A Half Century of Medical Genetics—Where Do We Go from Here?*

David L. Rimoin

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Thank you so much! This award celebrates my 52nd year in genetics.

When I was 17 years old, as a college sophomore, I entered a new honors program in genetics at McGill—all I wanted to do was find a way to get into medical school! My costudent was Dorothy Warburton, and we took turns making lunch for the faculty!

I started to work for Clarke Fraser, filing reprints and helping with his cleft lip and palate mouse work. Every morning, I would examine several hundred mice for vaginal plugs to time their gestation. I was certain that I would be a hit on "What's My Line!" I soon learned that I liked human bottoms better than mouse bottoms—no wonder I didn't go into OB/GYN. Clarke taught me about the joys of research and how to think critically. When I was accepted to McGill Medical School, Clarke arranged a new program where I could do a master's degree over the summers of medical school. I worked on the genetics of epilepsy with the Metrakoses and received my M.D.C.M. and M.Sc. degrees in 1961.

The giants in medical genetics at that time were primarily internists—McKusick, Motulsky, and Neel—and I chose to do my residency in medicine. Little did I know that I would later become a pediatrician by adoption!

At Victor McKusick's invitation, I went to complete my residency at Johns Hopkins and realized what a wonderful place it was. Victor had just started a Ph.D. program in Human Genetics, and I was able to pursue a fellowship and receive a Ph.D. in 3 years. Just ahead of me in the program was Alan Emery. A decade later, we met in the Hotel Russya in Moscow and formulated plans for "Principles and Practice of Medical Genetics"; the fifth edition, which includes an E edition, is being introduced at these meetings.

Victor taught me the power of clinical research and the value of studying rare diseases to prove basic biological principles. I accompanied him to meetings of the Little People of America (LPA) and even the "freak show" at the Barnum and Bailey circus at Madison Square Garden to find new research subjects.

He also highlighted the conflict between the "lumpers" and "splitters." We now know that both sides are correct—the splitters demonstrating enormous locus and allelic heterogeneity and the lumpers showing that the same phenotype can be produced by different genes that operate on the same pathway. This demonstrates the tremendous need for clinicians and lab scientists to work collaboratively. Not only can genotyping without phenotyping lead to missense or nonsense, but phenotyping without genotyping can also result in inappropriate prognostication, counseling, and treatment.

While doing a consult on the wards at Johns Hopkins, I saw a little person who looked just like a pituitary dwarf, but she was sexually mature and had a normal daughter. However, up until that time, there was no growth-hormone assay, and it was thought that all pituitary dwarfs were hypogonadal. Tom Merimee had just returned from the Berson and Yalow lab, and, with the new human-growth-hormone (HGH) immunoassay, we demonstrated that isolated growth-hormone deficiency did exist. These patients reminded me of the National Geographic pictures I had seen of pygmies, and Victor contacted Luca Cavalli-Sforza, who was doing population-genetics studies in the Central African Republic. I joined Luca's team on three occasions, and we showed that the pygmies were resistant to HGH or IGF1. My daughter Anne is an epidemiologist

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who is currently studying monkeypox in the Congo, and she plans to collect pygmy DNA so that we can now search for their molecular defect.

When I would go to LPA meetings looking for more growth hormone–deficient dwarfs, the disproportionate ones complained that I was ignoring them. I realized how little was known about their biology and gradually switched my interests.

I was recruited to Washington University in St. Louis to start the genetics clinic, where I was able to jump start my independent research career. I created the International Skeletal Dysplasia Registry, which still provides samples for our molecular research, almost 40 years later!

I soon realized that I wanted to develop my own genetics program, and, after exploring many possibilities in more-traditional university settings, I ended up choosing Harbor General Hospital, a county hospital with World War II barracks converted into labs. I received an RO1 grant for my skeletal dysplasia work, and the National Institutes of Health (NIH) support for this project has lasted 36 years to date.

I was extremely fortunate to recruit Mike Kaback to join me, and I helped him start the California Tay-Sachs screening program, which became the prototype for genetic-disease prevention. We were able to "Shanghai" my former student, Larry Shapiro, on his way back to St. Louis from the NIH, and he accepted a faculty position at Harbor and quickly became a leader in the field. Jerry Rotter was one our own graduates to join the faculty. A number of these Harbor graduates became leaders in cartilage biology, including David Hollister, Ilkka Kaitila, William Horton, and David Sillence.

My first national leadership position was as national secretary-treasurer of the American Federation of Clinical Research (AFCR) (now the AFMR), and I helped run the national clinical research meetings in Atlantic City. I was then elected president of the Western Society for Clinical Research, which ran the annual meetings in Carmel, and, 20 years later, I became president of the Western Society for Pediatric Research.

In the late '70s, ASHG President Arno Motulsky asked me to form a committee to look into credentialing medical geneticists and accrediting training programs. I was able to put together a committee of the giants in field—and we created the American Board of Medical Genetics. Since the American Board of Medical Specialties (ABMS) was not admitting any new Boards at the time, in order to make the new ABMG credible, we hired the National Board of Medical Examiners (NBME) to administer the exams. After the first exam, we asked the new ABMG diplomats whether our original Board could be grandfathered in, and, much to our dismay, they voted no—so almost all of us took the next exam.

In the mid-1980s, I was elected president of the ASHG. One of my accomplishments that year was to institute a new political action committee.

In 1986, I moved across town to Cedars-Sinai Medical Center to become chair of Pediatrics and build a new Medical Genetics Center in partnership with Jerry Rotter. I joined forces with the geneticists at the UCLA Campus and Harbor-UCLA and created the UCLA Intercampus Medical Genetics Training Program, which has trained scores of excellent clinical and laboratory geneticists.

At the turn of the decade, I was asked by the ASHG to form a clinically oriented organization, as they wanted to concentrate on genetics research. The laboratory directors were feeling disenfranchised at that time and were planning to form their own guild. I assembled a group of leaders in the field and, with the help of Mike Watson, drafted a constitution for the American College of Medical Genetics (ACMG) and its Foundation, making the College equally responsive to the needs of clinicians and lab people. We applied for membership in the Council of Medical Specialty Societies and became the 24th recognized medical specialty. We instituted an annual meeting, and, to avoid too many meetings each year, we combined the ACMG meeting with the ongoing March of Dimes (MOD) meeting and changed the time to the spring—6 months around the calendar from the ASHG meetings.

The ABMS finally admitted the ABMG as the first new board in 20 years, and as a full specialty. However, nondoctoral individuals were not eligible for ABMS membership, and we had to spin off the American Board of Genetic Counselors (ABGC). In order to maintain partnership and full integration with the genetic counselors, we formed the Council of Medical Genetics Organizations (COMGO)—the initial group being presidents of the ASHG, ABMG, ACMG, National Society of Genetic Counselors (NSGC), and the ABGC. We also helped fund the new ABGC.

The ACMG Foundation (ABMGF) was created to fund raise for education. We formed the Industry Liaison Council, hoping to attract diagnostic and therapeutic companies involved in genetic disease, to help them in setting policy and gain their financial support. Rodney Howell expanded this function greatly during his presidency, and the Foundation coffers have increased considerably. Mike Watson was hired as executive director of ACMG and immediately set off to grow the College's influence and finances.

There are a number of burning issues today facing medical genetics: How many medical geneticists do we need? How do we recruit them—with less than half of the training positions filled? We must start young—push for much more exposure to medical students. However, medical genetics is not a lucrative specialty, and recruits must be turned on by scientific excitement. We should not bitch and moan about the trials and tribulations of NIH funding and reimbursement (at least in front of the students). To save and populate our species, we must attract, seduce, train, employ, and sustain our youth!

It is curious that the so-called yuppie specialties that have attracted many of the top medical students in the past decade because of their income potential all start with a vowel! I think that is the reason that radiology changed

its name to "imaging." Perhaps we ought to change our name from genetics to "inheritology."

Do we remain as generalists? Should we be consultants or primary-care docs? We can't claim the genome as our territory. It is now part of every specialty of medicine. Can we hold off the commercial labs? Why should we be any more successful at this than the endocrinologists and immunologists, which were once lab-based academic specialties?

There is no way that generalist medical geneticists will be able to serve the increasing needs of society in providing genetics services for all diseases. I believe that we should create joint training programs with other specialties, such as perinatologists, neurologists, and clinical oncologists—similar to the new molecular medicine certificate with the pathologists. One year of specialized training is better than none; for example, most perinatologists now do prenatal diagnosis without any genetics training. The ABMG used to offer perinatologists credit for one year of research training in perinatology, and thus they could sit for their clinical genetics boards with only 1 year of genetics fellowship. This type of joint program with other boards, whereby one can save a year in obtaining dual certification, should be explored! Our goal should be to ensure that genetics services are available to everyone—and not just attempt to preserve our species.

We should take advantage of ethnic differences in genetics. The Tay-Sachs program made major changes in disease prevalence and has served as the model for greatly reducing the prevalence of thalessemia in Sardinia. Little else has been done in this regard. This should be true for common diseases as well—BRCA testing in Ashkenazi Jews costs 20% of what it does in other ethnic groups, since we can pinpoint three major mutations rather than have to sequence the entire gene. We should detail genomic differences between all ethnic groups and utilize this information for early detection and prevention of disease and improved personalized medicine. Let us celebrate our differences rather than hide behind a politically correct cloak. We are currently developing such a multicultural genetics center at Cedars-Sinai.

We are entering a new age where all medicine will use genetic methodology. If we do our job properly, all future M.D.s will be conversant in genetics and genomics and able to interpret molecular lab results effectively. We should stay at the forefront of our science—discovering new knowledge, developing new technology, and hoping that it gets disseminated throughout academic medicine, private medical practice, and industry, so that we are always ready to take on new challenges and not be burdened by what has become routine.

So what are the lessons I have learned over these 50-plus years?

1. Choose the right mentors.
2. Never let specialty boundaries deter you.
3. If your original plan doesn't work out, immediately bounce back and take the next fork in the road.
4. Set your sights high—if you don't aim for the sun, you will never get to the moon.
5. Treat your students and staff with respect and they will be glad to help you attain your goals.
6. Choose the best people to work with—hope that they all outshine you, and you can take credit for the integrated finished product.
7. Nothing stays the same—don't try to preserve the old tried-and-true methods, but let someone else take them over and shoot for the next level.
8. Be lucky in love, cherish and take pride in your spouse and children, and don't let your job or ambitions interfere with a happy family life.

This award is a great honor, and I have many people to thank—my mentors Clarke Fraser and Victor McKusick; my dear friend and partner Mike Kaback; the many people who helped me form the board and college, especially Mike Watson and Kurt Hirschhorn; my skeletal dysplasia team, including Dan Cohn, Bill Wilcox, and Debbie Krakow, who have kept me from becoming a dinosaur; and especially my wonderful wife, Ann, who is clearly the wind beneath my wings.