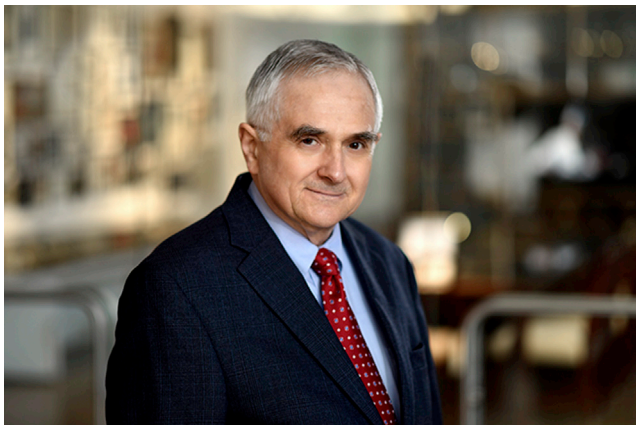
2017 Victor A. McKusick Leadership Award[1]

Arthur L. Beaudet[2,*]



It is an extraordinary honor to receive this award. I want to thank the ASHG Board and all who had any part in making the award possible. I first encountered Victor McKusick in 1967 while I was a pediatric resident, and I would like to recognize the recent passing of his always present partner, Anne. I view this award as recognition for my participation in building a medical genetics program at Baylor College of Medicine in Houston. This effort has involved hundreds of individuals and 46 years. So the recognition goes to a team effort. This award is also special because the ASHG is my academic home base—I have not missed a meeting since 1970.

I will try to tell you a little bit about myself and how the Baylor program was built. I started out as a New Englander through and through; I was raised in Rhode Island, but I like to think of Vermont as my adopted home state, as reflected in my tie today. My ancestors were French Canadian and migrated into New England with no Cajun connection. My interest in science was well established in high school and was nurtured by an after-school opportunity to learn some additional chemistry.

I started college in 1959, and sometime in my first or second year, I read Watson and Crick's famous 1953 paper. I said to myself, "This double helix can explain the replication of life, and I want to pursue a career in genetics."

In medical school at Yale, summers were for research. After a couple of unfruitful summers in a pediatric lab, I asked a faculty member for advice about finding a summer research position in genetics elsewhere. He said, "Well, you could go to the Jacob and Monod lab, but it will be shut down in August, so maybe it would be better to go to the NIH. Marshall Nirenberg is there, and he will be winning a Nobel Prize soon, so that would be a good choice, and as there is a doctor draft, it could help get you into the NIH Public Health Service to fulfill your military obligation." These were the most valuable few minutes of advice of my entire life. I sent off a letter to the NIH but received no response, so I called at spring break and said that I would be happy to come for an interview. A secretary who I would later know well yelled, "Marshall the kid from Yale is on the phone." Five or ten seconds passed, and she said "You can come."

When I arrived in Bethesda, I was assigned to Tom Caskey, who handed me a reprint and said that I should build a two-story column to fractionate tRNAs and get a hole drilled through to the floor above us to install it. This led to my first publication as a middle author with Tom and Marshall as coauthors. The NIH environment was research at its best. During this same summer, I also met my wife, Margie, who is here today, so it was a spectacularly positive summer.

When it came time for pediatric residency training, I was ecstatic to join the Harriet Lane program at Johns Hopkins. I was able to meet many people in genetics, including Mike Kaback, Rod Howell, Haig Kazazian, and others. My closest encounter with clinical genetic training was to attend at least two March of Dimes Birth Defects Conferences and perhaps some others where Victor McKusick and John Opitz, ever present, were escorting patients across the stage. I was also able to attend the Moore Clinic a couple of times to see Victor in his natural setting.

After 2 years at Hopkins, Nirenberg had won a Nobel Prize as predicted, and I returned to the NIH as planned and again found myself in the Caskey group, which now was focused on peptide chain termination. I shared half of a bench for 1 year with Joe Goldstein while Ed Scolnick and Tom and two to three others were all in a cramped lab. The excitement for science was palpable as Ed Scolnick led the cheering and booing as appropriate as the scintillation counter in the room flashed its morning and afternoon counts. The Nirenberg lab taught compulsiveness given that every solution was numbered in 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 17, 2017, in Orlando, FL, USA. The video of the original address can be found at the ASHG website.

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solution book, and every experiment was meticulously documented. This exposed me to an incredibly stimulating environment.

As my required 2 year stay at the NIH was winding down, Tom Caskey announced that he was accepting a position in Houston and asked whether I would join him. I did not look at other opportunities. I think that it was total serendipity to end up in Houston. When we arrived, exons and recombinant DNA methods had yet to be discovered, and there was no genetic board certification. There was virtually no clinical genetics in Houston, although Al Knudsen, Marjorie Shaw, and others were based at MD Anderson. If a family had a newborn with Down syndrome, there was no one trained in clinical genetics in the entire city of Houston to meet with them, but neither Tom Caskey nor I was trained in clinical genetics. Despite this, people started asking us to see patients. Over the next 5–10 years, I saw many, many patients in self-teaching mode. Laboratory services were nearly nonexistent, but Tom took the lead in starting a cytogenetics lab. Again, of course, neither of us had any training in cytogenetics.

Soon we had thriving cytogenetics and biochemical labs, and at least the first made money. This started what was to be a core feature of our success in growing the program: developing genetic labs that gave the program some very significant financial support. In the early years, the labs paid no dean's tax, and any surplus was poured into growing, strengthening, and broadening genetics. I was always fond of saying, "The more patients we see, the more money we lose. The more lab samples we process, the more money we make." This was true and is a sad indictment of the US healthcare system.

Tom Caskey and I both wanted to be involved in basic science, but recruiting basic science faculty was difficult because the activities were based in internal medicine and pediatrics. As part of a package to reverse a decision that Tom had made to move to Duke in 1985, Baylor created an Institute for Molecular Genetics, essentially with full department status and Tom as director. The institute was renamed the Department of Molecular and Human Genetics in 1994. Tom was always an excellent talent scout and recruiter, and he brought Allan Bradley and Phil Soriano to Houston; these two made enormous contributions to make the institute feel like a basic science environment. A Ph.D. program in genetics was put in place by Gretchen Darlington. Soon we had more and more trainees, including graduate students, clinical genetic fellows, and diagnostic lab postdocs.

When the institute was founded, I argued for a model that had evolved at Yale under Leon Rosenberg, the key feature of which was that faculty ranging from the most basic to the most clinical had primary appointments in genetics. Yale then had the best NIH postdoc training grant score, and it attracted the Francis Collins type of trainees.

In Houston, we were fortunate that genetics was a relative academic vacuum at Baylor and its affiliated hospitals. We just grabbed every bit of turf that we thought might be useful. At this time, I spent 4–5 years on an NIH National Institute of General Medical Sciences committee that reviewed all predoc and postdoc genetic grants. This was an era when almost every application was site visited, and I went on five to six site visits per year. This was an extraordinary learning opportunity, and I tried to bring the best attributes of each program back to Houston.

Fast forward, and we did end up with a gigantic department with probably more American Board of Medical Genetics and Genomics trainees than any other in recent years, enormous amounts of NIH grant support thanks to the combined efforts of the department and the Human Genome Sequencing Center, probably the largest academic parties at ASHG, and a preferred exhibit hall location at ASHG for our lab booth. While serving in an advisory capacity at the National Human Genome Research Institute, I observed their skits and singing at the retreat and brought the skits to our retreat, which ultimately led to the now famous "Bad Project" video. At times I think we did achieve the best NIH postdoc training grant score.

Two activities showed the Baylor program at its best: being very early to launch chromosomal microarray analysis and being early to offer whole-exome sequencing in the diagnostic lab. The status as one of the first to market resulted in high-profile publications, many new discoveries, a good profit margin for the lab, and the attraction of outstanding trainees and faculty. Particularly exome sequencing was a high point because it brought wonderful collaboration between the department and the Genome Center.

So what made this possible? First, an unquenchable thirst to build the strongest possible genetics program at a medical school, and second, building hybrid academic and semi-commercial genetic testing labs to generate revenue solely devoted to making the programs better. We also were fortunate enough to have hundreds of contributors over decades and dozens of superstar faculty. Many people choose not to name names in thanking people in this setting for fear of omitting people. However, I feel obliged to recognize certain people who are still with the department after at least 20 years and have received widespread recognition. I have mentioned Tom Caskey repeatedly, and he planted the seeds. Richard Gibbs is responsible for the success of the Genome Center. We have two outstanding cases of larceny from New York City: Jim Lupski, whose career-long contributions in terms of genetic concepts and manuscripts have been incredible, and Brendan, who you heard from and is proving to be a dynamic and talented successor as department chair. Hugo Bellen has been the basic science, hard-core genetics pillar of the department. Finally, Huda Zoghbi, who spent time in my lab as a K08 trainee, has made extraordinary contributions and now mentors me and keeps me out of trouble. My self-assignment as chair

for about 20 years was to keep these stars and many others in Houston.

We find ourselves alive during remarkable times in terms of genetics and medicine. We are living in the golden age of genetics. My advice is that each of you explore every possible opportunity in genetics and try to make the world a better place by virtue of genetic knowledge.

Finally, my family: I want to thank my wife, Margie, who has put up with me through thick and thin and without whose support I could not have accomplished any of this. She and my two daughters carried on through three editions of the Online Metabolic & Molecular Bases of Inherited Disease, to which I committed years of weekend time to editing chapters. Too often I have taken too little family time and asked too much of them, but they were always supportive despite this, and now my daughters and their husbands have added four wonderful grandchildren to our lives. Thank you.