that year allowed me to recognize that the traditional laboratory setting was not for me, even though I had developed enormous respect for laboratory-based genetics. So the natural thing was to go study with the "other father" of medical genetics, Dr Victor McKusick, at the Johns Hopkins University Medical School.

Among other things, Dr McKusick was intensely interested in the genetics of short stature, and so we genetics fellows almost necessarily became involved in the patient advocacy organization Little People of America. Through this combination of McKusick and Little People of America, we learned not only about the various disorders of short stature but also learned directly about parent support groups and the importance of reliable and knowledgeable medical advisors to such groups. The clinic became my laboratory, every family teaching me something about its disorder, including the natural history and how patients and families adjust. As the concepts and principles of genetics began to clarify for me, I saw that the multiple organ systems affected by a missing or abnormal gene and/or its protein product provided early clues to systems biology and the complexity of gene action.

Moreover, I became aware of how little I knew about normal human growth and development; thus, I went on to do a pediatric residency, as well as a fellowship in endocrinology (mentored by Dr Robert Blizzard) at Johns Hopkins. It was then I realized that every one of the many stages in human development has different underlying physiologies and susceptibilities. In short, I became interested in congenital anomalies long before developmental genetics revealed the underlying origins of those "experiments of nature."

When I returned to Washington to start a clinical genetics program based at the Seattle Children's Hospital, inborn errors of metabolism and chromosomal anomalies were the high-profile genetic disorders. As a consequence, I and a group of medical genetics fellows initiated a study on the natural history of Turner syndrome, which helped me realize the importance of natural history studies in revealing the effects of abnormal genes on multiple organ systems. In addition, the first two families I saw in Seattle as a bona fide "grown up" medical geneticist set the path for years to come. The first was a family with a child with spina bifida, a challenge at the time because this was before the utilization of prenatal ultrasound and before the recognition of the role of folic acid in preventing neural tube defects. All we knew was that spina bifida was a "multifactorial disorder"; thus, we were more or less limited to explaining the known 3–5% recurrence risk. The second family involved monozygotic twins, including one with arthrogryposis and the other apparently normal. These twins led me down the path of trying to understand intrauterine (embryo and fetal) limb movement, on the one hand, and how and why monozygotic twins can be discordant, on the other hand.

My professional career has been highlighted by three sabbatical leaves: each one renewing my interest in genetics and revealing brand new (for me) fascinating areas. I highly recommend

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sabbatical leaves as part of an academic career, in providing exposure to new areas, time away from other hectic demands (administrative or clinical), and time for reflection about where one is headed in life. My first sabbatical was aimed at understanding both the breadth of disorders associated with arthrogryposis (multiple congenital contractures—some 400 disorders at last count) and at least some of the pathogenetic mechanisms involved (e.g., itemization of what "needs to be in place" for normal embryo/fetal movement to occur). From this work, we began to distinguish and characterize a large series of disorders involving congenital contractures, including, for example, the fetal akinesia sequence, amyoplasia, the "distal" arthrogryposes, and the pterygium syndromes.

The second sabbatical, commencing in 1988, with a Killam Senior Fellowship, was in Oxford, UK. It represented not only a cultural change but also a chance to understand the utilization of mouse models for selected human disorders and the homologies of imprinting/epigenetic disorders in mice and humans. It also provided the opportunity to know and collaborate with numerous fine medical geneticists in the United Kingdom and Europe. Working with them, I realized that genomic imprinting opened the door to other nontraditional types of inheritance as well.

Finally, after finishing 10 years as the Department of Pediatrics chair at the University of British Columbia, I undertook a sabbatical at Christ's College in Cambridge, UK. There I discovered the principles of the developmental origins of health and disease, i.e., fetal determinants of adult disease and their epigenetic transgenerational programming effects—areas that are now transforming our understanding of genetic mechanisms.

How much genetics has changed! From barely knowing what DNA was, to unraveling the human genome and the complex mechanisms that control gene expression, genetics has come a long way. The distant promise of genetic therapy is now about altering regulatory pathways and using small molecules rather than replacing entire genes. The likely apocryphal, but nonetheless compelling, clinical adage that "if you know the basic defect, a therapy may already be available" is becoming a truism. I marvel at the surprises that have occurred along the way and look forward to those yet to come.

There will always be a role for health-directed geneticists to explain and interpret complex findings to families, to serve as advisors to support groups, to define the natural history of genetic disorders (with and without therapy), and to learn from the families about how they manage and cope, their ideas about mechanisms and therapy, and their ability to cherish the unusual. I truly honor the many trainees, colleagues, and mentors I have had along the way, but perhaps I have learned the most from the families.

Now I am at the stage of thinking about—pondering—the value of senior academicians. How to utilize their (our) broad perspectives and institutional memories? When I was born, my life expectancy was 59 years. Currently, as a mature woman on the west coast of North America, I have accumulated an extra 30 years: my life expectancy is now 89 years (and that is just the average—I'm hoping for more)! Amazing human capital exists among our senior human/medical geneticists. A special challenge is to find new avenues to use their accumulated skills rather than displace them to retirement or to jobs meant for younger professionals. Being paid is not nearly as important as being able to use the enormous wisdom and experience that exists among senior academicians. A new and interesting challenge is before us.

DISCLOSURE

The author declares no conflict of interest.