

2016 Victor A. McKusick Leadership Award<sup>1</sup>Stanley M. Gartler<sup>2,\*</sup>

Stanley Gartler (left) and Gail Jarvik (right).

Thank you, Gail, for that wonderful introduction, and I also want to thank the ASHG for awarding me the McKusick Award.

I started my career in human genetics as a postdoctoral fellow in 1952 with Franz Kallman, a psychiatric geneticist who specialized in twin studies. He had fled Germany in the 1930s and established himself in New York City, where he became a professor of psychiatry at the Columbia University Medical School. He was one of the founders of our society in 1948, and in 1952, the year I arrived to join his group, he was society president. He was carrying out a twin study on sexual behavior and had identified an identical pair of twins who were discordant. One was married and had children, whereas the co-twin was homosexual. In what could have been my first day in the department, Kallman went out to interview the homosexual co-twin, and I accompanied him. The interview did not go well because the twin did not respond to any of Kallman's queries. Finally, Kallman lost his cool, and in a number of words, lectured the co-twin by essentially saying, "Your brother, who has identical genes to yours, is leading a perfectly normal life—why are you behaving this way?" The co-twin seemed somewhat startled by this outburst and looked at Kallman and said, "I don't know, Professor—it must be the environment." Within a very short time, we left the scene.

I did not get on with Kallman very well, and for most of my postdoctoral career, I was at the Institute for the Study

of Human Variation at Columbia University, where L.C. Dunn was the director. A number of Columbia faculty, including Kallman, were members of the Institute. Dunn was a mouse geneticist with a strong interest in human genetics and an equally strong anti-eugenics philosophy. He was an early member of our society and served as president in 1961. Dunn's close colleague in the Zoology Department at Columbia was Theodosius Dobzhansky, a famous evolutionist working with *Drosophila*. As a side line to his major interest in *Drosophila* evolution, he was interested in trying to detect genetic variation in human urinary amino acid excretion patterns, and I became his postdoc on this project. Other faculty members of the Institute included Philip Levine of blood-group genetic fame and Harry Shapiro, a well-known physical anthropologist. One of Dunn's friends was Henry Wallace, the former secretary of agriculture and vice president for two of Franklin Delano Roosevelt's famous four terms as president of the United States. Wallace came from a commercial plant-breeding background and could ask some very penetrating questions at seminars. While at the Institute, we all got to meet many other visitors from around the human genetics world. It was a great postdoctoral experience.

In 1956, Arno Motulsky was one of those visitors. He gave a seminar, and afterward he and I had a lengthy conversation. He was organizing a Division of Medical Genetics in the Department of Medicine at the Medical School of the University of Washington, and he invited me out there to be considered for a position in the new division. I got the position, and Arno was a great division head—full of ideas and encouragement. I am only sorry that he couldn't be here today. Arno received the McKusick Award in 2009, just one of the many awards he has received. Only 2 years after the Division of Medical Genetics was founded in 1957, the Department of Genetics was founded at the University of Washington in the Arts and Science College. Arno and I were founding members of that department.

Although positions and funding in academia were very tight when I received my degree in 1952 and started position searching, by 1959 conditions had improved considerably. A major reason for this improvement was Sputnik, the first artificial earth satellite launched in 1957, marking the start of the space age. This was done by the Russians

<sup>1</sup>This article is based on the address given by the author at the meeting of the American Society of Human Genetics (ASHG) on October 18, 2016, in Vancouver, Canada. The audio of the original address can be found at the ASHG website.

<sup>2</sup>Departments of Medicine (Medical Genetics), Genome Sciences, and Pathology, University of Washington, 850 Republican Street, Seattle, WA 98109, USA

\*Correspondence: [gartler@u.washington.edu](mailto:gartler@u.washington.edu)

<http://dx.doi.org/10.1016/j.ajhg.2017.01.010>

© 2017

and not the US. There's nothing like competition with Russia to open up the congressional coffers: grants and positions became much easier to get for some time. I know that funding is difficult now, but I am confident that it will get better.

I have spent a little time telling you about the early part of my career, and I now want to tell you a little bit about our research, which makes an academic career so interesting.

In the early 1960s, human chromosome studies were still a big thing, and I had a wild idea about the possible cytological basis of individuals with different eye colors. I mentioned this to a pediatric resident, Sorrel Waxman, in the next lab, and he responded that he had just seen a little girl who had different eye colors. Within a very short time, we found that she was chimeric for XX and XY cells in most body parts that we could examine. She had a normal ovary on one side and an ovotestis on the other side. The ovotestis was removed, and this infant grew up to become a functioning female. She was a full-bodied chimera who arose from an opposite-sex twin conception, and then in some way the two embryos fused early in development. In cattle, opposite-sex twins often exchange blood cells but not other tissues, the so-called freemartin effect.

Besides the XX:XY chromosomal variation, we were interested in looking at other genetic markers in this chimera, so we turned to Eloise Giblett, who ran the blood bank in Seattle and was the local expert in blood-group genetics, as well as other genetic variants. Elo was one of the most intelligent and careful workers I have ever met. She wrote a fine textbook on genetic markers and discovered the relationship between adenosine deaminase deficiency and cellular immunity. She was president of our society in 1973 and was a member of the National Academy of Sciences. The work we did on this chimera was very rewarding, and the added pleasure of working with Elo was truly frosting on the cake.

I find it hard to think of anything I would have rather done in my life than research and teach in human genetics. When something works, it is simply great. All the negative results of the past disappear. Let me tell you of another case. Much of my work was based on the X chromosome inactivation mechanism of dosage compensation, which involves turning off one X chromosome randomly in each cell of the early female embryo. At some point in the life cycle of the female, both X's must be active, and this most likely occurs in the oogonia. We were able to obtain ovarian material from a woman heterozygous for the X-linked glucose-6-phosphate dehydrogenase (G6PD) variant, and the oocyte extract showed a clear hybrid band, indicating activity of both G6PD alleles in each cell. The control pattern from the follicle cells of the same individual showed only the parental bands—no hybrid band—indicating that only a single allele was active in each of those somatic cells. Later, we showed the presence of the hybrid band in fetal oocytes, suggesting that

reactivation could have been occurring at the time of fetal differentiation of the oocyte pool. This was the first time that the hybrid G6PD band had been detected, so we were quite excited. Most of this work was carried out with a very talented graduate student, Mike Liskay.

Another wonderful, stimulating aspect of my university life was that individuals from other institutions worked with me. In the early 1960s, when our G6PD work was in its early stages, David Linder, a pathologist from the Children's Hospital in San Francisco, was spending a year in the pathology department at our medical school. David was going around the medical school to interview workers about their research activities. When I told him what we were doing, he asked whether he could join our lab for the year. I said yes, and David jumped right in. Soon, besides analyzing normal tissue structure with G6PD variation, we were analyzing leiomyomas of the uterus from G6PD heterozygotes. This work led to the first strong demonstration of primary tumors arising from single cells. David was one of the most intelligent and even-tempered persons I had ever met, and rather than use this work as a stepping stone for an academic career, he went back to his beloved San Francisco and pathology at Children's Hospital. Phillip Fialkow, a young assistant professor in our division at the time and a close colleague of mine, eagerly took over the tumor work with G6PD. Phillip made it his full-time activity and rose very quickly in the academic ranks to become dean of the medical school.

I was president of our society in 1987, and I was struck by the extensive role played by our action committees. One public policy action that we took that year involved a letter to Governor Thompson of Illinois in which we urged him to veto a modification of a right-of-conscience act. This bill would have permitted a physician to not counsel a patient regarding the possibility of abortion if abortion were contrary to the physician's religious or moral beliefs. Our letter, which was drafted primarily by Drs. Short and Fleisher and sent over for my signature, was one I had no difficulty in signing. And the governor vetoed the bill!

When I turned 70 in 1993, you had to retire from a state-supported professorship and stop lecturing, but you could continue your non-state-funded research—not such a bad idea. Earlier, I had spent some time in Art Riggs' lab trying to get caught up on DNA methylation and its possible role in X chromosome inactivation. Scott Hansen joined my lab, and we also began collaboration with Charles Laird, a biology colleague who was strongly interested in DNA methylation and replication timing. With Charles Laird, we studied the association between fragile X syndrome and delayed replication of *FMR1*. A few years later, we collaborated with associates in Holland to analyze the ICF syndrome, which involves immunodeficiency, centromeric instability, and facial anomalies. We were able to demonstrate a mutation in the DNA methyltransferase gene.

Finally, I want to tell you very briefly about one of my early ideas for a human genetic study: a somatic cell-culture approach. This idea was far from unique, but in the

early 1960s, little progress had been made. I collected a number of apparently independent permanent human cell lines—cultures that cloned easily and did not have a limited lifespan. I characterized them as to their genetic markers and found out quickly that they were all alike. Not that many different genetic markers could be used in cell culture at that time, but one (G6PD variation) was available, and all the so-called independent cultures were G6PD-A, a variant found only in individuals of African descent. Because the HeLa culture was from a woman of African descent and it was the first permanent human cell line established, it was obvious that all other permanent cell lines were contaminants of HeLa. I had been invited to the 1966 Cell Tissue and Organ Culture meeting and was going to present these results as a short note. I was chatting with my friend and colleague, Herschel Roman, a yeast geneticist, and he asked me what I was going to talk about at this meeting. When I told him, he looked at

me in amazement and said, “You are going to talk about cell contamination at a scientific meeting? They will laugh you out of the hall!” So before I left for the meeting, I added a fair amount of unrelated topics to my talk. As it turned out, hardly anyone was interested in the unrelated topics. No one tried to laugh me out of the room, but I think that some of the audience would have liked to have thrown me out of the room! And some 50 years later, instances of cross-culture contamination still turn up in the literature.

I have had a wonderful life, and my work has been a great part of it. My former colleague, Larry Sandler, a *Drosophila* geneticist, and I used to chat about how fortunate we were in our work. We would come up with ideas and chat about them with young bright students, fellows, and colleagues, and sometimes the ideas would actually work. They could have hired us for half the price! Thank you for this wonderful honor.