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2001 ASHG PRESIDENTIAL ADDRESS
On Black Boxes and Storytellers: Lessons Learned in Human Genetics*

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Like so many before me, I stand here expressing gratitude for the opportunity to serve as your president during the past nine months. It is a great honor, of course, but, more than that, it is also the privilege of a career for one who has never wanted anything more than to belong to the community of human genetics. I will have much to say this afternoon about the nature of this community, both for me as an individual and for us as investigators, scholars, and educators who have chosen to spend our professional lives as part of this community. I have learned many lessons from human genetics and would like to highlight several of these this afternoon, as well as to offer you a challenge for our future.

Before I begin on this peaceful afternoon in San Diego, it is important to reflect on just how much our world has changed in the last month. A new view of the world and a new view of the future have been thrust upon us. We are left to wonder exactly how each of us fits into this new world and how our work can best go on. We wonder how our individual and collective efforts in research, education, and the practice of human and medical genetics can best be presented and perceived at a time of both national and international—and, for some, very personal—turmoil and tragedy. We are, at the same time, scientists—with much to contribute by way of understanding the nature of the human condition—and individuals—with much to lose because of the nature of the human condition.

We are not the first generation of scientists to be asked to meet during the early stages of a war that promises—or should I say threatens—to occupy our thoughts and energy for many years to come. And we are not the first scientists to have to consider thoughtfully how science can best be served or can best contribute during a period of altered political and human priorities. There was widespread disruption to science in Europe in the late 1930s and 1940s, as Europe responded to events at that time in Germany. Not to increase the anxiety level among those of you who have flown here from overseas, but travelers to the Seventh International Congress of Genetics in Edinburgh in 1939 were torpedoed while crossing the Atlantic at the outset of World War II. Many scientists known to us, including some in this room, suffered greatly during that period and were asked to make both scientific concessions and personal sacrifice.

The American Society of Human Genetics played a role in the aftermath of that war—at least vicariously through several of its members—by contributing to the discourse at that time on radiation exposure and social policy. A number of our members—Jim Neel (ASHG president in 1953–1954), Jim Crow (ASHG president in 1963), Bentley Glass (ASHG president in 1967), and H. J. Muller (the first ASHG president, in 1948–1949)—were named to the national Committee on Biological Effects of Atomic Radiation and various other committees of the National Academy of Sciences, the World Health Organization, and the United Nations that were formed to address health concerns about radiation.

Out of these wartime efforts grew a new research focus: to study the effects of radiation on genes, chromosomes, and the genome. Public health concerns about the effects of ionizing radiation and chemical mutagens gave birth to a new generation of research tools to create novel mutations in model organisms. These efforts led to the emergence of the national laboratory system—at Oak Ridge, Berkeley, Livermore, and Los Alamos—each of which has played a catalytic role in the development of genetic and, more recently, genomic technologies, from which the field of human genetics has so clearly benefited. As one example that is particularly relevant to us at this meeting, it was studies on the effects of radiation that led Dan Pinkel and Joe Gray—then at the Lawrence Livermore Labs in Livermore, California—to develop fluorescence in situ hybridization methods as a cytogenetic approach to evaluate chromosome damage. It is their work that we honor, at this meeting, with the first Curt Stern Award of this Society. Stern himself would have been pleased that, in a very real sense, their

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work is a successor to his own Manhattan District project to study genetic effects of radiation at low doses, testing for the possible effects of exposure to fallout from nuclear weapons (Stern 1974).

What new areas of science and genetics will emerge as a result of our new awareness of terrorism? Perhaps we've seen a glimpse of this in only the past few weeks. Public and government attention to the threats of biological and chemical warfare—heightened this week with the discovery of several cases of anthrax infection in Florida and New York—may lead to increased efforts to understand how organisms respond to exposure to such agents. As one example, different strains of mice exhibit striking differences in susceptibility to lethal toxins, including anthrax. The recent identification of the gene responsible for differences between anthrax-susceptible and -resistant strains, by Bill Dietrich and his colleagues (Watters et al. 2001), received significant attention in the lay press, perhaps more than one might have anticipated prior to September 11. Are there similar variants in the human population that might be revealed in large-scale SNP association studies? Research on model organisms, one hopes, may provide us with new insight into the nature of the anthrax response, in order to develop newer, more effective vaccines.

Or will we be asked to play a more practical role in preparing us for—or safeguarding us against—future terrorist attacks? After all, each of our genomic DNAs, with its unique collection of SNPs, may be the perfect informational substrate for possible national identification cards. Even today, as revealed in a recent survey (fig. 1), while many Americans are willing to consider national ID cards, a full 50% of the American public is unwilling to have DNA information stored on such cards. This may reflect general ignorance about DNA uniqueness and what it means or, perhaps, less specific concern about privacy issues. Clearly, there is a role our Society could play, both in developing the technology and databases necessary for such ID cards and in educating and reassuring the public about the uses of genetic information.

Another, more somber possibility: there may be a need for more efficient, high-throughput methods of DNA genotyping to match and identify personal remains. Our Society is already engaged in discussions with the Institute of Justice, a scientific group within the U.S. Department of Justice that is collaborating with the New York State Forensics Laboratory to develop a plan to identify personal remains in the aftermath of September 11. Many members of our Society are highly qualified and, one hopes, will be willing to contribute their expertise to this effort.

These shifting priorities and the challenges of getting about business as usual aside, let me particularly welcome and acknowledge those of you who have traveled

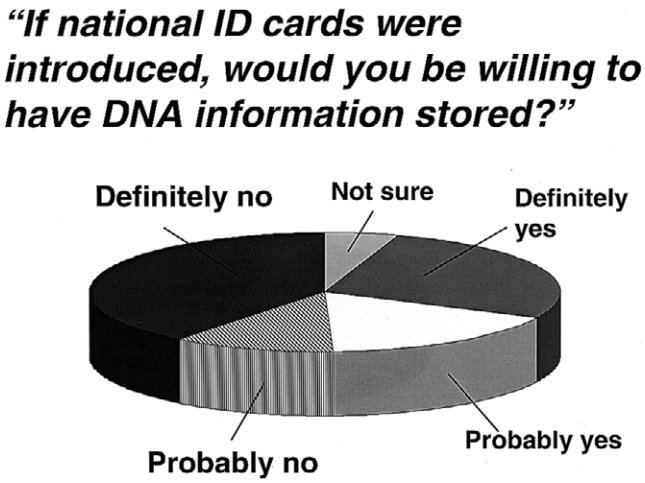

Figure 1 Public opinion on storage of DNA information on national identification cards. Source: Fabrizio, McLaughlin and Associates poll of 1,100 adults conducted September 24–26, 2001. Margin of error ±3%.

from overseas to join us at this meeting and who, no doubt, like those who traveled to the Genetics Congress in 1939, had to think hard about whether you would be able to attend this meeting at all. This week, we will hear presentations from all over the world. It may surprise many of you to know that less than three-quarters of the presentations here will be made by those from the Americas. We will hear from scientists from England, France, Germany, Japan, Italy, Finland, Belgium, Spain, the Netherlands, Sweden, China, Australia, Denmark, Austria, Switzerland, Scotland, Israel, Iceland, and Jamaica. We're delighted to have you all with us.

This annual meeting of the American Society of Human Genetics, then, is in a very real sense an *international* meeting of geneticists and is therefore a celebration of the unity of men and women of science from around the globe—scientists of different national origins, scientists of different personal beliefs, scientists of different religious backgrounds. Let the clearest and loudest message of this week be that, at a time when others would take away freedom of thought and action, more than 4,400 geneticists from over 20 countries came together to share new information and to speak their shared conviction that the open pursuit of knowledge is far more powerful than the fear of terror.

It is a sad irony—but one worth remembering—that this is the year of one of our greatest achievements as human geneticists: the public release of the first draft sequence of the human genome (International Human Genome Sequencing Consortium 2001, Venter et al. 2001). This is a time when scientists, philosophers, media pundits, and politicians alike, from around the world, all celebrated the single most obvious fact to

emerge from the human genome sequence: that our genetic similarities are much more profound than our differences. It is a sad irony that, in this same year, we are confronted with the starkest example yet seen in modern times that there is so much more to learn about at least some of the differences that mark humankind.

This week, we must attempt to place the work of human genetics into a larger and broader perspective, one both scientific and social. Part of my title for this address alludes to the "storytellers," those who—both in science and in the lay press—contribute so much and so well to our deeper understanding of the human condition. Throughout this address, I will refer to or quote directly from some of the "stories" that were influential in determining my own path in genetics or in shaping my outlook on what is important in science. I am reminded of the writings of E. O. Wilson, the Harvard entomologist and somewhat controversial social Darwinist. Some 20 years ago, he published a book, "On Human Nature," concerning the biological and genetic basis for human behavior and the concept of altruistic genes that are chosen for benefiting society as a whole, not just the individual (Wilson 1978). In this book, he wrote, "No species, ours included, possesses a general purpose beyond the imperatives created by its genetic history…. To chart our destiny means that we must shift from automatic control based on our biological properties to precise steering based on biological knowledge (pp 2–6)."

Whether one agrees with the basic tenets that Wilson espouses or not, we are left with our belief that only greater knowledge and understanding of genetics and its contributions to the human condition will help us truly decipher the meaning and potential of the human genome and lead us to ways of better influencing health and the state of mankind. That, after all, is *our* basic tenet, as stated in the bylaws of this Society (American Society of Human Genetics Web site):

- to encourage and integrate research, scholarship, and education in all areas of human genetics,
- to bring into close contact investigators in the many general fields of research that involve human genetics, and
- to encourage discourse on the applications of human genetics as they apply to society at large.

So, who are we in human genetics and where are we going? As one of the most popular storytellers of all time said, "it was the best of times, it was the worst of times." First, the "best."

Lesson 1: It Is the Best of Times

There can hardly be a better time to be in genetics. We have seen dramatic advances over the past few decades in our understanding, at a molecular and genetic level, of the role of genes in disease and in our ability to dissect genetically complex pathways and phenomena that could hardly be appreciated by generations of scientists before us. We have explored, at great depth and with great sophistication, the inner workings of our cells, chromosomes, and genes, and yet retained enough innocence and enough ignorance to be pleasantly shocked to find that we have perhaps only a third as many genes as we thought we had! By following patterns of DNA polymorphisms in both our mitochondrial and nuclear genomes, we have learned much in the last two decades about the evolution of our species and the migrations and emergence of different human populations around the globe.

We have seen the dramatic beginnings—but only the beginnings—of what one might call "translational genetics," taking fundamental discoveries from the laboratory and applying them to new advances in medicine in the diagnosis, management, and treatment of disease. We have brought genetics to medicine, from before conception to the neonatal period and, increasingly, into adulthood. Even in the aftermath of a genetic tragedy in the death of a human research subject at the University of Pennsylvania, we have witnessed the very first demonstrations of clinical efficacy in gene therapy.

And, finally, in the last year, we have seen the unveiling of the human genome and the telling of some of its secrets that shape our genome and its contribution to human biology and disease. We have dared to proclaim that we have seen the future, and it is us. The "best of times," indeed.

Lesson 2: Black Boxes

As a group—and even as individuals—we show astonishing breadth in human genetics. What other field can boast virtuosity over such a dynamic intellectual range? It is, of course, precisely this breadth that many of us find so attractive and compelling about our field. Human genetics offers the opportunity of both medicine and basic laboratory research. It remains the best of both worlds. The challenge, however, is to find effective bridges that connect basic science to medicine. Human genetics offers a better opportunity to do this effectively than most fields, but it is still an enormous, and largely unfulfilled, challenge.

It is the breadth of our field that brings many of us to this meeting year after year, and it is the breadth of our field that provides the fodder for discovery in human genetics. This breadth marks us not only collectively, but marks even as individuals many of the best scientists and scholars in our field. Our breadth spans pure basic scientific inquiry into the formal genetics, as well as molecular genetics, of both *Homo sapiens* and a variety of versatile model organisms, disease-oriented and pa-

tient-oriented research into the basis for human disease, and translational and clinical research at the doorstep of medical practice. It is a tapestry wide enough to cover both the most fundamental advances in basic science and the most potentially meaningful applications in medicine.

It is this breadth that invites and enriches the conceptual leaps that any field needs to make real progress. I refer not to progress of the sort as one travels down a well-marked path, with reasonably predicable outcomes and advances. Rather, it is the discovery of what I've called in my title "black boxes." These are the totally unforeseen and unpredictable discoveries that come only from a willingness to wander—at least intellectually—well off the path in search of explanations for the unexplained; in search of broader implications for what may, at first, seem like an incidental observation; or in search of new tools needed to chip away at or peer into the black box of uncertainty that surrounds so much of genetics. It is these conceptual and technical leaps that not only open doors but point to the existence of doors where there were none.

Let's look at some examples of what I mean. We could go back to Sir Archibald Garrod, the father of inborn errors of metabolism, who nearly 100 years ago first articulated the significance of those rare individuals whose, in his words, "alternative course of metabolism…must be looked upon as somewhat inferior to the ordinary plan" (Garrod 1902). His notion of "chemical individuality" provided a conceptual understanding in humans—for the first time in *any* organism—of the metabolic and biochemical consequences of genetic deficiency in individual genes, a lasting concept with profound implications for both biology and medicine.

Or we could look to Al Knudson's statistical evaluation of epidemiological data in the rare childhood tumor retinoblastoma and his careful articulation of the two-hit hypothesis of cancer that has served the fields of human genetics and cancer molecular biology so well for the past 30 years (Knudson 1971). Or to the theoretical enunciation of the power of restriction fragment length polymorphisms and linkage maps by Botstein, Skolnick, White, and Davis, published in *The American Journal of Human Genetics* in 1980 (Botstein et al. 1980). Or the demonstration by Kan and Dozy of the practical value of such RFLPs for studying the evolution and diagnosis of sickle-cell anemia (Kan and Dozy 1978).

This is a particularly good example to explore, because it not only underscores the dizzying speed of converting basic discovery in human genetics to clinical benefit but also proves the old maxim that chance favors the prepared or, in this case, the broadly educated mind. First recognizing and then cracking this particular black box required mindful physician-scientists, driven by a clinical need and aware of the theoretical value of polymorphisms in prenatal diagnosis. This concept wasn't new; after all, it was proposed initially by Haldane in the context of protein polymorphisms (Haldane and Smith 1947). But it took another 30 years to develop the theory more formally and generally in the context of DNA polymorphisms, building upon the discovery of human DNA polymorphisms in 1978 by two groups. One was the chance observation of a single nucleotide difference between independent genomic clones by Lawn and Maniatis when they first cloned the human β-globin gene (Lawn et al. 1978); little was made of this observation or of its potential human genetic implications. The second discovery, however, was Kan and Dozy's careful elucidation in the same year of a different RFLP downstream of the sickle-cell mutation (Kan and Dozy 1978). This paper was a model of prescient thinking and provided a clear outline for much of molecular genetic analysis in our field during the 1980's. It took the breadth of the field—encompassing medicine, formal genetics, and molecular genetics—to capture the true significance and promise of this particular conceptual breakthrough.

For those of you students whose eyes are rolling up because you've never heard of some of these people and can't believe I'm prattling on about events way back in the 1970s (much less the 1940s), let me assure you that there are more-recent examples too. There was Sir Alec Jeffreys, who discovered, in 1985, the existence of highly polymorphic minisatellite DNA loci in the human genome and gave birth to an entire new industry based on DNA fingerprinting (Jeffreys et al. 1985).

There are any number of clinical geneticists who demonstrate repeatedly the value of the rare, and sometimes unique, patient for illuminating black boxes. One of my favorite examples of this involves Bonnie Pagon and Uta Francke (ASHG president in 1999), who understood implicitly the significance of an unusual patient, B.B., who presented with four normally distinct X-linked diseases simultaneously (Francke et al. 1985). It was this patient's deleted X chromosome and DNA that led to the elucidation and eventual positional cloning of genes for all four of these disorders (chronic granulomatous disease, retinitis pigmentosum, McLeod syndrome, and Duchenne muscular dystrophy).

There were the cytogenetics and clinical genetics communities, starting with David Ledbetter, whose careful persistence to follow-up on chromosome 15s that looked just a little bit shorter under the microscope revealed the cytogenetically tiny deletion that marks Prader-Willi syndrome. It was this finding, followed by Merlin Butler's insight that virtually all of the deletions were paternally derived, that laid the groundwork for the eventual documentation by Rob Nicholls of im-

printing as a black box concept in human genetics (Nicholls et al. 1989).

There was Art Beaudet (ASHG president in 1998), who recognized an unusual female patient with cystic fibrosis whose father appeared not to be a carrier. Rather than assume nonpaternity, which, no doubt, many would have done, his group demonstrated that the girl had inherited two full copies of her mother's chromosome 7 and no copies of her father's chromosome 7 (Spence et al. 1988). This was the first fully documented case of uniparental disomy in humans—a black box, at the time, if ever there was one!

There was Haig Kazazian, whose discovery of an L1 repeat element inserted into the factor VIII gene in two cases of hemophilia A (Kazazian et al. 1988) established the relevance of this class of repeats in medical genetics and uncovered the surprising degree of dynamic movement of L1 elements in our genome.

There was Carolyn Brown, then a postdoctoral fellow in my lab, who persisted in trying to explain an observation that had no obvious explanation: an X-linked gene that seemed to be expressed only in females, not in males (Brown et al. 1991). Her persistence (very much in the face of my initial skepticism, I must confess) led to the description of the *XIST* gene, now known to play a pivotal role in X chromosome inactivation.

And, as a final example, there was Stephanie Sherman—also still a trainee at the time—who outlined what became widely known as the "Sherman paradox" (the observation that the penetrance of fragile X mental retardation differed in different carriers within the same pedigree and appeared to depend on one's position in the pedigree [Sherman et al. 1985]). This concept, derived (it should be stressed) only from formal genetic considerations, defied explanation until the gene was cloned a few years later and one of the most famous of the black boxes to emerge from human genetics was uncovered—namely, trinucleotide repeat expansion.

Who in the next generation of trainees, in this age of genomic reductionism—where everything, it seems, has to have an explanation embedded in our genome sequence—who will propose the next new genetic concept with no obvious precedent or molecular explanation?

What marks each of these discoveries is the imagination and intellectual courage that it takes to stray off the path and look for black boxes. Real progress—in this or any field—requires that we don't just walk through open doors; we must be open to the possibility that there are doors we haven't even seen yet and be open to the data that first hint at the existence of those doors. I like black boxes, because they challenge one's thinking to the extreme and invite us to muse about what mind-boggling, possibly crazy, probably even wrong in detail, explanations could conceivably explain the data. I like black boxes, because you can draw sometimes wildly speculative models, and no one can look up the answer in the back of the book and tell you are wrong. No one can look to other systems or precedents and tell you that you must be crazy. You *might* be crazy, of course, but, then again, you just might be right. My delight with black boxes probably shouldn't come as a surprise. After all, I've spent much of the last 20 years ignoring proteins and instead chasing after repetitive, so-called "junk" DNA and noncoding transcripts in our genome. Those were—and to a large extent still are—black boxes.

Lesson 3: When Nothing Else Works, Stop and Think

The early decades of human genetics were full of such musings. After all, today's younger scientists might hasten to point out, there wasn't much else to do! There were no cloned genes and databases of genome sequence. There weren't transgenic mice or yeast models to test critical predictions of hypotheses. There weren't fancy confocal microscopes or deconvolution software to provide high-resolution images in three dimensions or in living cells. Without a catalogue of enzymes and genes, one had the freedom to infer the existence of new activities and the role they might play in metabolism or development. Often, of course, as I've just illustrated, such insights came from a collection of patients or even that one unique patient whose phenotype begged for an explanation. Absent complete data, one had to rely on one's cunning and, well, just plain thinking, to milk all that one could out of limiting amounts of clinical or laboratory data. How different the challenge is now, when we are, at times, inundated with mountains of data, and the task is to sort through them to find the most cogent and the most meaningful. It takes great intellectual discipline to put your pipette down and just think about the data. The best and most impactful scientists do this regularly.

In those premolecular and pregenome years in human genetics, there were often just the hypotheses. Some of them were truly creative and mind-stretching exercises, free from the confining scaffold of well-understood molecular, cellular, and genomic principles that now enlighten us all but tend to constrict our freedom of movement intellectually. In the 1960s and 1970s especially, the literature was full of wonderful genetic models to explain how things might work. They greatly advanced our thinking and prepared the field to accept the notion of a totally novel and unanticipated mechanism once the data were advanced enough to demonstrate it convincingly.

Many of the black boxes that I've discussed are now well known (and, in some cases, even well understood), and it may be difficult for some trainees in the audience to consider a day when these concepts were not a fully

established part of human genetics. It is a sign of their significance, however, that each of these formerly-black boxes is now so firmly rooted in our field. These discoveries, and so many others like them, opened new doors where there were none before and where there is now an open passage for exploration and further discovery. The impact of such discoveries goes well beyond either basic science or clinical observation; their hallmark is that their significance blends the basic science of genetics with the keen eye and practical imperative of human and medical genetics.

Lesson 4: The View from Outside the Tent

So, what's wrong with this picture? Why do I not share the enthusiasm and optimism of so many of my colleagues? As I've just illustrated, my sense of concern is certainly not for the field of human genetics in general or for its capacity to contribute in increasingly significant ways to our deeper understanding of human biology or medicine. Rather, my concern is for the challenges that await this organization—the American Society of Human Genetics. My concern is for its vitality, for its ability to continue to grow and thrive and to assume or maintain a leadership position in applying genetics to human biology and medicine. In a sense, our successes—both scientific and political—in bringing human and medical genetics into the limelight and in proving that we are indeed "relevant" threaten to be our downfall.

The state of our field and the prospects for its future are stronger than ever, but the state of our Society, I fear, is less certain. Let me explain.

My concern is that the view from inside the tent and that from outside the tent are very different. The single clearest manifestation of what it means to be a member of this Society, of what it means to be a human geneticist as any of us would define it, is our yearly attendance at this meeting. I have been attending this meeting every year since 1975, my first meeting, when I presented a paper based on my work as an undergraduate with the late Sam Latt. It was he who taught me that this was the one meeting that you pointed your work towards each year. I cannot imagine a fall going by without attending this meeting and without members of my laboratory presenting their work for consideration and evaluation by this community. I know there are many of you who share this conviction and have attended far more meetings than I have! We are truly a Society of many generations, and this is one of the great successes of this community.

My concern isn't about those of us who are here. My concern is about those who are *not* here, those who consider themselves human geneticists—or at least biologists or physicians interested in human genetics—but who do not consider this meeting to be either important or exciting enough for them to attend.

My concern is twofold. First, with human genetics and genomics finding itself in so many venues, the temptations, if you will, for the next generation are great. Students and other trainees show, in many cases, an indifference to this Society and its meeting. The breadth of human genetics—precisely what I just described as being our strength and defining quality—gives us an air of being a bit (how shall I say this?) "old-fashioned" and "stuffy." Even among those of us on the inside, we have argued for years about whether our meeting was getting to be "too molecular" or "too clinical" and whether we were adequately and equally serving all of the various constituencies that make up human genetics. But, for all our internal debates, we should acknowledge that many of those on the outside have already voted with their feet. There are just too many alternatives—genome meetings, Gordon Conferences or Keystone Symposia in specialty areas, or meetings of other scholarly societies—that are perceived to be more exciting and somehow more modern and relevant to them than this one.

My second concern is that those outside of the tent mean something very different than we do when they refer to human genetics or when they talk about the impact of genetics on the future of medicine. When many of them talk in this way, what they really mean is the molecular biology of human genes or perhaps "functional genomics," to use the most common modern buzz phrase. Their perspective may be from the standpoint of physiology or cardiology or neurology, rather than from a strong foundation in human genetics.

However, this concern of mine can also be stated as an opportunity and a challenge. We should broaden our perspective and be inclusive. It is only by doing so that we will be able to demonstrate our vitality and deliver on the great promise that our field holds. Not only should we openly welcome others to our field, but we must work harder to ensure that they feel welcome inside our tent. As stewards of the field of human genetics, we have much to lose if they don't. We run the risk that—in contrast to what I said earlier—we have seen the future, and it is *not* us! We run the risk—a very real one, in my opinion—that we will wake up and find ourselves on the sidelines, not at center court.

So what's the evidence? For starters, let's look at our own membership numbers (fig. 2). To be sure, our membership has increased every year for decades, and we can boast of a 20% increase over the past five years and a 10% increase in the last year alone. But compare this with the period from 1991 to 1996, when membership grew by almost 40%. And put this in the context of our field. Human genetics is supposed to be the hottest ticket in town, if you believe the press releases! We

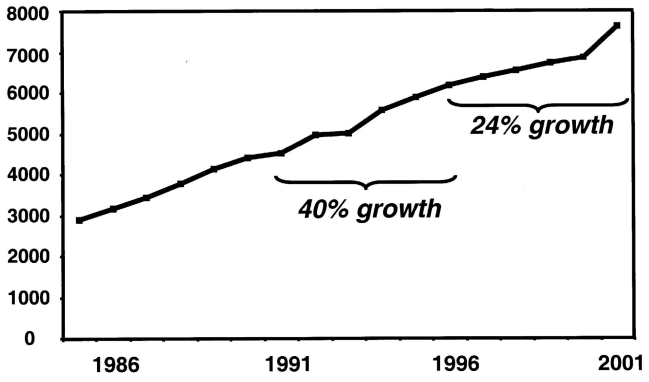

Figure 2 Membership trends in the American Society of Human Genetics, 1986–2001.

have enjoyed spectacular successes, with the promise of even more spectacular ones—and ones of more general interest and significance—to come.

So where are all the converts? Attendance growth at this meeting during the past decade—during this period of increasing profile, various *Time* and *Newsweek* covers, and even the Human Genome Project—has actually been fairly modest. Over the past nine years, the average growth rate in attendance at this meeting is only about 4% per year. Not bad, but hardly what one might expect for the hottest field in the business. The inescapable conclusion is that the converts are outside the tent, not inside!

Where did everyone go? Compare our numbers with those in the Society for Neuroscience (fig. 3). Here, membership has exploded, more than doubling since 1990. It is a similar story for the American Society for Cell Biology. The combined membership of these two groups is some five times that of our Society. Want to go to a meeting with lots of human genetics talks? Check out the abstract book for the Neuroscience meeting! To cite another example—in another area that overlaps human genetics—consider gene therapy. The American Society of Gene Therapy is only five years old, having been established in 1996. But its membership has already increased to about 3,000 members during that time. (By comparison, it took us 35 years to get to that level!) Does this mean that neuroscience, cell biology, and gene therapy are more exciting than human genetics? No, not at all. But it does mean that we have some work to do.

Let's consider next the Human Genome Project and the annual Cold Spring Harbor meeting on the genome. The overwhelming success of that meeting, which began in 1988, can, I believe, be attributed, in no small part, to actions (or inaction) on our part. After all, it was the conclusion of members of this Society that the Human Genome Project being proposed in the late 1980s was largely *outside* the purview of the American Society of Human Genetics. Support for the project from this Society derived largely from our interest in the medical implications of the project, rather than our participation in the research per se at the interface of human genetics and genomics. In retrospect, we should have recognized that we couldn't count on one without first investing in the other.

Consider this statement from the report of our Human Genome Committee (ASHG Human Genome Committee Report 1991): "The Human Genome Project is…of particular interest to the ASHG." So far so good. But the reason? Because "ASHG has within its membership the vast majority of American and Canadian health care personnel involved in the development and delivery of genetic services to the North American public." The Committee formed three working groups at that time to address health care issues, educational issues, and legal, ethical, and social issues related to the genome project. But missing was a working group on genome science! Clearly the science of the project itself was not perceived to be in our purview. It was pushed outside our tent, and the Cold Spring Harbor meeting and many other genome meetings and organizations sprang up to capture the excitement and the science of human genome research. I believe we are now paying a price for those decisions. We needed a bigger tent.

I do not intend to be overly critical of the Committee and its deliberations. It was, after all, the considered opinion of leaders in our Society at that time, and the process followed was deliberate and thoroughly democratic and driven by the membership. I was on the Program Committee then, and we wrestled diligently and thoughtfully with the extent to which genomics belonged at this meeting. In our efforts to preserve the special flavor of our Society and its meeting, we unwittingly contributed to one of the problems that I be-

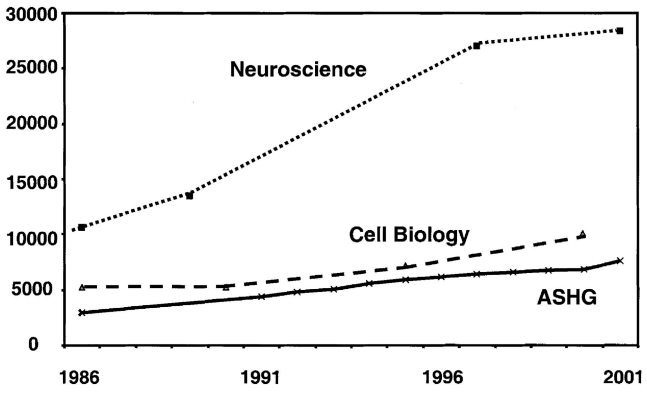

Figure 3 Comparison of membership trends in the American Society of Human Genetics, the American Society for Cell Biology, and the Society for Neuroscience.

lieve we are now confronting. Much of the commonly perceived excitement and vitality is on the outside.

There are no easy answers, and hindsight is, of course, 20:20. But I believe we made the wrong choice 10 years ago. Should we have then—or should we now—consider a more expansive Society and a different type of meeting that would enlarge the tent? Are we content with a meeting of the current size and diversity? Would our field be better served or would it be hurt if we were the size of, say, the Neuroscience meeting? And, if it would be better served, how do we do enlarge the tent while preserving those aspects of this meeting and our Society that are central to who we are? Without prejudging the answers, I believe these are questions that we must debate and consider.

Lesson 5: We Need a Bigger Tent

To begin this dialogue, I would argue that not only do we need a bigger tent but we need to change how we present ourselves, how we state our interests, and what we offer to scientists who are currently in fields that we now indicate are largely outside our purview. Simply put, if we want to attract a broader audience with diverse but legitimate interests in genetics and genomics, particularly as they apply to the future of medicine, then we will need to change our body language. While we meet annually to celebrate the advances in our field—and they are substantial ones of which we should be proud—there is an entire world going on outside our tent. Our voice is loud and resonant inside the tent, but we are less effective at being heard outside.

I believe that we must consider strategies to throw open the doors and invite the others in. We must better articulate what human genetics is, and we must identify a group of thought leaders who can argue effectively for "human genetics" as *we* mean it, integrated with "human genetics" in a broader sense as *they* mean it. I refer again to our by-laws and to one of the objectives of our Society: "to bring into close contact investigators in the many general fields of research that involve human genetics." If we believe our own words, then we must expand our attractiveness to those in other fields and other areas of science and technology. Everyone nowadays is doing genetics! This is good news, and we need to find a way to welcome them into the tent.

Let's consider some examples of who I mean. As successful as we are in attracting academic human geneticists from around the world, we have done an ineffective job, at best, of attracting geneticists from the for-profit sector. This is a meeting for the open presentation and discussion of data, and we should openly welcome scientists from the pharmaceutical and biotechnology industries, as well as those from genomics and diagnostics companies, to participate fully. Make no mistake—"fully" means "openly." They must be willing to present their data, just like the rest of us, and hold it up to scrutiny and discussion. Some do just that. But it is a fact that only 3% of the platform presentations at the meeting this week are primarily from companies. You can be sure that a much, much larger volume of human genetics research is going on in companies that is not presented here. Many of those scientists participate fully in other meetings, such as the American Society of Gene Therapy meeting and a variety of genomics meetings. Somehow, we have failed to deliver an effective invitation to the for-profit sector, or we have failed to offer an attractive message for them. They are very much a major part of the future of genetics in medicine, but they are outside our tent. I believe this must change.

There are other groups whom we must engage as well, outside of our usual audience. Bioinformatics is one such field that is just beginning in full force in academic circles but that is currently more closely affiliated with genomics meetings than with this meeting. There are emerging technologies that are appropriate to be represented here as well: technologies, for example, to develop better gene chips for population screening or technologies in proteomics that we are just beginning to hear about at this meeting. This science is tremendously exciting and certainly relevant to us. But they are currently outside the tent. I believe this must change.

And what about model organisms? Even Gregor Mendel and Charles Darwin worked with model organisms! There are spectacular advances in understanding the genetics of mice, rats, flies, worms, zebrafish, pufferfish, and even plants. All of this is highly relevant to human genetics and has enormous implications for human biology and medicine. However, we only occasionally hear of this work at these meetings. For the most part, they are currently outside the tent. I believe this must change.

I believe all this must change if this meeting and this Society are to retain our vitality, because it is the leaders of many of these companies and these other fields who will increasingly drive the revolution in medicine and in biology that we hope to be part of. I believe it does little good for us to meet by ourselves and make grand pronouncements about the future of genetics and genomics in medicine, while we ignore—or react belatedly to—the world around us. There is terrific science all around us, being presented at a variety of other venues by scientists and physicians who believe deeply in the impact of genetics on what they do and yet have little reason to think about or know about what goes on here.

Make no mistake: I think it's evident that the vast majority of those engaged in genetics research relevant to medicine will *not* be those we might consider to be "card-carrying" human geneticists. And I think it's ev-

ident that the vast majority of those who will practice genetics in medicine will *not* be board-certified medical geneticists. We had better get used to it. All the evidence argues that the revolution has already started and that we have yet to find an effective voice. We can do better. But to do this, our Society, its members, and its leadership will have to address what kind of Society we want to be, both now and 10 years from now.

Lesson 6: Two Cultures

To be sure, an alliance between academic societies and the for-profit sector is potentially an uncomfortable one. After all, the two cultures are founded on very different principles and beliefs. My thinking in this area has been shaped by two very different books. The first is perhaps the best novel ever written about the research enterprise and the differences between medical scholars, basic scientists, and those in the pharmaceutical industry—*Arrowsmith* by Sinclair Lewis (Lewis 1924). I first read this book as a high school student, and it was a source of inspiration that legitimized my interest in laboratory research as a career goal. The second book is a thoroughly informative and convincing discourse on America's universities, called *Academic Duty,* written by Donald Kennedy, former president of Stanford University and now editor-in-chief of *Science* (Kennedy 1997). In it, he explores the different pressures on universities and their faculty, viewed particularly against a background of intensive research activity. It focuses, as the title suggests, on what it means to be part of the Academy, what its freedoms are and what its responsibilities are. This should be required reading for every junior faculty member, at the time they take up their first job at a university, and again for every senior faculty member, at the time they consider or take up leadership or administrative roles.

All institutions of higher learning have as their primary mission one thing: to educate students. The biomedical research enterprise, substantial as it is, particularly at the top level of research-intensive universities and medical schools, is nonetheless secondary in the eyes of the public and of the boards of trustees who are charged with oversight responsibility for the academic trust. A uniquely academic solution to the potential conflicts between research and education is part of what distinguishes the research cultures of a university and thatof a for-profit company. The union between original research and research training—a tradition borrowed from the German university system and imported to the United States over 100 years ago—puts substantial emphasis on training young academics to take their places in the nation's universities. The belief behind the university culture, as Kennedy writes, is that "enlarging and disseminating knowledge are equally important activities and that each is done better when both are done in the same place by the same people." (Kennedy 1997, p. 28)

Contrast this with the experience, portrayed in *Arrowsmith,* of Max Gottlieb, a former medical school professor who, with some discomfort, moves his research to a Pittsburgh pharmaceutical firm. The potential conflicts inherent in attempting to perform basic research in such a setting are evident throughout this somewhat cynical tale. The cultural differences become apparent when the company's CEO confronts Gottlieb, the basic scientist. As the CEO reminds him, "Personally, I should like nothing so much as to spend my whole life in just producing one priceless scientific discovery…. But we have our duty toward the stockholders." (Lewis 1924, p. 135)

So, no matter what the motivation of individual scientists, we can't overlook that the primary mission of a university and the primary mission of a commercial enterprise are different. But within that context, meetings such as this can provide a common meeting ground, where scientists with a shared interest in the science can openly present their findings and discuss their implications.

We have our own Gottliebs of course. Over the years, a number of high-profile human geneticists have left academia, temporarily or permanently, to move to industry. But, rather than "vote them off the island" (to use a current phrase), we need to encourage their continued participation in our Society and our meeting and to ensure that we offer a meeting that meets their needs as well as our own. There is a gulf to bridge between universities and industry, and academic societies like ours can play a key role in this. This is not as impossible as it may seem. We are, after all, not the first discipline to have considered the value and importance of doing this. Chemists and engineers, to name two, have successfully bridged the gulf. So have pharmacologists and endocrinologists. The genomics community has been much more open to this and successful at it than has the genetics community. But as the ranks of those in industry who are interested in human genetics increase, we have a lot to gain by finding ways of continuing to break bread with them. And we have a lot to lose if we don't.

There is another reason to consider enlarging our tent. Genetics (and certainly genomics) is now "big science." Even Kennedy, himself a former University president, acknowledges that there is widespread skepticism "about the university's ability to reorganize, to marshal the diverse talents necessary to approach complex problems of large scale" (Kennedy 1977, p. 278). To be sure, human genetics—with its breadth of focus on basic science, practical applications to medicine, and increasingly important social policy implications—is one of

those "complex problems of large scale" that Kennedy refers to. To successfully tackle such a problem almost certainly will require input of energy and resources from a diverse set of organized units—universities, to be sure, but also independent research organizations, in both the academic and commercial worlds.

These are two different cultures, and the gulf between them needs to be bridged. This is where the American Society of Human Genetics can come in, if we are willing. None of this will happen without an attitudinal change, and our Society can help to catalyze this as an agent of change.

Lesson 7: Mentoring

In addition to the open exchange of information, one of the values that we must protect at all costs is mentoring our young trainees and ensuring the cultural transmission of our field from one generation to the next. This is very much a part of who we are as individual faculty members and scientists, but this is also one of the defining qualities of this Society and its annual meeting.

Kennedy's book provides a careful analysis of what is needed for proper mentoring, together with the potential pitfalls and traps that sloppy or inattentive, or just plain misguided, mentors can fall into, mostly to the detriment of their trainees. As Kennedy notes, "The student's experience depends heavily on the good will and conscientiousness of a single mentor. It requires total immersion in a demanding scholarly discipline.... The experience is often lonely and may be profoundly alienating. Yet at its best, with an inspiring and compassionate mentor, it can be positive and even transforming." (Kennedy 1977, p. 45)

I can attest to that. I was fortunate to have been mentored by passionate practitioners of the transforming quality of good mentoring. In keeping with Kennedy's comments, let me single out my experience as a graduate student under Leon Rosenberg in the then Department of Human Genetics at Yale in the late 1970s. My experiences with Lee, usually one-on-one early in the morning or on weekends, were almost uniformly uplifting and ultimately transforming. Like all effective mentors, he knew which buttons to push and when to push them. I cannot adequately express the debt I feel to him. Whatever I may have accomplished in this field, either as a scientist or as a member of this Society, I owe to him.

The mentoring experience in science takes on a singular, one-on-one quality, much like the relationship between master and apprentice. Those of you who are or who have been graduate students will recognize the true ring behind the following excerpts from popular accounts of this relationship.

First, Max Gottlieb again, when he was still a medical school professor, talking to Martin Arrowsmith as Martin begins his years of research training: "There are two kinds of students the gods give me. One kind they dump on me like a bushel of potatoes. I do not like potatoes, and the potatoes they do not ever seem to have great affection for me.... The other kind—they are very few!—they seem for some reason...to wish a little bit to become scientists.... Of the potatoes, I demand nothing; of the...ones like you, who think I could teach them something, I demand everything" (Lewis 1924, p. 15).

An absolutely wonderful book that tells this story well from the standpoint of a classic genetics story is *Mr. Darwin's Shooter* (McDonald 1998), an account of Darwin's travels on the HMS Beagle, leading up to his publishing *The Origin of Species*. The tale is told from the vantage point of Syms Covington, a historically accurate figure who was at Darwin's side from 1832 to 1838 on his voyage. Covington became Darwin's "shooter," the one responsible for shooting and then collecting various specimens, including the famous finches, for transport on the Beagle back to England.

Syms is, at first, a bit of a misfit, using the wrong powder or miscalculating the amount of shot to use for a particular target and often blasting Darwin's hoped for specimens to bits. But, like any first-year graduate student, he soon begins to get the hang of it and even to enjoy it. Covington works hard and eventually, as we would say, turns the corner. "He [finally] thought it advantageous to think like his master,...making connections and not just reporting facts, but whatever facts might seem to be important. How full of himself he was, all spunk and spittle." (McDonald 1998, p. 245)

We know the ending of this tale, of course. "Recall, thought Covington, [Darwin] and his catechism: 'Look for variations among common types'" (McDonald 1998, p. 260). Covington—and the world—is transformed. "Thus did 'what is life?' become a question in the mind of an ordinary young man" (McDonald 1998, p. 301).

And lastly, a bit lighter touch. Carl Djerassi, the award-winning Stanford chemist who invented the first oral contraceptive, has written a delightful little novel, called *Cantor's Dilemma,* about the ethics, politics, and practice of big-time research, starring a professor and his beleaguered trainee. (There are great lessons here about how *not* to mentor and about the potential conflicts of interest that can weigh heavily on the mentor-trainee relationship. This book also illustrates why readers of the popular press have such a distorted view of what we do for a living!) Professor Cantor attempts to explain his work habits to a nonscience friend of his, Paula:

"I would have called, but the last few weeks have been frantic. I've been working every day, and most evenings, in the lab...."

"I thought that you had a group of devoted slaves at your beck and call."

"Paula, we call them…coworkers" (Djerassi 1989, p. 100).

Lesson 8: Academic Duty

Life in human genetics is not all research and mentoring, of course. For most of us, there are committee meetings, grants to write or review, papers to review—all contributions to the academic way of life that most of us value so much. This is the "stuff of academic duty," as Kennedy calls it. No university and no academic Society like ours can survive without it. And yet, I confess, I am concerned that we are dividing into two groups of members. First, there are those who were trained to meet this duty and who do so willingly (for the most part), freely expending sometimes enormous amounts of time and energy to ensure that the system works and thrives. These are those who join study sections, who join committees at their universities or in various genetics organizations, who edit or review for our scientific journals, who volunteer to run courses.

But there are also those who, armed with the excuse that they are too busy, simply say no. My concern is that this second response seems increasingly to be considered a legitimate survival tactic, if you will, to protect enough time for one's research. To the contrary, in my opinion there is nothing legitimate about this, and it threatens the fabric on which our academic life is based. In my view, it is one of our jobs in the business of biomedical research, especially that which is based in academia, to ensure that there is an adequate supply of those whose sense of civic consciousness brings them to commit their best talents to the overall good. Maybe I've come full circle to return to the concept of altruistic genes, of which I spoke at the outset of this address!

This may seem to be an overly harsh assessment, but I reserve my greatest respect for those who have the strongest sense of academic duty. And, happily, there are many of them—many of you—in this room. We must encourage and reward those who are the most generous with their time, and we must ensure that we imbue in the next generation this same sense of citizenship. "Part of academic duty is the practice of civility in scholarly discourse—through which we may, by example, encourage the kinds of attitudes and behaviors we see among our most generous colleagues" (Kennedy, p. 184). The community depends on it.

Lesson 9: The Community

Let me conclude with a few thoughts about this community. I was trained in human genetics, have spent my entire professional life in human genetics, and have never wanted anything other than to be a part of this community. You have done me great honor by electing me to be your president, as you have done to those before me.

My time in this community has been enriched enormously by "the kinds of attitudes and behaviors we see among our most generous colleagues." I've already mentioned my mentors. But I'm equally indebted to a number of other colleagues who were unusually generous in helping me to find my voice. Sometimes, it was just a small thing, a gently encouraging word here or there, an invitation to dinner when in a strange city, someone taking or returning a phone call when they didn't have to, a "softball" question lobbed up to a nervous student giving his first talk, or a chance encounter that elevates the scientific soul and instills a sense of belonging to this community. Random acts of genetic kindness.

So my final plea is that we each spend a little extra energy to do what we should do best in this community—to encourage and welcome new members. This is especially true among the younger set. We should work hard to ensure that they have the opportunities to find their own voices in this community. This will be good for them, of course, but it is also good for us, as it will ensure the survival of our discipline. This Society and this meeting have always provided for many of those rites of passage that are critical to a young member finding his or her voice: reviewing an article for *The American Journal of Human Genetics;* being asked to moderate a session at our annual meeting; being invited by Victor McKusick to give a lecture at the Bar Harbor Short Course; or being asked to write a chapter for what used to be simply "Stanbury" or now "Scriver" (officially called *The Metabolic and Molecular Bases of Inherited Disease*). These were and are all big steps in the development of a professional career in human genetics. Those of us at the senior end of things have benefited enormously from being a part of this community; we should do our best to share those benefits with those just warming up their voices, still waiting in the wings.

This year's meeting will be a bit unusual for us all, because of world events that have preoccupied each of us over the course of the last month. The schedule of the meeting itself has been subject to a number of last-minute changes, to accommodate changes in plans by scheduled speakers. The schedule will have, as a result, a few holes here and there, when there will be a 15-minute gap because of a missing speaker. I would suggest that, during those breaks, you turn to a young colleague, introduce yourself, ask who they are and what they work on, ask what they want to do with their careers, tell them why human genetics is such a wonderful field to be part of, and welcome them to our community.

Ours is a community of personal and professional

generosity, notable achievement and great promise. As a field and as a Society, we have worked hard to put ourselves at the center of an immensely exciting revolution in thought, scientific understanding, and practical application. We should ensure that our community remains at the center. Let's get on with it.

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